

# Transethosomes: Novel Transdermal Drug Delivery Technology

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## ABSTRACT

The transdermal route is one of the effective routes for delivering drugs. It also overcomes many limitations associated with oral delivery. One of the limitations of this route is the drug's poor skin permeability—stratum corneum, the skin's outermost layer that also acts as a barrier for the drug to penetrate. Traditional liposomal formulation is utilized to overcome these limitations. However, these liposomes also have certain difficulty in delivering drugs across the barriers. Ultra-deformable vesicles are novel vesicular structures that are flexible and stable, they can easily bypass the skin barriers more efficiently and thus enhance bioavailability. These vesicles consist of ethosomes, transethosomes, and transferosomes. Transethosomes are more advanced than other vesicular systems because they contain ethanol, phospholipids, and edge activators, making them more deformable and easier to penetrate deeper skin membranes. These vesicular systems can be prepared by various methods, such as cold, hot, and thin film hydration. Characterization of transethosomes includes vesicular size, zeta potential, polydispersity index and encapsulation efficiency, stability, and drug release studies. These vesicular systems can be utilized to deliver a variety of medications transdermally, including analgesics, antibiotics, and arthritis medications. Since a few years ago, the delivery of drugs through the skin has gained popularity. By doing so, it gets around problems with the oral route. Despite the fact that only a few pathways are as appealing as the transdermal route, it is difficult to deliver drugs through the skin. Researchers have developed a technique that allows the medicine to be encapsulated into vesicles, which may then go deep into the layer of skin to reach the target spot. Consequently, bioactive agents can penetrate the skin more effectively. Liposomes, niosomes, transethosomes, and transferosomes are vesicular systems that frequently remain collected in the skin layers. Transethosomes can pass through multiple layers of skin because they have tiny particle sizes and can change the form of vesicles more easily than another vesicular system. Transethosomes allow the medicine to be conveniently delivered to the target place. Ethanol, phospholipids, and an edge stimulator make up transethosomes. Transethosomes' ability to penetrate the skin is improved by ethanol and edge stimulators. It increases patient cooperation because it is a non-intrusive procedure. It also improves the effectiveness of drug entrapment. These vesicles can hold a wide range of medications, including pain relievers, antitumor medicines, steroids, proteins, and peptides. Transethosomes minimize plasma fluctuations, first-pass metabolism, organ toxicity, and poor bioavailability. This comprehensive review provides an in-depth exploration of transethosomes, starting with an overview of the impact of formulation components on their properties and effective targeting. This article delves into the production techniques and evaluation properties employed to ensure efficient drug delivery. A significant contribution of this review lies in the analysis of various routes of administration for transethosomes, including transdermal, transvaginal, pulmonary, and ocular delivery, showcasing the versatility of transethosome-loaded with drugs and their potential to target specific tissues to achieve controlled release.

**Keywords:** Transethosomes, Novel, Transdermal, Drug Delivery Technology

## INTRODUCTION

The oral route of medication administration is the most practical, although some oral medications may have serious disadvantages, such as decreased bioavailability caused by hepatic first-pass metabolism, stomach irritability, and unpleasant taste. A transdermal strategy has been tried as a solution to

these problems because it offers advantages such as skipping the hepatic first-pass metabolism. When it comes to medications with a high first-pass metabolism, topical formulations can demonstrate greater bioavailability than oral routes. It has some restrictions, such as the fact that medications with greater molecular weights cannot reach the horny

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layer. Drugs with greater or lesser distribution coefficients have trouble entering the bloodstream. Drugs are delivered into the skin using liposomes, but their penetration is limited by their propensity to stay in the upper stratum corneum. New lipid vesicles called highly-deformable vesicles have been created to enhance medication delivery. There are many different forms of this type of vesicle, including ethosomes, transferosomes, and transethosomes, that are created for the administration of cosmetics and medications. Transferosomes are flexible vesicular transporters with a lipid dual-layer architecture and an edge stimulator. Edge stimulator is still present in the formulation in spite of the water which has evaporated. This formulation's principal drawback is that it is challenging to load hydrophobic medicines in this vesicular system with retaining their elastic characteristics. As a result of this, ethosomes are created. Ethosomes are vesicular transporters made of phospholipids that have a high alcohol content and are hydro-alcoholic. The main drawback of ethosomes is that when applied to surface under non-occlusive state, the ethanol in the mixture evaporates, leading to skin dryness. [3,5] Thus, transethosomes, a combination of transferosomes and ethosomes, are created. Transdermal drug delivery systems use the skin as a conduit for pharmaceuticals, allowing them to enter the bloodstream. A few benefits of this approach are that it avoids first-pass metabolism, is less invasive (some treatments are completely non-invasive), is simple to use, doesn't require the help of qualified specialists, and may require fewer dosages. Substances that are both lipophilic and lipophobic have been administered by transdermal devices. Because of these advantages, pharmaceutical researchers design transdermal drug delivery methods, focusing on enhancing drug penetration through the skin by modifying or avoiding the stratum corneum [1]. Transethosomes are modified ethosomes with an edge activator or permeation enhancer. These are employed to provide a variety of medications via transdermal methods. By increasing hydration and vesicular penetration, they can readily penetrate the skin by fluidizing its layers and enlarging its lipid bilayer. Numerous skin diseases, including vitiligo, psoriasis, atopic dermatitis, and skin cancer, are treated with these nanocarriers. [2,4]

## **Transdermal Pathway.**

### **Skin barrier.**

The stratum corneum, an outer layer of keratinocytes structured in a denser manner to prevent endogenous substances from penetrating the skin, is the important barrier that prevents medications from penetrating. It is a barrier of defense that keeps the majority of medications and foreign substances out of the skin and aids in homeostasis. Drugs can enter the skin through the intercellular, transcellular, and appendage channels thanks to the structural properties of the stratum corneum. Figure 1 illustrates these different paths. The intercellular route, which has been suggested to be the most significant drug delivery mechanism, involves the drug molecules moving between the densely packed lipophilic cells of the stratum corneum and negotiating the intricate lipid matrix between keratinocytes [6]. This pathway is usually used to transport medicinal molecules that are tiny and lipophilic (fat-soluble). Drugs travel straight through the stratum corneum's keratinocytes in the transcellular pathway. This path entails passing through both the watery cellular contents and the lipophilic membranes. The cellular components in between make it one of the most difficult medication delivery routes. The appendageal system uses hair follicles and sudoriferous glands to distribute medications. Although they make up a smaller portion of the skin's surface, hair follicles and sudoriferous glands provide an alternate pathway around the stratum corneum barrier. The platform can therefore deliver nanoparticles via this way [7]. Because of its high concentration of collagen (about 70%) and elastin fibers, the dermis layer—which varies in thickness across different body areas—is principally responsible for the skin's strength and elasticity. Its main job is to clear the lymphatic vessels of contaminants. The innermost layer of skin, known as the hypodermis, is made up mostly of fat cells and acts as a barrier between the skin and the body's structures underneath. These cells serve as shock absorbers, heat insulators, and conduction channels for blood vessels and nerves [7,8]. Fig.no.01

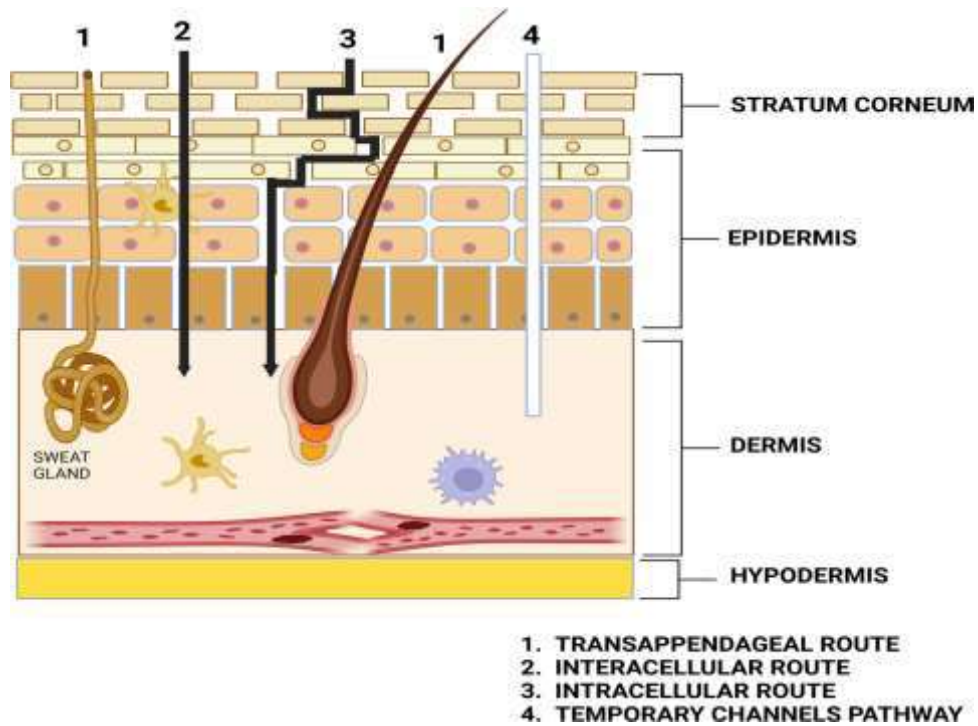


Fig.no.01

### Method to overcome.

Both active and passive methods get past these epidermal barriers to distribute the medication molecules. The active strategy includes both chemical and physical methods, which makes drug distribution easier. Chemical methods include the use of oleic acid (fatty acids) and surfactants, which break the strong bond between epidermal layers and increase the drug's transit speed and efficiency [9]. Sonophoresis, thermal ablation, microneedles, electroporation, and iontophoresis are physical methods of skin penetration. The medication can enter via disrupting the skin's membrane. This can be accomplished chemically or physically. With this physical method, specific tools are utilized to break down the membrane, which allows the medication to enter the skin more deeply and more efficiently enter the systemic circulation. Consequently, one of the alternate strategies to get around these restrictions is the passive approach. These methods are more patient-compliant and use carriers based on nanotechnology to administer medications without

the need for external devices. Because they are smaller, the nanoparticles have a greater surface area for absorption and penetration. These nanocarriers can have different sizes, shapes, and charges depending on how they are prepared [10]. Based on their makeup, the nanoparticles can be divided into a number of groups, including lipid, polymeric, and inorganic-based. Phospholipids, cholesterol, or fatty acids are examples of lipid-based nanoparticles that are utilized in cosmetics and local medicine delivery. Liposomes, lipid nanoemulsions, SLNs, NLCs, and other lipid-based nanoparticles are examples [34]. By coating the surface of the nanoparticles, these molecules can be directed to particular target areas, allowing the drug molecules to be actively targeted. Drug molecules may be able to pass through nanoparticles more easily if chemical moieties such as bile salts, surfactants, ethanols, and terpenes are added. The properties and functions of the therapeutic molecules are taken into consideration when choosing nanoparticles [11]. The different skin barriers and how to get past them are shown in Fig.no.2.

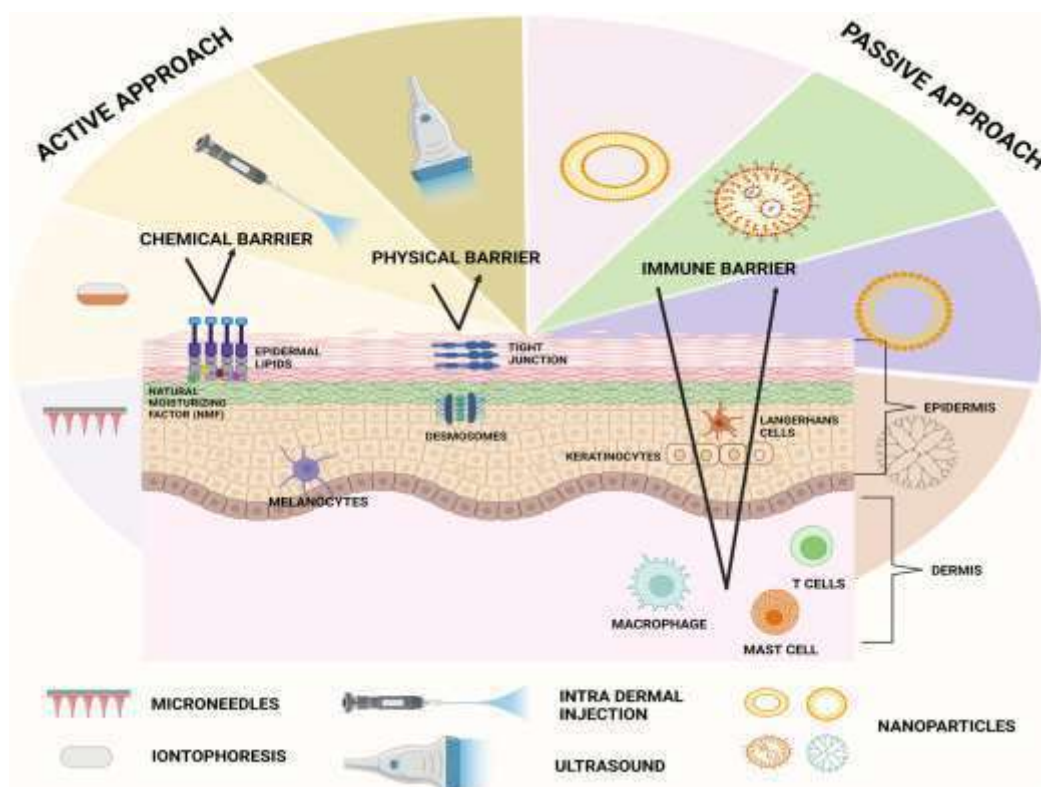


Fig.no.02

## Structure of Skin.

### The Three Layers of Skin

Your skin has three main layers: the epidermis, dermis, and hypodermis.

### Epidermis

The epidermis is the outermost layer, primarily made of keratinocytes. It consists of two distinct parts:

The stratum corneum, also known as the horny layer, is the non-viable (dead) epidermal layer. This outermost part of your skin is made of tightly packed lipid bilayers that surround corneocytes. It forms a vital barrier, preventing external substances from entering the body and significantly limiting medication absorption. The viable epidermal layers lie beneath the stratum corneum.

### Dermis

Beneath the epidermis lies the dermis, a layer composed of a connective tissue matrix. This is where medications are absorbed into the body. Structures like hair follicles, sebaceous (sebum) glands, and sweat glands extend from the dermis up into the epidermis, also playing a role in drug transport.

## Hypodermis

The hypodermis is the deepest layer, made up of subcutaneous fat tissue. It acts as a protective and nourishing cushion, shielding blood capillaries and nerve endings from shock.

### Methods for Preparation. Fig.no.03

#### Cold Method for Transethosome Preparation

The "cold method" is a widely adopted technique for formulating transethosomes, particularly beneficial for drugs sensitive to heat.

General Procedure for the Cold Method:

**Lipid Mixing:** Lipids, such as phospholipids, are combined with 10-30% ethanol and continuously stirred at room temperature.

**Edge Activator Addition:** An edge activator (e.g., Polysorbate 80, sorbitan monooleate 80) is then added to the mixture.

**Controlled Heating:** The mixture is subsequently heated to 30°C with continuous stirring. Separately,

water is also heated to 30°C before being added to the alcoholic lipid mixture.

**Sonication & Storage:** The resulting mixture undergoes sonication to reduce the size of the transethosomes. Finally, the finished product is stored in a refrigerator.

**Example:** Meiti Rosmiati et al. Study (2018)

Meiti Rosmiati et al. successfully developed a transethosomal vesicular system containing serum with 4-n-butyl resorcinol using a variation of the cold method. Their approach involved two distinct phases:

**Lipid Phase:** Soya lecithin was dissolved in an organic solvent with constant stirring for 5 minutes, followed by the addition of a surfactant, stirred for another 10 minutes.

**Aqueous Phase:** This phase consisted of aquadest and 4-n-butyl resorcinol.

**Vesicle Formation:** The aqueous phase was gradually added to the lipid phase while stirring at 700 rpm for one hour.

**Size Reduction & Characterization:** After vesicle formation, the dispersion was sonicated for 25 minutes to produce small, uniformly sized vesicles. Their optimized formulation exhibited excellent characteristics:

Particle size: 197.4±4.94 nm

Polydispersity Index (PDI): 0.421±0.02

Zeta potential: -56.8±4.24 mV

Encapsulation efficiency: 98.40±0.81% [32]

### Hot Method for Transethosome Preparation

The "hot method" is another approach for preparing transethosomes, involving controlled heating during the formulation process.

**General Procedure for the Hot Method:**

**Aqueous Phase Preparation:** Phospholipids (e.g., phosphatidylcholine, phosphatidylserine) are

dispersed in water and heated to 40°C in a water bath to form a colloidal solution.

**Alcoholic Phase Preparation:** Separately, ethyl and dihydric alcohol are combined and also maintained at 40°C.

**Mixing Phases:** The aqueous phospholipid solution is then gradually added to the alcoholic mixture with continuous stirring for 7-10 minutes.

**Drug Incorporation:** The active pharmaceutical ingredient (API) is dissolved in either ethanol or water, depending on its hydrophilic or hydrophobic nature. This API solution is then combined with the resulting colloidal mixture.

**Sonication:** The entire process is maintained at a consistent 40°C, and the transethosomes are sonicated to achieve smaller vesicle sizes.

**Example:** Heba Hesham et al. Study (2020)

Heba Hesham et al. successfully formulated Tofacitinib citrate-loaded transethosomes using the hot method. Their specific procedure involved:

**Lipid Film Formation:** Tofacitinib citrate (2.5 mg), phosphatidylcholine (150 mg), oleic acid (20 mg), and the edge activator Cremophor A25 (10 mg) were dissolved in 30% ethanol in a round-bottom flask until a thin lipid film formed.

**Hydration & Stirring:** The lipid film was then hydrated with distilled water, and the resulting suspension was stirred for 30 minutes.

**Maturation & Storage:** The formulation was left for an hour before being stored in a refrigerator at 4°C for subsequent characterization studies.

Their optimized formulation demonstrated favorable properties:

Vesicular size: 359.46±11.82 nm

Encapsulation efficiency: 83.76±7.95%

Polydispersity Index (PDI): 0.378±0.073

Zeta potential: 33.17±1.34 mV. [33]

## Thin Film Hydration Method for Transethosome Preparation

The Thin Film Hydration Method is a widely utilized technique for preparing transethosomes.

General Procedure:

**Film Formation:** Phospholipids (like phosphatidylcholine) and edge activators (e.g., Tween 80, Span 80) are dissolved in an organic solvent (e.g., chloroform or a 3:1 chloroform-methanol mixture) within a round-bottom flask.

**Solvent Evaporation:** The organic solvent is then removed using a rotary evaporator, leaving a thin lipid film on the inner surface of the flask. To ensure complete solvent removal, nitrogen gas is introduced into the flask, which is then left at room temperature for 24 hours.

**Hydration:** The dried lipid film is gradually hydrated over an hour using a phosphate buffer solution with ethanol, or a mixture of distilled water and ethanol.

**Temperature:** The hydration medium's temperature is crucial; it must be above the lipid's gel-to-liquid crystalline phase transition temperature. This influences surfactant molecule packing, thereby affecting the size and morphology of the resulting vesicles.

**Hydration Time:** Longer hydration times generally lead to smaller vesicle sizes, as vesicles swell during this period.

**pH:** The pH of the hydration medium is also vital, as it impacts the drug's solubility and, consequently, its encapsulation efficiency within the vesicles.

Example: Kanika Arora et al. Study (2022)

Kanika Arora et al. successfully prepared silver sulfadiazine-loaded transethosomes (SSLT) coupled with vitamin E using the thin film hydration method. Their process involved:

**Dissolving Components:** Vitamin E, lipids, surfactants, and silver sulfadiazine were dissolved in organic solvents at a 2:1 ratio in a round-bottom flask.

**Thin Film Formation:** A rotary vacuum evaporator was used to evaporate the organic solvent, forming a thin lipid film.

**Hydration & Sonication:** The film was then hydrated with phosphate-buffered saline and probe sonicated to reduce the vesicular size.

**Storage:** The resulting suspension was lyophilized and stored under refrigerated conditions for further characterization.

Their study found that the particle size of SSLT was  $208.98 \pm 18.49$  nm before extrusion, which slightly decreased to  $205.14 \pm 14.13$  nm after extrusion. The formulation also exhibited an elasticity of 4.10 and a deformability index of 0.981. [34].

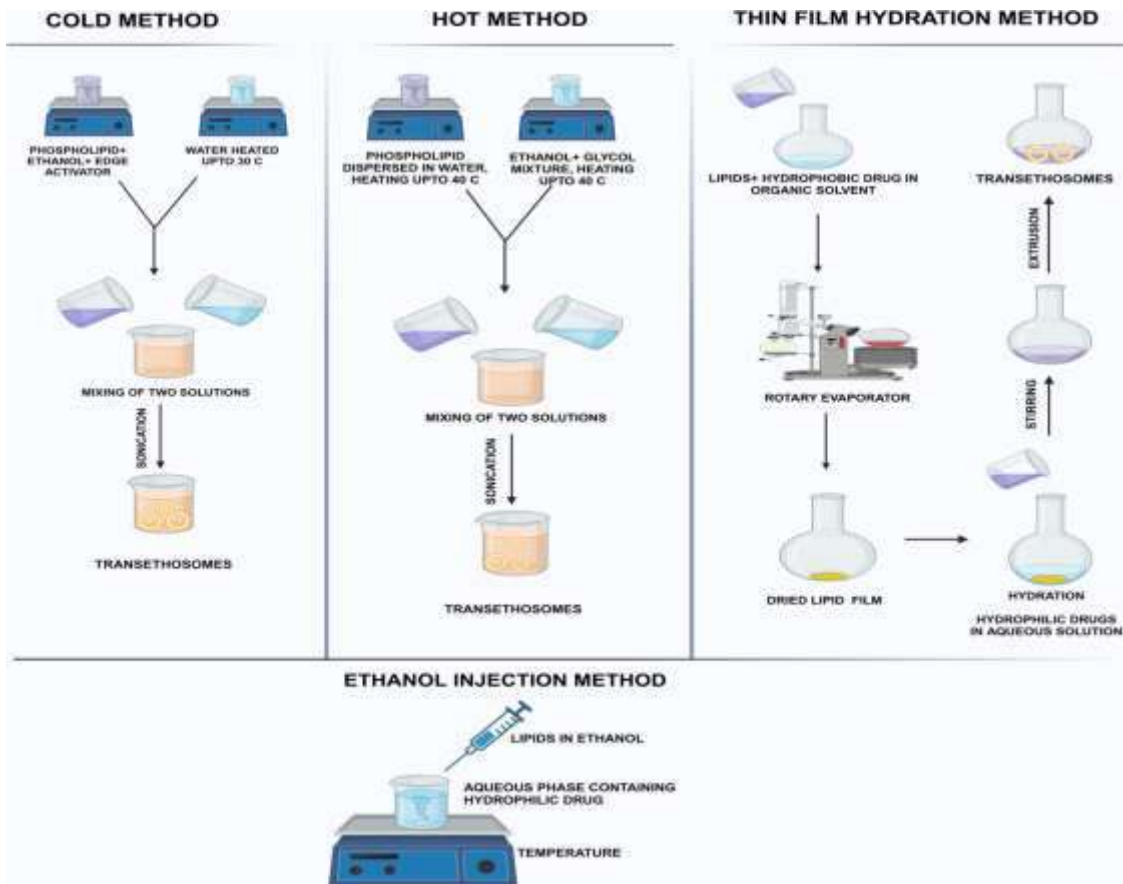


Fig.no.03

**About Transethosomes.**

**Structure of Transethosomes**

Transethosomes are an advanced drug delivery system combining features of transferosomes and ethosomes. They are highly deformable and flexible, allowing for enhanced penetration and drug release across various routes like transdermal, ophthalmic, transvaginal, and

pulmonary. Composed of phospholipids, edge activators, ethanol, and water, they offer improved stability (with added cholesterol), can encapsulate both hydrophilic and hydrophobic drugs, and can be modified for targeted delivery. While their high alcohol content might cause skin irritation, their overall benefits in biocompatibility, efficacy, and scalability make them a promising option for drug delivery. Fig.no.04

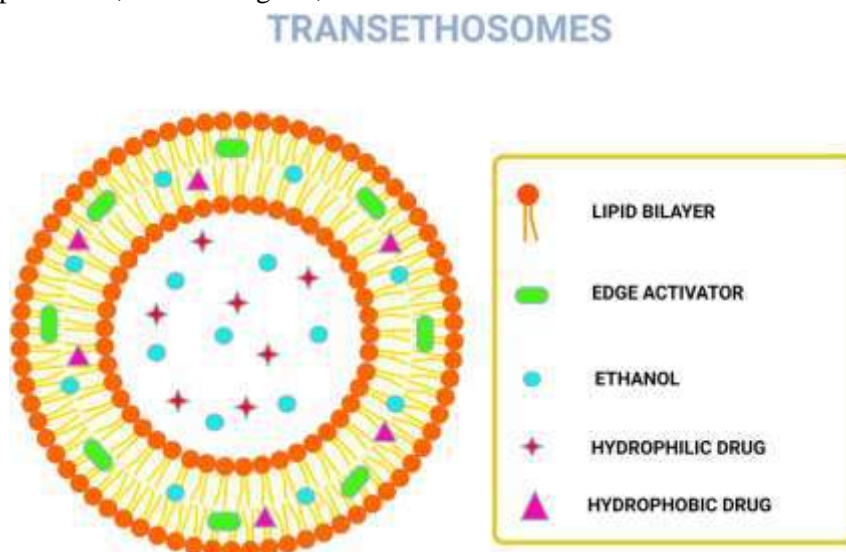


Fig.no.04

## Composition.

### Phospholipids

Vesicular development requires phospholipids, which can be produced naturally. By fluidizing the stratum corneum layer, natural phosphoglycerides or phospholipids—found in foods like sunflower seeds, soybeans, and egg yolks—improve skin penetration. Additionally, saturated (hydrogenated) phospholipids extend medication retention by assisting in the restoration of the skin's barrier function. For example, phosphatidic acid, phosphatidylcholine, phosphatidylinositol, phosphatidylethanolamine, phosphatidylserine, and phosphatidylglycerol are all forms of phospholipids [12,13]. Because natural phospholipids contain unsaturated hydrocarbon chains, they are less stable than manufactured phospholipids. Dimyristoyl phosphatidylcholine, distearoyl phosphatidylcholine, dipalmitoyl phosphatidylcholine, and others are examples of synthetic phospholipids. The drug loading, vesicular size, zeta potential, penetration, and stability of the nanoparticles are all impacted by the kind and concentration of phospholipids. Transethosomes are made with phospholipids at quantities of 0.5% to 5%. According to research by Ahmed et al., a larger drug-phospholipid molar ratio caused vesicles to enlarge, which in turn produced MLVs with enhanced penetration effectiveness [14]. Researchers Fang et al. looked at the phospholipid acyl chain's degree of unsaturation and how it affected transethosomes loaded with curcumin. Compared to transethosomes manufactured with saturated phospholipids, those formulated with unsaturated phospholipids demonstrated greater epidermal penetration and entrapment effectiveness [15].

### Ethanol

Ethanol is a key component in transethosomes, significantly contributing to their effectiveness as a drug delivery system. It enhances the softness and deformability of the vesicular membrane, allowing the vesicles to easily navigate and penetrate biological barriers. Beyond its structural role, ethanol also acts as a potent permeation enhancer, facilitating drug movement across the skin. The concentration of ethanol is a critical factor influencing various properties of transethosomes, including their particle

size, zeta potential, skin penetrability, drug entrapment efficiency, and overall stability. Transethosomal formulations typically incorporate ethanol in concentrations ranging from 10% to 50%. However, there's a delicate balance to strike with ethanol concentration. While it offers numerous benefits, excessively high concentrations can lead to the more ready dissolution of phospholipids. This interaction with the lipid bilayer can unfortunately reduce the drug entrapment efficiency within the vesicles. To counteract this, the inclusion of cholesterol in the formulation can help to maintain or even improve the stability and flexibility of the transethosomes, even when higher ethanol levels are present. [16,17]. Research provides specific insights into optimal ethanol concentrations. For example, Tamer et al. found that transethosomal formulations containing 10–20% ethanol exhibited superior stability and flexibility compared to those with higher concentrations (30–50%). Similarly, Abdulbaqi et al. observed that increasing ethanol concentration from 10% to 30% (w/v) initially reduced vesicular size. However, concentrations exceeding this range led to bilayer leakage, which in turn caused a slight increase in vesicular size. These findings highlight the importance of carefully optimizing ethanol concentration to achieve the desired balance of properties for effective transethosome performance. [18]

### Cholesterol

Cholesterol plays a vital role in transethosomal formulations by enhancing their stability and improving the efficiency with which drugs are entrapped within the vesicles. It acts as a crucial stabilizer, preventing the undesirable clumping (agglomeration) of particles, maintaining the consistent size and cohesion of the vesicles, and ultimately extending the overall shelf life of the formulation. While beneficial for stability, it has been observed that the addition of cholesterol may also increase the vesicle size of transethosomes. A common concentration used in studies to stabilize these vesicular systems is 3% cholesterol. [19] However, there's a limit to its utility. Increasing the cholesterol content beyond a certain point can actually lower the encapsulation efficiency, likely due to its limited solubility within the system. Beyond cholesterol, other stabilizers can also impact

transethosome performance. For example, Cao et al. investigated the effect of sodium deoxycholate (SDC) on transethosomes carrying the antiparasitic drug ivermectin. Their findings indicated that SDC concentrations exceeding 1% negatively impacted the stability of the transethosomes and led to drug leakage, which could compromise the therapeutic effectiveness of the drug delivery system. This highlights that while stabilizers are essential, their optimal concentration and type must be carefully determined for each specific transethosomal formulation. [20]

### Edge Activator

The transethosomal formulations' edge activators improve the flexibility and deformability of phospholipid vesicles. The permeability profile of the medication is significantly influenced by the kind and amount of edge activators. The zeta potential may rise with excess edge activators, suggesting improved stability and a threefold increase in encapsulation efficiency. This is probably because the interaction between the medication cations and deoxycholate anions results in decreased polarity. Polysorbate 20, sodium cholate, dipotassium glycyrrhizinate, bile salts, Sorbitan laurate 80, 9-Octadecenoic acid, and Polysorbate 80 are common surfactants used as edge activators. A recent study used surfactants such as Cetyl Stearyl Polyether-25, Polysorbate 20, Sorbitan laurate 20, and Polysorbate 80 at low concentrations (0.1% and 0.3% w/v) in conjunction with 20% w/v ethanol and phosphatidylcholine to create Fe-chlorophyllin transethosomes. Vesicles in transethosomes typically ranged in size from 456 to 685 nm [21].

### Transethosomes Mechanism in the Skin

Fick's law of diffusion states that a diffusion process is frequently responsible for medication penetration through the skin. Additionally, the skin has several channels, including diffusion shunts and appendages, that can facilitate the passage of big, extremely hydrophobic molecules or specific electrolytes across the membranes. Maintaining this barrier function depends on the stratum corneum's highly vascularized lipoidal layer. Because liposomal formulations contain cholesterol, they are unable to pass through the epidermal layers. The liposomes break apart due to the stratum's stiff, compact shape, releasing the medications into the layer of the epidermis. Their ethanolic and non-invasive properties may allow medications to permeate the systemic circulation or even deeper into the skin's layers without harming other cells. [22] Ethanol can easily enter the lipophilic regions of bilayered lipids due to the lipophilicity of its carbon tail. Transethosomes first adhere to the stratum corneum's surface before expanding intracellular connections to pierce it. Transethosomes can pierce the skin because of the tight intracellular junction's expansion. Transethosomes' initial penetration stage occurs when they are applied topically, drying and partially dehydrating the skin. To maintain total hydration, the vesicles penetrate deeply into the layers of skin that are more hydrated by following the local hydration gradient. The increased penetration of transethosomes into the dermis is facilitated by two primary mechanisms [23]. The method of transethosome-mediated epidermal penetration is depicted in Fig.no.05

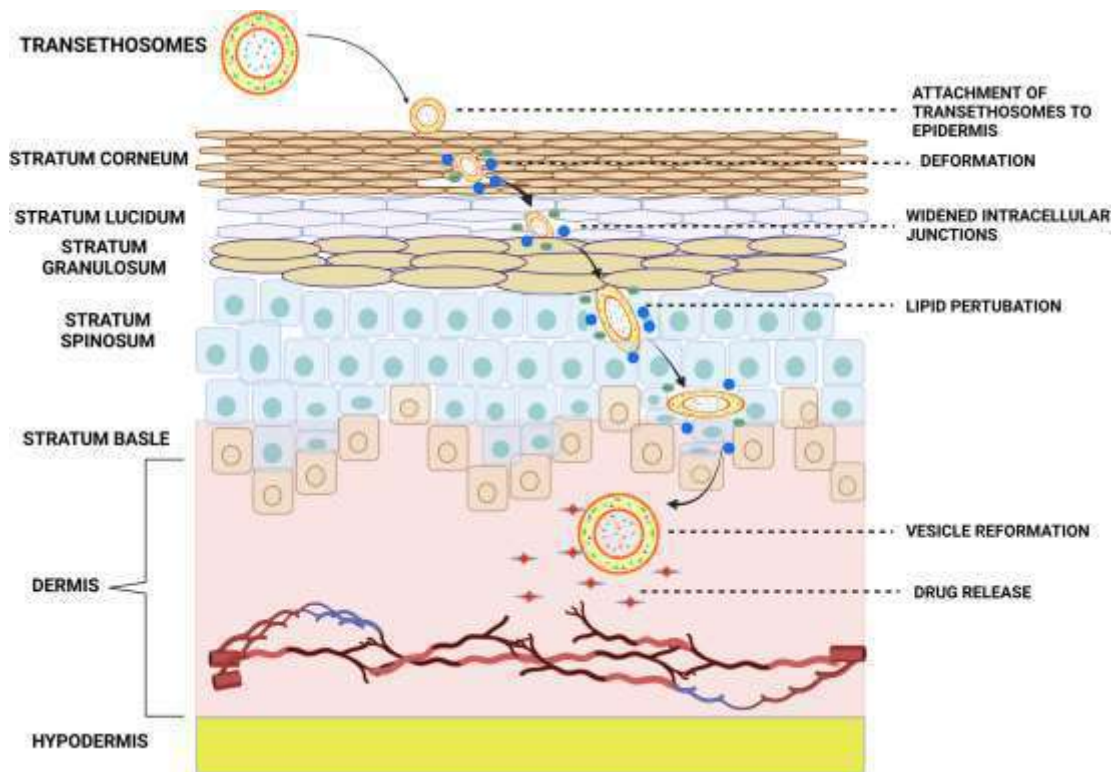


Fig.no.05

### Modified Transethosomes.

Additionally, transethosomes can be coated or modified to target them to particular areas. To increase the therapeutic effect, transethosomes can be coated with specific materials including proteins, peptides, polymers, and carbohydrates to target a specific region. By altering the transethosomes, just one study has shown this. Mannosylated Imiquimod-Terbinafine (MIT) co-loaded transethosomes were created by Humzah Jamshaid et al. to treat cutaneous leishmaniasis, overcoming drawbacks such as inadequate skin penetration, low efficacy, and drug toxicity. [28] With a low half-maximal inhibitory concentration value of  $19.56 \pm 3.62 \mu\text{g/ml}$ , the optimized MIT co-loaded transethosomes showed robust anti-leishmanial activity, targeted macrophages, and improved cutaneous retention after being coated with monnosamine HCl and loaded onto a chitosan gel. In BALB/c mice infected with *Leishmania major*, the formulation decreased the size of the lesion by  $1.52 \pm 0.430 \text{ mm}$ . It demonstrated immunomodulatory effects, such as elevated nitric oxide production and nuclear factor kappa B, and a more noteworthy safety profile.

### Therapeutic

### Anti-fungal drug delivery

The antifungal activity of the medicine is assessed by comparing commercially available econazole nitrate topical cream with transethosomal gel loaded with the drug. Transethosomal gel's superior cutaneous maintenance and antifungal properties were found. When using the transethosomal gel to treat cutaneous candidiasis, the medicine is released in a consistent pattern. [30]

### Anti-cancer drug delivery

Researchers finished testing dual loading medications into a transethosomal formulation to treat cutaneous melanoma. When compared to the other pharmaceutical formulations, they selected two drugs that had a synergistic effect, such as tretinoin and dacarbazine, which reduced cell toxicity. Dual-loaded transethosomes demonstrated increased antitumor activity in comparison to a single drug encapsulated. They noticed that it is possible to enhance skin penetration. In another study, it was found that adding 5-fluorouracil to the transethosomal gel formulation led to better skin targeting and increased superficial penetration, both of which were associated with ethosomes. [29].

## Antihypertensive Medications

Although antihypertensive drugs are frequently taken orally, hepatic first-pass metabolism can reduce their bioavailability. For instance, when olmesartan medoxomil was used as the primary component of a transethosomal gel, the transdermal approach increased drug penetration through the surface. [31]

## CONCLUSION

Transethosomes are innovative drug delivery systems designed to overcome the skin's barrier. They use ethanol to make their membranes flexible and reduce vesicle size, and edge activators to help distort skin pores. This allows them to penetrate deeply into the skin, delivering drugs (even large biomolecules) through both intercellular and intracellular pathways. Transethosomes are a promising drug delivery system capable of transporting diverse therapeutics, including small molecules, proteins, and phytochemicals, deep into tissues. Their unique structure allows them to carry both water-loving (hydrophilic) and water-fearing (hydrophobic) drugs, offering improved penetration, solubility, absorption, and stability.

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