

# Ethosomes: A Novel Approach to Overcoming Skin Barriers for Efficient Drug Delivery

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## Abstract

Ethosomes represent an advancement in transdermal drug delivery systems, offering enhanced skin penetration and drug delivery capabilities. This review explores the composition, structure, preparation methods, and evaluation techniques of ethosomes, highlighting their benefits and mechanisms of action. Ethosomes, comprised of phospholipids, ethanol, and water, disrupt the stratum corneum's lipid structure, facilitating drug permeation. Various preparation methods, including cold, hot, mechanical dispersion, and thin-film hydration techniques, are discussed. Evaluation methods such as transmission electron microscopy, scanning electron microscopy, and dynamic light scattering are crucial for characterizing ethosome properties. The mechanism of ethosome-mediated skin penetration involves interaction with stratum corneum lipids, vesicle flexibility, and fusion with skin lipids, enabling efficient drug release. Ethosomes offer versatility in delivering both hydrophilic and lipophilic drugs, with applications in treating various conditions. Their biocompatibility, safety, and advantages over other delivery systems make them a promising choice for improved transdermal drug delivery.

**Key words:** Drug delivery, ethosomes, skin penetration, stratum corneum, transdermal drug delivery systems

## INTRODUCTION

Transdermal drug delivery systems (TDDS) release drugs into the body through the skin at a sustained rate. Skin has been used for centuries as a method for medical use, but TDDS, as a technology-based system of delivery, was developed during the 20<sup>th</sup> century when the first Food and Drug Administration-approved patch, transderm-scop (scopolamine), was approved in 1979/1981.<sup>[1]</sup>

TDDS is beneficial over conventional approaches such as oral or intravenous delivery, i.e., non-invasiveness, elimination of first-pass metabolism, enhanced bioavailability, extended drug release, and less frequency of dosing.<sup>[2]</sup> Available over-the-counter patches are motion sickness (scopolamine) and angina (nitroglycerin), and areas of use include pain relief, hormone replacement, and other diseases.<sup>[3]</sup>

The major obstacle of TDDS is the barrier property of the stratum corneum, the outermost layer of skin, which restricts drug penetration.<sup>[4]</sup> Chemical enhancers and physical methods such as iontophoresis and microneedles have been established to increase skin permeability.<sup>[5]</sup>

Ethosomes are developed from ethanol, phospholipids, and water and act through their ethanol content that disrupts the lipid structure in stratum corneum, so that it facilitates drug diffusion while providing softness and integrity to the vesicles.<sup>[6]</sup>

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**Received:** 19-03-2025

**Revised:** 04-08-2025

**Accepted:** 25-08-2025

## COMPOSITION AND STRUCTURE

Ethosome structure is likely the most significant characteristic that explains their ability to function as drug carriers. Ethosomes comprise a series of concentric rings that constitute plastic phospholipid bilayers, as shown in Figure 1. Ethanol incorporation plays the dual role of enhancing lipid membrane fluidity as well as the deformability of the vesicles. This enables ethosomes to migrate through intercellular space without compromising the integrity of their payloads.<sup>[7]</sup>

### Phospholipids

The central position of phospholipids in ethosome architecture is the pivotal role played by them, which are amphipathic molecules possessing both hydrophilic (water-attracting) and lipophilic (fat-attracting) moieties. Their inherent duality allows them to spontaneously self-assemble into bilayer structures upon being transferred to an aqueous environment. Bilayer formation creates vesicular architecture in ethosomes as a protective sheath for drug encapsulation. There are several classes of phospholipids commonly employed in the formulation of ethosomes. Table 1 highlights the unique properties and contributions of each phospholipid to ethosome formulations, enhancing their stability, biocompatibility, and drug delivery efficiency.<sup>[8]</sup>

### Ethanol

Ethanol ( $\text{CH}_3\text{CH}_2\text{OH}$ ) is one of the main components of ethosomes with a concentration typically ranging from 20% to 45% (v/v). It is a short-chain alcohol that can be a permeation enhancer and a critical determinant of the vesicle properties. The non-aqueous phase may vary from 22% to 70%.<sup>[10]</sup>

### Water

Water is a water carrier with which phospholipids and ethanol are dissolved. Water supplies the environment of the moment to enable phospholipids to create bilayers as well as accommodate drugs.<sup>[13]</sup>

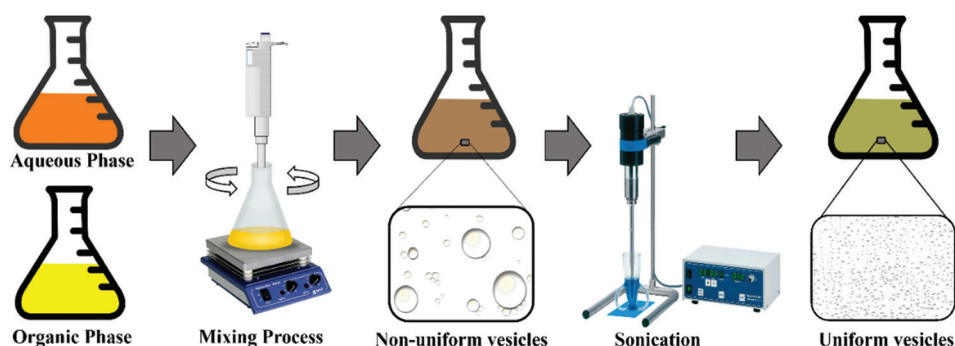
### Other voluntary ingredients

#### Stabilizers

They may be incorporated to enhance the physical and chemical stability of ethosomes. Among them are antioxidants (e.g., Vitamin E) to inhibit lipid peroxidation, and polymers (e.g., polyethylene glycol) to inhibit vesicle aggregation.

#### Charge inducers

Charged molecules (e.g., stearylamine for the cationic charge, dicetyl phosphate for an anionic charge) can be



**Figure 1:** Illustration of the preparation of the ethosome

**Table 1:** Summarizing the phospholipids used in ethosome formulations

Phospholipid	Characteristics	Benefits of ethosome formulations	References
Phosphatidylcholine	Zwitterionic, charge-neutral at physiological pH, biocompatible, similar to natural cell membranes.	Ideal for producing stable and tolerated vesicles.	[9]
Hydrogenated Phosphatidylcholine	Hydrogenated fatty acid chains enhance stability against oxidation and hydrolysis.	Increases shelf life by preventing lipid degradation.	[10]
Phosphatidylethanolamine	Involved in membrane fusion and protein anchoring, facilitates interaction with cell membranes.	Enhances drug delivery by promoting vesicle-cell membrane fusion.	[11]
Phosphatidylglycerol and phosphatidylinositol	Negatively charged anionic phospholipids influence surface charge and skin interaction.	Increases interaction with cell membranes, leading to enhanced drug uptake and stability.	[12]

included to alter the surface charge of ethosomes, governing skin interaction and stability.<sup>[14]</sup>

### Amphiphilic fluorescent probes

Amphiphilic fluorescent probes such as dyes or D-289, Rhodamine-123, and fluorescence isothiocyanate are added routinely for characterization Figure 2. Illustrated the structural diagram of the ethosome and its parts:

Table 2 summarizes the formulation of ethosomes, including the percentage amount of each component and their respective roles:

## PREPARATION OF ETHOSOMES

Ethosomes are new vesicular carriers that have been designed for improved transdermal delivery of drugs. Their preparation is done by different methods, and each method has its own procedure and conditions.<sup>[15]</sup> Figure 1 illustrates the basic method of preparation of an ethosome.

### Cold method

The cold method is the most common method employed for the preparation of ethosomes. In the cold method,

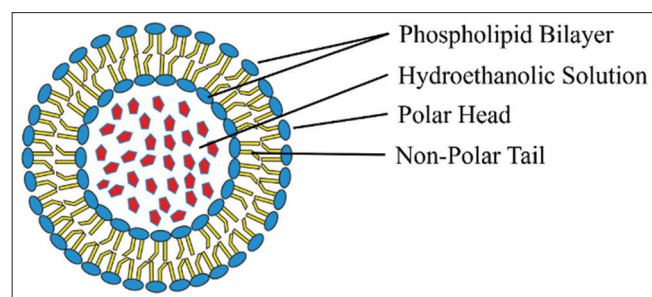


Figure 2: Structure of ethosome

phospholipids, drugs, and other lipid materials are dissolved in ethanol at room temperature by vigorous stirring. The mixture is then heated to 30°C using a water bath. Preheated double-distilled water at 30°C is added slowly into the lipid mixture under constant stirring under agitation for 5 min. This leads to a colloidal suspension of ethosomes. Smaller diameters of vesicles can be obtained by subsequent processing, such as sonication or extrusion. Finally, the ethosomal preparation is cooled to ensure stability.<sup>[16]</sup>

### Hot method

The hot method is carried out by dissolving the drug in a solution of ethanol and propylene glycol and then mixing this with a water dispersion of phospholipid at 40°C. This mixture is agitated for 5 min and afterward sonicated in cycles to produce nano-sized ethosomes. High-pressure homogenization (approximately 15,000 psi) is the last step to ensure homogeneity and decrease the size of vesicles 14. It is a good method to make small-sized vesicles, but it needs rigorous temperature control to avoid degradation of unstable components.<sup>[17]</sup>

### Traditional mechanical dispersion method

Dispersal by the mechanical process includes the dissolution of soya phosphatidylcholine in chloroform-methanol solution (3:1) in a round-bottom flask. The organic solvents are evaporated off by rotary vacuum evaporation above the transition temperature of lipids, thus leaving a thin lipid film adhering to the flask wall. The film is hydrated with an aqueous drug solution by rotating the flask at an optimum temperature till a colloidal suspension is generated. The technique provides fine control over the lipid composition but can require sophisticated equipment.<sup>[16]</sup>

Table 2: Formulation of ethosomes

Component	Percentage (% w/w)	Role
Phospholipids	0.5–10%	Form the lipid bilayer structure of ethosomes, providing stability and encapsulation for drugs. Common types include phosphatidylcholine, hydrogenated phosphatidylcholine, phosphatidylethanolamine, phosphatidylglycerol, and phosphatidylinositol.
Ethanol	20–45%	Acts as a permeation enhancer by disrupting the lipid structure of the stratum corneum, increasing fluidity, and enhancing drug penetration through the skin.
Water	Balance to 100%	Serves as the solvent for the other components, facilitating the formation of the ethosomal structure and allowing for drug encapsulation.
Stabilizers	Variable (e.g., 1–5%)	Improve the physical and chemical stability of ethosomes. Examples include antioxidants (e.g., Vitamin E) and polymers (e.g., polyethylene glycol).
Charge inducers	Variable (e.g., 0.1–2%)	Modify the surface charge of ethosomes to enhance interaction with skin and improve stability. Examples include stearylamine (positive charge) and dicetyl phosphate (negative charge).
Drug/active ingredient	Variable (typically 1–10%)	The therapeutic agent is intended for delivery through the skin. The specific percentage depends on the drug's solubility and desired therapeutic effect.

### Thin film hydration method

It is a process that involves solubilizing phospholipids and cholesterol in a small quantity of a combination of chloroform and methanol in a round-bottom flask. The organic solvent is evaporated under a vacuum to leave a thin lipid film on the flask surface. Lipid film is hydrated under stirring at room temperature using an aqueous drug solution. This procedure yields stable ethosomes but is associated with some special precautions regarding handling solvents and vacuum.<sup>[18]</sup>

## EVALUATION OF ETHOSOME

Ethosomes are identified by several methods for ascertaining their characteristics, such as size, shape, and encapsulation efficiency.

The following methods are used for the evaluation of ethosomes:

### Transmission electron microscopy (TEM)

Ethosomes vesicles are examined by TEM under an accelerating voltage of 80 kV. A small amount of ethosomal sample is dropped onto a carbon-coated grid, left to dry, and negatively stained with 1% phosphotungstic acid to increase contrast.<sup>[19]</sup>

### Scanning electron microscopy (SEM)

SEM is used to examine the surface morphology, e.g., roundness, smoothness, and aggregate formation.<sup>[19]</sup>

### Dynamic light scattering (DLS)

DLS is used to measure particle size, zeta potential, and polydispersity index (PDI) using instruments such as the Malvern Nano-ZetaSizer 3. The zeta potential determines vesicular stability and skin-vesicle interactions. PDI values below 0.8 represent a very monodispersed formulation.<sup>[19]</sup>

### Fourier transform infrared spectroscopy (FTIR)

FTIR is conducted to detect functional groups and interactions in the ethosomal preparation.<sup>[20]</sup> The spectrum range is typically 4000–500  $\text{cm}^{-1}$ .<sup>[20]</sup> Potassium bromide is commonly used to grind the samples into pellet form for analysis.

### Thermogravimetric analysis (TGA)

TGA is conducted to analyze mass change or sample loss upon heating to a temperature range typically between 25°C and 300°C.<sup>[21]</sup>

### Differential scanning calorimetry (DSC)

DSC is utilized to determine the glass transition temperature ( $T_g$ ) of ethosomes. The samples are scanned typically between 25°C and 300°C under purging with nitrogen gas.<sup>[22]</sup>

### Release study

Drug release from ethosomes is examined using the USP Dissolution Apparatus II at skin pH (5.5). Suspension of ethosomes is filled in dialysis membrane pouches, and samples are withdrawn periodically to determine drug release by high-performance liquid chromatography.<sup>[20]</sup>

## MECHANISM OF ETHOSOME-MEDICATED SKIN PENETRATION

Ethosomes are state-of-the-art lipid carriers designed to maximize the transdermal delivery of drugs beyond the insurmountable stratum corneum barrier. Due to their characteristic composition and the presence of ethanol, they achieve permeation beyond the skin, the mechanism of Skin penetration is clearly depicted in figure 6. This illustrates the process of how ethosomes enhance skin permeation:

### Interaction with stratum corneum lipids

Ethosomes interact with the stratum corneum, the outermost layer of the skin, by disrupting its lipid structure. Ethanol, which is a major component of ethosomes (typically present in concentrations between 20% and 45%), plays a crucial role in this process. It reduces the transition temperature ( $T_m$ ) of the stratum corneum lipids, making them more fluid and increasing the permeability of the skin. This disruption allows ethosomes to penetrate more easily through the intercellular spaces between corneocytes, the main cell type in the stratum corneum.<sup>[23]</sup>

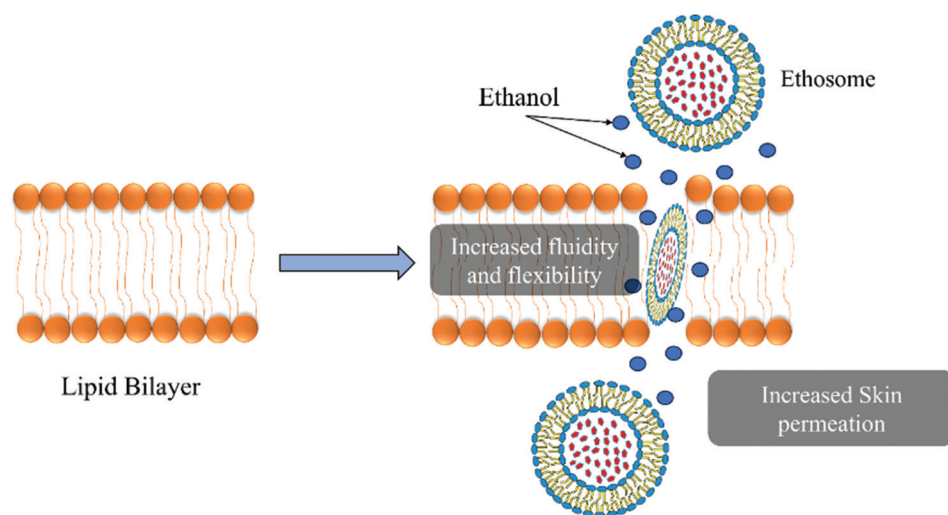
### Vesicle dynamics and flexibility

The presence of ethanol in ethosomes also imparts flexibility to these vesicles. This elasticity is crucial for their ability to deform and pass through pores that are smaller than their diameter. As a result, ethosomes can navigate through the narrow intercellular channels in the stratum corneum, facilitating deeper penetration into the skin. This flexibility is a key advantage over traditional liposomes, which are more rigid and may not penetrate as effectively.<sup>[24]</sup>

### Fusion with skin lipids

Ethosomes are designed to fuse with the lipids in the stratum corneum. This fusion process involves the phospholipids of the ethosomes merging with the skin's natural lipids. As this occurs, the drugs encapsulated within the ethosomes are released





**Figure 3:** Illustration of the process of how ethosome enhances skin permeation

progressively into the deeper layers of the skin. This gradual release mechanism helps maintain therapeutic drug levels over an extended period, enhancing the efficacy of the treatment.<sup>[23]</sup>

### Drug release mechanism

The drug release from ethosomes is facilitated by the initial penetration of ethanol into the skin. Ethanol acts as a permeation enhancer, creating pathways for the ethosomes to follow. Once the ethosomes penetrate deeper into the skin, they release their drug payload at multiple points along the way. This sustained delivery mechanism ensures that therapeutic levels of the drug are maintained in the target area for a longer duration, which is beneficial for both hydrophilic and lipophilic drugs.<sup>[25]</sup>

### Enhanced penetration via hair follicles

Ethosomes can also utilize hair follicles as an alternative pathway for deeper delivery. Hair follicles provide a less resistant route compared to the compact stratum corneum, allowing ethosomes to reach deeper skin layers more easily. This dual pathway (intercellular and follicular) enhances the overall penetration efficiency of ethosomes, contributing to their effectiveness in transdermal drug delivery.<sup>[26]</sup>

## BENEFITS OF ETHOSOMES

Ethosomes are a breakthrough in transdermal drug delivery that offers numerous benefits over conventional methods:

### Enhanced drug penetration

Ethosomes improve skin permeability by disrupting the lipid structure with ethanol, allowing drugs to penetrate deeper without causing damage. Their flexibility enables them to

deform and pass through narrow spaces in the skin.<sup>[27]</sup>

### Versatility in drug delivery

Ethosomes can deliver both hydrophilic and lipophilic drugs, making them versatile for various therapeutic agents. They provide a non-invasive delivery method, enhancing patient compliance and reducing systemic side effects.<sup>[27]</sup>

### Therapeutic applications

Ethosomes are used for diverse conditions such as psoriasis and hypertension, offering better and longer-lasting effects compared to traditional methods. They ensure sustained drug release, maintaining therapeutic levels over time.<sup>[28]</sup>

### Biocompatibility and safety

Ethosomes are biocompatible and non-toxic, ensuring safety for human use. They are easy to formulate into user-friendly dosage forms such as gels and creams, enhancing patient adherence.<sup>[28]</sup>

### Advantages over other systems

Ethosomes penetrate deeper than traditional liposomes and offer better skin penetration than niosomes. They are similar to transferosomes in deformability but achieve deeper systemic effects, making them a preferred choice for enhanced drug delivery.<sup>[29]</sup>

## APPLICATION OF ETHOSOMES

Ethosomes are a new generation of phospholipid-based drug delivery systems and high levels of ethanol (20–45%) for the preparation of vesicular carriers to facilitate transdermal drug

delivery. The unique structure of ethosomes enables them to penetrate deeper into the layers of the skin when compared to conventional liposomes, making them ideally suited for the treatment of several skin conditions. This review is on the uses of ethosomes in the treatment of psoriasis, hypertension, melanoma, acne, atopic dermatitis, skin infection, and macromolecule delivery, including peptides, proteins, and plasmids. Figure 4 shows the application of ethosomes in various fields:

### Ethosomes in the treatment of psoriasis

Psoriasis is a chronic skin disorder characterized by the overproduction of skin cells and immune responses.<sup>[30]</sup> Traditional treatments often involve systemic medications or local applications, which can be less effective or have side effects. Ethosomes enhance the delivery of anti-psoriatic drugs by altering the lipid bilayer for better skin penetration.<sup>[31]</sup> Clinical trials show that ethosomal creams and gels significantly reduce psoriasis severity compared to standard treatments, with patients experiencing fewer side effects and improved comfort.<sup>[32]</sup>

The study by Mehmood *et al.*, published in Scientific Reports in 2024, explores the synthesis of Vitamin D3-loaded ethosomes gel for treating chronic immune-mediated inflammatory skin diseases such as psoriasis. The research aims to formulate and evaluate a Vitamin D3-loaded ethosomal gel to enhance skin delivery for therapeutic purposes. It involves synthesizing ethosomes encapsulating Vitamin D3, integrating them into a gel, and conducting physical characterization. The study will include *in vitro* assessments of drug release and permeation, along with *ex vivo* evaluations using skin models to test penetration and efficacy. By utilizing ethosomes, the goal is to improve skin penetration and bioavailability of

Vitamin D3, potentially enhancing treatment outcomes for chronic inflammatory skin conditions. This approach offers a promising therapeutic strategy with improved efficacy and patient compliance.<sup>[33]</sup>

### Ethosomes for anti-hypertensive therapy

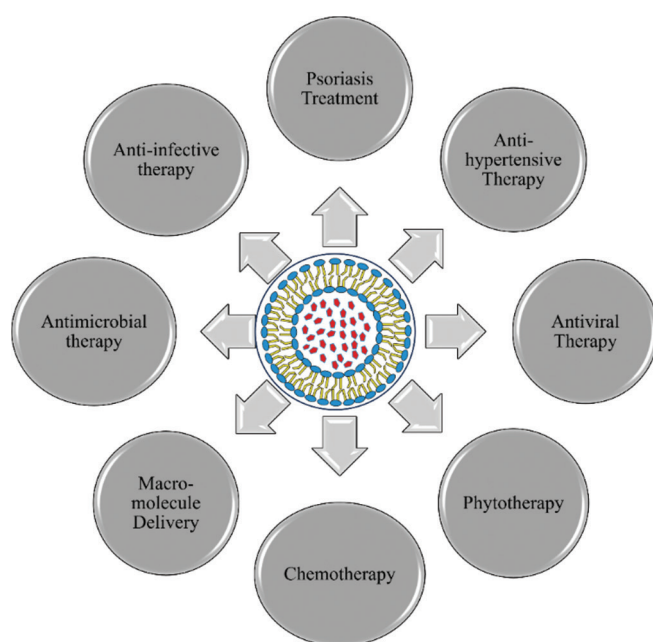
Hypertension typically requires long-term medication, but oral anti-hypertensive drugs can have side effects.<sup>[34]</sup> Ethosomes are a transdermal delivery system that offers a non-invasive method to deliver these medications, improving patient adherence and maintaining consistent drug levels. This approach leads to more stable blood pressure and fewer side effects compared to oral medications.<sup>[35]</sup>

A study by Amarachinta *et al.*, published in J Nanobiotechnology in 2021, focuses on the development of carvedilol-loaded transdermal ethosomal hydrogel using a central composite design. The goal was to improve the anti-hypertensive effect of carvedilol, a drug used for hypertension, heart failure, and angina. Due to its poor oral bioavailability from low solubility and high first-pass metabolism, transdermal delivery is a promising alternative. Ethosomes are lipid vesicles that enhance skin penetration and drug delivery. The ethosomal hydrogel formulation aims to provide sustained release and improved skin permeation of carvedilol, potentially increasing efficacy and patient compliance. This approach showcases the versatility of ethosomes in drug delivery systems for various therapeutic applications.<sup>[36]</sup>

### Ethosomes for treatment of melanoma

Melanoma is an aggressive skin cancer that needs effective localized treatments.<sup>[10]</sup> Ethosomes are a promising drug delivery system that targets chemotherapy directly to tumor cells, increasing drug concentration and reducing side effects. They may also enhance immune checkpoint inhibitors, improving therapy outcomes.<sup>[37,38]</sup> The study by Romani *et al.*, published in Cells in 2024, investigates the enhanced anti-melanoma effects of nutlin-3a delivered through ethosomes, focusing on p53-mediated apoptosis in HT144 cells. Nutlin-3a, a potent MDM2 inhibitor, activates the p53 pathway essential for cancer cell apoptosis. The researchers characterized nutlin-3a-loaded ethosomes for their properties and tested them on melanoma cell lines, including HT144 (p53 wild-type) and SK-MEL-28 (p53 mutated).

The results indicated that these ethosomes effectively induced morphological changes, cell cycle arrest, and apoptosis in p53 wild-type cells while modulating p53-regulated proteins. In addition, ethosomes reduced melanoma cell migration, suggesting antimetastatic properties. Overall, the study highlights ethosomes as effective delivery systems for nutlin-3a, enhancing its therapeutic efficacy against melanoma by targeting p53-mediated apoptosis and paving



**Figure 4:** Application of ethosome

the way for potential nutlin-3a-loaded ethosome-based treatments.<sup>[39]</sup>

### Ethosomes for acne, atopic dermatitis, and skin infections

Ethosomes have shown potential in treating skin conditions such as acne, atopic dermatitis, and skin infections.<sup>[40]</sup> A case study revealed that cryptotanshinone (CPT)-loaded ethosomes improved acne treatment with minimal irritation. They may also enhance drug delivery for atopic dermatitis and improve antimicrobial effectiveness for skin infections by reaching deeper layers. Overall, ethosomes offer a promising method for drug delivery across the skin barrier.<sup>[41]</sup> The study by Yu *et al.*, published in PLoS ONE in 2016, explores the use of ethosomes loaded with CPT for acne treatment through a topical gel formulation. The researchers developed ethosomes loaded with CPT to formulate a topical gel for acne treatment. They evaluated the ethosomes for vesicle size, CPT loading, and encapsulation efficiency, finding an average vesicle size of  $69.1 \pm 1.9$  nm, with CPT loading at  $0.445 \pm 0.007$  mg/mL and encapsulation efficiency of  $40.31 \pm 0.67\%$ . The ethosomal gel exhibited significantly higher transdermal flux and skin deposition than conventional gels, being 2.5 and 2.1 times greater, respectively. It demonstrated improved anti-acne activity with minor skin irritation, effectively reducing inflammation and restoring skin structure in rabbits. Both CPT-loaded and blank gels showed minimal irritation without significant histological changes. The study suggests that ethosomal formulations are an effective delivery system for CPT and hold promise as future acne treatments.<sup>[41]</sup>

### Ethosomes for delivery of macromolecules (peptides, proteins, and plasmids)

The delivery of macromolecules such as peptides, proteins, and plasmids through the skin is a significant advancement in treating genetic and chronic diseases. Ethosomes are effective carriers due to their soft structure and improved permeability.

Using ethosomes to deliver peptides protects them from enzymatic degradation while allowing for skin absorption, which is vital for their effectiveness. Research shows that encapsulating proteins in ethosomes stabilizes them and enhances their local bioavailability.<sup>[42]</sup> There is increasing interest in using ethosomes for gene therapy, particularly for plasmid DNA delivery. This approach aims to transport plasmids transdermally, potentially treating genetic skin diseases and systemic conditions in a non-surgical way.<sup>[43]</sup>

The study by Fu *et al.*<sup>[44]</sup> focuses on the development of an ethosomal gel designed to enhance the transdermal delivery of thymosin  $\beta$ -4 (T $\beta$ -4), a macromolecular protein drug with significant potential in wound healing. T $\beta$ -4's therapeutic use is often limited by poor membrane permeability and instability. Researchers developed ethosomes, lipid-based vesicles that enhance drug delivery by improving cell membrane fluidity. They optimized the ethosomal formulation using the ethanol infusion method and characterized the gels through various analyses. *In vitro* studies with Franz diffusion cells showed the optimized T $\beta$ -4 ethosomal gels released 1.67 times more drug than conventional gels in 5 h. Furthermore, these gels reduced wound healing time to half that of the T $\beta$ -4 gel group. The study concludes that ethosomal gels enhance the absorption of macromolecular drugs such as T $\beta$ -4, indicating potential for wider applications in transdermal delivery and traditional medicine.

Table 3 summarizes studies that highlight the versatility and effectiveness of ethosomes in enhancing drug delivery across various therapeutic applications.

## CHALLENGES

While promising, ethosomes also pose several challenges that must be addressed. One of the primary limitations is drug leakage risk, which is due to the high concentration of ethanol in the vesicles.<sup>[10]</sup> Some measures to counter this include optimizing the lipid composition, chemically

**Table 3: Recent research on ethosomal formulations aimed at treating various diseases**

Researcher	Drug/active ingredient	Key Findings	Application	References
Mehmood <i>et al.</i>	Vitamin D3	Enhanced drug penetration and absorption, improved therapeutic outcomes for psoriasis by reducing keratinocyte hyperproliferation and inflammation.	Psoriasis treatment	[33]
Amarachinta <i>et al.</i>	Carvedilol	Optimized ethosomes showed sustained release and enhanced skin penetration, leading to prolonged anti-hypertensive effects in rats.	Hypertension management	[36]
Romani <i>et al.</i>	Nutlin-3a	Enhanced anti-melanoma activity by preserving drug effectiveness and inducing apoptosis in melanoma cells.	Melanoma treatment	[39]
Yu <i>et al.</i>	Cryptotanshinone	Demonstrated superior transdermal permeation and skin deposition, associated with a better anti-acne effect.	Acne treatment	[41]
Fu <i>et al.</i>	Thymosin $\beta$ -4	Improved transdermal delivery of T $\beta$ -4 significantly reduces wound healing time.	Wound healing	[43]

crosslinking the lipid bilayer for enhanced stability, or employing lyophilization techniques for improved long-term storage. The high ethanol content can also cause skin irritation in certain subjects and may require lowering ethanol concentrations in the formulation or even entail the use of irritant-reducing agents.<sup>[32]</sup> In addition, manufacturing-related aspects such as the typically low production yield of ethosomes and transfer loss from organic to aqueous mediums need to be tackled through process optimization and more efficient equipment design. Finally, the currently limited routes of administration of ethosomes, mainly transdermal, need to be expanded by exploring other routes such as oral, nasal, or pulmonary delivery to maximize their therapeutic application.<sup>[45]</sup>

## FUTURE OUTLOOK

The future of ethosome research is in some significant areas. Of prime importance will be the performance of more complex *in vivo* studies, particularly with human subjects, to confirm efficacy seen in pre-clinical models, critically evaluate safety profiles, optimize dosing regimens, and fully elucidate the pharmacokinetic and pharmacodynamic properties of ethosomes in the human body.<sup>[46]</sup> In addition, ethosomes are envisaged to hold strong potential for personalized medicine and targeted drug delivery. This encompasses ethosome design for formulation to meet specific patient needs, e.g., different lipid ratios based on skin types or inclusion of targeting ligands for drug delivery in a targeted manner to targeted tissues or cells based on individual disease profiles.<sup>[47]</sup> Further innovation will come from the studies on new modifications and combinations for better ethosome performance, e.g., the application of transethosomes for better skin permeation, functionalized ethosomes for improved stability and controlled release, combination therapy for synergistic action in the treatment of multifactorial diseases, and combination with physical approaches such as microneedles to facilitate drug penetration across the skin barrier.<sup>[29]</sup>

## CONCLUSION

Ethosomes represent a giant step ahead as transdermal nanocarriers to transform drug delivery through the skin into an entirely new science. Their structure and nature make them especially suited to dramatically enhance drug penetration, efficiently deliver a wide range of therapeutic entities, and hold great promise for curing dermatoses. In line with continuous scientific investigation and development, great prospects for future breakthroughs shine ethosomes brilliantly in the way of more effective, targeted, and individualized transdermal therapy.

## ACKNOWLEDGMENTS

The authors would like to thank the School of Pharmaceutical Sciences, Chhatrapati Shahu Ji Maharaj University, Kanpur, for providing all the facilities and resources that are required.

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**Source of Support:** Nil. **Conflicts of Interest:** None declared.