



Transethosomes: Novel Technology for Skin Delivery of Drugs

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ABSTRACT

The human body's contact with the outside world is the skin, which has a total surface area of roughly 1.8 m². Because it removes many of the difficulties associated with the oral route, the transdermal mode of medicine administration has aroused a lot of interest in pharmaceutical research. Although the skin, particularly the stratum corneum, is a barrier to most medicine absorption, it does provide a large (1.2 m²) and easily accessible surface area for drug diffusion. Several approaches for improving bioactive delivery through transdermal distribution have recently been investigated. Some of the most frequent examples are iontophoresis, electrophoresis, sonophoresis, chemical permeation enhancers, magnetophoresis, microneedles, and vesicular systems (niosomes, liposomes, elastic liposomes such as transfersomes, ethosomes, and transethosomes). Transethosomes seem to be the most promising of the group, since they include both lipophilic and hydrophilic sections and can take therapeutic compounds with a wide range of solubility. Transethosomes may bend and pass through constrictions that are 5 to 10 times smaller in diameter than their own. Intact vesicles may be pierced more readily due to their high deformability. These vesicles may transport analgesics, anesthetics, corticosteroids, sex hormones, anticancer drugs, insulin, and other pharmaceuticals transdermally.

Key Words: Transethosomes, Transdermal, Skin, Drug Delivery, Preparation, Applications

INTRODUCTION

Oral administration is presently the most common way of medicine delivery. While this has the advantage of being simple to administer, it also has a number of drawbacks, including poor bioavailability due to hepatic metabolism (first pass) and the potential for rapid blood level spikes (both high and low), necessitating high and/or frequent dosing, which can be both costly and inconvenient. Continuous intravenous infusion is seen to be a superior mode of drug administration, not only because it avoids hepatic "first pass" metabolism, but also because it keeps the drug level in the body steady and long-lasting. However, this entails the patients' hospitalisation and medical surveillance by the administration. Simultaneously, the transdermal technique offers some advantages over conventional delivery methods, including lower plasma drug levels volatility, gastrointestinal side effects, and high patient compliance. The Stratum Corneum, with

the exception of lipophilic and low molecular weight medications, is the most difficult barrier to cross. Ultra deformable vesicles (UDV) have recently risen to prominence as a promising strategy for producing new and improved cutane-

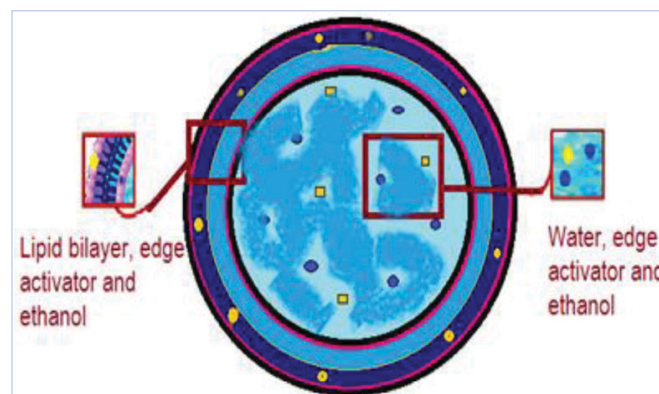


Figure 1: Structure of transethosome.

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ous and transdermal therapies. Transethosomes, for example, are thermodynamically stable deformable vesicles that are harmless. Dermal and transdermal delivery have been used to transport a variety of substances, including peptides and proteins. Furthermore, scaling up their production is simple and rapid. UDV's such as transfersomes, ethosomes, and, more recently, transethosomes have been successfully generated for both medications and cosmeceuticals. The name "transethosomes" was coined by Song et al. in 2012, and they are characterised by a high ethanol concentration (up to 30%) paired with an edge activator. Transethosomes may help both transfersomes and ethosomes. Both techniques may be used to penetrate the skin [1].

MECHANISM OF TRANSETHOSOMES

Transethosomes are a novel lipid formulation that contains phospholipids, high-concentration ethanol (30–40%), edge activators such as tween 20/60/80, span 60/65/80, sodium cholate or sodium deoxycholate, and water. As they indicate, both ethosomes and transfersomes have advantages. The size varies from 40 nm to 200 nm, depending on the medicine. The presence of ethanol separates the transethosomal system from other vesicular systems. The 'ethanol effect', which occurs when ethanol is intercalated into intercellular lipids and enhances lipid fluidity while decreasing lipid bilayer density, is thought to be the first step in the process. The action of ethanol and its high concentration in transethosomes fluidizes the stratum corneum's lipid layer, boosting the malleability and flexibility of these systems and enabling them to infiltrate via microscopic holes generated by fluidization. Alcohol reduces the size of the vesicular system by imparting a net negative charge on the surface of the vesicle. The ideal ethanol concentration range for the generation of stable

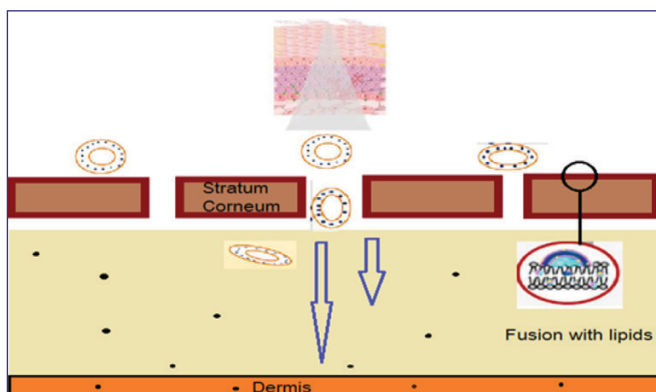


Figure 2: Dermal permeation and penetration mechanism.

ethosomes is 30–40%. Lowering the ethanol concentration to 20% may result in increased vesicular size. Phospholipids' hydrophilic head and hydrophobic tail are vital in the formation of bilayers [2].

ADVANTAGES OF TRANSETHOSOMAL DRUG DELIVERY

Other transdermal and dermal delivery methods fail in contrast:

- The transethosomal system is made up of non-toxic raw components and is passive, non-invasive, and ready for immediate commercialization.
- Transethosomal drug delivery has potential applications in animal medicine and aesthetics.
- It has a high degree of patient compliance since it is administered as a semisolid gel or a cream.
- Unlike deformable liposomes, transethosomes improve medicine delivery to the skin in both occlusive and non-occlusive circumstances.
- This drug delivery technique is more stable than other standard vesicles.
- This is a straightforward method of medication delivery compared to iontophoresis, laser surgery, cryosurgery, and other sophisticated procedures.

DISADVANTAGES OF TRANSETHOSOMAL DRUG DELIVERY

- The drug must be soluble in both lipophilic and aqueous conditions in order to permeate the dermal microcirculation and get access to the systemic circulation.
- The drug's molecular size must be acceptable to be absorbed percutaneously.

METHODS OF PREPARATION

Mechanical dispersion, cold procedure, and hot method are all methods for producing transethosomes. The cold approach is the most often used technique [3].

Hot Method

To make a colloidal solution, disperse the phospholipid in water in a water bath at 40°C. The ethanol and glycol combination is heated to 40°C. The organic phase is combined with the aqueous phase. Stirring for 7 to 10 minutes Depending on their hydrophilic/hydrophobic properties, drugs may be dissolved in either water or ethanol. The temperature is maintained at 40°C throughout the procedure. Sonication of the probe lowers the size of the vesicles.

Cold Method

Dissolve the phospholipid in the ethanol with vigorous stirring. This mixture is heated to 30°C in a water bath. Water

is heated to 30°C in a separate pot before being carefully poured into the alcoholic mixture in a fine stream. The drug may be dissolved in either water or ethanol, depending on its solubility. The mixture is maintained moving at 700 rpm on a magnetic stirrer during the addition of the aqueous solution to the ethanolic solution. To modify the size of vesicles, a probe sonicator may be utilized.

Classical method

The active medicament and phospholipid are dissolved in ethanol after consuming a combination of ethanol, active medicaments, and phospholipid. The solution mixture is then heated to about 30°C in a water bath. After that, double distilled water is added to the solution mixture while it is continually agitated at 700 revolutions per minute. With the use of a hand extruder and a polycarbonate membrane, the resultant vesicles are homogenized three times.

Mechanical Dispersion Method

Lipid and surfactant are placed in a clean, dry round bottom flask. As a solvent, the lipid mixture is dissolved in a chloroform/methanol mixture. A rotary evaporator is used to create a thin lipid layer above the lipid transition temperature. It is kept under pressure for 24 hours to remove organic solvent residues. The deposited film is hydrated with 10% v/v ethanol in phosphate buffer pH 6.5 by rotating at 60 rotations per minute. The medication is included into the mixture. Sonication is utilised to shrink the vesicles to a more manageable size.

CHARACTERIZATION OF TRANSETHOSOMES

Vesicle Shape

The shape of vesicles may be determined using both transmission electron microscopy (TEM) and scanning electron microscopy (SEM).

Particle Size and Zeta Potential

Particle size analyzers, dynamic light scattering, and photon correlation spectroscopy may all be used to measure the size of transethosomes. A zetasizer may be used to determine a

formulation's zeta potential.

Entrapment Efficiency

The percentage entrapment of the additional medicament is used to determine entrapment efficiency. The ultracentrifugation method might be used to determine this. The percent EE may be calculated as follows:

$$[Q_t - Q_s / Q_t] \times 100$$

Where Q_t is total theoretical amount of drug added and Q_s is the amount of drug found in supernatant.

Transition Temperature

The temperature at which transethosomes transition may be determined using differential scanning calorimetry (DSC).

Drug Content

To determine the medication content in transethosomes, a UV spectrophotometer might well be employed. To measure, a modified high-performance liquid chromatographic method may be utilized.

Vesicle Stability

The size and structure of vesicles may be measured over time to determine vesicle stability.

Surface Tension

The ring technique in a Du Nou ring tensiometer may be used to assess the surface tension activity of a medication in aqueous solution.

Penetration and Permeation

The depth of transethosome penetration may be measured using confocal laser scanning microscopy (CLSM).

In-vitro Drug Release

This is done in order to determine the penetration rate. Before more costly in-vivo experiments, the time required to attain steady state permeation and the permeation flux at steady state, as well as information from in vitro research, are utilized to improve the formulation.

Table 1. Materials Used in Preparation of Transethosomes.

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

Stability

The stability of the preparation may be determined if the vesicle size changes. Homogeneous preparations are regarded to be more stable than heterogeneous ones in terms of stability. Another method for determining a preparation's stability is to assess its membrane stability and molecular organization using X-ray scattering or differential scanning. Particle size analysis is solely used to assess the preparation's internal stability, not as a quality control measure [4].

APPLICATION OF TRANSETHOSOMES

Delivery of Non-steroidal Anti-inflammatory Drugs (NSAIDs)

When taken by oral, NSAIDs have been associated to a number of GI side effects. Ultradeformable vesicles with transdermal administration were selected as a consequence. Transethosomes carrying ketorolac tromethamine demonstrated higher penetration than ethosomes containing medicines. According to Garg et al., piroxicam transethosomal gel outperforms alternative vesicular systems in every way, including stability and elasticity.

Delivery of Antifungal Drugs

Transethosomes containing terbinafine, amphotericin B, and ketoconazole had better penetration. Voriconazole transethosomes showed skin penetration and deposition when compared to regular liposomes, deformable liposomes, and ethosomes.

Delivery of Anticancer Drugs

The usage of transethosome technology was employed to investigate the application of imiquimod as a transdermal drug. The results were encouraging, and they suggested a new treatment option for skin cancer. Transethosomes showed an increase in transdermal flow and penetration. Even after preservation, transethosomes retained their penetrating capacity.

Delivery of Antiviral Drugs

To investigate the efficacy of transdermal delivery of antiviral medications, Jain et al. produced nanoethosomes of lamivudine. When compared to a standard solution, the nanoethosomal formulation had a 25-fold increase in drug penetration. In T-lymphocytes, nanoethosomes demonstrated a greater absorption capacity than free drug solution.

Delivery of Cardiovascular Drugs

Touitou et al. investigated the efficacy of nanoethosomes containing minoxidil to evaluate the quantity of cardiovascular medicine delivered through a transdermal route. Nanoethosomes created with 2 percent phosphatidylcholine and

30% ethanol exhibited a greater permeability than those prepared with hydroethanolic and phospholipid minoxidil [5].

ISSUES AND FUTURE PROGRESS

The vast majority of active compounds never make it through the stratum corneum. Ethanol-based nanocarriers have opened a new window for delivering diverse bioactive chemicals transdermally since they have the ability to fluidize and break the stratum corneum's rigid lipid layer. These devices provide noninvasive medication administration for medium and large bioactive chemicals, as well as high patient compliance and low treatment costs. Clinical testing of ethanol-based nanocarrier technology, on the other hand, continues to be a challenge. Clinical testing is required to assess their potency. Because ethanol irritates the skin, ethanol-based nanocarriers must be studied in particular clinical scenarios, such as application to open eczema areas. As a consequence, further research in this area will aid in improving in vivo drug release and the development of transdermal therapy [6].

CONCLUSION

Skin permeation enhancement technology is a rapidly developing field that will result in a significant increase in the number of drugs that may be administered transdermally. As a result, skin might become an important delivery route in the next decade. By tweaking the edge activators and/or penetration enhancers, the formulator has the greatest flexibility in changing the ethosomal properties to fit the research needs. Transethosomes, for example, are extremely deformable vesicles that may carry peptides, low-penetration drugs, pharmaceuticals with a speedier and more targeted action, hormones, and antibiotics, among other chemicals. In terms of safety, efficacy, and patient compliance, they outperform other standard transdermal permeation approaches. Transethosomes have emerged as promising carriers for both local and systemic disease therapy. In the future, they might be utilized to provide various drugs through transdermal administration. To increase their viscosity and, as a consequence, their stay on the action site, these vesicles may be converted into gels.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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AUTHOR'S CONTRIBUTION

All authors have equally contributed to this manuscript. All authors did the literature survey from standard databases, collected all essential elements, and wrote this manuscript collectively.

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