wjpmr, 2025, 11(9), 192-204

WORLD JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH
www.wjpmr.com

SJIF Impact Factor: 6.842

Review Article

ISSN (O): 2455-3301
ISSN (P): 3051-2557

A CONCISE REVIEW ON ETHOSOMES

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Article Received on 08/07/2025 **Article Revised on 29/07/2025** **Article Accepted on 18/08/2025**

ABSTRACT

Ethosomes are cutting-edge nanocarriers made to effectively transfer active anti-aging and medicinal ingredients via the skin. While ethosomal systems are conceptually complex, they are simple to prepare, secure to use, and can be combined to greatly increase their utility. These innovative lipid-based vesicles, which are soft and flexible, are made mostly of phospholipids, ethanol, and water. These components give them special properties, such as increased skin permeability and deformability and the capacity to penetrate the stratum corneum and deliver active pharmaceutical ingredients. By rupturing the stratum corneum's lipid bilayer, ethanol allows active substances to penetrate deeper. Ethosomes have increased drug-loading capacity, enhanced bioavailability, and the ability to hold to encapsulate both Water-soluble and lipid-soluble molecules, in contrast to traditional liposomes. They are a viable platform for non-invasive therapeutic solutions because of their prospective uses in cosmeceuticals, transdermal medication administration, and the treatment of different skin conditions. Drugs, peptides, and macromolecules that are hydrophilic or lipophilic can be delivered using ethersomes with exceptional efficiency.

KEYWORDS: skin penetration enhancers, cutting edge nanocarriers,topical drug delivery, anti-aging,dermal drug carriers, and ethosomal system.

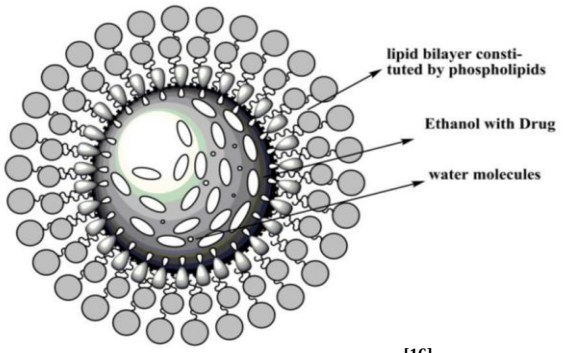
INTRODUCTION

Among the many benefits of transdermal medication delivery are patient compliance, regulated drug release, and prevention of first-pass metabolism. However, a significant obstacle to medication absorption is the corneum stratum. Because of their high ethanol content and adaptability, vesicular shape, ethersomes—which were first described by Touitou et al. (2000)—offer a fresh way to get around this restriction by improving medication penetration. These carriers have been investigated for a number of pharmaceutical and cosmetic uses, such as targeted therapy, pain relief, and medication delivery for skin conditions.[1] Transdermal medication delivery devices were developed recently to apply topical medication to the intact skin surface in order to accomplish the goal of systemic treatment.[2] When applied to intact skin, transdermal treatment systems—self-contained, discrete dose forms—release the medication into the bloodstream throughout the body at a regulated pace.[3] Transdermal distribution has a number of advantages, including improved patient compliance, enhanced efficacy, and increased safety. This drug administration approach reduces the discomfort and risks of parenteral medication while increasing patient adherence.[4] This makes the transdermal route an interesting option because of its safety and ease of use.[5] Transdermal medication delivery systems are an alternative means of getting medication into the bloodstream.[6-7] The advantages of transdermal medication administration over more traditional techniques, such parenteral and oral drug delivery, are numerous. The transdermal route is a better choice for sustaining constant plasma levels over longer periods of time, and it might also be advantageous because less frequent dosage schedules are required (Cal et al., 2008). The purported advantages include improved physiological and pharmacological response, avoiding first-pass metabolism, the efficacy of short-half-life drugs, a decrease in adverse effects, and a steady and extended duration of action. The main component that tags the vesicle for cell specificity is the barrier function of the stratum coneum, which enhances drug transport within their cavities. A major breakthrough in vesicle research was the discovery of vesicle derivatives.[8]

Ethosomes

Ethosomes are complex lipid-based vesicular networks designed to enhance the delivery of medications in the skin and transdermal routes. Recently, ethosomes, a vesicular delivery method, have garnered a lot of attention due to their ability to transfer drugs across the epidermal barrier. ethersomes have been the focus of extensive research and have shown great promise in the transmission of various drugs and cosmetics via the

epidermal layer. Early in the new millennium, Touitou et al. first demonstrated them. First created in 1997 by Touitou and her associates, ethersomes are further unique lipid carriers made of water, phospholipids, and ethanol. They are said to enhance the transport of certain drugs through the skin.[9] "Ethanolic vesicles give rise to ethersomes." One definition of ethersomes is a noninvasive medication delivery mechanism that enables the pharmaceuticals to better distribute medication over the skin's membrane, ethersomes are used. Touitou created a novel vesicular system, which he called ethosomes, because ethanol was present in the vesicular structure.[10] The vesicular system is currently the most researched method for transdermal medication administration.[11] Ethosomes are non-invasive delivery vehicles that allow medications to enter the systemic circulation or deep into the layers of the skin.[12] Ethosomes fulfill the necessary requirements for the effective and secure delivery of hydrophilic or lipophilic medications in addition to delivering the medication to the deep layer of the skin.[13–14] High molecular weight, lipophilic, and hydrophilic molecules are among the many types of molecules that ethersomes can ensnare. Ethosomes can transport the medication through the skin in both occlusive and non-occlusive circumstances.[15]



Structure of ethosomes.[16]

Ethosomes Composition

Ethosomes are made up of a variety of phospholipids, such as phosphatidylcholine, phosphatidylserine, phosphatidylinositol, phosphatidylglycerol, phosphatidic acid, etc., as well as different glycols, such as propylene glycol, and higher concentrations of ethanol and water. When it comes to administering drugs through the skin's membrane, ethosomal delivery systems are quite successful. Phospholipids, propylene glycol, and alcohol concentrations can be changed to create ethosomal vesicles. Soy lecithin, also known as phosphatidylcholine, is the most preferred phospholipid. It is used in concentrations between 0.5 and 10% w/w. Ethanol and isopropyl glycol are the most popular types of alcohol. Sometimes, cholesterol is also used in the preparation in certain amounts range of 0.1-1%. In expansion, the non ionic surfactants (PEG-alkyl ethers) are utilized along with the phospholipids. The alcohol concentration in final product is may be about 20 to 50%. The range of non- aqueous phase concentration (alcohol and glycol mixture) is may be about 22 to 70%.[17]

Ethosomal systems types

1. Conventional Ethosomes:- Ethosomes that are made of phospholipids, ethanol, and water are known as "conventional ethosomes".

2. Trans Ethosomes:- One kind of ethosomal system that has edge activators to increase the permeability and flexibility of the ethosomes is called a transethosome.

3. Binary Ethosomes:- These ethosomal systems use two kinds of phospholipids to increase their flexibility and stability.

4. Ternary Ethosomes:- One kind of ethosomal system is called a ternary ethosome, which is made up of three parts: ethanol, phospholipids, and a third part that may be a polymer or a surfactant.

5. Double-Walled Ethosomes:- This kind of ethosomal system features two lipid bilayers that enhance stability and regulate the release of the medicine that is encapsulated.

6. Gel - Core Ethosomes:- These are the type of ethosomal system that has a gel like core. Which provide improved stability and controlled release of encapsulated drug.[18-23]

Benefits

1. Enhanced skin penetration:-It has been demonstrated that ethersomes enhance skin permeability and penetration, enabling more efficient medication and cosmetic delivery.

2. Increased bioavailability:- Ethosomes have the ability to make medications more bioavailable, which enables the administration of smaller dosages.

3. Decreased side effects:- Ethosomes have the ability to lessen the negative effects of parenteral or oral administration.

4. Flexibility:- A variety of medications and cosmetics, including hydrophilic and lipophilic substances, can be delivered using ethersomes.

5. Stability:- By shielding encapsulated medications from oxidation and degradation, ethersomes can increase their stability.[18-22]

Drawbacks

1. Aqueous environment instability:- : Ethosomes may exhibit instability in aqueous environments, which could result in modifications to their size and makeup.

2. Limited scalability:- Ethosomes can be difficult to scale up production.

3. High cost:- The production of ethersomes can be more costly than that of conventional liposomes.

4. The behavior of ethosomes in the skin and other tissues is yet incompletely understood.

5. Potential for skin irritation:- If ethanol is present in high amounts in etherosomes, it may irritate the skin.[23-27]

Mechanism of action of ethosomes

1. Penetration of Ethosomes into the Skin:- Ethosomes penetrate into the skin through the stratum corneum, which is the outermost layer of the skin.

2. Disruption of the Lipid Bilayer:- Ethosomes disrupt the lipid bilayer of the stratum corneum, allowing for the release of the encapsulated drug.

3. Formation of a Concentration Gradient:- The released drug forms a concentration gradient across the skin, driving the drug to diffuse deeper into the skin.

4. Enhanced Permeability:- Ethosomes enhance the permeability of the skin, allowing for increased drug delivery.[18-21]

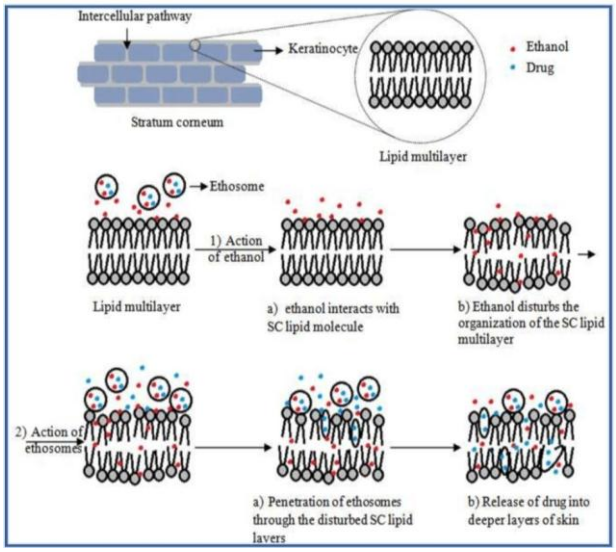


Fig -2:- Proposed mechanism of penetration of ethosomal drug delivery system.[28]

Techniques of preparation of ethosomes

1. Cold method:- This is the approach that is most frequently used for the preparation. of ethosomal definition. This approach uses phospholipids, drugs In a covered container, ethanol dissolves additional lipid materials. vigorously stirring the vessel at room temperature using mixer. It is added to propylene glycol or another polyol during stirring. A water bath is used to heat this mixture to 300C. What's In another vessel, water that has been heated to 300C is added to the mixture in a closed container, and it is then agitated for five minutes. The size of the ethosomal formulation's vesicles can be reduced to prefer to use the extrusion[30] or sonication[29] methods. The formulation is then refrigerated for storage.[31]

2. Hot method:- The hot approach involves dispersing phospholipid in water by heating it to 400 degrees Celsius in a water bath until a colloidal solution is achieved. Propylene glycol and ethanol are combined and heated to 400 degrees Celsius in a different tank. The organic phase is introduced to the aqueous phase once both solutions have reached 400C. Depending on whether the medicine is hydrophilic or hydrophobic, it dissolves in either ethanol or water. By employing the extrusion method or probe sonication, the ethosomal formulation's vesicle size can be reduced to the desired degree.[32]

Characterization of Ethosomes

1. Vesicle Morphology and Structure

-Ethosomes' surface structure and shape can be examined using transmission electron microscopy (TEM) and scanning electron microscopy (SEM).

-Atomic Force Microscopy (AFM): Provides 3D imaging and surface roughness analysis.[33]

2. Vesicle Dimensions and Distribution

Dynamic Light Scattering (DLS) & Photon Correlation Spectroscopy (PCS): Measure the size and polydispersity index (PDI) of ethosomes.[34]

3. Potential of Zeta

Assesses surface charge and stability; values above ±30 mV indicate good colloidal stability.[35]

4. EE%, or Entrapment Efficiency

Determined via ultracentrifugation or dialysis, followed by spectrophotometric analysis.[36]

5. Deformability Index (Elasticity Study)

Evaluated by applying pressure to vesicles as they pass through a microporous membrane using an extrusion technique.[37]

6. Studies on Drug Permeation and Release

In vitro release experiments employing dialysis bags.

Ex vivo skin permeation studies using human/animal skin and Franz diffusion cells.[38]

7. Stability Studies

Examined in varying humidity and temperature conditions.[39]

8. Surface Tension and Conductivity

Indicates vesicle integrity and interaction with skin lipids.[40]

9. FTIR and DSC Analysis Fourier Transform Infrared Spectroscopy (FTIR): Identifies chemical interactions between drug and excipients.

Differential Scanning Calorimetry (DSC): Determines phase transition temperatures of lipids.[41]

Evaluation

1. Investigation of the Filter Membrane-Vesicle Interaction Using Scanning Electron Microscopy

A filter membrane with 50 nm pores was coated with 0.2 mL of vesicle suspension and put in inside diffusion cells. The upper side of the filter was exposed to the air, whereas the lower side was in interaction with a pH of 6.5 (phosphate buffer saline solution), or PBS. An hour later, the filters were taken out. and prepared for SEM studies by fixation at 4°C in Karnovsky's fixative overnight followed by dehydration using graduated ethanol solutions (30%, 50%, 70%, 90%, 95%, and 100% vol/vol in water). After applying a gold coating, the filters were analyzed using a SEM.[42]

2. Study of Vesicle-Skin Interaction by TEM and SEM

Ultra-thin animal slices were cut (Ultracut, Vienna, Austria), gathered on grids coated with formvar, and viewed using a transmission electron microscope. The skin slices were dehydrated, then placed on stubs using adhesive tape and coated with gold palladium alloy using a fine coat ion sputter coater for SEM analysis. An electron scanning microscope was used to investigate the slices.[43]

3. Vesicle-Skin Interface Analysis via Fluorescence Microscopy

Fluorescence microscopy was conducted using the same methodology as the TEM and SEM studies. Paraffin blocks are employed, were formed, 5-µm thick slices were cut using microtome (Erma optical enterprises, Tokyo, Japan) and evaluated under a fluorescent micro Cytotoxicity Assay MT-2 cells (T- lymphoid cell lines) were cultivated in modified Eagle medium from Dulbecco (HIMEDIA, Mumbai, 10% fetal calf serum, 100 U/mL penicillin, 100 mg/mL streptomycin, and two additional mmol/L of L-glutamine at 37°C with 5% CO2. Cytotoxicity was measured as the A 50% decrease in absorbance at 540 nm was caused by the cytotoxic dose 50 (CD50).[44]

4. Research on drug absorption:- In 24-well plates (Corning Inc.), 100 µL of RPMI medium was applied, and the medication was absorbed into MT-2 cells (1×106 cells/mL). Following treatment of cells with 100 µL of the drug solution in ethosomal formulation, commercial formulation, or PBS (pH 7.4), drug uptake was measured. through the drug content's HPLC test analysis.[45,46]

5. HPLC Testing

The quantity of medication that entered the receptor compartment during in vitro skin penetration was ascertained by HPLC assay employing methanol:distilled-water in MT-2 cells. The mobile phase is an acetonitrile (70:20:10 vol/vol) mixture that is delivered by an LC 10AT vp pump at a rate of 1 mL/min. (Shimadzu, Kyoto, Japan).[47]

Applications

1. Transdermal Administration of Medicine

Effective systemic medication delivery is made possible by ethersomes, which increase a drug's permeability through the skin.

For instance, diclofenac ethosomal formulations have been created for the transdermal management of pain and inflammation.[33]

2. Topical Administration of Antifungal Substances

Ethosomes improve the effectiveness of antifungal medications by enhancing their distribution.

For instance, formulations of ethosomal fluconazole have demonstrated enhanced penetration and therapeutic efficacy for fungal infections of the skin.[48]

3. Distribution of Cosmetic and Anti-Aging Agents

In the cosmetics business, ethersomes are frequently employed to transport active chemicals into the deeper layers of the skin, such as peptides and antioxidants.

For instance, ethosomes enriched with coenzyme Q10 increase skin hydration and minimize wrinkles. In contrast to traditional formulations, and antitumor activities.[49]

4. Anticancer medication delivery

Chemotherapeutic chemicals are more effective in treating skin cancer when ethersomes help them penetrate deeper.

In contrast to traditional formulations, 5-fluorouracil (5-FU) ethosomes have demonstrated superior skin penetration and anticancer efficacy.[50]

5. Hormone Shipping

The transdermal administration of hormones such as testosterone and estradiol for hormone replacement treatment is improved by ethersomes.

Example: Studies have shown that estradiol ethosomes increase skin permeability, which lessens the requirement for frequent dosages.[41]

6. Antiviral Drug Delivery

Ethosomes increase the bioavailability of antiviral drugs, increasing their efficacy. To better treat herpes simplex virus (HSV) infections, for instance, acyclovir ethosomes have been produced.[51]

7. Delivery of Anti-Inflammatory Drugs

Ethosomal carriers enhance the penetration of anti-inflammatory drugs, reducing systemic side effects.

Example: Ibuprofen-loaded ethosomes have shown enhanced skin permeation and anti-inflammatory effects.[52]

A glance to the future

Though there is still opportunity for improvement, ethersomes have shown great promise in topical and transdermal medication delivery. Future studies and advancements could concentrate on the following topics.

1. Strengthening Scalability and Stability:- Ethamome stability during storage and large-scale manufacture is one of the main issues. In order to extend shelf life and preserve vesicle integrity, future research could investigate innovative stabilizers, cryoprotectants, or lyophilization methods.

2. Examining Novel Drug Molecules:- Drug molecules that are small to moderately large have been the main focus of ethersome research. The optimization of ethosomal formulations for macromolecules like

proteins, peptides, and nucleic acids may be the focus of future study, which could result in advances in vaccine delivery and gene therapy.

3. Incorporating Nanotechnology:- Drug targeting, controlled release, and deeper skin penetration may be improved by combining ethosomes with nanocarriers such as hydrogel-based systems, nanoparticles, and microneedles. This may be particularly helpful in the treatment of systemic disorders and persistent skin issues.

4. Intelligent Drug Delivery and Customized Medicine:- Biosensors and artificial intelligence (AI) developments may make it possible to customize ethosomes for patient-specific drug delivery, modifying release rates according to specific requirements. Treatment efficacy may be increased by clever ethosomal formulations that react to environmental cues like pH, temperature, or enzyme activity.

5. Growing Uses for Cosmetics and Cosmeceuticals:- The cosmetics industry has already taken notice of ethersomes because they can supply anti-aging and skin-repair chemicals. Future developments might include skin-lightening, UV protection, and sustained-release formulations for long-lasting skin hydration. 6. Research Studies and Regulatory Clearances:- Additional clinical trials are required to confirm the safety, effectiveness, and long-term benefits of ethosomes, despite their promising laboratory research. For them to be widely used in the cosmetics and pharmaceutical industries, regulatory permissions are essential.

7. Eco-Friendly and Biodegradable Ethosomal Products:- Finding eco-friendly, biodegradable ethosomal components could lead to more environmentally friendly drug delivery systems as environmental sustainability concerns grow.

CONCLUSION

The penetration of active pharmaceutical and cosmetic substances via the skin is greatly improved by ethersomes, a potential drug delivery technology. Because of their special makeup, which contains high levels of phospholipids and ethanol, they work very well for topical and transdermal treatments. With their increased bioavailability, decreased systemic adverse effects, and greater patient compliance, ethersomes have been effectively used to administer anti-inflammatory, antifungal, anticancer, antiviral, and cosmetic drugs. Notwithstanding their benefits, problems such formulation optimization, large-scale manufacturing, and stability concerns require more study. But with further development, ethosomes could completely transform drug delivery, especially for non-invasive medicinal uses. Enhancing their effectiveness, extending their use to more complicated medications, and combining them with nanotechnology for targeted drug delivery could be the main goals of future research.

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