Transethosomes: A Next-Generation Ultra-Deformable Vesicular System for Enhanced Transdermal Drug Delivery

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***Abstract*—Transdermal drug delivery offers a non-invasive alternative to oral and parenteral routes, but the stratum corneum remains a major barrier to effective drug permeation. Vesicular carriers such as liposomes, ethosomes, and transfersomes have been explored to overcome this barrier, each with specific advantages and limitations. Transethosomes (TEs) represent a hybrid, next-generation ultra-deformable vesicular system that combines the ethanol-rich composition of ethosomes with the edge-activator (surfactant)-mediated elasticity of transfersomes. This combination confers superior deformability, enhanced skin permeation, higher drug entrapment efficiency, and the ability to co-deliver both hydrophilic and lipophilic drugs. This review discusses the composition, mechanism of skin penetration, methods of preparation, characterization parameters, advantages over conventional vesicular systems, therapeutic applications, and current challenges associated with transethosomes.**

***Index Terms*—Transethosomes; ultra-deformable vesicles; transdermal drug delivery; edge activators; ethosomes; nanocarriers**

I. INTRODUCTION

The transdermal route has gained considerable attention as an alternative to oral and parenteral drug administration because it avoids hepatic first-pass metabolism, minimizes gastrointestinal degradation, improves patient compliance, and allows controlled, sustained drug release. However, the stratum corneum — the outermost, densely packed lipid layer of the skin — acts as a formidable barrier that restricts the penetration of most therapeutic molecules, particularly those with high molecular weight or poor lipophilicity (1).

To overcome this barrier, various lipid-based vesicular carriers have been developed, including liposomes, niosomes, transfersomes, and ethosomes. Among these, transethosomes have emerged as an advanced hybrid vesicular system. Structurally, they combine the high ethanol content and phospholipid bilayer of ethosomes with the surfactant-based "edge activators" that give transfersomes their elasticity. This dual mechanism allows transethosomes to squeeze through the intercellular lipid channels of the stratum corneum, achieving deeper and faster skin penetration than either ethosomes or transfersomes alone (2).

II. COMPOSITION OF TRANSETHOSOMES

Transethosomes are typically composed of:
Phospholipids (e.g., soya phosphatidylcholine, egg phosphatidylcholine, or synthetic lecithins) — form the vesicular bilayer.
Ethanol (and sometimes other alcohols such as isopropyl alcohol) — present in relatively high concentration (20–45% v/v); imparts fluidity to the lipid bilayer, gives the vesicle its negative surface charge, and interacts with the polar head groups of the stratum corneum lipids to enhance permeability (3).
Edge activators/surfactants (e.g., Tween 80, Span 80, sodium cholate, sodium deoxycholate, oleic acid) — destabilize the lipid bilayer locally, increasing membrane flexibility and vesicle deformability.
Water— the dispersion medium.
Drug (hydrophilic, lipophilic, or amphiphilic) — can be loaded in the aqueous core, the lipid bilayer, or at the interface, depending on its physicochemical properties.

Occasionally, penetration enhancers (e.g., propylene glycol) are added to further improve skin permeability (4).

III. MECHANISM OF SKIN PENETRATION

Transethosomes are believed to enhance drug delivery through skin via a combination of mechanisms:

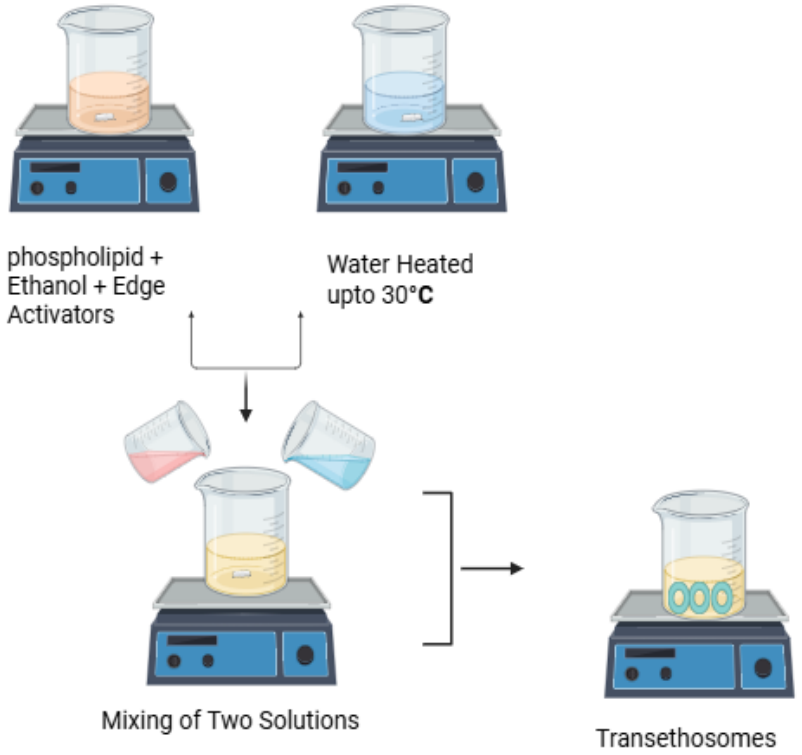
1. Ethanol effect: Ethanol fluidizes both the vesicle membrane and the intercellular lipids of the stratum corneum, temporarily disrupting the tightly packed lipid bilayers and creating transient channels for vesicle passage (5).
2. Elasticity/deformability effect: The presence of edge activators reduces interfacial tension and allows the vesicle to deform and squeeze through pores/channels much smaller than its own diameter, without rupturing — a property known as "self-optimizing deformability."
3. Vesicle fusion and penetration-enhancing pathway: Transethosomes may fuse with skin lipids, release their contents at various depths of the skin, and/or penetrate intact through intercellular and transappendageal (hair follicle/sweat gland) routes (6).
4. Synergistic "push–pull" mechanism: The combined ethanol–edge activator effect is generally considered synergistic rather than additive, producing greater flux than ethosomes or transfersomes individually.

IV. METHODS OF PREPARATION

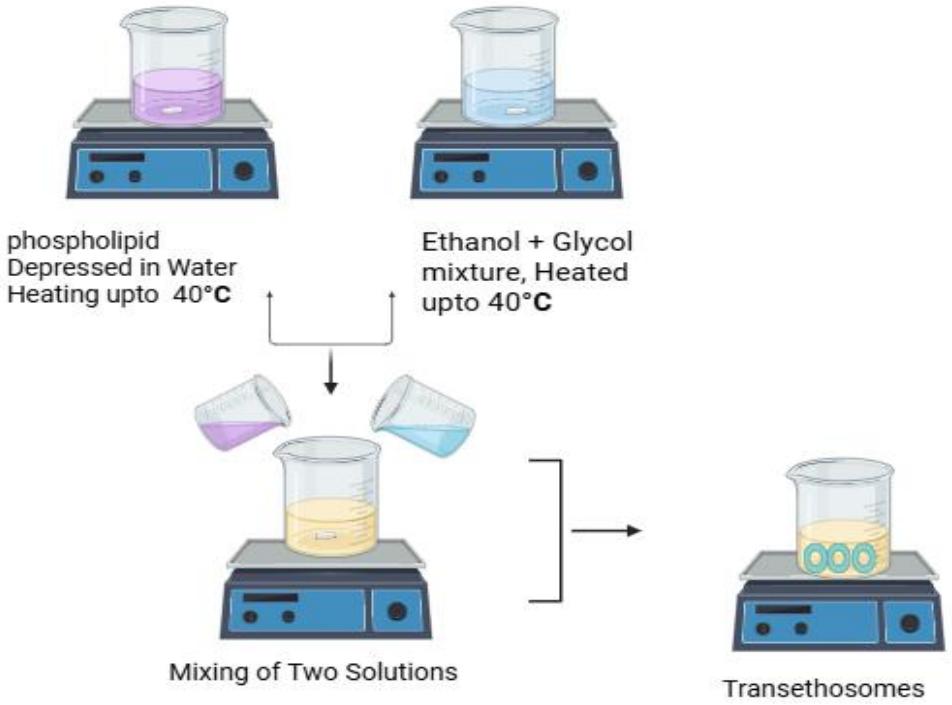
Several methods have been reported for the preparation of transethosomes, chosen based on drug solubility and desired vesicle characteristics:

Method

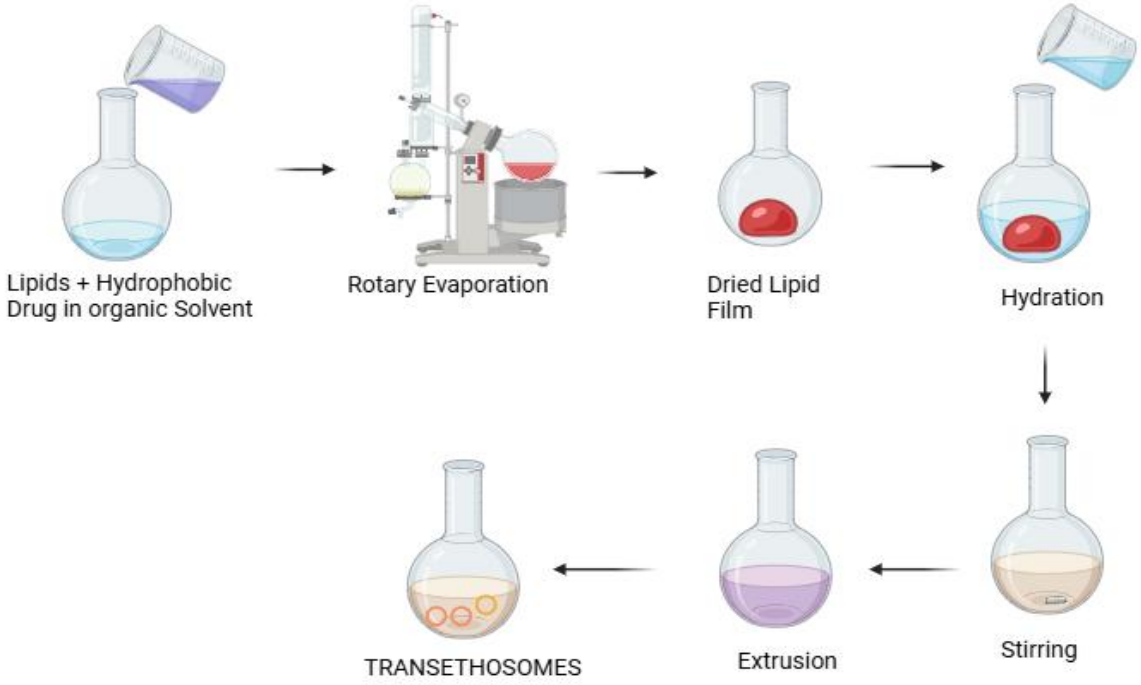
Cold method -Phospholipid, edge activator, and drug are dissolved in ethanol; water/drug solution is added slowly under stirring at controlled temperature. Most commonly used method (7).



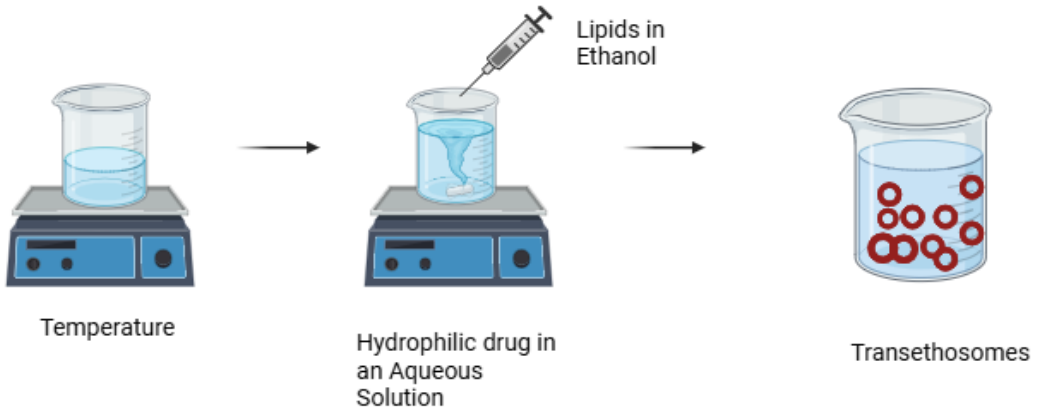
Hot method- Phospholipid is dispersed in water and heated; ethanol and edge activator are added to the hot aqueous phase followed by drug incorporation.



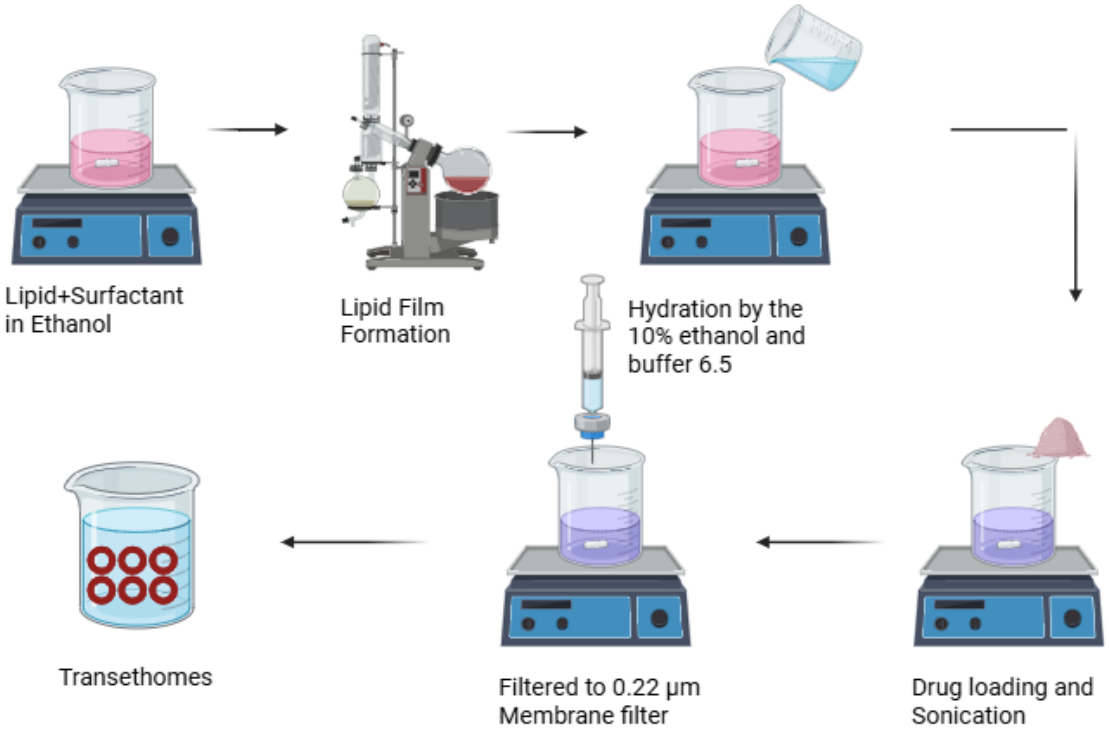
Thin-film hydration method- Lipid and surfactant are dissolved in organic solvent, which is evaporated to form a thin film; the film is then hydrated with an ethanol–water/drug solution.



Ethanol injection method - Lipid, drug, and edge activator dissolved in ethanol are injected into an aqueous phase under stirring, forming vesicles spontaneously (5).



Mechanical dispersion/sonication- Coarse vesicles are further reduced in size using probe or bath sonication, or extrusion through polycarbonate membranes.



Characterization Parameters

Transethosome formulations are typically evaluated for:

Vesicle size and morphology — dynamic light scattering (DLS)/photon correlation spectroscopy and transmission/scanning electron microscopy (TEM/SEM) (8).

Zeta potential — indicates surface charge and colloidal stability.

Entrapment/encapsulation efficiency — via ultracentrifugation, dialysis, or gel filtration followed by drug assay.

Vesicle elasticity/deformability index — measured by extrusion through membranes of defined pore size under pressure.

pH determination — to ensure skin compatibility (9).

Drug content and in-vitro drug release — using dialysis membrane/Franz diffusion cell.

Ex-vivo skin permeation studies — using excised animal or human skin mounted on Franz diffusion cells; parameters include cumulative drug permeated, flux, and enhancement ratio.

Skin retention/deposition studies — using tape-stripping or confocal laser scanning microscopy (CLSM).

Stability studies — under different storage conditions (temperature, light) over time (7).

Advantages of Transethosomes over Other Vesicular Systems

- Higher skin permeation and faster onset of action compared to liposomes, ethosomes, or transfersomes alone.
- Ability to encapsulate both hydrophilic and lipophilic drugs.
- Higher entrapment efficiency due to the combined solubilizing effect of ethanol and edge activators.
- Improved vesicle stability and reduced vesicle aggregation.
- Non-invasive route improves patient compliance compared with injectables.
- Potential for sustained/controlled drug release, reducing dosing frequency and systemic side effects.
- Avoidance of hepatic first-pass metabolism and gastrointestinal degradation associated with oral delivery (9).

Therapeutic Applications

Transethosomes have been investigated for the delivery of drugs across several therapeutic categories, including:

Analgesics/anti-inflammatory agents— e.g., piroxicam, for localized pain and inflammation management.

Antibiotics and antivirals — for improved local/systemic bioavailability.

Anticancer agents — for localized tumor therapy and reduced systemic toxicity.

Anti-arthritic agents — e.g., baicalin-loaded transethosomes explored for rheumatoid arthritis.

Hormone replacement therapyagents (11).

Natural/phytoconstituents (e.g., capsaicin) — for enhanced penetration of poorly permeable plant-derived actives.

Emerging exploration in transvaginal, pulmonary, and ocular delivery, in addition to the conventional transdermal route (10).

Current Challenges and Future Perspectives

Despite their promise, several challenges limit the clinical translation of transethosomes:

Formulation stability — long-term physical and chemical stability (vesicle aggregation, drug leakage) remains a concern.

Variability across skin types — differences in skin thickness, lipid composition, and barrier integrity among individuals can affect permeation consistency.

Scale-up and regulatory hurdles — reproducibility during large-scale manufacturing and lack of standardized regulatory guidelines for nanovesicular transdermal products.

Limited data on large biomolecules — delivery of peptides, proteins, and nucleic acids via transethosomes is still underexplored (12).

Need for combination and stimuli-responsive systems — future work is directed toward multi-drug loaded and stimuli-responsive (pH-, temperature-, or light-triggered) transethosomal systems for personalized medicine.

V. CONCLUSION

Transethosomes represent a promising evolution in vesicular transdermal drug delivery technology, merging the penetration-enhancing properties of ethanol-based ethosomes with the elastic

deformability conferred by edge activators in transfersomes. Their ability to deliver diverse drug molecules with enhanced permeation, bioavailability, and controlled release makes them an attractive platform for a wide range of therapeutic applications. Continued research addressing formulation stability, scalability, and regulatory standardization will be essential to translate transethosome-based systems from laboratory research into clinically approved products (13).

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