

A Comprehensive Review on The Emerging Potential of Transethosomes as Innovative Vesicular Drug Delivery System

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Abstract

Transethosomes represent a novel class of lipid-based vesicular carriers that have shown significant potential for both dermal and transdermal drug administration. Evolving from ethosomal vesicular system, these systems integrate ethanol and edge activators to improve vesicle deformability and promote enhanced skin penetration. The growing demand for non-invasive and effective drug delivery, particularly for macromolecular and poorly absorbable drugs has accelerated research into transethosomes. Traditionally, the stratum corneum has posed a major obstacle to efficient topical delivery. Transethosomes overcome this barrier by navigating through both intracellular and intercellular routes. Their capability to encapsulate diverse therapeutic agents, including both hydrophilic and lipophilic drugs, as well as large biomolecules, distinguishes them from conventional delivery systems. Recent advancements highlight their effectiveness in managing various skin conditions, microbial infections, and certain cancers. Superior drug stability, enhanced penetration depth and improved systemic availability supports their growing importance in pharmaceutical nanotechnology.

Kew Words: transdermal; transethosome; vesicles; carrier; drug delivery; edge activator; flexibility; penetration

Introduction

Medications can be delivered to the human body in several ways, with oral administration being the most widely used. Nonetheless, this approach has certain drawbacks, including the possibility of the drug being lost before it enters the bloodstream and potential interactions with other medications. As a result, different methods of drug delivery have been encouraged. Transdermal drug delivery is one alternative, that offers multiple benefits compared to other administration routes. Compared to oral and injectable routes, this technique offers greater convenience for patients, bypasses first-pass metabolism, and tends to improve patient compliance.[1] Innovative lipid vesicles known as highly deformable vesicles have been developed to improve drug delivery efficiency. Various types of these

vesicles such as ethosomes, transferosomes, and transethosomes have been developed for delivering both pharmaceuticals and cosmetic products. Transferosomes are adaptable vesicular carriers composed of a dual-layer lipid structure along with an edge activator. A major limitation of this system is the difficulty in encapsulating hydrophobic drugs while maintaining its flexibility. Ethosomes are vesicular carriers composed of phospholipids and characterized by their high alcohol content in a hydroalcoholic solution. Their primary disadvantage is that, when used on the skin without occlusion, the ethanol tends to evaporate, which can result in skin dryness. Hence transethosomes were developed in order to overcome these drawbacks.[2]

Feature	Ethosomes	Transfersomes	Transethosomes
Composition	Mainly composed of phospholipids, high concentration of ethanol, and water.	Contain phospholipids and edge activators (e.g., surfactants like Tween or Span)	Contain phospholipids, ethanol, and edge activators (a hybrid of ethosomes and transfersomes)
Mechanism of skin penetration	Ethanol disrupts the skin lipid bilayer and enhances flexibility of vesicles.	Edge activators make vesicles highly deformable, allowing them to squeeze through narrow pores.	Combines ethanol's penetration enhancement with edge activators' deformability
Vesicle Flexibility	Moderately flexible	Flexible enough	Highly Flexible
Stability	Relatively stable with proper ethanol concentration.	Stable enough	Highly stable

Table 1: Comparison Of Ectosomes, Transfersomes and Transethosomes

Feature Ethosomes Transfersomes Transethosomes

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Flexible Flexible Enough Highly Flexible Stability Relatively stable with proper ethanol concentration. Stable enough Highly stable

Structure Of Transethosomes: [3,4]

Transethosomes are lipid based vesicular drug delivery system which includes phospholipids, edge activator, ethanol and water as aqueous phase. The main component comprises the phospholipid which is responsible for vesicle formation and serves as a carrier to deliver the drug through the skin.

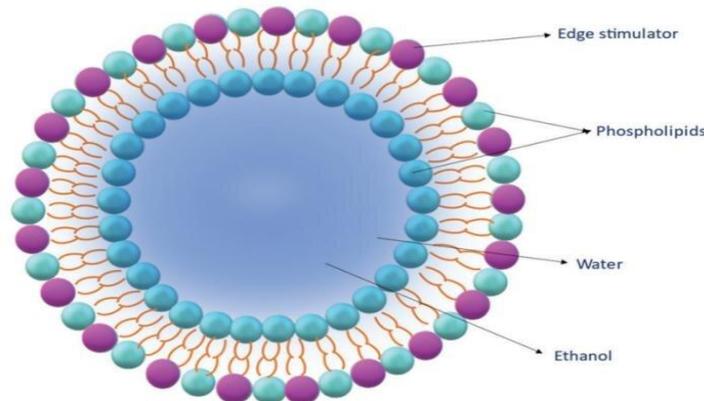


Figure 1: Structure of transethosomes

Composition [5,6]

Phospholipid:

Choosing the appropriate phospholipids plays a vital role in formulating ethosomal systems, as it greatly influences the vesicle size and the permeation characteristics of the delivery system. Phospholipid levels usually range between 2% and 5% for formulation of transethosomes.

Ethanol:

Transethosomes, a type of topical formulation, typically include 10–20% ethanol, which gives these vesicles their flexible and soft properties.

Edge activator:

Choosing the right edge activator is essential in the production of transethosomes (TEs) because it greatly impacts their properties. Although various substances can be used in TE preparation, tweens and spans are frequently chosen as the preferred edge activators.

Penetration Of Transethosomes Through Skin [7,8]

Transethosomes are known to have greater penetration than both transfersomes and transethosomes

□ Ethanol effect:

Ethanol upon interaction with the phospholipids in the stratum corneum causes disruption, fluidization and expansion of intracellular zone present between the corneocytes which allows greater penetration.

□ Edge stimulator effect:

They make the vesicles flexible and elastic enough to penetrate through the tiny pores of the skin.

Advantages: [9,10]

- Facilitates delivery of both hydrophobic and hydrophilic drugs.
- Improvement of drug absorption across the skin in transdermal drug delivery systems.
- Formulation involves use of harmless, natural materials.
- Enables smooth absorption through the layers of the skin.
- Bypasses hepatic first-pass metabolism, reducing the likelihood of side effects.
- Characterized by a non-invasive approach.

Disadvantages: [11]

- Can lead to skin irritation or allergic reactions, making it unsuitable for individuals with sensitive dermatitis.
- The drug should possess an appropriate molecular size to enable effective absorption through percutaneous layer skin.
- Excessive use of surfactants can be toxic, so their concentration must be kept within safe limits.
- Incomplete formation of vesicles may lead to the coalescence of transethosomes.

Methods For Preparation of Transethosomes

Cold Method: [12]

In this technique, to form vesicles, phospholipid is mixed with ethanol through vigorous shaking. The resulting solution is then warmed to 30°C using a water bath. Separately, water is heated to 30°C and gradually introduced into the ethanol mixture. Throughout this procedure, a magnetic stirrer set at 700 rpm is used to maintain consistent mixing.

Hot Method: [13]

Phospholipid preparation begins by dispersing it in water and heating the mixture to 40°C. At the same time, a blend of ethanol and glycol is warmed to the same temperature. The organic phase is then gradually combined with the aqueous phase under continuous stirring. The choice of solvent, either water or ethanol, depends on the drug's solubility. The temperature kept at 40°C during the entire procedure.

Thin Film Hydration Method: [14]

In this technique, the precisely measured drug, lipid, and edge activator are dissolved in an organic solvent blend. Using a rotary evaporator, the solvent is evaporated under reduced pressure, creating a thin film. This film is subsequently hydrated with a pH 7.4 buffer containing varying ethanol concentrations. This results in formation of vesicles which are then observed under projection microscope.

Ethanol Injection Method: [15]

Phospholipid, edge activator, and the drug are dissolved together in an organic solvent, such as ethanol, with thorough mixing. This solution is then quickly injected in a thin stream through a fine needle into water while

stirring continuously. As a result, the lipid molecules precipitate and assemble into bilayer planar fragments that encapsulate the aqueous phase. Finally, the sample undergoes centrifugation and filtration then formed transethosomes are checked under microscope.

Characterization of transethosomes:

Vesicle size:

One of the primary assessments involves determining the vesicle size and size distribution using techniques such as Dynamic Light Scattering (DLS). This provides insight into the average particle size and polydispersity index, both of which significantly influence drug release and absorption characteristics. [16]

Surface morphology:

The morphology and structural integrity of transethosomes are examined using sophisticated imaging methods such as Transmission Electron Microscopy (TEM), Scanning Electron Microscopy (SEM), and Atomic Force Microscopy (AFM) which help confirm vesicle formation and assess their uniformity. [17]

Zeta potential:

The zeta potential is also measured to evaluate the surface charge of the vesicles, offering an indication of their physical stability; higher absolute zeta potential values typically suggest better stability resulting from electrostatic forces of repulsion between vesicles.

Entrapment efficiency:

The entrapment efficiency of transethosomes can be determined using ultra centrifugation technique which is done at 15000 rpm for up to 40 minutes at temperature 4°C which separates out the untrapped drug. The amount of drug entrapped can be determined through UV-spectroscopy. [18]

Drug content:

In order to assess the amount of drug present in formulation UV spectroscopy can be used, which is determined by dissolving 1ml of formulation with 10 ml of solvent. Whereas to quantify HPLC can be employed. [19]

Invitro drug release studies:

This study includes use of Franz diffusion cell. A presoaked diffusion membrane in pH 7.4 phosphate buffer placed between the donor and receptor compartment. The receptor compartment consists of the buffer while 1ml of formulation is placed in the donor compartment. This is placed on magnetic stirrer at 100 rpm and temperature maintained at 37±2°C, 1ml of sample is withdrawn every one hour up to 12 hrs and replaced with same quantity of buffer and analysed under microscope. [20]

Applications:

1. Antifungal Drug Delivery:

Comparison of an econazole-loaded transethosomal gel with a commercially available econazole nitrate topical cream was reported. The study aimed to evaluate the antifungal efficacy of the formulation. Findings revealed that the transethosomal gel demonstrated superior skin retention and notable antifungal effects. Additionally, the gel exhibited a consistent and controlled drug release profile successfully treated superficial Candida infection of the skin. [21]

2. Anticancer Drug Delivery

Researchers conducted studies aimed at treating cutaneous melanoma using a transethosomal formulation containing a dual drug combination. Two drugs with synergistic effects, dacarbazine and tretinoin were selected, as they

showed reduced cellular toxicity compared to other drug formulations. Dual-loaded transethosomes exhibited enhanced anticancer activity in comparison to those containing a single drug. It was noted that the drug penetrated through the skin could be due to transethosomal formulation[22]

3. Antiarthritic Drug Delivery

Antioxidant-coated transethosomes were developed by loading them with Sinomenine hydrochloride and then applying an ascorbic acid coating. This formulation enhanced transdermal absorption and drug delivery, targeting oxidative stress associated with rheumatoid arthritis.[23]

4. Antihypertensive Drug Delivery

Although antihypertensive drugs are commonly taken orally, their effectiveness can be reduced by first-pass metabolism in the liver. For example, incorporating olmesartan medoxomil into a transethosomal gel improved its skin permeability, allowing for enhanced delivery via the transdermal route and overcomes the drawback of first pass metabolism.[24]

Conclusion:

Certain drugs are unable to penetrate the skin's outer barrier. However, when incorporated into transethosomal formulations, the drug can traverse through the stratum corneum via both intercellular and intracellular pathways. Transethosomes consist of ethanol and an edge activator. Ethanol enhances the fluidity of the lipid bilayer and contributes to a reduction in vesicle size, while the edge activator facilitates skin pore disruption and boosts penetration. Transethosomes show promise for use in cancer therapy, especially for skin cancer. When large biomolecules are encapsulated within transethosomal formulations, their ability to penetrate deeper skin layers is enhanced. These characteristics establish transethosomal vesicular carriers as valuable tools in pharmaceutical nanotechnology and drug delivery systems.

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