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Review Paper

Transethosomes: Vesicular Carriers in Transdermal Drug Delivery Systems - A Review

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ABSTRACT

Transdermal drug delivery is a good substitute for oral administration, particularly for medications that have low bioavailability because of gastrointestinal problems or first-pass metabolism. Ultra-deformable lipid vesicles called transethosomes are intended to improve transdermal medication administration by enhancing skin penetration and prolonging drug release. Transethosomes, which are made up of phospholipids, ethanol, stabilizers, edge activators, and water, encapsulate hydrophilic and lipophilic medications, improving therapeutic effectiveness and minimizing adverse effects. Because of their great flexibility, they can move across the stratum corneum with the help of ethanol-induced lipid fluidization. Vesicle characteristics are influenced by a variety of preparation techniques, including thin film hydration and ethanol injection-sonication. Evaluation parameters include morphology, zeta potential, entrapment efficiency and drug release studies. Despite minor disadvantage like potential skin irritation, Transethosomes provide promising benefits in controlled and non-invasive drug delivery.

INTRODUCTION

Oral administration is the most often used mode of administration. Although the oral method of medication administration is the most practical, some oral medications may have significant drawbacks, including stomach irritation, disagreeable taste, and lower bioavailability due to hepatic first-pass metabolism.[1]

To overcome these difficulties, transdermal route has been tried having merits such as bypasses first pass metabolism. For medications with a high first pass metabolism, transdermal formulation can demonstrate superior bioavailability compared to oral administration, as well as increased efficacy, safety, convenience, and patient compliance. Transdermal system, which provide a study flow

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of drugs into the bloodstream for a prolonged period of time, could circumvent the "peak and valley" impact of oral injectable therapy. Additionally, it provides more controlled and efficient treatment.[2,3]

Structure of Skin

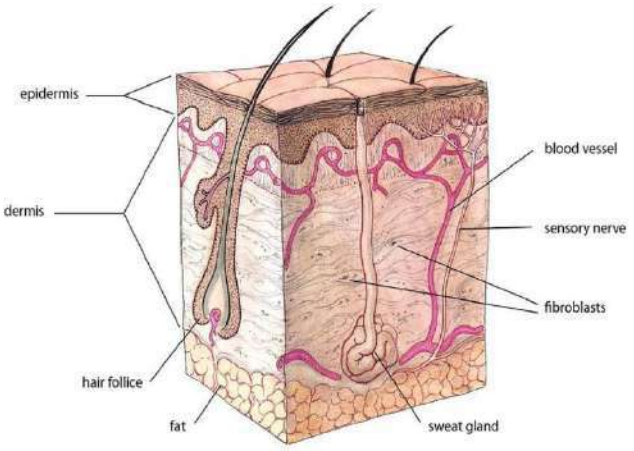

Fig. 1: Structure of skin.[4]

Epidermis: It is composed of keratinocytes and is the outermost layer of skin. It has two different kinds of epidermal layers: viable and non-viable. The stratum corneum is the name for the non-viable epidermal layer.[2] Stratum corneum made up of 10–25 longitudinal, dead corneocyte layers that are heavily keratinized and anchored in the matrix of lipid bilayers. The stratum corneum has been found as the primary skin barrier that stops penetration. When a topical formulation is applied to skin, the active drug has to enter through the stratum corneum. The slow diffusion of the substance through the dead horny layer of skin is the factor that limits these processes. As a membrane, the stratum corneum is hydrophobic. In the stratum corneum, the transit rate of organic non-electrolytes with low and high molecular weights is generally determined.[5]

Dermis: The primary functions of the dermis are strength and flexibility; its thickness varies by different region. This property is ascribed to its composition, which consists of 70% collagen and elastin fibers.[6]

Hypodermis:

The third layer below the dermis is called the hypodermis. The elastic layer known as the subcutis contains a lot of fat cells that act as shock absorbers for nerve endings and blood vessels. This layer is typically between 4 and 9 mm thick. The actual thickness, however, varies from person to person and is also dependent on the different body region.[7]

VESICULAR DRUG DELIVERY SYSTEM

Vesicular carriers used in transdermal delivery system of 2 types: lipid-based carrier system and polymer-based carrier system. Vesicular and non-vesicular lipid carriers are two further subcategories of lipid-based carriers. Vesicular lipid carriers include liposomes, niosomes, transferosomes, sphingosomes, aquasomes, photosomes, ethosomes, transethosomes etc, while lipospheres, solid lipid nanoparticles, nano lipid constructs, micelles, dendrimers, etc. are examples of non-vesicular lipid carriers. Polymeric nanoparticles, microspheres, dendrimers, polymeric micelles, nanocapsules, and nanospheres are example of polymer based carriers.[8]

Vesicles are particles prepared using amphoteric molecules such as surfactants or phospholipids surrounding an aqueous phase creating colloids of one or more concentric lipid bilayers. Both hydrophilic and lipophilic drugs can be encapsulated in vesicles in the aqueous core or lipid bilayer, respectively. They have the ability to deliver drugs to the targeted action site, thus decreasing the risk of drug toxicity. Vesicular delivery methods have also been shown to be superior than conventional system.[9] Ultra-

deformable vesicles (UDV), also known as vesicular nano-carrier recently represent a promising approach for the advanced and improved transdermal delivery of drugs.[5]

Ethosomes are non-invasive delivery carriers that enable drugs to reach deep into the skin layers or the systemic circulation. This system can permeate intact through the human skin due to its high elasticity. Ethosomes are soft, malleable lipid vesicles that are mainly composed of water, phospholipid, and alcohol in comparatively high concentrations (20–45%). Ethosomes may vary in size from tens of nanometers to microns. Ethosomes permeate through the skin layers more rapidly and possess significantly higher transdermal flux. In addition to delivering the drugs to the deep layer of the skin, ethosomes also satisfy the necessary requirements for the safe and effective administration of hydrophilic or lipophilic medications. Ethosomes are able to entrap a wide range of molecules, including hydrophilic, lipophilic and high molecular weight entities. Under both occlusive and non-occlusive conditions, ethosomes can transport the medication through the skin.[10]

Based on their composition, ethosomes can be categorized into several types:

1. Classical Ethosomes:

Classical ethosomes are the moderation of so called classical liposomes and contains phospholipids, a high concentration of upto 45% w/w, and water. When compared to classical liposomes, classical ethosomes had superior skin penetration and stability profiles. Drug entrapped in classical ethosomes have molecular weights ranging from 130.077 Da to 24kDa.[11]

2. **Binary Ethosomes:**

Another type of alcohol was added to the classical ethosomes to create binary ethosomes. Propylene glycol (PG) and isopropyl alcohol (IPA) are the most often used alcohols in binary ethosomes. The purpose of this change is to improve skin penetration and drug encapsulation efficiency.[12]

3. Transethosomes:

These are advanced ethosomal systems that contain penetration enhancers or edge activators, such as surfactants. Transethosomes are especially useful for delivering drugs to deeper skin layers or systemic circulation since the presence of these agents increases the vesicles' deformability and further improves their skin penetration abilities.[13] These novel vesicles were developed in an attempt to mix the benefits of classical ethosomes and deformable liposomes (transfersomes) in one formula to produce transethosomes. Drugs having molecular weights ranging from 130.077 Da to 200–325 kDa have been found to be entrapped by transethosomes.[14]

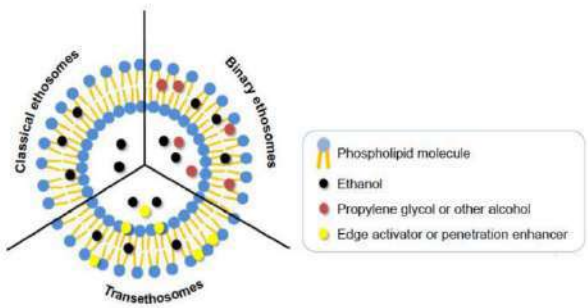

Fig. 2: Different types of ethosomal system.[15]

Advantages of Transethosomes

- High flexibility.
- High permeability.
- High stability.
- Biocompatible and biodegradable.
- High patient compliance.
- It is a non-invasive technique.

- It is more stable than other ultra-deformable vesicles; it avoids adverse effects such as vomiting due to a disagreeable taste and irritation of the stomach mucosa by avoiding first-pass metabolism.
- Transethosomes can be used to encapsulate drugs, allowing for both sustained and controlled release.[2, 9]

Disadvantages of Transethosomes

- Since the formulation contains ethanol, it may result in dermatitis, allergic reactions, and skin irritation.
- The coalescence of transethosomes may result from incomplete vesicle formation.[16]

MECHANISM OF SKIN PENETRATION

Transethosomes have shown an irregular spherical shape and higher values in both vesicle elasticity and skin permeation/penetration studies. This occurrence might be the result of a reorganization in the lipid bilayer of these vesicles brought on by the combination of ethanol and edge activator. The aqueous vesicle compartment is often where hydrophilic molecules are expected to remain; whereas, hydrophobic compounds are expected to interact with lipid membranes and incorporate into the carriers to a higher extent.[17]

Ethanol fluidizes the lipid bilayers of the transethosomal vesicles and the stratum corneum simultaneously, changing the arrangement and decreasing the density of skin lipids. As a result, a transethosomal system's malleable and soft vesicles will penetrate the stratum corneum's altered structure and create a pathway through the skin. These vesicles fuse into cell membranes in the deeper layers of the skin, releasing the therapeutic substance.[18]

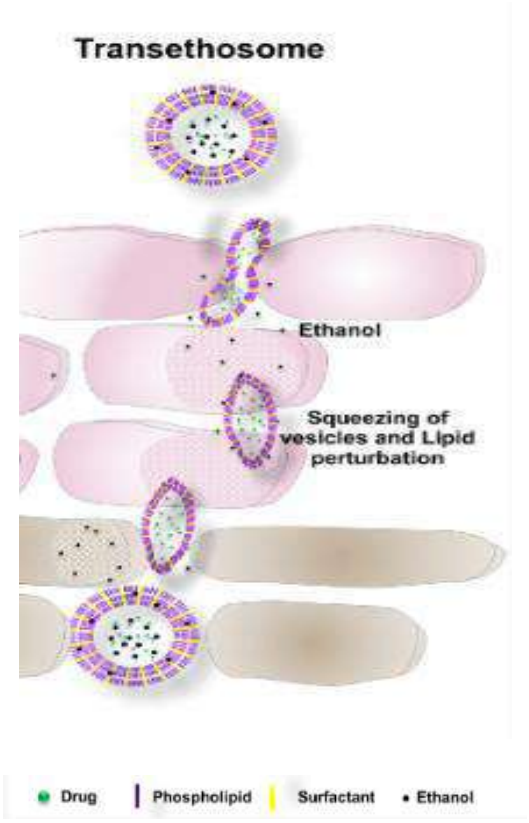

Fig 3: Mechanism of penetration.[19]

Transethosomes mainly made up of phospholipids, ethanol, edge activator, stabilizer and water.

Phospholipids are essential vesicle-forming agents that can be classified as natural or synthetic based on their sources. Unsaturated forms of natural phospholipids, which are obtained from sunflower seeds, soybeans, and egg yolks, improve skin permeability by fluidizing the stratum corneum. On the other hand, saturated (hydrogenated) natural phospholipids aid in the restoration of the skin barrier, which keeps APIs localized for extended periods of time. For example, phosphatidylcholine (PC), phosphatidylinositol, phosphatidylserine, phosphatidylethanolamine, phosphatidic acid, and phosphatidylglycerol. Because of their unsaturated hydrocarbon chains, natural phospholipids are less stable than synthetic ones. More stability is provided by synthetic phospholipids, such as dipalmitoyl phosphatidylcholine (DPPC), which may be

customized by altering both polar and non-polar regions. Vesicle properties such as size, ζ-potential, penetrating ability, and entrapment efficiency (EE) are strongly influenced by the type and concentration of phospholipids, which are (normally 0.5% to 5 %.)[20]

Ethanol plays a pivotal role in the formulation and function of transethosomes, enhancing their flexibility and efficacy in transdermal drug delivery. By fluidizing the lipid membranes, it increases the vesicles' flexibility and facilitates deeper skin penetration, act as a penetration enhancer. The stability, entrapment efficiency, zeta potential, and vesicle size of transethosomes are all strongly impacted by the ethanol concentration. While excessive ethanol can result in leaky bilayers and reduced entrapment efficacy, optimal ethanol levels decrease vesicle size and improve flexibility.[18] Nonionic, ionic, or cationic surfactants are examples of edge activators. Non-ionic surfactants like Tween20 help to achieve steric stability, by creating a protective layer on the particle surface that prevents interactions between the vesicles. Ionic surfactants, like sodium lauryl sulfate (SLS), offer electrostatic stability, by forming a charged layer around the nanoparticles and preventing aggregation. [21] In transethosomes (TE) formulations, stabilizers are essential for retaining size and structure, preventing vesicle aggregation, and prolonging shelf life. Cholesterol is the most widely used stabilizer and has been demonstrated to increase stability and deformability, especially at higher ethanol concentrations. Although it's limited solubility can lower entrapment efficiency (EE) at larger doses. Therefore, to prevent compromising the stability and efficacy of the Transethosomes, the choice and concentration of stabilizers must be carefully optimized based on the specific drug and formulation.[22]

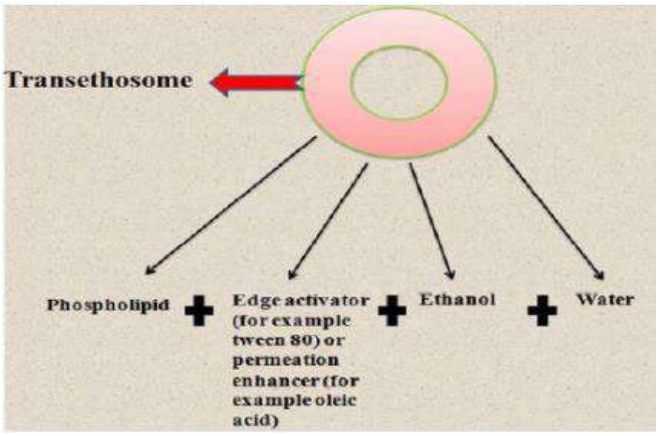

Fig. 4: Composition of transethosomes.[23]

METHOD OF PREPARATION:

Ethanol injection-sonication method:

This method has many advantages over other techniques as it is easy to prepare and scale up. Ethanol is used as organic solvent because it is harmless. This process involves dissolving the active ingredient, phospholipids, and surfactants in ethanol. Using a syringe system this organic phase is injected at a predetermined flow rate into an aqueous phase. An ultrasonic probe sonicator is then used to homogenize the resulting mixture.[24, 20]

Cold Method:

In this method, phospholipids are added to ethanol, well combined, and heated to 30°C (organic phase). Subsequently, the drug, water, and edge activator are mixed and heated to 30°C (aqueous phase) in a different container. Then, the aqueous phase is added to the alcoholic phase with constant stirring for 5 to 10 minutes, and the temperature is maintained at 30°C throughout the procedure. The mixture mentioned above is then sonicated in a sonicator.[25]

Hot method:

Phospholipid, after being dispersed in water, is heated to 40°C. A mixture consists of glycol and ethanol and is heated to 40°C. The aqueous and organic phases are combined while stirring continuously. Based on the solubility of drugs, the solvent system is chosen (water or ethanol). Throughout the procedure, a constant temperature of 40°C is maintained. The vesicular size can be altered by probe sonication.[26]

Reverse phase evaporation method:

The drug and edge activator are dissolved in an aqueous solvent, whereas the phospholipids are dissolved in an organic solvent. After that, the aqueous phase is added to the organic phase, and the mixture is placed in an ultrasonic bath set at 0°C until two-phase separation takes place. The organic phase is removed, and gel formation occurs under low pressure. The lipid layer is incorporated into the aqueous layer following constant agitation. The sample is filtered at the end.[27]

Thin film hydration method:

The lipid, edge activator, and drug are weighed accurately and dissolved in chloroform: methanol (2:1). This solution is evaporated under reduced pressure at 50°C to 55°C on a rotary evaporator. The thin film obtained is hydrated with pH 7.4 phosphate buffer saline with or without ethanol. For the vesicles to be fully hydrated, the suspension is left overnight.[28]

Direct method:

The required quantity of phospholipids, edge activator, and drug is dissolved in an organic solvent. An aqueous solution is added to the organic solvent. The required mixture is homogenized for 5 to 10 minutes. The sample is then filtered. It is easy to perform and scale up.[29]

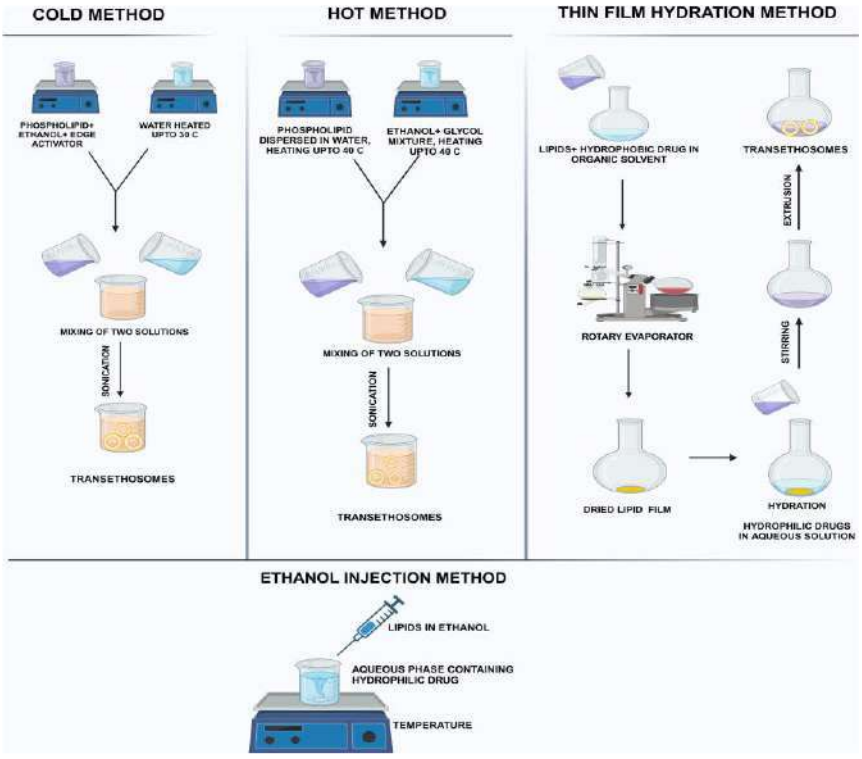

Fig 5: Method of preparation of transethosomes.[30]

EVALUATION OF TRANSETHOSOMES

Morphology:

Morphology defined as study of shape and size of vesicular carriers. Vesicular carriers generally have a regular spherical shape, physically soft, flexible and core is enclosed. On the basis of formulation, vesicular carrier may be small, unilamellar or multilamellar. The morphology of the vesicular carrier is examined with the aid of a microscope. Scanning electron microscopy is used to view the morphology because the majority of the vesicles are nano-sized. In addition to identification study, morphology also explains the detection the pattern of packing of particles and aggregation.[31]

Entrapment Efficiency (EE):

The EE% of the drug within the transethosomes is estimated by centrifuging the samples for three hours at 15,000 rpm in a cooling centrifuge. The EE% is determined by comparing the amount of drug added to the transethosome formulation with the amount that remains in the aqueous phase after centrifugation. The supernatant is collected from the sample and examined with a UV spectrophotometer to determine the drug content at a specific nm.[32]

A formula for calculating EE% is shown below:

$$EE\% = \frac{\text{(Total amount of drug taken-drug detected in supernatant)}}{\text{Total amount of drug taken}} \times 100$$

Zeta potential (ZP):

The ZP determination is evaluated by studying the electrophoretic mobility of the charged vesicles.[33] A laser is used as a light source to illuminate the sample's vesicles and quantify the zeta potential. The laser beam travels from the center of the sample cell being examined at a particular angle. There is an inverse relationship between TE's charge and mobility rate.[34]

Drug Content:

Drug can be quantified by a modified high performance liquid chromatographic method (HPLC) and UV spectrophotometer.[10, 35]

$$\% \text{ Drug content} = \frac{\text{Actual drug content in vesicles}}{\text{Theoretical weight of drug content in vesicles}} \times 100$$

Fourier-Transform Infrared Spectroscopy (FT-IR) Analysis:

The compatibility of drug with the transethosomal components was tested through infrared (IR) spectroscopy.[36]

Phase transition temperature:

Phase transition temperature is studied to understand the release of the drug from the vesicles. The Differential Scanning Calorimeter (DSC) is used to identify it. Each sample is analyzed at a specific temperature range under a constant nitrogen stream. The samples are compared using differential thermal curves.

In vitro drug release:

In vitro drug release studies of transethosomes are essential for evaluating the rate and extent of drug release from the vesicular system. These studies are usually conducted using membrane diffusion techniques, dialysis bag diffusion, or Franz diffusion cells.

The dialysis bag technique is utilized to study the drug release pattern. This method involves applying the transethosome formulation to the dialysis membrane, which is then placed in a conical flask with a buffer solution and incubated. At predefined intervals, aliquots are removed and

centrifuged using the column centrifugation method. The released drug is evaluated using an appropriate procedure. Drug discharge can continue for 24 hours. By doing this, the frequency of doses is reduced, improving patient comfort.[37]

APPLICATION OF TRANSETHOSOMES

Delivery of Antifungal drugs:

Voriconazole (VRC), a BCS class II antifungal with poor solubility, was successfully formulated into transethosomes (VRCT) using the cold method and incorporated into a Carbopol 940 gel. The optimized formulation showed favourable characteristics, including a particle size of 228.2 nm, zeta potential of –26.5 mV, and improved entrapment efficiency. In vitro and ex vivo studies demonstrated enhanced drug release, skin permeation, and transdermal flux, with a 4-fold increase in permeation efficiency.[38]

Delivery of NSAIDs drugs:

The study focused to enhance the transdermal delivery of Dexketoprofen trometamol (DKT), a painkiller, using transethosomes (TEs) as a novel vesicular carrier. A factorial design was employed to evaluate the impact of formulation variables on solubilization efficiency, vesicle size, and release efficiency. The optimized formulation (F1) exhibited a vesicle size of 133.2 nm, high solubilization efficiency (86.08%), and significantly improved skin permeation—2.6 times greater than DKT solution. The formulation remained stable over time and showed no significant changes during the stability study. These findings suggest that TE-based delivery of DKT offers a promising alternative to oral administration with better bioavailability and patient compliance.[39]

Delivery of Anticancer drugs:

This study explored the use of nano lipid vesicles (transethosomes, TES) for the topical delivery of celecoxib (CXB), a selective COX-2 inhibitor, to treat skin cancer. The optimized CXB-TES formulation showed high entrapment efficiency (88.8%), small vesicle size (75.9 nm), and a strong negative surface charge, indicating good stability. When incorporated into a hydrogel, it provided sustained drug release over 24 hours and significantly enhanced skin permeation compared to free drug formulations. The CXB-TES hydrogel showed selective cytotoxicity against skin cancer cells while sparing normal cells and downregulated the CDKN2A gene, a marker associated with tumor growth. These findings support CXB-TES hydrogel as a promising and targeted chemotherapeutic approach for managing skin carcinoma.[40]

Delivery of Depigmentation agent:

This study developed and optimized a transethosome-based delivery system for 4-n-Butylresorcinol (4nBR) using the Box–Behnken design. The optimized formulation consisted of 5.53% soya lecithin, 3% surfactant (Tween80:Span80 at 1:3), and 30% ethanol, yielding vesicles with a particle size of 197.4 nm, a PDI of 0.421, a zeta potential of –56.8 mV, and an entrapment efficiency of 98.4%. The transethosome serum demonstrated excellent physical stability and significantly enhanced skin penetration in vitro compared to ethosomes, transfersomes, and non-vesicle systems. It achieved the highest cumulative drug penetration (41.43%) among all tested formulations. These findings confirm that transethosomes are ultra-deformable vesicles capable of improving 4nBR delivery through the skin.[41]

Delivery of Anti-arthritis drug:

In this study, TE was modified with ascorbic acid to form antioxidant surface-transethosome (AS-TE), which improved drug entrapment, deformability, and skin penetration compared to traditional ethosomes. Although AS-TE and TE had similar plasma pharmacokinetics, AS-TE achieved higher drug concentrations in synovial fluid. In RA rat models, AS-TE significantly alleviated joint swelling and reduced inflammatory markers over a 3-week treatment. These findings suggest AS-TE has strong potential as an advanced TDDS for RA therapy.[42]

FUTURE PROSPECTS

The future of transethosomes looks promising as researchers continue to explore their potential. To ensure quality and safety, continuous efforts are being made to enhance manufacturing procedures and set regulatory standards. Furthermore, advancements like the addition of specific targeting mechanisms may make it possible to deliver drugs even more precisely. Overall, transethosomes hold great potential to change how we administer medications, making treatments more effective and patient-friendly in the years to come.

CONCLUSION

Transethosomes are advanced vesicular systems that combine the qualities of transfersomes and ethosomes to provide effective transdermal drug delivery. Phospholipids, ethanol, and edge activators form these ultra-deformable vesicles, which improve vesicle flexibility and disrupt the stratum corneum to improve skin penetration. Compared to traditional systems, transethosomes provide better drug encapsulation efficiency, stability, and biocompatibility, allowing for the effective delivery of therapeutic agents while reducing first-pass metabolism and increasing bioavailability.

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