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Review Paper

Review On Ethosome: As A Nanocarrier

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ABSTRACT

The evolution of nanotechnology has revolutionized the field of transdermal and dermal drug delivery. Among various vesicular carriers, ethosomes have emerged as highly efficient, soft, and deformable lipid-based systems designed to enhance the delivery of bioactive compounds through the skin barrier. Ethosomes are composed of phospholipids, ethanol, and water, which synergistically improve drug solubility, permeability, and bioavailability compared to traditional liposomes(1,2). Due to their unique structure, ethosomes can encapsulate both hydrophilic and lipophilic molecules and penetrate deeply into skin layers. Recent research highlights their application in dermatology, cosmetology, oncology, and photodynamic therapy, making ethosomes one of the most promising nanocarriers for topical and transdermal delivery(3,4). This review provides a comprehensive overview of ethosomal structure, mechanism of skin penetration, preparation methods, applications, advantages, limitations, and future prospects, supported by extensive literature from 2010–2024

INTRODUCTION

Transdermal and dermal drug delivery systems have gained significant attention as non-invasive routes for systemic and localized drug administration. However, the stratum corneum, the outermost layer of the skin, acts as a major barrier that limits the penetration of most drugs (5). Traditional vesicular systems such as liposomes and niosomes often face challenges of rigidity and limited permeability through skin layers (6). To overcome these limitations, Touitou et al. (1996) introduced the concept of ethosomes — soft, malleable vesicular systems containing high concentrations of ethanol that enhance lipid fluidity and skin permeability(7) .

Ethosomes are composed primarily of phospholipids**,** ethanol, and water**,** with optional additives like cholesterol or surfactants that improve stability and elasticity(8) . Ethanol acts as a penetration enhancer and imparts negative charge to the vesicles, preventing aggregation(9) . The presence of ethanol disrupts the stratum

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corneum lipid organization, facilitating deep dermal drug delivery (10).

Over the past two decades, ethosomes have been explored as carriers for a variety of therapeutic agents, including **anti-hypertensive drugs** (8), **antifungal agents** (11), **anti-psoriatic formulations** (10), **anticancer agents** (12), and **cosmeceuticals**(1,13). Furthermore, their high deformability allows efficient drug delivery even through skin appendages and damaged tissues (14,15).

Flowchart: Evolution of Vesicular Drug Delivery Systems

Liposomes (Rigid vesicles)

↓

Niosomes (Non-ionic surfactant vesicles)

↓

Transfersomes (Highly deformable lipid vesicles)

↓

Ethosomes (Ethanol-based soft vesicles)

↓

Transethosomes (Hybrid system: ethosome + edge activators)

Schematic Representation of Ethosome Structure.

"An ethosome vesicle comprises a bilayer of phospholipids interspersed with ethanol molecules. The core may contain hydrophilic drug molecules, while lipophilic drugs reside within the lipid bilayer. The external ethanol-rich phase ensures fluidity, allowing ethosomes to deform and penetrate skin layers effectively."

Ethosomes bridge the gap between traditional and advanced delivery systems, combining the **biocompatibility of liposomes** with the **penetration power of ethanol** (2,16) . Their ability to enhance both dermal retention and transdermal flux makes them suitable for **systemic therapy**, **cosmetic enhancement**, and **targeted skin treatments** (15–17) .

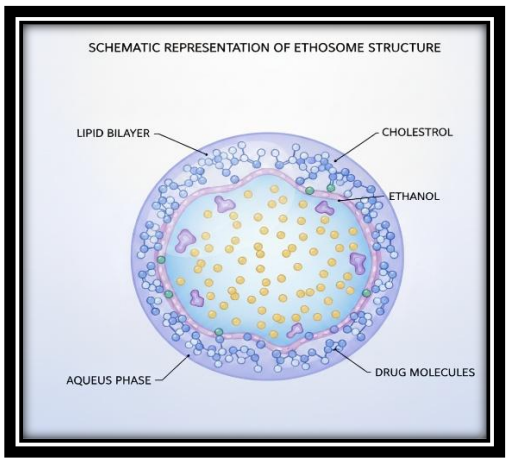


Figure 1:Schematic representatiom of ethosome structure

3. Structure and Composition of Ethosomes.

3.1. Structure of ethosome

Ethosomes are **soft, malleable vesicular systems** primarily composed of **phospholipids**, **ethanol (20–45%)**, and **water** (2,5). Optional components such as cholesterol, surfactants, or stabilizers are added to enhance the structural integrity and control vesicle size. The ethanol content distinguishes ethosomes from other vesicular carriers like liposomes or niosomes (1,16).

Phospholipids form a bilayer membrane that entraps both **hydrophilic** and **lipophilic** drug molecules. Ethanol, being a small polar molecule, integrates within the bilayer, imparting high deformability and flexibility (6). Water serves as the dispersion medium and ensures vesicle hydration.

Ethosomes exist as **unilamellar or multilamellar vesicles** depending on the preparation conditions and phospholipid concentration (9,17). Their average particle size ranges from **100–400 nm**, which favors deep skin penetration and sustained drug release (4,15).

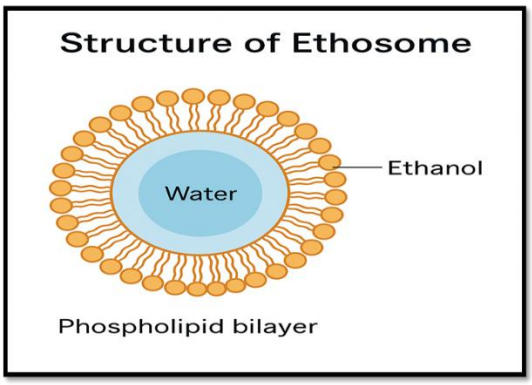


Figure 2:Structure of ethosome

3.2. Composition of Ethosomes

Table 1:Composition of ethosome

Component	Function	Examples
Phospholipids	Form vesicular bilayer	Phosphatidylcholine, Phosphatidylserine
Ethanol (20–45%)	Enhances permeability and vesicle fluidity	Ethanol, Isopropanol
Water	Dispersion medium	Purified water
Cholesterol	Improves membrane rigidity and stability	Cholesterol
Additives	Stabilizers or surfactants	Propylene glycol, Tween 80

(2,8,9,14,16)

3.3. Structure of an Ethosomal Vesicle.

"An ethosomal vesicle consists of a lipid bilayer in which ethanol molecules are embedded. The central core may encapsulate hydrophilic drugs, while lipophilic drugs are entrapped within the bilayer region. The outer surface carries a negative charge, preventing vesicle aggregation and improving colloidal stability."

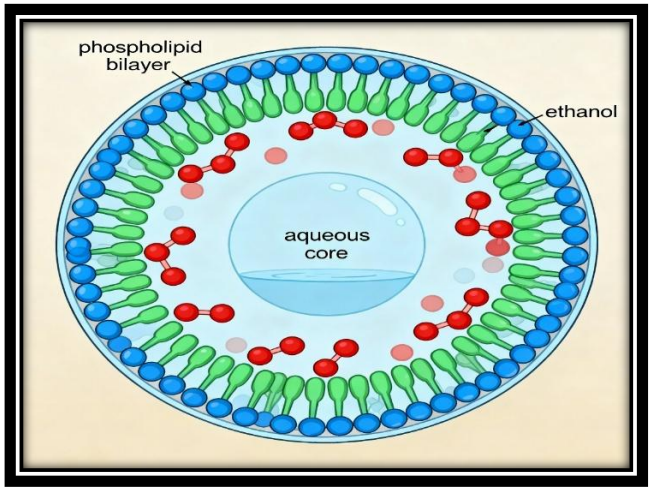


Figure 3 : Structure of an ethosome vesicle

4. Mechanism of Skin Penetration

The **enhanced permeation mechanism** of ethosomes is primarily attributed to the synergistic action of **ethanol** and **phospholipids** (3,4). Ethanol interacts with skin lipids in the stratum corneum, increasing their fluidity and decreasing the density of the lipid multilayers (1,18). Simultaneously, ethosomal vesicles, due to their flexible bilayer, penetrate the skin through intercellular pathways.

The **mechanism** can be explained in three sequential stages:

1. **Ethanol effect on skin lipids:**

Ethanol disrupts the tightly packed lipid domains of the stratum corneum, enhancing the permeability of the skin (2,5).

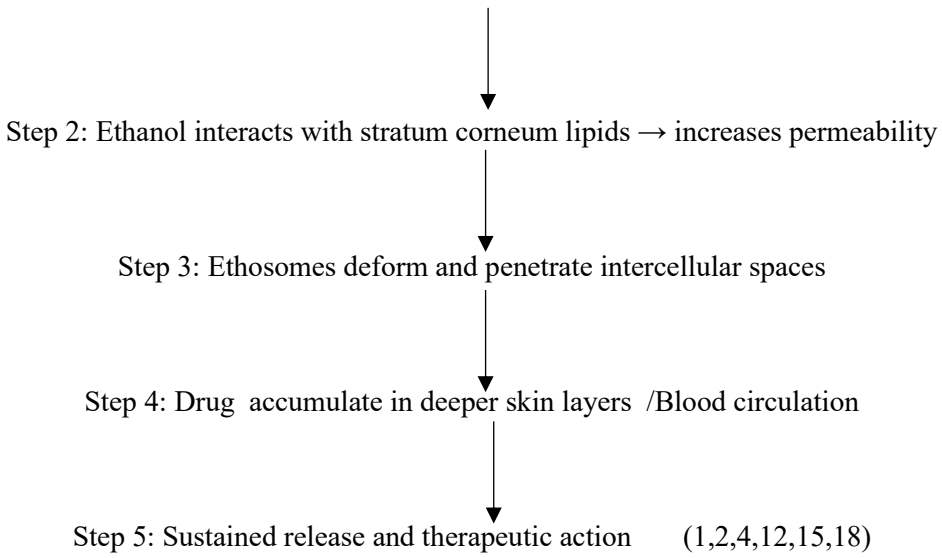
2. **Ethosome Deformability:**

The high ethanol content confers ultra-flexibility to ethosomal vesicles, allowing them to squeeze through narrow intercellular spaces without rupture (12,13)

3. **Deep dermal deposition:**

Once inside, the vesicles act as drug reservoirs, releasing the active molecules gradually to deeper skin layers or systemic circulation (9,15)

Mechanism of Ethosomal Penetration through Skin



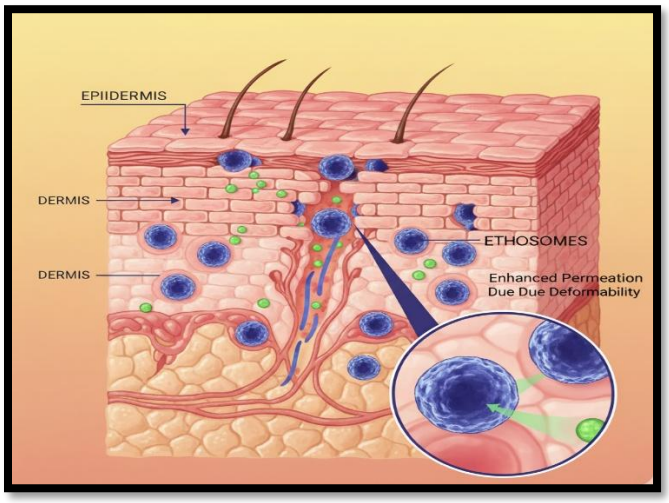


Figure 4:Mechanism of skin penetration of ethosome

Comparison Between Liposomes and Ethosomes

LIPOSOME:
[Phospholipid Bilayer] → Rigid, low permeability
Drug retained mainly on skin surface

ETHOSOME:
[Phospholipid + Ethanol Bilayer] → Flexible, deep penetration
Drug reaches viable epidermis and dermis (3,10,13,16) .

5. Methods of Preparation

Various methods have been developed for the preparation of ethosomal systems. The choice of technique affects **vesicle size**, **entrapment efficiency**, **stability**, and **drug release characteristics** (5,8,15). Commonly used methods include:

5.1 Cold Method (Touitou Method)

The **cold method** is the most widely used and efficient technique (18).

Procedure:

1. Dissolve phospholipids and drug in ethanol at room temperature with continuous stirring.
2. Add propylene glycol or other polyols if required.
3. Heat water separately to 30°C and add slowly to the ethanol-lipid mixture under continuous stirring.
4. Continue mixing for 5–10 minutes until a milky ethosomal suspension forms.
5. The resulting vesicles can be stored at 4°C.

Advantages: Simple, reproducible, and suitable for thermolabile drugs.
Limitations: Requires controlled ethanol concentration to maintain vesicle integrity (3,8,18).

5.2 Hot Method

In this method

1. the phospholipids are dispersed in water maintained at 40°C, and ethanol is added dropwise under constant stirring .
2. The temperature helps improve lipid solubilization, but excessive heat may cause drug degradation (9).

5.3 Classic Mechanical Dispersion

1.Here, the drug and lipids are dissolved in organic solvent (ethanol or chloroform) and subjected to rotary evaporation to form a thin film, which is then hydrated with aqueous ethanol solution .
2.The resulting vesicles are sonicated or extruded for size reduction (14,16).

5.4 Thin-Film Hydration Technique

1. An adaptation of the liposomal preparation method, this involves the **formation of a thin lipid film** on a rotary evaporator flask, followed by hydration with hydro-ethanolic solution (15,19).
2. The ethosomal suspension is then subjected to sonication to achieve uniform particle size.

5.5 Injection Method

1.In this technique, an ethanolic solution of lipids and drug is injected rapidly into an aqueous phase maintained at a specific temperature under continuous stirring.
2.The sudden change in polarity results in spontaneous vesicle formation(20,21).

Table 2 : Summary of Ethosome Preparation Methods

Method	Temperature Range	Key Feature	Advantages	References
Cold Method	25–30°C	Simple, widely used	Suitable for heat-sensitive drugs	(2,18)
Hot Method	40–45°C	Quick formation	Better solubilization of lipids	(9,15)
Thin-Film Hydration	40°C (hydration)	Controlled size	High encapsulation efficiency	(16,19)
Injection Method	Room temp	Rapid vesicle formation	Good reproducibility	(20,21)

6. Characterization of Ethosomes

Comprehensive **characterization** of ethosomes is essential to ensure optimal performance, stability, and therapeutic efficacy. Physicochemical parameters such as **vesicle size**, **zeta potential**, **entrapment efficiency**, **morphology**, and **drug release profile** are critical indicators of formulation quality (8,15,17).

6.1 Vesicle Size and Size Distribution

The vesicle size of ethosomes typically ranges from **100 to 400 nm**, depending on the ethanol concentration and phospholipid composition (2,16). Size reduction is commonly achieved through **probe sonication** or **extrusion techniques**. A smaller vesicle size contributes to deeper skin penetration and uniform drug distribution (15,19).

Measurement Technique:

- **Dynamic Light Scattering (DLS)** or **Photon Correlation Spectroscopy (PCS)** are used to determine average vesicle size and polydispersity index (PDI) (5,22)

6.2 Zeta Potential

The **zeta potential** indicates the surface charge of ethosomal vesicles and plays a vital role in colloidal stability. Ethosomes generally exhibit a **negative zeta potential** (−30 to −50 mV) due to ethanol's interaction with phospholipid head groups, preventing vesicle aggregation (9,12).

6.3 Entrapment Efficiency (EE%)

Entrapment efficiency represents the percentage of drug successfully encapsulated within the ethosomal vesicles. EE% depends on the physicochemical properties of the drug and formulation parameters [8,10].
It can be determined using **ultracentrifugation** or **dialysis methods** followed by drug quantification through **UV spectroscopy** or **HPLC analysis** (14,16).

6.4 Morphology

Ethosome morphology is typically **spherical or oval**, with a smooth and uniform surface (15,23). Visualization is performed using **Transmission**

Electron Microscopy (TEM) or **Scanning Electron Microscopy (SEM)** (6,9). Cryo-TEM provides detailed insights into vesicle lamellarity and uniformity (13).

6.5 Drug Release and Permeation Studies

Drug release from ethosomal formulations is evaluated using **Franz diffusion cells** with synthetic membranes or excised animal skin (8,15). The release profile often follows a **controlled or biphasic pattern**—an initial burst release followed by sustained diffusion into deeper layers (4,24).

In vivo studies on animal models (e.g., rats, rabbits) and **in vitro** human skin permeation tests demonstrate the superior penetration capability of ethosomes compared to conventional liposomes (1,6,17).

Table 3: Key Characterization Parameters of Ethosomes

Parameter	Instrument / Technique
Vesicle Size	**→ DLS, PCS**
Zeta Potential	**→ Zeta Sizer**
Entrapment Efficiency	**→ Ultracentrifugation + UV/HPLC**
Morphology	**→ TEM, SEM, AFM**
Drug Release Profile	**→ Franz Diffusion Cell**

(5,8,9,13,15,16)

7. Applications of Ethosomes in Drug Delivery

Ethosomes have emerged as a versatile nanocarrier platform for multiple therapeutic and cosmetic applications. Their **soft, flexible, and ethanol-rich** structure allows deep penetration through skin layers, facilitating **enhanced transdermal flux** and **improved bioavailability** (1,4,9,13,24). The major application domains of ethosomes are summarized below.

7.1 Transdermal Drug Delivery

Ethosomes are widely used for **transdermal drug delivery**, enabling systemic absorption without invasive administration (2,6). For example, **Ibrahim et al. (2019)** developed a **transdermal ethosomal gel of carvedilol**, demonstrating enhanced antihypertensive effects compared to oral formulations (8). Similarly, **Rao et al. (2008)** used ethosomal vesicles for **finasteride delivery**, achieving improved dermal retention and controlled release (6).

Mechanism of Transdermal Ethosomal Delivery

Step 1: Application of ethosomal gel/cream on skin

↓

Step 2: Ethanol fluidizes stratum corneum lipids

↓

Step 3: Ethosomes deform and penetrate epidermal layers

↓

Step 4: Drug released into viable epidermis or systemic circulation(2,6,8,15)

7.2 Dermal and Cosmetic Applications

Ethosomes play a significant role in **cosmeceutical formulations**, enhancing the skin absorption of bioactive ingredients such as **vitamins, antioxidants, and herbal extracts** (1,13,24).

Abu-Huwaij & Zidan (2024) emphasized the growing trend of using ethosomal nanocarriers in cosmetic dermatology for anti-aging and skin rejuvenation (1). Ethosomes improve dermal delivery of compounds like **vitamin D3**, **coenzyme Q10**, and **retinoids**, which are otherwise poorly soluble in conventional creams (23).

Esposito et al. (2024) demonstrated that ethosomes and transethosomes can "feed the body through the skin" by delivering nutritional bioactives, highlighting their use in nutracosmetics (24).

7.3 Anticancer Applications

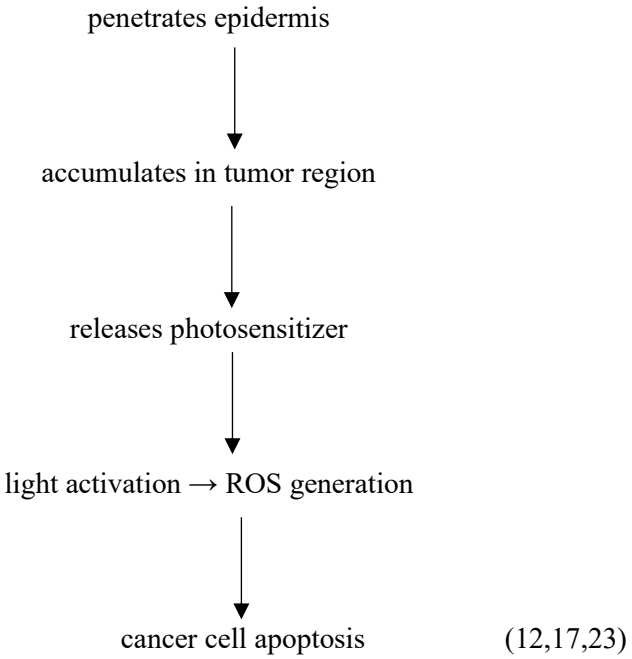
Ethosomes have shown immense promise in **skin cancer therapy** due to their ability to deliver cytotoxic or photodynamic drugs selectively to tumor sites (12,25).

Nasr et al. (2019) formulated ethosomes loaded with a chlorophyll derivative for **photodynamic therapy of squamous cell carcinoma**, achieving significant tumor cell apoptosis (17).

Likewise, **Shinde et al. (2023)** explored the **anticancer potential of ethosomal formulations** in skin malignancies, demonstrating improved drug targeting and minimal systemic toxicity (12).

Mohanty et al. (2024) also reported synergistic benefits when combining **photodynamic therapy with ethosomal nanocarriers**, reinforcing their potential as next-generation oncologic delivery systems (25).

Ethosomes in Skin Cancer Therapy[Ethosomal Vesicle]



(12,17,23)

7.4 Antifungal and Anti-inflammatory Applications

Ethosomes are highly efficient in **delivering antifungal agents** such as ketoconazole and clotrimazole across skin layers (11,26).

Aljohani et al. (2023) developed **binary ethosomes** to enhance the topical delivery and antifungal efficacy of ketoconazole, showing

superior skin deposition compared to conventional creams (11).

Verma & Utreja (2019) also demonstrated the ethosomal delivery of antifungal drugs as a potential approach for **deep-seated skin infections**, achieving sustained drug release and improved patient compliance (26). Furthermore, ethosomes have been used for **anti-inflammatory** and **anti-psoriatic** therapies. **Fathalla et al. (2020)** developed **anthralin-loaded ethosomal gels**, which significantly reduced psoriatic lesions and improved patient tolerance (10).

7.5 Delivery of Herbal and Natural Compounds

The ethosomal platform is compatible with **plant-based extracts** and **ethnopharmacological formulations**, allowing better skin permeation of natural actives(22,27).

Sivapriya et al. (2018) reported the incorporation of herbal agents in ethosomes for enhanced bioavailability and therapeutic effect (27).

This characteristic makes ethosomes an ideal vehicle for **herbal-based nanocosmetics** and **natural topical therapies**.

7.6 Delivery of Vitamins and Nutraceuticals

Ethosomes have been used to improve the delivery of **vitamin D3**, **vitamin E**, and other nutraceuticals to skin layers. **Costanzo et al. (2021)** performed a **formulative study on vitamin D3 ethosomes**, showing efficient intracellular uptake and controlled release (23).

Such formulations not only address vitamin deficiencies but also improve skin health and photoprotection (24).

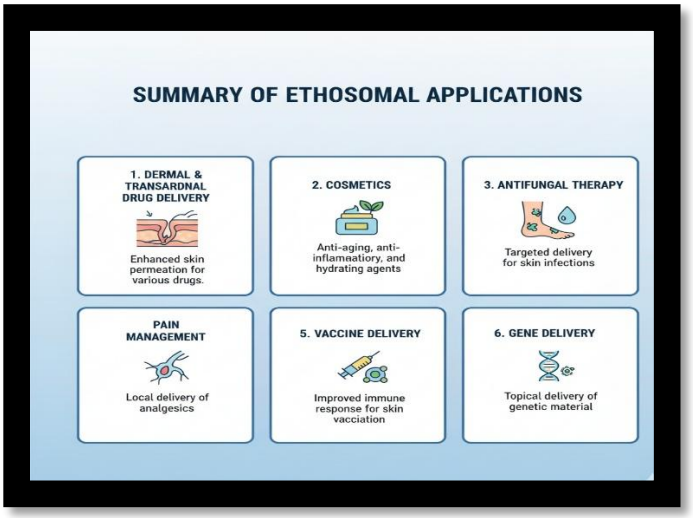


Figure 5 : Summary of ethosomal application.

Table 4:Summary of ethosomal application

Drug/Agent	Target Disease/Application	Outcome	Reference
Carvedilol	Hypertension	Enhanced antihypertensive activity	(8)
Finasteride	Alopecia	Increased skin accumulation	(6)
Anthralin	Psoriasis	Improved skin tolerability	(10)
Chlorophyll derivative	Skin cancer (PDT)	Effective tumor ablation	(12,17)
Ketoconazole	Fungal infection	Improved antifungal efficacy	(11)
Vitamin D3	Skin nourishment	Sustained dermal release	(23)

8. Advantages of Ethosomes

Ethosomes represent a major breakthrough in the field of vesicular drug delivery systems. Their unique combination of ethanol and phospholipids offers several physicochemical and therapeutic advantages over conventional liposomes, niosomes, and transferosomes (2,4,15).

8.1 Enhanced Skin Permeation

The high ethanol content in ethosomes disrupts the stratum corneum lipid structure, improving skin permeability and allowing deeper penetration of both hydrophilic and lipophilic drugs (3,9). Ethosomes have been shown to increase drug flux up to **20 times** compared to liposomes (18).

8.2 High Drug Loading Capacity

Due to the solubilizing effect of ethanol, ethosomes can encapsulate a wide range of molecules including peptides, proteins, steroids, and hydrophobic drugs (1,5,16).

8.3 Non-Invasive and Patient Friendly

Ethosomal formulations (gels, creams, or patches) provide **non-invasive administration**, avoiding gastrointestinal degradation and first-pass metabolism, thus improving patient compliance (8,15,28).

8.4 Improved Stability

Ethanol acts as a natural preservative, increasing the chemical and microbial stability of ethosomal systems compared to traditional aqueous vesicles (6,22).

8.5 Versatility in Formulation

Ethosomes can be formulated into **gels, creams, sprays, emulsions, or patches**, making them adaptable for dermal, transdermal, and cosmetic applications (1,13,23,27).

Advantages of Ethosomes

Ethosomes vs. Liposomes

Table 5:Advantages of ethosomes

High ethanol content → Better permeability
Flexible structure → Deeper skin delivery
Dual solubility → Lipophilic + Hydrophilic drugs
Stable formulation → Longer shelf life
Patient compliance → Non-invasive application

(1,6,15,17,27)

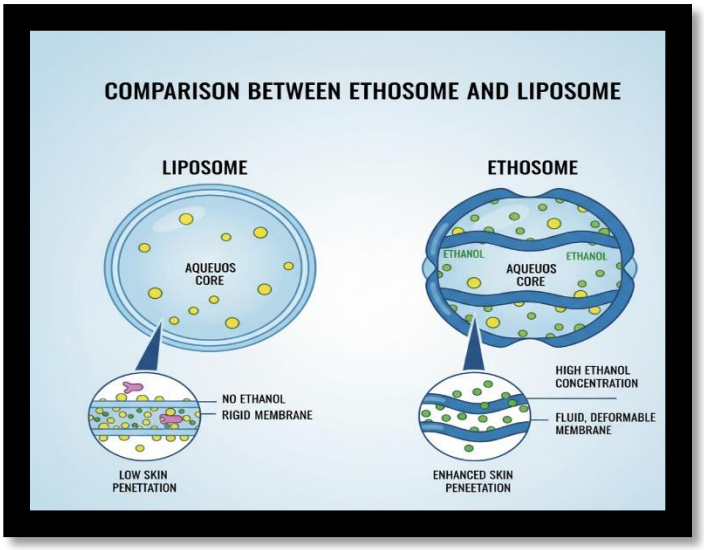


Figure 6 : comparison between ethosome and liposome

9. Limitations and Challenges

Despite their promising properties, certain challenges limit the widespread use of ethosomes in clinical practice (7,14,20).

9.1 Stability Issues at High Temperature

Ethosomes may exhibit **reduced stability** under high temperature or humidity due to ethanol evaporation and vesicle fusion (15,21). Storage below 8°C is often necessary to maintain integrity.

9.2 Skin Irritation Potential

Excess ethanol content may cause **irritation or erythema** in sensitive individuals, particularly for long-term topical application (22,28).

9.3 Scale-Up Challenges

The industrial **scale-up** of ethosomal formulations remains complex because ethanol's volatility can alter vesicle composition during manufacturing (7,29).

9.4 Limited Drug Compatibility

Highly hydrophilic or unstable biomolecules may not always achieve high encapsulation efficiency in ethosomes (15,19,20).

Table 6:Limitations of ethosomal system

High Ethanol Concentration → Possible skin irritation
Temperature Sensitivity → Instability during storage
Manufacturing Constraints → Scale-up difficulties
Drug Solubility Limitations → Low EE% for certain drugs

(7,15,20,22,29) .

10. Future Perspectives

Ethosomes continue to evolve as **next-generation nanocarriers** for targeted and personalized transdermal therapy. Emerging research trends focus on:

10.1 Development of Hybrid Systems

The integration of ethosomes with **transfersomes**, **niosomes**, and **polymeric nanoparticles** is leading to hybrid systems such as **transethosomes**, offering superior deformability and dual mechanism penetration (15,23,24).

10.2 Smart and Stimuli-Responsive Ethosomes

Innovations are being explored to design **stimuli-responsive ethosomal systems**, capable of responding to **pH, temperature, or light**, for controlled and site-specific drug release (13,25).

10.3 Ethosomal Carriers in Gene and Vaccine Delivery

Recent advancements indicate potential applications of ethosomes in **DNA, RNA, and vaccine delivery**, leveraging their soft vesicular structure for nucleic acid protection and transfection (15,30).

10.4 Clinical Translation and Regulatory Approval

While numerous preclinical and in vitro studies demonstrate efficacy, **large-scale clinical trials** are still limited. Future research must focus on **standardization**, **toxicity evaluation**, and **regulatory acceptance** to facilitate market translation (2,5,24).

Future Prospects of Ethosomal Technology

Emerging Fields of Ethosome Research

• Transethosomes for hybrid delivery
• Stimuli-responsive ethosomes
• Gene and vaccine transporters
• Cosmeceutical and nutraceutical delivery
• Personalized nanomedicine applications (13,15,24,25,30)

Ethosomes have entered clinical evaluation for various dermatological applications, including psoriasis and fungal infections. Their non-invasive nature and compatibility with biocompatible lipids make them suitable for personalized medicine (5,12,19). However, large-scale clinical trials and regulatory validation remain essential. Future directions include smart ethosomal systems responsive to stimuli such as pH, temperature, or light, potentially revolutionizing targeted dermal therapies (15,25).

11. Recent Developments

Recent research focuses on binary ethosomes, transethosomes, and hybrid vesicular systems combining ethanol with surfactants or penetration enhancers. Binary ethosomes (ethanol + propylene glycol) provide improved stability and penetration (11). Studies by Zhan et al. (15) and Mazhar et al. (22)suggest ethosomes' clinical potential for chronic skin disorders and targeted drug delivery. Moreover, computational modeling and imaging techniques have enhanced understanding of ethosome-skin interactions (1,15,28). In cosmetic dermatology, ethosomal formulations are being evaluated for anti-aging, pigmentation control, and photoprotection (13,24).

Table 7:Ethosomal formulation and disease treated.

Drug/Formulation	Disease/Use	Key Findings	Reference
Anthralin ethosomal gel	Psoriasis	Improved efficacy and reduced irritation	(10)
Carvedilol ethosomal gel	Hypertension	Enhanced skin permeation and effect	(8)
Finasteride ethosomes	Alopecia	Higher follicular drug accumulation	(6)
Ketoconazole binary ethosomes	Fungal infections	Improved antifungal activity	(11)
Chlorophyll ethosomes	Skin cancer (PDT)	Efficient targeting and light activation	(17,25)
Vitamin D3 ethosomes	Nutrient supplementation	Controlled release and absorption	(23)
Cosmetic bioactives (e.g., vitamins)	Skin nourishment	Enhanced cosmetic efficacy	(13,24)

CONCLUSION

Ethosomes represent a **revolutionary approach** in the field of transdermal and dermal drug delivery. By combining the **penetration-enhancing ability of ethanol** with the **biocompatibility of phospholipids**, ethosomes offer superior drug permeation, high entrapment efficiency, and improved patient compliance compared to traditional carriers (1,2,4,8,9).

Their versatile application across **pharmaceutical, dermatological, and cosmeceutical fields** underscores their

adaptability as an advanced nanocarrier system. Despite certain limitations related to ethanol content and stability, ongoing innovations such as **transethosomes** and **smart responsive systems** are paving the way for future clinical translation.

Thus, ethosomes hold immense promise as **nanocarriers for efficient, non-invasive, and targeted skin drug delivery**, bridging the gap between modern nanotechnology and therapeutic dermatology (15,23,24).

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