REVIEW PAPER

Ethosomes: nanostructures for enhanced skin penetration

S Ruchitha[1], Gourav R[1], Pradip Nirbhavane[2], Prashant kurkute*[1]

[1]Shobhaben Pratapbhai Patel School of Pharmacy & Technology Management, SVKM's NMIMS, V.L. Mehta Road, Vile Parle (W), Mumbai, India
[2]Amity Institute of Pharmacy, Amity University Haryana, Gurgaon, India

ABSTRACT

The skin is a prominent and easily accessible organ in the human body. Despite providing the most straightforward and non-invasive drug administration method, the skin's limited permeability restricts the range of medications effectively delivered transdermally. The use of ethosomes as innovative vesicles for transdermal drug delivery has shown considerable promise in enhancing the permeation of drugs through the biological membrane. Ethosomes offer a preferable alternative to liposomes due to their ability to penetrate the skin more rapidly. Researchers have shown significant interest in ethosomes because of their exceptional capacity to deeply penetrate the skin, improve drug delivery, and achieve high entrapment efficiency. This study provides a comprehensive exploration of ethosomes as a drug delivery system. It aims to present detailed information on various aspects of ethosomes, including their manufacturing process, advantages, composition, properties, and applications in treating multiple diseases such as rheumatoid arthritis, psoriasis, hormonal imbalances, and other skin infections.

***Keywords**: Ethanol; Ethosomes; skin; Transdermal; Drug delivery system; Skin penetration; Phospholipids.*

How to cite this article
Ruchitha S, Gourav R, Nirbhavane P, kurkute P. Ethosomes: nanostructures for enhanced skin penetration. Nanomed J. 2026; 13(1): 54-71. DOI: 10.22038/nmj.2025.82905.2070.

INTRODUCTION

The skin, being the largest and most accessible organ, presents a promising route for delivering medications intended to produce systemic effects. However, the skin's outermost layer, the stratum corneum, acts as a formidable barrier that prevents drugs from penetrating the skin [1] (Figure 1). As a result, the ability of medications to be absorbed into the bloodstream through the skin is limited, leading to reduced transdermal bioavailability. Therefore, the use of specialized carriers is essential to overcome the natural resistance of the skin barrier and facilitate the efficient transport of drug molecules with diverse physicochemical properties into the systemic circulation [2].

The transdermal route offers numerous advantages, including avoiding first-pass metabolism by the liver, controlled drug release, reduced dosing frequency, and improved patient adherence [3]. These methods are non-invasive and can be self-administered, thereby enhancing patient compliance. The first transdermal patch containing scopolamine for managing motion sickness was approved in the United States in 1979 [3,4].

The initial use of liposomes for the topical delivery of triamcinolone marked the beginning of a new phase of research in this field [5]. Since then, numerous innovative lipid-based vesicular systems have been developed.

According to various specialists, traditional liposomes are generally considered ineffective carriers for transdermal drug delivery [6–8]. This is primarily due to their limited ability to penetrate the epidermis deeply, as they tend to remain principally within the superficial layer of the stratum corneum.

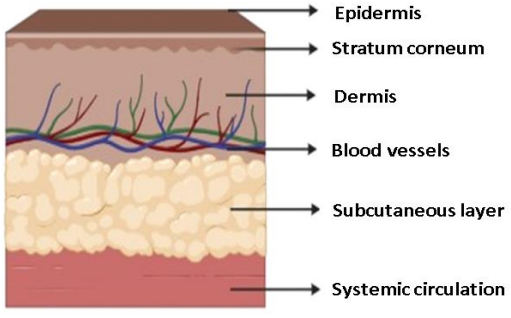

Fig. 1. Depicts the layered structure of human skin, showcasing the epidermis, dermis, and subcutaneous tissue, each layer contributing to skin's protective and sensory functions.

* *Corresponding author:* Prashant kurkute, Associate Professor, Shobhaben Pratapbhai Patel School of Pharmacy & Technology Management, SVKM's NMIMS, V.L. Mehta Road, Vile Parle (W), Mumbai, India. E-Mail address: prashkurkute@gmail.com.
Note. This manuscript was submitted on August 13, 2024; approved on July 01, 2025.

Transfersomes were first discovered by Cevc and Blume in 1992. This was followed by the groundbreaking research of Touitou et al., who introduced a new lipid vesicular system known as ethosomes [9,10]. Ethosomes penetrate the skin more easily than transfersomes due to their higher ethanol content, which enhances fluidity and facilitates drug transport.

However, it is widely recognized that vesicles and high ethanol concentrations are generally incompatible due to the disruptive effects of ethanol on lipid bilayers [11]. This issue can be mitigated by lowering the ethanol concentration (20-45%), adding co-solvents or stabilizing agents, and modifying the lipid composition.

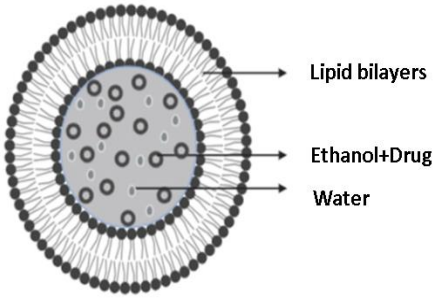

Fig. 2. Illustrates the structure of an ethosome, a lipid-based vesicle composed of phospholipids and ethanol.

Ethosomes

Touitou developed a new type of vesicular system called ethosomes in 1997 [9,10]. The term "ethosomes" is derived from the presence of ethanol within the vesicular structure. Ethosomes provide a non-invasive method for drug delivery, as they can deeply penetrate the layers of the skin. These vesicles are primarily composed of water, phospholipid, and alcohol, which comprise a significant portion (20-45%) of their composition (Figure 2). Ethosomes are characterized by their softness and flexibility, allowing them to pass through the skin without causing any damage, in parallel with the remarkable flexibility of human skin.

Ethosomes exhibit a wide range of sizes, from tens of nanometers to microns. They meet the necessary criteria for the safe and efficient administration of hydrophobic and hydrophilic drugs, while enabling drug delivery to the deepest layers of the epidermis [12]. They are also suitable carriers for delivering medications to treat occlusive and non-occlusive skin conditions [13,14].

Ethosomal system types

Ethosomal systems can be classified into three categories based on composition (Figure 3). Table 1 outlines the key differences among the various ethosomal systems.

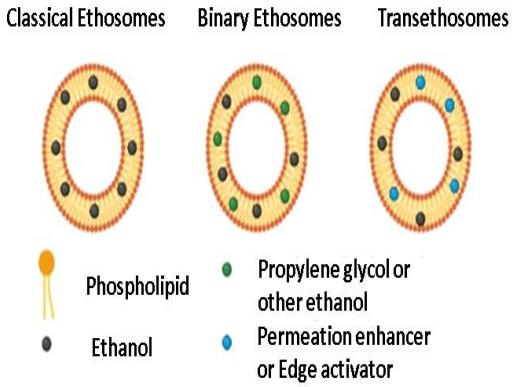

Fig. 3. Illustrates the different types of ethosomes, including classical ethosomes, binary ethosomes, and transethosomes, each with unique compositions and properties tailored for specific drug delivery applications.

Table 1. Compares different ethosomal systems based on their composition, size, shape, and stability. These factors significantly impact their ability to encapsulate drugs, penetrate the skin, and deliver the drug effectively.

Feature	Classical Ethosomes	Binary Ethosomes	Transethosomes
Composition	Phospholipids, Ethanol (up to 45% w/w), Water	Phospholipids, Ethanol (lower concentration), Another Alcohol (e.g., propylene glycol), Water	Phospholipids, Ethanol (lower concentration), Edge activators (e.g., surfactants), Water
Size	Relatively smaller than traditional liposome	Same or smaller than the classical ethosomes	Size depends on penetration enhancer or edge activator type and concentration
Morphology	Spherical	Spherical	Regular or irregular Spherical shapes
Stability	Less stable, prone to aggregation	Exhibits more stability compared to classical ethosomes	Highly stable compared to classical and binary ethosomes
Drug Entrapment	High	More than classical ethosomes	Greater than classical and binary ethosomes
Skin Penetration	Enhanced	More enhanced than classical ethosomes	May be most enhanced
References	[10,12,15,22–24]	[9,19,22–25]	[22–26]

Classical ethosomes

In classical ethosomes, water, phospholipids, and a high ethanol content (up to 45% w/v) are the main components. These ethosomes are designed to enhance skin penetration by fluidizing the lipids of the stratum corneum, thereby improving drug delivery. Classical ethosomes have been shown to offer advantages over traditional liposomes due to their smaller size, higher entrapment efficiency, and negative zeta potential [15]. Medications with molecular weights between 130.077 Da and 24 kDa are optimal for entrapment in classical ethosomes [16,17].

Binary ethosomes

The concept of binary ethosomes was first described by Zhou *et al.* [18]. Their development involved combining conventional ethosomes with different types of alcohol. In binary ethosomes, the most commonly used alcohols are isopropyl alcohol (IPA) and propylene glycol (PG) [19]. The combination of these solvents further enhances the ethosomes' ability to penetrate the skin and stabilize the vesicles [20].

Transethosomes

Transethosomes, a novel type of ethosomal system, were developed to combine the benefits of transfersomes and classical ethosomes into a single formulation. This includes a combination of ethanol and surfactants. The surfactants further reduce the vesicle size and enhance skin penetration efficiency compared to classical ethosomes [21].

Advantages of ethosomes

1. Ethosomes enhance the ability of drugs to penetrate the skin via transdermal and dermal delivery methods [27,28].
2. Ethosomes can facilitate the delivery of a wide range of drugs, including protein molecules and peptides [29,30].
3. Ethosomal systems enable the practical and deep application of quantum dots to the skin [29,31].
4. The use of ethosome technology in large-scale drug production poses minimal risk due to the well-documented toxicological profiles of its components in the scientific literature, indicating a low risk profile [31].
5. The administration of ethosome-based medications in semisolid forms, such as gels or creams, leads to improved patient compliance [32,33].
6. The ethosome system is ready for commercialization and can function through both passive and active mechanisms [29,31,34].

Limitations of ethosomes

1. Drug molecules that require higher blood concentrations cannot be administered; the only permitted potent molecules are those with a maximum dosage of 10 mg per day [28].
2. The medication must exhibit sufficient solubility in both hydrophobic and aqueous environments to efficiently penetrate systemic circulation and cutaneous microcirculation [28,29,34].
3. The drug must have a molecular size small enough to allow absorption via the skin [28,30].
4. Cost-effectiveness may be compromised by inadequate yield [28,35]. However, optimizing the formulation and preparation process, exploring alternative materials, and scaling up production can help mitigate these costs.
5. To reduce the risk of skin irritation, it is essential to select excipients with minimal allergenic potential and to optimize the formulation to limit skin exposure [28].
6. A decrease in product quantity occurs when shifting from an organic medium to an aqueous medium [28].

MATERIALS AND METHODS

Various methods can be employed to prepare ethosomes, depending on the specific conditions and requirements of the ethosome formulation (Figure 4). The cold and hot methods (Figure 5) and the hot method (Figure 6) are the most straightforward and convenient. Table 2 provides a summary of ethosomal preparation techniques and their defining features.

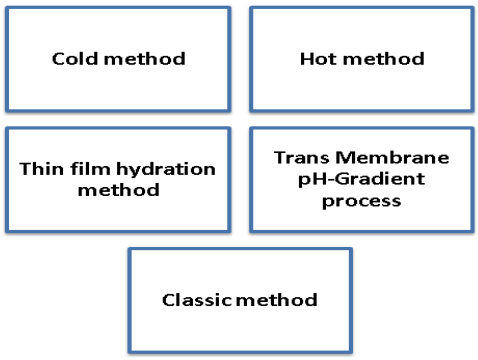

Fig. 4. Depicts the various techniques employed to prepare ethosomes, including cold method, hot method, trans membrane pH-Gradient method, thin-film hydration methods and classic method, each offering distinct advantages and considerations for specific formulations.

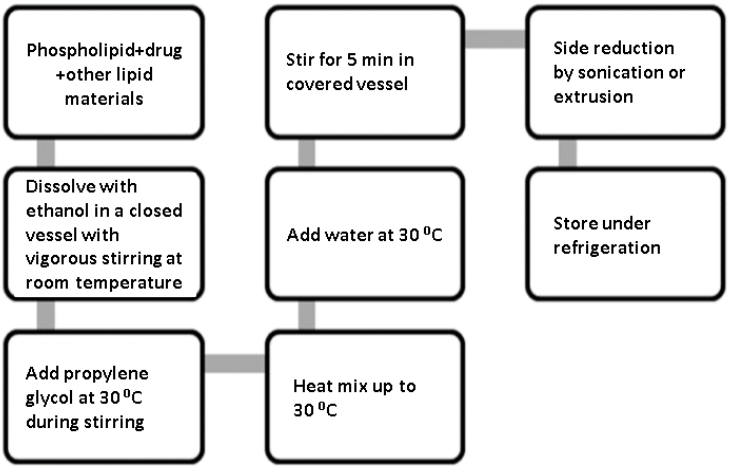

Fig. 5. Depicts the step-by-step process of preparing ethosomes using the cold method, involving the dissolution of phospholipids and drug in ethanol, followed by the addition of an aqueous phase and subsequent stirring to form ethosomes.

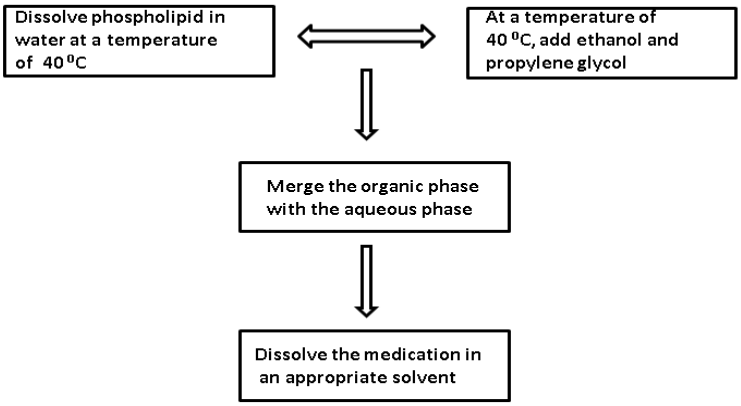

Fig. 6. Illustrates the step-by-step process of preparing ethosomes using the hot method, involving the dissolution of phospholipids and drug in ethanol, followed by the addition of organic phase with the aqueous phase and subsequent homogenization to form ethosomes.

Table 2. Overview of ethosomal manufacturing techniques and their distinguishing characteristics

Method	Advantage	Limitation	Cost	Manufacturing scale	References
Cold method	1. Easy and gentle preparation technique 2.Stable at room temperature 3. Capable of holding both hydrophilic and hydrophobic drugs 4. Good scalability	1. Poor encapsulation efficiency 2. Particle size is larger 3. Preparation time required is longer	Low to moderate	Small to large	[10,37,41,44]
Hot method	1. Simple and quick 2. Small particle size 3. High encapsulation efficiency 4. Capable of holding both hydrophilic and hydrophobic drugs	1. Chance of degradation of the drug 2. High consumption of energy 3.Particle aggregation	Low to moderate	Small to large	[10,37,38,44]
Classic method	1. Moderate and easy way to prepare 2. Capable of holding both hydrophilic and hydrophobic drugs	1. Greater particle size	Low to moderate	Small to large	[36,39]

Method	Advantage	Limitation	Cost	Manufacturing scale	References
Thin film hydration method	1. More drug loading capacity 2. High Stability 3. Suitable for Lipophilic drugs	2. Limited or low encapsulation efficiency 1. Specialized equipment requirement 2. Consumption of energy is more 3. Chance of drug degradation	Moderate to high	Small to moderate	[37,40,41]
Trans membrane pH-Gradient process	1. Suitable for hydrophobic drugs 2. Good stability 3. Good drug loading capacity	1. More time consumption 2. Specialized equipment and faculty is required	High	Small to moderate	[41,42]

Cold method

The cold method is the most commonly used approach for formulating ethosomes. In this process, phospholipids, the drug, and other lipid components are dissolved in ethanol within a covered vessel at ambient temperature while stirring vigorously with a mixer. During stirring, propylene glycol or another polyol is incorporated. The mixture is then heated to 30°C in a water bath. Afterward, water heated to 30°C in a separate vessel is added to the mixture, stirring for 5 minutes in the covered vessel. The vesicle size of the ethosomal formulation can be reduced to the desired level using either the sonication technique or the extrusion method. Finally, the formulation is stored in a refrigerated environment [19,35–37].

Hot method

This procedure involves the formation of a colloidal solution by dispersing the phospholipid in water using a water bath maintained at 40°C. Ethanol and glycols are mixed and heated to 40°C in a separate container. Once the temperature of both phases reaches 40°C, the organic phase is added to the aqueous phase. The final step is somewhat similar to the cold method (Figure 5) [19,37,38].

Classic method

The medication and phospholipid are combined in ethanol and then heated to 30°C ± 1°C using a water bath. Twice-distilled water is gradually added to the lipid mixture in an enclosed vessel while stirred at 700 revolutions per minute. A hand extruder and three cycles through a polycarbonate membrane are used to homogenize the resulting vesicle solution [36,39].

Thin film hydration method

The lipids are dissolved in an organic solvent within a round-bottom flask (RBF), and the solvent is removed by evaporation at a temperature above the lipid transition temperature using an evaporator. The interior surfaces of the RBF are coated with a thin layer, which is wetted with an ethanolic mixture and then dispersed using a probe sonicator to produce an ethosomal suspension [37,40].

Trans membrane pH-Gradient process

The process consists of two separate steps: the active loading of the drug and the formation of empty binary ethosomes. The phospholipid, such as Phosphatidylcholine (PC), is initially solubilized in an alcoholic solution containing PG and ethanol. Next, this solution is gradually mixed with a citrate buffer solution and stirred continuously at 700 rpm. During this process, the system is maintained at approximately 30 ± 1°C and cooled to room temperature. Subsequently, the drug is forcefully infused into the ethosomes. To ensure proper dissolution and distribution of the drug, the system is shaken continuously at 700 rpm. The external pH of the ethosomal system can be adjusted using a 0.5 M sodium hydroxide (NaOH) solution to create a pH gradient between the interior (acidic) and exterior (alkaline) phases [41]. Finally, the system is incubated at the appropriate temperature and for the required duration to allow the unionized drug molecules to actively penetrate the phospholipid bilayer of the ethosomes and become entrapped within the vesicles [42,43].

Mechanism of drug penetration

There are likely two ways that drugs are absorbed (Figure 7):

1. Ethanol effect
2. Ethosomes effect

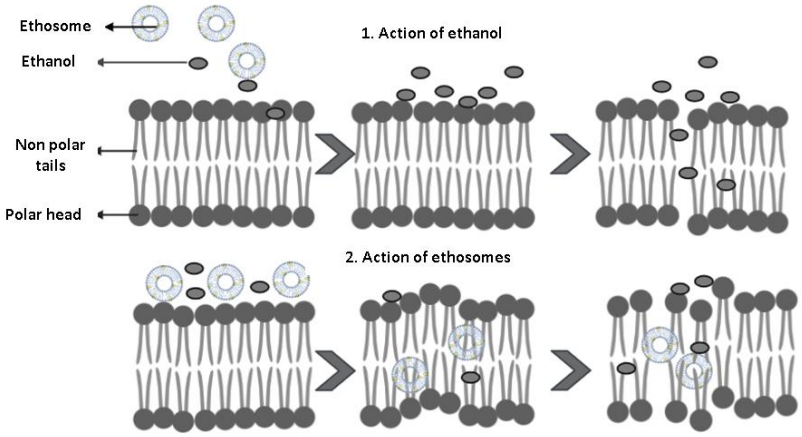

Fig. 7. Illustrates the two mechanisms by which drugs penetrate the skin: the ethanol pathway and the ethosomes pathway.

Ethanol effect

The ethanol concentration in ethosomes disrupts the arrangement of stratum corneum lipids. Ethanol enhances the fluidity of lipids in cell membranes and reduces the density of the multilayer as it permeates the intercellular lipids [33,45].

Ethosomal effect

The presence of ethanol in ethosomes increases their fluidity, enhancing skin permeability. As a result, ethosomes efficiently penetrate the deeper layers of the skin, where they interact with skin lipids to facilitate drug release (26).

Various additives used in the ethosomes formulation

Various additives are incorporated into those formulations to enhance stability, penetration, and the overall efficacy of the drug delivery system. These additives play crucial roles in optimizing the performance and characteristics of the ethosomes, ensuring effective drug encapsulation and release. Table 3 provides a list of the various additives used.

Characterization of ethosomal formulation

The following properties characterize ethosomal formulations:

Vesicular shape

The vesicular morphology of ethosomal systems can be examined using transmission electron microscopy (TEM) and scanning electron microscopy (SEM), which often involves negatively staining the formulation with an aqueous solution of chemicals such as phosphotungstic acid [51–54].

Zeta potential and vesicle size

Photon correlation spectroscopy (PCS) and dynamic light scattering (DLS) can be used to estimate the particle size of ethosomes. A zeta meter can be employed to determine the formulation's zeta potential [52,54–56].

Transition temperature

The transition temperature of ethosomes is crucial for assessing their stability and fluidity, which directly affect drug release and skin penetration. Accurate characterization ensures the formulation is optimized for effective and stable drug delivery. The transition temperature of vesicular lipid systems can be determined using differential scanning calorimetry (DSC). The aluminum crucibles are heated at a rate of 10°C per minute to determine the transition temperature, which typically falls within the 20°C to 300°C range [57].

Table 3. Various additives utilized in the ethosomal formulation and their applications within the formulation

Class	Example	Uses	References
Phospholipid	Soya phosphatidyl choline(SPC) Egg phosphatidyl choline	Components that create vesicles	(19,25,36,41)
Alcohol	Ethanol ,isopropyl alcohol	To boost vesicle membrane penetration by giving it a softer texture	[17,31,41,42]
Polyglycol	Transcutol RTM, Propylene glycol.	To increase the penetration of the skin	[21,31,41,46]
Cholesterol	Cholesterol	To increase the penetration of the skin	[31,41,46,47]
Dye	Rhodamin red, Rhodamine-123	With regard to the characterisation purpose	[31,46,48,49]
Vehicle	Carbapol 934	Used as gel forming agent	[41,46,50]

Configuration of vesicular bilayer

The ethosomal system's vesicle bilayer determines drug entrapment efficiency, making an in-depth investigation into optimal bilayer development essential. Studies using nuclear magnetic resonance (NMR) can be employed in this regard [37].

Drug entrapment

One way to determine the drug entrapment efficiency in ethosomes is by using the ultracentrifugation method [37]. This process consists of two steps. The first step involves preparing the vesicles the night before and centrifuging them at a specific speed (RPM) for a predetermined time. The second step involves analyzing the pure drug using advanced techniques such as high-performance liquid chromatography (HPLC). The entrapment efficiency is then calculated using the following formula:

$$EE = \frac{D_t - D_S}{D_t} X\ 100 \qquad \textbf{Equation 1}$$

Entrapment efficiency (EE) is determined by the ratio of the amount of drug present in the supernatant (Ds) to the theoretical amount of drug administered (Dt) [52,58].

Penetration and permeability studies

Confocal Laser Scanning Microscopy (CLSM) determines the extent of ethosome penetration. Skin deposition is significantly higher with ethosomes, possibly due to the synergistic effects of ethanol and phospholipids. This provides an effective method for delivering substances to the skin via both dermal and transdermal routes [23,54,59,60].

Drug content

The drug content of ethosomes can be determined using a UV spectrophotometer. An enhanced method of high-performance liquid chromatography (HPLC) can also be employed to measure the drug content [55].

Stability studies

The drug-retentive behavior of ethosomal preparations can be assessed by exposing the formulations to various temperatures, specifically 25 ± 2°C (room temperature), 37 ± 2°C, and 45 ± 2°C, for durations ranging from 1 to 120 days. The ethosomal formulations were stored in airtight vials (10 ml capacity) after being flushed with nitrogen gas. The stability of the ethosomes was quantitatively assessed by monitoring the size and morphology of the vesicles using Dynamic Light Scattering (DLS) and Transmission Electron Microscopy (TEM) [52,61].

Evaluation of ethosomes

Ethosomes formulations are evaluated for the following characteristics:

Interaction study of Filter membrane-vesicle by scanning electron microscopy (SEM)

A 0.2 mL suspension of vesicles was applied to a filter membrane with a pore size of 50 nm and placed in diffusion cells. The top surface of the filter was left uncovered. The upper side of the membrane was exposed to air, while the lower side was in contact with PBS (phosphate-buffered saline) at a pH of 6.5. After 1 hour, the filters were extracted and prepared for SEM analysis by fixing them overnight at 4°C in Karnovsky's fixative. The filters were then dehydrated using a series of increasing ethanol concentrations (30%, 50%, 70%, 90%, 95%, and 100% v/v in water). Finally, the filters were coated with a layer of gold and analyzed using a scanning electron microscope (SEM) manufactured by Leica, Bensheim, Germany [59].

Skin permeation studies

The hair of the test animal (rat) was carefully trimmed to a length of less than 2 mm using scissors. The skin from the abdomen was carefully excised from the underlying connective tissue with a knife. Once the skin was separated, it was placed on aluminum foil, and the dermal side was gently examined to remove any subcutaneous tissue or fat adhering to the skin. The effective permeation area of the diffusion cell was 1.0 cm^2, with a receptor compartment volume of 10 mL. The temperature was maintained at 32°C ± 1°C. The receptor compartment contained a 10 mL phosphate-buffered saline solution (PBS) at pH 6.5. The excised skin was positioned between the receptor and donor compartments. 1.0 mL of the ethosomal formulation was applied to the skin's epidermal surface. At 1, 2, 4, 8, 12, 16, 20, and 24-hour intervals, 0.5 mL samples were withdrawn from the diffusion cell through the sampling port and analyzed using high-performance liquid chromatography (HPLC) [31,42].

Interaction study of Vesicle-skin by TEM and SEM

Thin sections of animal tissue were prepared using an ultramicrotome. These sections were then placed on grids coated with Formvar and observed using a transmission electron microscope (TEM). The slices of dehydrated skin were affixed to stubs using adhesive tape and coated with a gold-palladium alloy using a fine coat ion sputter coater

for scanning electron microscopy (SEM) analysis [52,59,60]. The sections were analyzed using a scanning electron microscope (SEM).

Interaction study of Vesicle-skin by fluorescence microscopy

Fluorescence microscopy was performed using the same methodology as TEM and SEM analysis. Skin sections, 5 micrometers thick, were sliced using a microtome and analyzed via fluorescence imaging. A micro cytotoxicity assay was conducted using MT-2 cells, a T-lymphoid cell line. The cells were cultured in Dulbecco's modified Eagle medium supplemented with 10% fetal calf serum, 100 U/mL penicillin, 100 µg/mL streptomycin, and 2 mmol/L L-glutamine. The cells were incubated at 37°C in a 5% CO2 atmosphere. Cytotoxicity was quantified by determining the 50% cytotoxic dose (CD50), which corresponds to the concentration that caused a 50% decrease in absorbance at 540 nm [59,60,62,63].

Drug uptake studies

The drug was introduced into MT-2 (T-lymphoid cell line) cells by incubating them with 100 µL of the drug solution in phosphate-buffered saline (PBS, pH 7.4), either in an ethosomal formulation or a commercial formulation. The amount of drug taken up by the cells was then analyzed by measuring the drug content using high-performance liquid chromatography (HPLC) analysis [18,47,60].

Stability study

The stability of the vesicles was assessed by storing them at 4°C ± 0.5°C. The dimensions of the vesicles, their zeta potential, and their entrapment efficiency were evaluated after 180 days using the previously reported method (58).

HPLC assay

The drug binds to its receptor, and the amount of drug that enters the receptor compartment in both in vitro skin permeation studies and in MT-2 cells is evaluated using high-performance liquid chromatography (HPLC). The HPLC assay uses a mobile phase consisting of a mixture of methanol, distilled water, and acetonitrile in a volume ratio of 70:20:10. The mobile phase is delivered at a 1 mL/min flow rate by the LC-10AT pump. A 20 µL injection is eluted through the column at ambient temperature. The eluent is analyzed at a wavelength of 271 nm using the SPDM10A VP diode array UV detector. The standard curve's variance coefficient ranged from 1.0% to 2.3%, with a correlation coefficient (R^2) 0.9968 [55].

Dermopharmaceutical uses of ethosomes

Numerous skin conditions can be effectively managed using ethosome-based medications, including acne vulgaris, atopic dermatitis, skin infections, psoriasis, skin cancer, inflammation, pain, erectile dysfunction, and hormone imbalances (Figure 8). It has been shown that adding functionalizing agents, such as polymers and targeting ligands, to the colloidal surface structure of traditional ethosomes enhances their skin penetration, particularly for these dermatological applications.

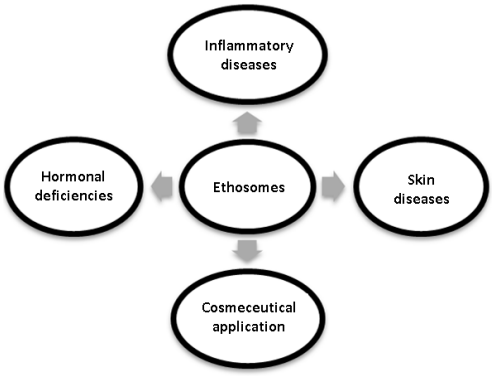

Fig. 8. Showcases the wide-ranging applications of ethosomes across dermatology, cosmetics, and pharmaceuticals.

Ethosomes in the treatment of inflammatory diseases

The immune system initiates an inflammatory response to various stimuli, such as infection or tissue damage. The recruitment of innate immune cells, tissue injury, and the release of pro-inflammatory mediators all contribute to inflammation, a critical defense mechanism. Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used treatments for osteoarthritis, chronic musculoskeletal conditions, and both acute and chronic rheumatoid arthritis (RA) [64]. However, prolonged use of NSAIDs is generally not recommended due to the serious side effects associated with oral administration, including damage to the stomach epithelium, gastric ulcer formation, and renal impairment. Dermal or topical administration of active ingredients offers a viable alternative for treating inflammation.

Du Li et al. developed a novel microneedle system encapsulating colchicine and iguratimod ethosomal formulations to simulate and treat recurrent gout. This system effectively modulates inflammatory cytokines, inhibits osteoclast activity, and enhances transdermal drug delivery,

demonstrating significant analgesic, anti-inflammatory, and bone-protective effects in animal models. The study findings suggest that this therapeutic approach holds promise for the clinical management of recurrent gout [65].

Ma HD et al. developed paeonol-loaded ethosomes to enhance the delivery of this promising bioactive compound, which has poor solubility and bioavailability. The optimized ethosomes exhibited high encapsulation efficiency, small particle size, and a negative charge. In vitro studies demonstrated improved transdermal absorption and skin retention of paeonol compared to conventional formulations. These findings suggest that paeonol-loaded ethosomes are a promising strategy for enhancing the therapeutic efficacy of paeonol [66].

Alfehaid et al. developed apremilast-loaded ethosomes using a single-step injection technique to overcome the low solubility and permeability challenges associated with oral therapy for psoriatic arthritis. The optimized ethosomal gel demonstrated enhanced transdermal flux, prolonged drug release, and significantly greater absorption than oral administration. This study underscores the potential of ethosomal transdermal delivery as an effective alternative to oral therapy, offering improved clinical outcomes in psoriatic arthritis [67].

Divya Aggarwal et al. reviewed how ethosomes can improve the delivery and absorption of anti-inflammatory herbal medications, such as curcumin, resveratrol, and quercetin. The study highlights that ethosomes enhance skin penetration by addressing challenges like poor solubility and bioavailability, showing promise in optimizing anti-inflammatory treatments. The review also discusses challenges related to formulation and regulatory considerations, with future research focusing on advanced technologies and personalized medicine [68].

Ramadhani et al. discuss the advantages of ethosomes in improving the transdermal delivery of ketoprofen for osteoarthritis (OA), providing a solution to the gastrointestinal side effects associated with oral NSAIDs. The review highlights recent advancements in transdermal systems, emphasizing the potential of ethosomes and microneedles for effective OA management [69].

Lodzki et al. developed a cannabidiol (CBD)-ethosomal formulation for transdermal delivery to treat rheumatoid arthritis. The formulation demonstrated significant CBD accumulation in the underlying muscles and maintained steady plasma levels for 3 days following application. In a rat paw edema model, the ethosome-encapsulated CBD exhibited enhanced anti-inflammatory activity by improving skin penetration and accumulation, significantly increasing the biological effectiveness of CBD [70].

Paolino et al. evaluated ethosomes loaded with ammonium glycyrrhizinate for treating inflammatory skin conditions. When human volunteers with methyl nicotinate-induced erythema were treated with the ethosomal suspension instead of hydro-ethanol solutions, the erythema was significantly less severe and lasted much shorter. Additionally, the ethosomes demonstrated enhanced skin accumulation, improved percutaneous penetration, and extended release of ammonium glycyrrhizinate for up to 48 hours after application [44].

In a preclinical study, ethosomes encapsulating ketoprofen were developed for transdermal delivery. Using 1-3% soya phosphocholine and 20-40% ethanol, ethosomes with vesicular diameters ranging from 120.3 to 410.2 nm were produced, with the smallest size achieved using 40% ethanol and 1% soya phosphocholine. The study found that higher ethanol concentrations enhanced drug entrapment efficiency, highlighting the potential of ethosomal systems to improve the delivery of hydrophobic NSAIDs like ketoprofen [69].

In a follow-up study, an ethosomal preparation of meloxicam was developed as a new transdermal approach. Meloxicam, a potent NSAID, is commonly used to treat osteoarthritis, arthritis, and degenerative joint disease. However, oral administration is associated with poor patient compliance and gastrointestinal issues, such as dyspepsia and stomach pain. The optimized formulation was produced using Phospholipon® 90G (3% w/v) and ethanol (42.5% v/v). After five minutes of sonication, the formulation was gelled and incorporated with 1% w/w Carbopol® 934. After 12 hours, this ethosomal gel achieved a 65% suppression of edema, compared to 25.23% with oral therapy, indicating a significant reduction in skin inflammation [71].

In animal models, ethosomal gels loaded with ibuprofen were studied to evaluate their analgesic and antipyretic effects. The ibuprofen-loaded ethosomes, with an average particle size of 249.83 nm and 97% entrapment efficiency, achieved rapid plasma concentration and prolonged presence compared to oral administration, reducing common side effects such as bleeding and ulcers [72].

Ethosome in the treatment of skin disorders

Acne, one of the most prevalent skin conditions, primarily affects teenagers. It is considered a

chronic inflammatory disorder with four stages: Propionibacterium acnes proliferation, inflammation, excessive sebum production, and follicular hyperproliferation [73]. P. acnes, a Gram-positive anaerobic bacterium, causes inflammation in sebaceous follicles, playing a significant role in the pathophysiology of acne [74]. Over time, new therapeutic options, including topical and systemic treatments, have been developed. Topical therapy, which includes antibacterial agents (such as erythromycin and clindamycin) and anti-keratinizing agents (such as tretinoin and azelaic acid), is typically the first line of treatment [75].

A study by Vishwakarma et al. developed cationic ethosomes to enhance the topical delivery of bleomycin sulfate (BLM) for skin cancer treatment. Using thin film hydration and optimization techniques such as Artificial Neural Networks (ANN) and Response Surface Methodology (RSM), the ethosomes achieved 27.1% entrapment efficiency, a vesicle size of 144.3 nm, and a positive zeta potential. Characterization and evaluation demonstrated improved skin retention and localized drug delivery, suggesting that this approach effectively addresses challenges related to systemic toxicity and limited skin penetration in skin cancer therapy [76].

A study by Ferrara et al. explored the use of ethosomes to deliver curcumin and piperine and protect the skin from damage caused by diesel particulate matter. Ex vivo studies on human skin demonstrated that curcumin- and piperine-loaded ethosomes effectively prevent skin damage caused by diesel exhaust, highlighting the potential of ethosomes in improving the delivery and efficacy of protective compounds against environmental stressors that cause skin damage [77].

The intracellular and cutaneous transport of ethosomes loaded with bacitracin, a polypeptide antibiotic that targets Gram-positive bacteria with bactericidal activity, was examined by Godin and Touitou (2004). Ethosomes were formulated using Phospholipon® 90, 25% (w/w) ethanol, and bacitracin concentrations ranging from 1-3%. Dynamic light scattering (DLS) analysis revealed that the size of the vesicles carrying 1% and 3% medication ranged from 114.9 ± 3.5 nm to 96.4 ± 6.9 nm, demonstrating a homogeneous distribution [78].

An ethosomal gel containing clindamycin phosphate and salicylic acid (CLSA) was evaluated for treating mild to moderate acne in a clinical trial involving 40 participants. Patients were randomly assigned to receive either the CLSA gel or a placebo, applying the treatment twice daily for eight weeks. Those treated with the CLSA gel experienced significant improvements in acne treatment, with notable reductions in pustules, comedones, and overall lesions. In contrast, 48% of placebo participants reported no change in their acne. Additionally, the CLSA gel was well tolerated, with few adverse effects observed [79].

Topical application of azelaic acid is another potential therapeutic option for acne. Azelaic acid exhibits bacteriostatic and anti-keratinizing properties when applied to P. acnes. A cream containing azelaic acid, formulated with ethosomes and 35% ethanol, was developed to assess its antibacterial effects. The ethosomes demonstrated exceptionally high entrapment efficiency, measuring 94.48 ± 0.1%. The estimated particle size of the ethosomes was 179 nm. The addition of phospholipids and ethanol compromised the integrity of the bacterial cell wall, enabling ethosomes to penetrate and accumulate at optimal levels in the bacterial cytoplasm. This mechanism played a crucial role in bacterial inhibition [80].

Maheshwari et al. demonstrated that clotrimazole-loaded ethosomes offer superior penetration enhancement and greater inhibitory efficacy against Candida species compared to liposome formulations [81].

Fathalla et al. investigated the potential of liposomal and ethosomal gels containing anthralin for treating psoriasis. The study found that ethosomes were more effective than liposomes, achieving an average Psoriasis Area and Severity Index (PASI) reduction of approximately 81.84%, compared to 68.66% for liposomes [82].

Fang et al. conducted a comparative study to evaluate the efficacy of liposomal and ethosomal formulations of 5-aminolevulinic acid in delivering the drug to target melanoma cells. Their findings demonstrated that ethosomes, with their unique lipid bilayer structure and enhanced skin penetration properties, significantly outperformed liposomes in terms of drug delivery efficiency [83].

Ethosome-based formulations for hormonal deficiencies

Inadequate testosterone levels are commonly associated with androgen insufficiency in both men and women. In women, testosterone enhances vaginal blood flow and lubrication, while in men, it plays a key role in male sex organ development. However, testosterone also affects non-reproductive systems, including prostatic hyperplasia, calcium homeostasis, lipid and glucose metabolism, and bone health. Androgen replacement therapies are available in various

formulations, including oral, intramuscular, and transdermal routes. Transdermal administration is the most suitable delivery method as it avoids the pain associated with intramuscular injections, improves oral bioavailability, and bypasses first-pass metabolism**.**

In a preliminary trial, a transdermal testosterone ethosomal patch (Testosome) was developed and compared with the commercially available testosterone patch (Testoderm®). The ethosomal patch demonstrated a thirty-fold increase in skin permeability after application to the rabbit's pinna skin. In an in vivo study, applying the same patch daily for five consecutive days significantly increased the Area Under the Curve (AUC), maximum concentration (Cmax), and related pharmacokinetic values. A subsequent study aimed to create and evaluate a transdermal testosterone ethosomal gel to further enhance transdermal absorption. A pharmacokinetic study assessed the systemic absorption of testosterone using a gel formulation (AndroGel®) in an animal model. The Cmax and AUC values for AndroGel® were significantly lower (601 ± 88 ng/dL and 5678 ± 385 ng/dL/h, respectively) compared to the ethosomal formulation (1970 ± 251 ng/dL and 9313 ± 385 ng/dL/h, respectively) [84].

The efficacy of buspirone in managing menopausal syndrome, which is commonly associated with anxiety and hot flashes, was investigated by Shumilov et al. (2010). Buspirone hydrochloride, widely used as an anxiolytic, interacts with two main types of 5-hydroxytryptamine-1A receptors, which are believed to regulate body temperature. Due to significant first-pass metabolism when taken orally, transdermal delivery is considered a viable alternative to bypass this metabolic effect. A transdermal device containing ethosomes loaded with buspirone was tested in an animal model. The pharmacokinetic analysis revealed that the Cmax value of buspirone following transdermal delivery was 120.07 ± 87 ng/ml after two hours, compared to 93.44 ± 76.5 ng/ml following oral administration after one hour. Three hours post-administration, the ethosomal formulation significantly reduced body temperature, and this effect persisted for up to six hours [85].

Cosmetic/ skin care applications of ethosomes

When ethosomes are incorporated into cosmetic formulations, they not only enhance the stability of the chemicals but also reduce skin irritation caused by potentially irritating ingredients and improve transdermal permeability, particularly in elastic forms. The key factors to consider for achieving these benefits in cosmeceutical applications are the sizes and compositions of the elastic vesicles.

Fang et al. developed Prinsepia utilus seed oil (PUSO)-loaded ethosomes (PEs) to enhance transdermal delivery for treating skin diseases. The optimized PEs, prepared using a cold method, exhibited a small particle size (39.12 ± 0.85 nm), high entrapment efficiency (95.93 ± 0.43%), and good stability. PEs significantly increased skin deposition of PUSO and demonstrated protective effects against UVB-induced skin damage in mice. These findings suggest that PEs could be a promising approach for treating UVB-induced skin inflammation, with potential for industrial application [83].

Vitamin E in cosmetics and dermatological products reduces epidermal lipid peroxides and protects against UV radiation, harmful chemicals, and physical agents. In their study, Koli et al. (2008) developed antioxidant ethosomes to deliver vitamin E into the deeper layers of the stratum corneum. Vitamins A, E, and C were applied topically to leverage their synergistic effects. These vitamins work together in the lipid bilayer to protect ethosome formulations from oxidation, while the water-based core offers additional protection. Although elastic and non-elastic liposomes may not be effective for delivering α-tocopherol through the epidermis, entrapping the vitamin in either formulation can enhance its photo-stability under UVB irradiation [86].

In 2004, Esposito et al. conducted a study on azelaic acid, a compound that inhibits keratinization and is commonly used to treat acne. The researchers used this substance to formulate ethosomes and liposomes. The results showed that ETHOS 40 (containing 40% ethanol) was associated with a higher concentration of azelaic acid compared to ETHOS 20 (containing 20% ethanol) liposomes [87].

Commercial products based on ethosomal formulations

The commercialization of ethosome technology began in 2000. Several companies have developed products utilizing ethosomes (Table 4).

Patented formulations

The ethosome was created and patented by Professor Elka Touitou and her students in the Department of Pharmaceutics at the School of Pharmacy, Hebrew University. Table 5 presents a selection of more recent patents.

Table 4. Commercial products based on ethosomal formulations and their uses

Name of the product	Uses	Manufacturer	References
Supravir cream	For use in herpes virus intervention. At 25 ^{0}C, the acyclovir medicine formulation remains stable for at least three years and has a long shelf life. The cream's penetration-enhancing properties were preserved even after three years, according to experiments on skin penetration.	Nottingham, UK Trima,Israel	[61,88]
Nanominox	The first product to use ethosome technology to incorporate minoxidil contains 4% minoxidil, a popular element in hair growth promoters that must be sulphated in order to work.	Sinere, Germany	[88,89]
Noicellex	Topical anti-cellulite cream used topically.	Novel therapeutic Technologies, Israel	[59,88]
Cellutight EF	A potent blend of chemicals found in topical cellulite cream increases metabolic rate and breaks down fat.	Hampden Health,USA	[59]
Decorin cream	Anti-aging creams treat, prevent, and postpone the appearance of age spots, wrinkles, sagging skin, loss of elasticity, and hyperpigmentation.	Genome Cosmetics, Pennsylvania, US	[90]

Table 5. Recent patents in ethosomal drug delivery provides an overview of recent intellectual property developments in the field of ethosomes, highlighting innovative formulations and techniques for enhancing drug delivery.

Title	Patent number	Applicant	Year of publication	Findings	References
Methods for treating inflammatory skin conditions and other topical conditions or disorders	US2024180837A	Selner marc[US]	06-06-2024	This invention introduces a topical treatment for conditions like dermatitis or migraines, using gels, creams, or ointments with active drugs delivered via nanovesicles like ethosomes or transethosomes for enhanced efficacy.	[91]
Ceramide ethosome as well as preparation method and application thereof	CN115919680A	Yutai biology Dongguan co Ltd	07-04-2023	This invention describes a ceramide ethosome for improved skin delivery. It's a tiny sphere made with ceramides, surfactants, phospholipids, and other ingredients to enhance penetration of beneficial components.	[92]
Method of preparing bioactive substance-encapsulated ethosome, ethosome composition, and cosmetic composition including ethosome composition	US11452679B2	Yu Mi Kim, Gi Hyun Jang	27-02-2022	This invention outlines a method for making ethosomes, tiny carriers for bioactive substances, by dissolving lipids in ethanol, mixing them with the bioactive substance in water, and then adding more water to create the final solution.	[93]
Ketoconazole ophthalmic preparations containing trans-ethosomal drug nanoparticles	US11285148B1	King abdulaziz University	29-03-2022	This invention details an in-situ gelling eye drop for sustained delivery of ketoconazole, using positively charged transethosomes for enhanced delivery and a gelling agent for prolonged effect.	[94]

Title	Patent number	Applicant	Year of publication	Findings	References
Retinyl Palmitate-loaded Ethosomes i n Acne Vulgaris	NCT04080869	Sara Mohamed Awad, Assiut University	14-11-2022	The study aims to assess the effectiveness and side effects of Retinyl Palmitate-loaded ethosomes in treating acne vulgaris, comparing with the traditional retinoid treatments.	[95]
Ethosomal composition including ethosomes encapsulating vitamin and dexpanthenol and method for preparing the same	AU2020389480A1	Hyundai biosciencecco Ltd[KR]	27-02-2021	This patent outlines an ethosome composition for hair growth, containing vitamins, amino acids, and a peptide, encapsulated by ethosomes made with ethanol, phosphatidylcholine, and an amino acid compound. It also describes the preparation method	[96]
An anti-aging cosmetic product	WO2021040645A1	TC Erciyes university[TR]	04-03-2021	This invention is an anti-aging cosmetic product featuring lemon balm extract encapsulated in ethosomes to boost its antioxidant effects.	[97]
Poloxamer based in-situ nasal gel of Naratriptan hydrochloride deformable vesicles for brain targeting	AU2021107008A4	Shelke santosh dattatraya	16-12-2021	Composition containing deformable vesicles of Naratriptan hydrochloride for use in the treatment of migraine attacks.	[93]
Gel skin care product containing NMN and preparation method thereof	CN108969396A	Hoboom life Shenzhen co Ltd. Hoboomlife technology(Shenzh en)co,Ltd.	11-12-2018	This invention is an NMN-containing gel skincare product where NMN is encapsulated in Ethosome vesicles for better delivery.	[98]
Capsaicin ethosome gel and preparation method thereof	CN106074365(A)	Xi an aierfei biological science & tech co ltd	09-11-2016	The invention discloses a capsaicin ethosomes gel for local weight loss. The gel enhances transdermal delivery of capsaicin, improving its penetration and reducing skin irritation.	[100]
Tretinoin ethosome gel and preparation method thereof	CN104983675(A)	Xi an aierfei biotechnology co ltd	21-10-2015	The invention discloses a tretinoin ethosomes gel that enhances transdermal delivery of tretinoin, improving its penetration and reducing skin irritation.	[101]

Future Directions

As research on ethosomes progresses, it is becoming increasingly evident that this technology holds significant potential for drug delivery and cosmetic applications. However, challenges remain that must be addressed to fully realize the potential of ethosomes.

Combination therapies and personalized medicine

Research on ethosomes is increasingly focusing on personalized and combinatorial medicines. By tailoring ethosome formulations to meet the specific needs of individual patients, informed by genetic data and customized treatment strategies, therapeutic outcomes can be enhanced. The ability to incorporate multiple medications or bioactive agents within a single ethosome offers opportunities for synergistic effects and comprehensive treatment approaches. This aligns with the growing emphasis on precision medicine and recognizing individual variability in drug response [102,103].

Advanced formulation technologies

Advancements in formulation technologies, including nanotechnology, microfluidics, and 3D printing, can potentially enhance the design, optimization, and scaling of ethosomal preparations. Innovative techniques for encapsulation, targeting, and controlled release

can further improve therapeutic outcomes and patient compliance [68].

Potential for targeted delivery to specific cell types and deeper skin layers

Ethosomes, with their unique deformability, offer significant potential for targeted drug delivery to specific skin layers or individual cell types. Researchers are actively developing formulations exploiting specific receptors or signaling pathways to precisely target cells, maximizing efficacy and minimizing side effects. This targeted approach holds particular promise for achieving optimal therapeutic outcomes [104].

Overcoming the challenges of scalability, cost-effectiveness, and stability

Addressing stability, scalability, and cost-effectiveness challenges is crucial to fully realizing the potential of ethosome formulations in pharmaceutical and cosmetic applications. Ensuring the stability of ethosomes during storage, transportation, and application is essential for consistent performance. Additionally, improving the production process while maintaining quality presents a significant challenge. To promote widespread acceptance, developing cost-effective ethosome-based formulations is vital [105].

CONCLUSION

Scientists have recently shown increasing interest in using ethosomes in dermatology and cosmetics due to their remarkable ability to change shape, high efficiency in encapsulating active ingredients, and enhanced capacity to penetrate deeper layers of the skin. This document comprehensively reviews various ethosomal formulations researched and developed for treating many conditions, including acne, psoriasis, skin infections, rheumatoid arthritis, and hormone imbalances.

The findings suggest that ethosomes, lipid-based vesicles, are effective non-invasive nanotransporters for various medicinal substances. Due to their unique composition, ethosomes exhibit remarkable elasticity and flexibility, allowing them to efficiently penetrate the skin and enhance the delivery and absorption of medications through multiple skin layers. Ethosomes are most effective when incorporated into semi-solid formulations, such as creams and gels, as these provide the optimal thickness and adherence to the skin surface, thereby improving substance delivery. The proposed mechanism involves the disruption of phospholipid and stratum corneum (SC) lipid bilayers in the vesicles, facilitated by ethanol's fluidizing effect, enabling the effective distribution of medication throughout the skin.

Ethanol enhances stability by preventing vesicle aggregation through electrostatic repulsion, creating a negative surface charge that makes ethosomes more stable than liposomes. Ethosomes have also demonstrated significant potential as delivery systems for cosmetic and pharmacological products. When applied to the skin, ethosomes can reduce the amount of medicine or cosmetic chemicals that enter the bloodstream, while extending their residence time in the stratum corneum and epidermis. These characteristics improve the ability of pharmaceutical or cosmetic ingredients to penetrate the deeper layers of the skin and, ultimately, enter the bloodstream.

Ethosomes are promising drug delivery systems with significant potential for targeted drug delivery and cosmetic applications. However, challenges such as scalability and stability must be addressed. Future research should focus on personalized medicine, combination therapies, and advanced formulation techniques to fully harness their potential.

AUTHOR CONTRIBUTIONS

S Ruchitha and Gourav R wrote the draft. Pradip Nirbhavne collected the data and edited the draft. Prashant kurkute edited the draft and conceived the idea.

ETHICAL APPROVAL

Not applicable

FUNDING

Not applicable

CONFLICTS OF INTEREST

The authors declare no competing interests.

REFERENCES

1. Abdulbaqi IM, Darwis Y, Khan NAK, Assi RA, Khan AA. Ethosomal nanocarriers: the impact of constituents and formulation techniques on ethosomal properties, in vivo studies, and clinical trials. Int J Nanomedicine. 2016;11:2279-2304.
2. Barry BW. Novel mechanisms and devices to enable successful transdermal drug delivery. Eur J Pharm Sci. 2001;14(2):101-114.
3. Prausnitz MR, Langer R. Transdermal drug delivery. Nat Biotechnol. 2008;26(11):1261-1268.
4. Scheindlin S. Transdermal drug delivery: past, present, future. Mol Interv. 2004;4(6):308-312.
5. Mezei M, Gulasekharam V. Liposomes—a selective drug delivery system for the topical route of

administration: I. Lotion dosage form. Life Sci. 1980;26(18):1473-1477.
6. Pierre MBR, Costa ISM. Liposomal systems as drug delivery vehicles for dermal and transdermal applications. Arch Dermatol Res. 2011;303(9):607-621.
7. Siler-Marinkovic S. Liposomes as drug delivery systems in dermal and transdermal drug delivery. In: Dragicevic N, Maibach HI, editors. Percutaneous Penetration Enhancers: Chemical Methods in Penetration Enhancement. Berlin, Heidelberg: Springer; 2016; 15-38.
8. Tapfumaneyi P, Imran M, Mohammed Y, Roberts MS. Recent advances and future prospective of topical and transdermal delivery systems. Front Drug Deliv. 2022;2:957732.
9. Touitou E, Godin B. Ethosomes for skin delivery. J Drug Deliv Sci Technol. 2007;17(5):303-308.
10. Touitou E, Dayan N, Bergelson L, Godin B, Eliaz M. Ethosomes—novel vesicular carriers for enhanced delivery: characterization and skin penetration properties. J Control Release. 2000;65(3):403-418.
11. Patrekar PV, Inamdar SJ, Mali SS, Mujib MT, Ahir AA, Hosmani AH. Ethosomes as novel drug delivery system: a review. The Pharma Innovation Journal. 4, 9, 2015; 10-21.
12. Kumar A, Dubey A. Ethosomes: a novel approach in transdermal drug delivery system. Int J Pharmacy and Life Sciences. 2020;11(5):6598-6608.
13. Romero EL, Morilla MJ. Highly deformable and highly fluid vesicles as potential drug delivery systems: theoretical and practical considerations. Int J Nanomedicine. 2013;8:3171-3186.
14. Sala M, Diab R, Elaissari A, Fessi H. Lipid nanocarriers as skin drug delivery systems: properties, mechanisms of skin interactions and medical applications. Int J Pharm. 2018;535(1-2):1-17.
15. Chauhan N, Vasava P, Khan SL, Siddiqui FA, Islam F, Chopra H, et al. Ethosomes: a novel drug carrier. Ann Med Surg. 2022;80:104595.
16. Zhang Z, Wo Y, Zhang Y, Wang D, He R, Chen H, et al. In vitro study of ethosome penetration in human skin and hypertrophic scar tissue. Nanomedicine. 2012;8(6):1026-1033.
17. Mishra D, Mishra PK, Dabadghao S, Dubey V, Nahar M, Jain NK. Comparative evaluation of hepatitis B surface antigen-loaded elastic liposomes and ethosomes for human dendritic cell uptake and immune response. Nanomedicine. 2010;6(1):110-118.
18. Zhou Y, Wei Y, Liu H, Zhang G, Wu X. Preparation and in vitro evaluation of ethosomal total alkaloids of Sophora alopecuroides loaded by a transmembrane pH-gradient method. AAPS PharmSciTech. 2010;11(3):1350-1358.
19. Ascenso A, Raposo S, Batista C, Cardoso P, Mendes T, Praça FG, et al. Development, characterization, and skin delivery studies of related ultradeformable vesicles: transfersomes, ethosomes, and transethosomes. Int J Nanomedicine. 2015;10:5837-5851.
20. Zhang JP, Wei YH, Zhou Y, Li YQ, Wu XA. Ethosomes, binary ethosomes and transfersomes of terbinafine hydrochloride: a comparative study. Arch Pharm Res. 2012;35(1):109-117.
21. Finnin BC, Morgan TM. Transdermal penetration enhancers: applications, limitations, and potential. J Pharm Sci. 1999;88(10):955-958.
22. Yang Y, Wu F, Liu J, Fan L, Zhu Y, Zhai G. A novel drug delivery gel of terbinafine hydrochloride with high penetration for external use. Drug Dev Ind Pharm. 2015;41(11):1782-1788.
23. Bragagni M, Mennini N, Maestrelli F, Cirri M, Mura P. Comparative study of liposomes, transfersomes and ethosomes as carriers for improving topical delivery of celecoxib. Drug Deliv. 2012;19(7):354-361.
24. Touitou E. Composition for applying active substances to or through the skin. US Patent 5716638A. 1998.
25. Abu-Huwaij R, Zidan AN. Unlocking the potential of cosmetic dermal delivery with ethosomes: a comprehensive review. J Cosmet Dermatol. 2024;23(1):17-26.
26. Song CK, Balakrishnan P, Shim CK, Chung SJ, Chong S, Kim DD. A novel vesicular carrier, transethosome, for enhanced skin delivery of voriconazole: characterization and in vitro/in vivo evaluation. Colloids Surf B Biointerfaces. 2012;92:299-304.
27. Jafari A, Daneshamouz S, Ghasemiyeh P, Mohammadi-Samani S. Ethosomes as dermal/transdermal drug delivery systems: applications, preparation and characterization. J Liposome Res. 2023;33(1):34-52.
28. Zahid SR, Upmanyu N, Dangi S, Ray SK, Jain P, Parkhe G. Ethosome: a novel vesicular carrier for transdermal drug delivery. J Drug Deliv Ther. 2018;8(6):318-326.
29. Gangwar S, Singh S, Garg G. Ethosomes: a novel tool for drug delivery through the skin. J Pharm Res. 2010;3(4):688-691.
30. Nikalje AP. Ethosomes: a novel tool for transdermal drug delivery. Int J Res Pharm Sci. 2012;2(1):1-20.
31. Zahid SR, Upmanyu N, Dangi S, Ray SK, Jain P, Parkhe G. Ethosome: a novel vesicular carrier for transdermal drug delivery. J Drug Deliv Ther. 2018;8(6):318-326.
32. Chen M, Gupta V, Anselmo AC, Muraski JA, Mitragotri S. Topical delivery of hyaluronic acid into skin using SPACE-peptide carriers. J Control Release. 2014;173:67-74.
33. Paiva-Santos AC, Silva AL, Guerra C, Peixoto D, Pereira-Silva M, Zeinali M, et al. Ethosomes as nanocarriers for the development of skin delivery formulations. Pharm Res. 2021;38(6):947-970.
34. Razavi H, Janfaza S. Ethosome: a nanocarrier for transdermal drug delivery. Arch Adv Biosci. 2015;6(2):38-43.
35. Shahwal VK, Samnani A, Dubey BK, Bhowmick M. Ethosomes: an overview. Int J Biomed Adv Res. 2011; 2(5):159-166.
36. Ascenso A, Raposo S, Batista C, Cardoso P, Mendes T, Praça FG, et al. Development, characterization, and skin delivery studies of related ultradeformable vesicles: transfersomes, ethosomes, and transethosomes. Int J Nanomedicine. 2015;10:5837-5851.
37. Pandey V, Golhani D, Shukla R. Ethosomes: versatile vesicular carriers for efficient transdermal delivery of therapeutic agents. Drug Deliv. 2015;22(8):988-1002.

38. Pakhale NV, Gondkar SB, Saudagar RB. Ethosomes: transdermal drug delivery system. J Drug Deliv Ther. 2019;9(3):729-733.
39. Verma P, Pathak K. Therapeutic and cosmeceutical potential of ethosomes: an overview. J Adv Pharm Technol Res. 2010;1(3):274-282.
40. Agrawal G, Chouthe R, Damale M, Kulkarni D, Panzade P, Pathan I, et al. Ethosomes: an exciting and promising alcoholic carrier system for treating androgenic alopecia. In: Androgenic Alopecia. IntechOpen; 2018.
41. Cevc G, Schätzlein A, Blume G. Transdermal drug delivery: Innovative transdermal delivery using ultradeformable vesicles. Eur J Pharm Biopharm. 2003; 58(2):281-299.
42. Zhou Y, Wei Y, Liu H, Zhang G, Wu X. Preparation and in vitro evaluation of ethosomal total alkaloids of Sophora alopecuroides loaded by a transmembrane pH-gradient method. AAPS PharmSciTech. 2010;11(3):1350-1358.
43. Zhang Z, Chen Y, Xu H, Wo Y, Zhang Z, Liu Y, et al. 5-Aminolevulinic acid loaded ethosomal vesicles with high entrapment efficiency for in vitro topical transdermal delivery and photodynamic therapy of hypertrophic scars. Nanoscale. 2016;8(46):19270-19279.
44. Paolino D, Lucania G, Mardente D, Alhaique F, Fresta M. Ethosomes for skin delivery of ammonium glycyrrhizinate: in vitro percutaneous permeation through human skin and in vivo anti-inflammatory activity on human volunteers. J Control Release. 2005;106(1-2):99-110.
45. Akiladevi D, Basak S. Ethosomes – a noninvasive approach for transdermal drug delivery. Int J Curr Pharm Res. 2013; 2(4):1-4.
46. Mishra D, Balekar N, Dhote V, Mishra P. Ethosomes: a novel carrier for dermal or transdermal drug delivery. In: Recent Advances in Novel Drug Carrier Systems. 2017: 1-26.
47. López-Pinto JM, González-Rodríguez ML, Rabasco AM. Effect of cholesterol and ethanol on dermal delivery from DPPC liposomes. Int J Pharm. 2005;298(1):1-12.
48. Yang L, Wu L, Wu D, Shi D, Wang T, Zhu X. Mechanism of transdermal permeation promotion of lipophilic drugs by ethosomes. Int J Nanomedicine. 2017;12:3357-3364.
49. Touitou E, Dayan N, Bergelson L, Godin B, Eliaz M. Ethosomes—novel vesicular carriers for enhanced delivery: characterization and skin penetration properties. J Control Release. 2000;65(3):403-418.
50. Indira S, Reddymalla P, Srinivas P. Formulation and evaluation of ethosomal topical gels of etoricoxib. Int J Pharm Res Scholars. 2015;4(4):93-103.
51. Dubey V, Mishra D, Dutta T, Nahar M, Saraf DK, Jain NK. Dermal and transdermal delivery of an anti-psoriatic agent via ethanolic liposomes. J Control Release. 2007;123(2):148-154.
52. Jain S, Tiwary AK, Sapra B, Jain NK. Ethosomes as elastic vesicles in transdermal drug delivery: an overview. Int J Pharm Sci Res. 2012;3(4):1-10.
53. Soba SV, Babu M, Panonnummal R. Ethosomal gel formulation of alpha phellandrene for the transdermal delivery in gout. Adv Pharm Bull. 2021;11(1):137-149.
54. Dhakar RC. Formulation development and evaluation of ethosome of stavudine. Indian J Pharm Edu Res. 2021.
55. Touitou E, Dayan N, Bergelson L, Godin B, Eliaz M. Ethosomes—novel vesicular carriers for enhanced delivery: characterization and skin penetration properties. J Control Release. 2000;65(3):403-418.
56. Bendas ER, Tadros MI. Enhanced transdermal delivery of salbutamol sulfate via ethosomes. AAPS PharmSciTech. 2007;8(4):E107.
57. Godin B, Touitou E. Erythromycin ethosomal systems: physicochemical characterization and enhanced antibacterial activity. Curr Drug Deliv. 2005;2(3):269-275.
58. Zhu X, Li F, Peng X, Zeng K. Formulation and evaluation of lidocaine base ethosomes for transdermal delivery. Anesth Analg. 2013;117(2):352-357.
59. Jaiswal PK, Kesharwani S, Kesharwani R, Patel DK. Ethosome: a new technology used as topical & transdermal delivery system. J Drug Deliv Ther. 2016;6(3):7-17.
60. Jain S, Tiwary AK, Sapra B, Jain NK. Formulation and evaluation of ethosomes for transdermal delivery of lamivudine. AAPS PharmSciTech. 2007;8(4):E111.
61. Mohanty D, Mounika A, Bakshi V, Haque MA, Sahoo CK. Ethosomes: a novel approach for transdermal drug delivery. Int J Chem Tech Res. 2018;11(8):219-226.
62. Akib NI, Novianti C, Ritonga H, Apt S, Adjeng AN. Optimization of method and proportion of phosphatidylcholine and ethanol for preparation of kojic acid ethosome. Res J Pharm Technol. 2020;13(11):5251-5256.
63. Havaldar VD, Mali SS, Mali KK, Shinde SS, Jadhav NY, Shinde AA. Ethosomes: an overview. Int J Med Pharm Res. 2012;2(5):1-8.
64. El-Alim SHA, Kassem AA, Basha M, Salama A. Comparative study of liposomes, ethosomes and transfersomes as carriers for enhancing the transdermal delivery of diflunisal: in vitro and in vivo evaluation. Int J Pharm. 2019;563:293-303.
65. Li D, Dong J, Xiong T, Zhou X, Li Y, Chen C, et al. Transdermal delivery of iguratimod and colchicine ethosome by dissolving microneedle patch for the treatment of recurrent gout. Colloids Surf B Biointerfaces. 2024;242:114087.
66. Ma H, Guo D, Fan Y, Wang J, Cheng J, Zhang X. Paeonol-loaded ethosomes as transdermal delivery carriers: design, preparation and evaluation. Molecules. 2018;23(7):1756.
67. Alfehaid FS, Nair AB, Shah H, Aldhubiab B, Shah J, Mewada V, et al. Enhanced transdermal delivery of apremilast loaded ethosomes: optimization, characterization and in vivo evaluation. J Drug Deliv Sci Technol. 2024;91:105211.
68. Aggarwal D, Jain T, Saini C, Devi N, Boora N, Murali K, et al. Enhanced delivery of herbal medications by

using ethosomes. Arch Biochem Biophys. 2024;1(5):541-552
69. Ramadhani D, Harahap Y, Sagita E, Sari KCDP, Andranilla RK, Trisina J, et al. Transdermal delivery of ketoprofen for osteoarthritis treatment and management: a literature review on current progression. Pharm Sci Res. 2024;11(1):18-26.
70. Lodzki M, Godin B, Rakou L, Mechoulam R, Gallily R, Touitou E. Cannabidiol-transdermal delivery and anti-inflammatory effect in a murine model. J Control Release. 2003;93(3):377-387.
71. Ahad A, Raish M, Al-Mohizea AM, Al-Jenoobi FI, Alam MA. Enhanced anti-inflammatory activity of carbopol loaded meloxicam nanoethosomes gel. Int J Biol Macromol. 2014;67:99-104.
72. Shumilov M, Bercovich R, Duchi S, Ainbinder D, Touitou E. Ibuprofen transdermal ethosomal gel: characterization and efficiency in animal models. J Biomed Nanotechnol. 2010;6(5):569-576.
73. Kligman AM. An overview of acne. J Invest Dermatol. 1974;62(3):268-287.
74. Kolarsick PAJ, Kolarsick MA, Goodwin C. Anatomy and physiology of the skin. J Dermatol Nurses Assoc. 2011;3(4):203-213.
75. Nguyen R, Su J. Treatment of acne vulgaris. Paediatr Child Health. 2011;21(3):119-125.
76. Vishwakarma M, Haider T, Soni V. Next-generation skin cancer treatment: a quality by design perspective on artificial neural network-optimized cationic ethosomes with bleomycin sulphate. J Drug Deliv Sci Technol. 2024;96:105705.
77. Ferrara F, Bondi A, Pula W, Contado C, Baldisserotto A, Manfredini S, et al. Ethosomes for curcumin and piperine cutaneous delivery to prevent environmental-stressor-induced skin damage. Antioxidants. 2024;13(1):91.
78. Godin B, Touitou E. Mechanism of bacitracin permeation enhancement through the skin and cellular membranes from an ethosomal carrier. J Control Release. 2004;94(2-3):365-379.
79. Touitou E, Godin B, Shumilov M, Bishouty N, Ainbinder D, Shouval R, et al. Efficacy and tolerability of clindamycin phosphate and salicylic acid gel in the treatment of mild to moderate acne vulgaris. J Eur Acad Dermatol Venereol. 2008;22(5):629-631.
80. Apriani EF, Rosana Y, Iskandarsyah I. Formulation, characterization, and in vitro testing of azelaic acid ethosome-based cream against Propionibacterium acnes for the treatment of acne. J Adv Pharm Technol Res. 2019;10(2):75-80.
81. Maheshwari RGS, Tekade RK, Sharma PA, Darwhekar G, Tyagi A, Patel RP, et al. Ethosomes and ultradeformable liposomes for transdermal delivery of clotrimazole: a comparative assessment. Saudi Pharm J. 2012;20(2):161-170.
82. Fathalla D, Youssef EMK, Soliman GM. Liposomal and ethosomal gels for the topical delivery of anthralin: preparation, comparative evaluation and clinical assessment in psoriatic patients. Pharmaceutics. 2020;12(5):446.
83. Fang Q, Li Y, Xiong F, Hu X, Song Y, Shen W, et al. Formulation and characterization of ethosomes for transdermal delivery of Prinsepia utilis rogle seed oil with ameliorative effects against UVB-induced skin damage. AAPS PharmSciTech. 2024;25(5):122.
84. Ainbinder D, Touitou E. Testosterone ethosomes for enhanced transdermal delivery. Drug Deliv. 2005;12(5):297-303.
85. Shumilov M, Touitou E. Buspirone transdermal administration for menopausal syndromes, in vitro and in animal model studies. Int J Pharm. 2010;387(1-2):26-33.
86. Uchechi O, Ogbonna JD, Attama AA. Therapeutic and cosmeceutical potential of ethosomes: an overview. J Basic Clin Pharm.2011;2(1):1-8.
87. Esposito E, Menegatti E, Cortesi R. Ethosomes and liposomes as topical vehicles for azelaic acid: a preformulation study. J Cosmet Sci. 2004;55(3):253-264.
88. Upadhyay N, Mandal S, Bhatia L, Shailesh S, Chauhan P. A review on ethosomes: an emerging approach for drug delivery through the skin. Recent Res Sci Technol. 2011;3(7):19-24.
89. Farhath S, Fels S, Athira J, Syamasree S, Neena P, et al. Ethosome: a novel approach to enhance drug permeation. Int J Pharm Sci Rev Res. 2019;55(1):18-22.
90. Pang D. Use of decorin in a cosmetic or dermatologic composition. US Patent US20030124152A1. 2003.
91. Selner M. Method for treating inflammatory skin conditions and other topical conditions or disorders. US Patent US20050287185A1. 2005.
92. Preparation technology and application of composite ceramide liposomes. CN Patent CN115919680A. 2023.
93. Kim YM, Jang GH. Method of preparing bioactive substance-encapsulated ethosome, ethosome composition, and cosmetic composition including ethosome composition. US Patent US11452679B2. 2022.
94. Ahmed TA, Alzahrani MM, Alhakamy NA, Felimban RI. Ketoconazole ophthalmic preparations containing trans-ethosomal drug nanoparticles. US Patent US11285148B1. 2022.
95. Awad SM. Formulation of retinyl palmitate-loaded topical ethosomes for treatment of acne vulgaris: a split-face comparative clinical study. Clinical Trials.gov. 2022.
96. Jun YJ, Kim HJ. Ethosomal composition including ethosomes encapsulating vitamin and dexpanthenol and method for preparing the same. AU Patent AU2020389480A1. 2021.
97. Karatoprak G, Yucel C, Baskal G. An anti-aging cosmetic product. WO Patent WO2021040645A1. 2021.
98. 9A kind of gel skin care item and preparation method thereof containing NMN. CN Patent CN108969396A. 2018.
99. Agrawal G, et al. Poloxamer based in-situ nasal gel of naratriptan hydrochloride deformable vesicles for brain targeting. AU Patent AU2021107008A4. 2021.
100. Hu C, Liu Y, Zhao W, Wang J. Capsaicin ethosomes gel and preparation method thereof. CN Patent CN106074365A. 2016.

101. Hu C, Liu Y, Wang J, Li R. Tretinoin ethosomes gel and preparation method thereof. CN Patent CN104983675A. 2015.
102. Lu J, Guo T, Fan Y, Li Z, He Z, Yin S, et al. Recent developments in the principles, modification and application prospects of functionalized ethosomes for topical delivery. Curr Drug Deliv. 2021;18(5):570-582.
103. Dave V, Kumar D, Lewis S, Paliwal S. Ethosome for enhanced transdermal drug delivery of aceclofenac. Int J Drug Deliv. 2010;2(1):81-92.
104. Chauhan N, Vasava P, Khan SL, Siddiqui FA, Islam F, Chopra H, Emran TB. Ethosomes: A novel drug carrier. J Pharm Care Health Syst. 2022; 9(3):1-7.
105. Mahajan K, Nagpal M, Kaushik D, Vohra P. Ethosomes as a carrier for transdermal drug delivery system. J Liposome Res. 2024; 34(1):18-29.