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Green Ethosomics: Towards Sustainable and Eco-Friendly Manufacturing of Nano-Vesicular Systems

Mahmoud Elkot Mostafa[1], Shaimaa Atef Badawi [2], Fatima Ahmed Ali[3], Ghada Mahmoud Ahmed, Taghian E. Taghian[5], Hossameldin A. Aziz[6]

[1]Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, New Valley University, Al-Kharga 72511, Egypt
[2]Faculty of Pharmacy, New Valley University, Al-Kharga 72511, Egypt
[3]Faculty of Pharmacy, New Valley University, Al-Kharga 72511, Egypt
[4]Faculty of Pharmacy, New Valley University, Al-Kharga 72511, Egypt
[5]Department of pharmacology and toxicology, Faculty of Pharmacy, New Valley University, Al-Kharga 72511, Egypt
[6]Department of Pharmaceutical Chemistry, Faculty of Pharmacy, New Valley University, New Valley, 72511, Egypt.

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ABSTRACT

"As the pharmaceutical industry pivots toward sustainability, 'Green Ethosomics' is emerging as a transformative paradigm in transdermal drug delivery. Ethosomes, renowned for their exceptional skin-penetration capabilities due to their high ethanolic content and vesicular flexibility, are now being reimagined through the lens of Green Chemistry. This review article critically examines the transition from traditional, solvent-heavy synthesis methods to eco-friendly manufacturing protocols for nano-vesicular systems. We explore the integration of bio-based surfactants, sustainably sourced phospholipids, and 'green' solvents that minimize environmental toxicity without compromising the vesicles' structural integrity or therapeutic efficacy. Furthermore, the review highlights innovative, low-energy fabrication techniques such as microfluidics and supercritical fluid technology as alternatives to conventional high-energy homogenization. Key challenges, including long-term physical stability, scalability under green parameters, and the evolving regulatory landscape for bio-nanomaterials, are thoroughly discussed. By synthesizing current advancements, this article provides a strategic roadmap for developing the next generation of ethosomes balancing high-performance transdermal delivery with environmental responsibility."

Keywords: Green Chemistry, Ethosomes, Sustainable, Nanotechnology, Transdermal Drug Delivery, Eco-friendly Manufacturing and Bio-based Vesicles

INTRODUCTION

Drug delivery systems are important components in the strategy to carry drugs for the treatment of several diseases, including cancer and other dermatological conditions. Among these, ethosomes are a type of nanocarrier used for topical and transdermal applications because they combine the properties of their organic components (phospholipids and ethanol 20–45 %) to overcome low skin permeability and achieve therapeutic efficacy while reducing adverse effects **[1]**.

The landscape of modern therapeutics has been radically transformed by the advancement of Transdermal Drug Delivery Systems (TDDS) **[2]**. Historically, the skin was viewed primarily as an impermeable barrier designed to protect the body from external threats **[3]**. However, the realization that this barrier could be bypassed to provide systemic or localized delivery avoiding the pitfalls of first-pass hepatic metabolism and gastrointestinal degradation sparked a multi-generational evolution in pharmaceutical science. From the first-generation simple chemical enhancers to the third-generation nanocarriers, the goal has remained constant: to navigate the Stratum Corneum (the skin's outermost layer) with precision and safety **[4]**.

Ethosomes (lipid vesicular carriers) were developed as novel lipid carriers, composed of phospholipids, ethanol, and water as presented in Figure 1. At the forefront of this evolution are Ethosomes, a sophisticated class of lipid-based vesicular carriers. Unlike traditional liposomes, ethosomes are characterized by a high concentration of ethanol (typically 20% to 45%) combined with phospholipids. This unique composition triggers what is known as the "Ethanol Effect" **[5]**. On one hand, ethanol increases the fluidity of the skin's lipid bilayers; on the other, it provides the vesicle with a soft, malleable structure that allows it to "squeeze"

through narrow intercellular spaces. This dual mechanism enables deep penetration of both hydrophilic and lipophilic drugs, making ethosomes a gold standard for challenging dermatological and systemic treatments **[6].**

Despite their clinical prowess, the environmental footprint of conventional nano-manufacturing has become an urgent concern. Traditional synthesis of ethosomes often relies on high-energy homogenization, organic solvents derived from petrochemicals, and synthetic surfactants that persist in the environment **[7]**. In an era defined by the climate crisis and the push for a circular economy, the pharmaceutical industry faces a critical crossroads: maintaining high therapeutic efficacy while minimizing ecological harm **[8]**.

This necessity has given rise to the paradigm of "Green Ethosomics." Defining a new frontier in nanomedicine, Green Ethosomics integrates the principles of Green Chemistry with vesicular engineering **[9]**.

The philosophy of Green Ethosomics rests on three fundamental pillars:

1. Sustainable Sourcing: Transitioning from synthetic lipids to bio-based, biodegradable phospholipids and natural surfactants (biosurfactants) derived from renewable resources **[10, 11]**.

2. Solvent Engineering: Replacing hazardous organic solvents with "green" alternatives or optimizing ethanol recovery systems to minimize the carbon footprint of production **[11]**.

3. Low-Energy Fabrication: Moving away from energy-intensive methods toward innovative techniques such as microfluidics, supercritical fluid technology, and self-assembly processes that operate under ambient conditions **[12]**.

Despite the promising potential, the transition to green manufacturing is not without obstacles. Maintaining structural integrity, vesicular stability, and entrapment efficiency of ethosomes while adhering to strict "green" parameters requires a deep understanding of molecular interactions at the nanoscale. Furthermore, the clinical translation of these eco-friendly systems is governed by a complex regulatory environment that demands rigorous proof of safety and bioequivalence **[13]**.

This review aims to provide a comprehensive analysis of the current state of ethosomal technology through the lens of sustainability. It explores the latest breakthroughs in green synthesis, evaluates the performance of bio-derived components, and discusses the socio-economic impacts of adopting eco-friendly nanomedicines **[14]**.

By bridging the gap between nanotechnology and environmental responsibility, this article outlines a roadmap for the future of transdermal delivery systems in a world that increasingly values both human health and ecological preservation **[15]**.

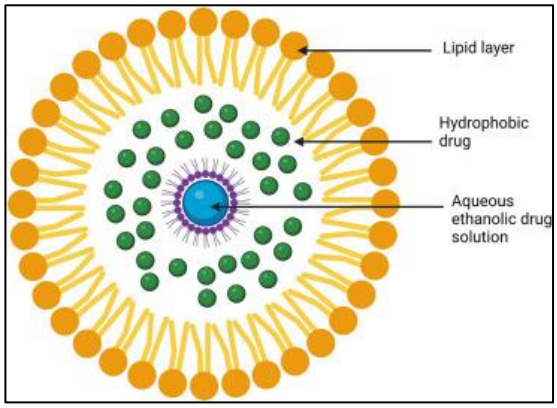

Figure 1: Diagram illustrating the Ethosome structure **[15]**.

Advantages of Ethosomes

Ethosomes offer definite advantages over traditional transdermal drug delivery systems due to their unique composition. Their high ethanol content enhances skin permeability by fluidizing the stratum corneum, allowing efficient delivery of both hydrophilic and lipophilic drugs. Compared to liposomes and niosomes, ethosomes exhibit greater flexibility, enabling deeper penetration through skin barriers. They provide high entrapment efficiency and stability, minimizing vesicle aggregation. Ethosomes are safe, cost-effective, and suitable for immediate commercialization, requiring no invasive techniques, which enhances patient compliance and broadens their therapeutic and cosmetic applications.

Limitations of Ethosomes [15]

- Molecular size needs to be appropriate for percutaneous absorption.
- Only powerful compounds with a daily intake of 10 mg or less are allowed.
- High Ethanol Content: May cause irritation or dryness in sensitive skin types.
- Stability Issues: Ethosomal formulations are prone to aggregation and leakage during storage.
- In case if shell locking is ineffective then the ethosomes may coalescence and fall apart on transfer into water.

Types of Ethosomes

Ethosomes can be classified according to their composition into several categories, including classical ethosomes, binary ethosomes, trans ethosomes, composite phospholipid ethosomes and active targeting ethosomes **[15]**, as presented in Figure 2.

a. Classical Ethosomes

Classical ethosomes are lipid-based nanocarriers of phospholipids, ethanol (20 - 45%), and water **[16]**. They offer high permeability and ease of formulation compared to other varieties of ethosomes. Classical ethosomes offer better skin stability and compatibility, whereas other forms, such as binary ethosomes, need the addition of penetration enhancers or transethosomess, which incorporate surfactants that may cause irritation. The classical form of ethosomes is superior to polymer based ethosomes in terms of the cost of manufacturing **[17]**. Different types of ethosomes are available, such as classical ethosomes, binary ethosomes, and transethosomes as presented in Figure 2.

b. Binary Ethosomes

Incorporating a secondary alcohol similar as propylene glycol into the formulation of binary ethosomes enhanced their durability enhances drug solubility and facilitates increased skin penetration, making them a more effective delivery system, **[15]** as presented in Figure 2.

c. Transethosomes

Transethosomes are the latest generation of ethosomal systems and were first recorded in 2012 by Song et al. The composition of this ethosomal system comprises the basic elements of classical ethosomes by incorporating a penetration enhancer or surfactant, the formulation's transdermal drug delivery capabilities are significantly augmented these novel vesicles were formed Studies have consistently shown that trans ethosomes exhibit superior properties compared to traditional ethosomes, driving research into optimizing their formulation, **[17]** as presented in Figure 2.

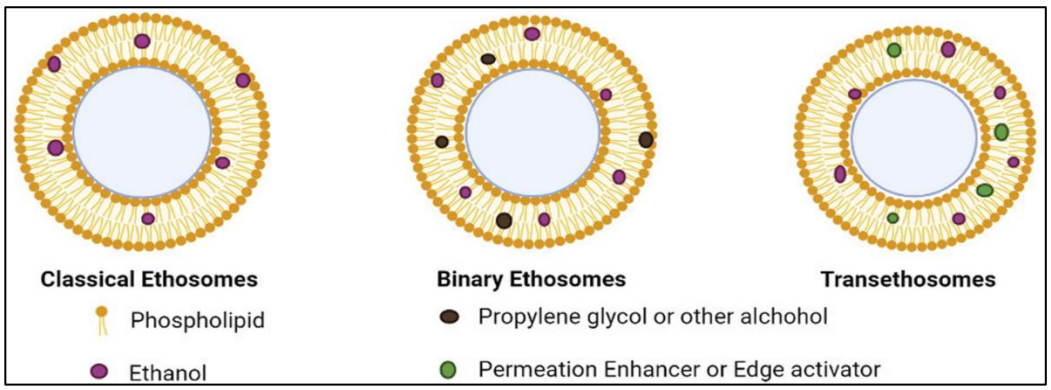

Figure 2: Diagram illustrating Types of Ethosomes

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Mechanism of Action of Ethosomes

The mode of action and delivery from ethosome formulation is due to an interaction between ethanol, lipid layers, and vesicles as presented in Figure 3. In general, the mechanism of ethosomes can be broadly divided into two stages. One stage is called the 'ethanol effect', in which ethanol directly interacts with the lipid bilayer hydrophilic head. By that, it reduces the transition temperature, increases lipid layer fluidity, and reduces layer density. They act in this stage by (1) drug solubilizing enhancement, in which ethanol acts as a penetration enhancer, increasing the solubility of the drug in the lipid bilayer of the ethosomes **[15]**. This ensures the efficient encapsulation of both hydrophilic and hydrophobic drugs; (2) interaction with the stratum corneum, in which the high ethanol content disrupts the lipid organization of the stratum corneum, the outermost layer of the skin **[17]**. In addition, ethanol fluidizes the lipids, reducing the barrier function and allowing ethosomes to penetrate deeper into the skin; (3) vesicle flexibility and deformability, in which ethosomes are highly flexible due to the presence of ethanol, which reduces the rigidity of the phospholipid bilayer, which therefore enables it to squeeze through the narrow intercellular spaces of the stratum corneum, a process known as vesicle-driven transdermal penetration. The second stage, termed the 'ethosome effect', involves the malleability and fusion of ethosomes with the skin's lipid layers, facilitating drug release. They act in this stage by (1) fusing with skin lipids, in which ethosomes can fuse with the lipids in the stratum corneum and deeper skin layers, releasing the drug directly into the skin; (2) deep penetration into the skin, in which ethosomes can penetrate deeper into the dermis and even reach systemic circulation if designed for transdermal delivery; and (3) controlled and sustained release, in which the ethosome inside the skin acts as a reservoir for the controlled and sustained release of the drug in order to keep a steady state level of the drug in blood circulation **[15]**.

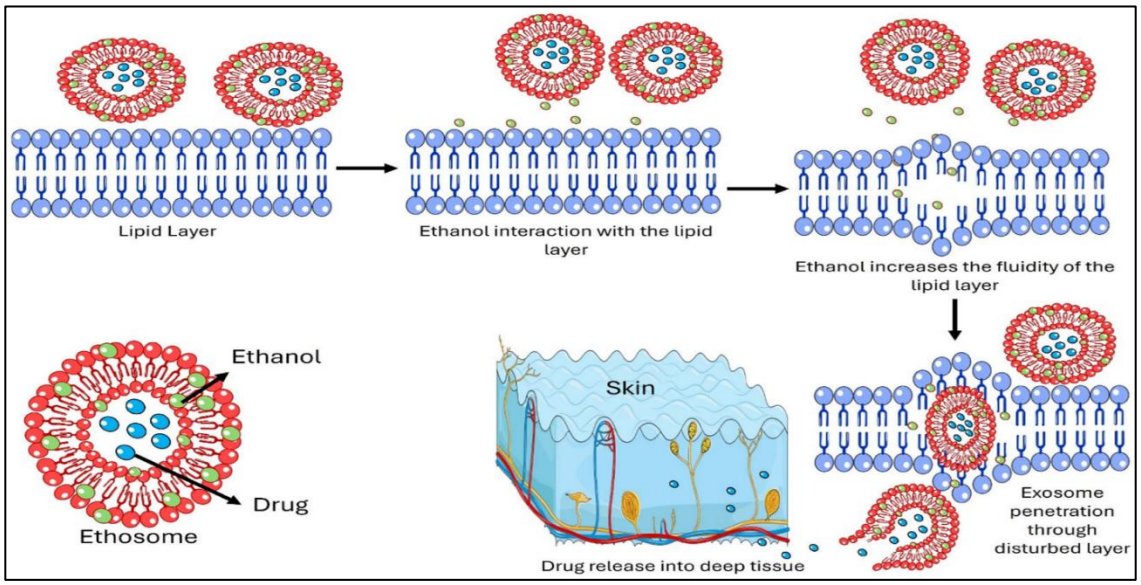

Figure 3. Diagram illustrating the Mechanism of action of ethosomes as transdermal drug delivery **[15]**.

Preparation of Ethosomes

Ethosomes can be prepared using several formulation techniques depending on the composition and desired vesicle properties. The most commonly used approaches include cold method, hot method, classical mechanical dispersion method, ethanol injection method, and transmembrane pH gradient method, **[17]** as presented in Figure 4.

a. Cold Method

The cold method is the simplest and most common method of preparing ethosomes. In this method, the organic and aqueous phases are made separately. At 25 ◦C, with vigorous agitation, ethanol 20% to 45% (w/w) is solubilized into a mixture of phospholipids, pharmaceutical agents, and other lipid constituents **[17]**. The container is then heated to 30 ◦C. This method, commonly termed the 'cold approach', is widely employed. Water is preheated to 30 ◦C in a separate vessel and is gradually incorporated into the initial mixture with continuous stirring. Vesicle formation initiates after approximately 5 min of mixing. Maintaining the resulting vesicles at a low temperature is critical. Optionally, the resulting ethosomal dispersion can be sonicated for a specified duration to further reduce the vesicle size and enhance uniformity, **[16]** as presented in Figure 4A.

b. Hot Method

The hot method of ethos me preparation involves dissolving the phospholipids in ethanol at an Elevated temperature and then adding water to the mixture while continuously stirring. Initially, the phospholipids are dissolved in ethanol at 40–60 ◦C with constant stirring. Then, a heated aqueous phase (e.g., water or a drug solution) at the same temperature is slowly added to the ethanolic phase under constant stirring. The mixture is mixed at a controlled speed to form the ethosome vesicle. The vesicle formed may be sonicated to achieve uniform-sized vesicles for 5 min or for the desired time to achieve the optimum size **[17]**. This method is simple and efficient, especially for thermally stable drugs, and ensures good ethosome formation with high encapsulation efficiency. However, it may not be suitable for heat-sensitive drugs, **[16]** as presented in Figure 4 B.

c. Thin Film Method

Ethosomes can also be prepared using the classical mechanical dispersion method, in which phospholipids are dissolved in an organic solvent mixture to form a thin lipid film. The solvent is evaporated using a rotary evaporator, and the film is then hydrated with a hydroethanolic solution containing the drug to produce vesicles as presented in Figure 4 C **[17]**.

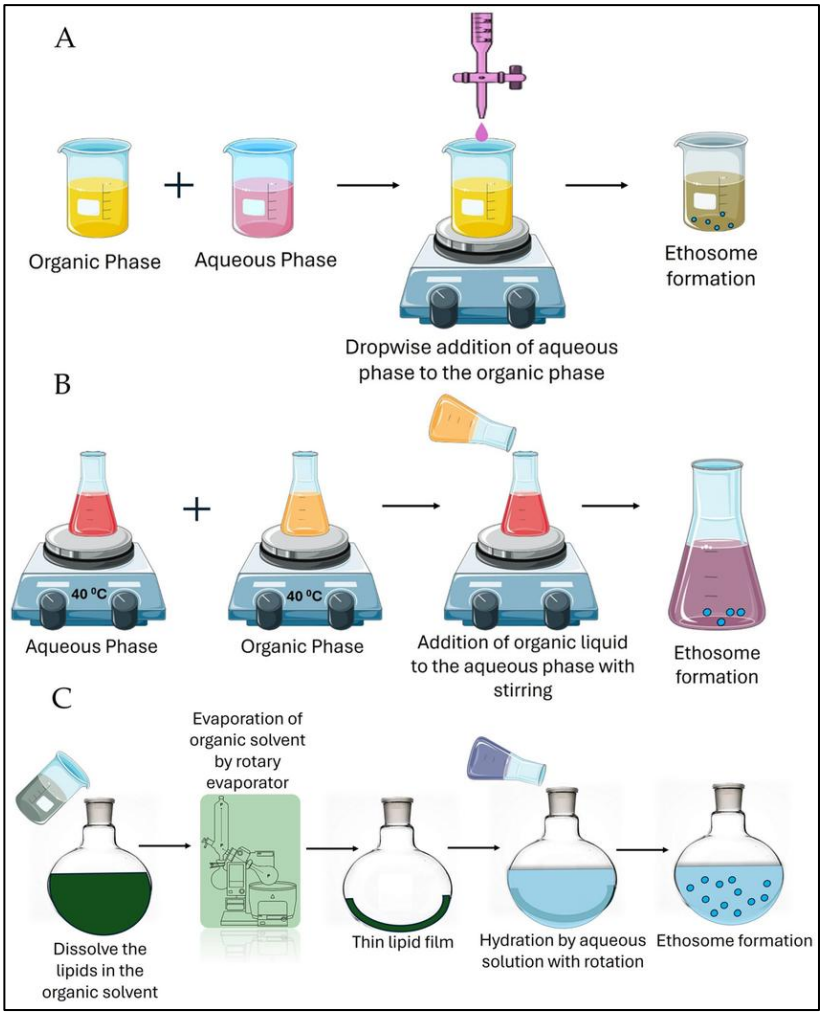

Figure 4. Diagram illustrating the method of Preparation of Ethosomes, Cold Method (A), Hot Method (B) and Thin Film Method (C) **[17]**.

Characterization Of Ethosomal Formulations

The characterization of ethosomes is crucial to ensure their stability and efficacy in transdermal delivery.

1. Vesicle Morphology and Shape

The structural integrity and spherical nature of ethosomes are primarily confirmed using high-resolution imaging techniques. Transmission electron microscopy (tem) and scanning electron microscopy (sem) are employed to visualize the vesicles' morphology and provide evidence of their soft, pliable structure **[18]**.

2. Particle Size and Zeta Potential

The mean diameter and size distribution (polydispersity index) are determined using dynamic light scattering (dls) or photon correlation spectroscopy (pcs). Additionally, the surface charge, which indicates the physical stability of the colloidal dispersion, is measured as zeta potential using a zeta meter **[19]**.

3. Drug Entrapment Efficiency (Ee%)

The capacity of the ethosomes to retain the active pharmaceutical ingredient is evaluated using methods such as ultracentrifugation or the dialysis bag technique. These methods allow for the separation of the free drug from the encapsulated fraction to calculate the efficiency percentage **[18]**.

4. Transition Temperature

The thermodynamic properties and the fluidity of the lipid bilayers are analyzed using differential scanning calorimetry (dsc). This characterization helps in understanding the interaction between ethanol and the phospholipid components within the vesicular system **[20]**.

5. Drug Content and Quantification

To ensure the total amount of drug present in the entire formulation, specific analytical methods are used. This is typically achieved through uv-visible spectrophotometry or validated high-performance liquid chromatography (hplc) procedures **[19]**.

6. Skin Permeation and Penetration Studies

The functional performance of the ethosomal carrier in crossing the skin barrier is often assessed using confocal laser scanning microscopy.

This technique helps track the depth of penetration and the distribution of the formulation within the various epidermal layers **[20]**.

Overall, the characterization of ethosomal formulations plays an essential role in evaluating their stability, drug loading capacity, and effectiveness in transdermal drug delivery.

Dermopharmaceutic Applications of Ethosomes

Ethosome-based systems are utilized across a broad clinical spectrum, ranging from dermatological conditions like psoriasis and skin cancer to systemic issues such as inflammation and hormonal imbalances. Research indicates that incorporating functionalizing agents specifically polymers and targeting ligands onto the ethosomal surface significantly enhances their therapeutic efficacy and skin penetration compared to traditional formulations, **[20]** as presented in Figure 5.

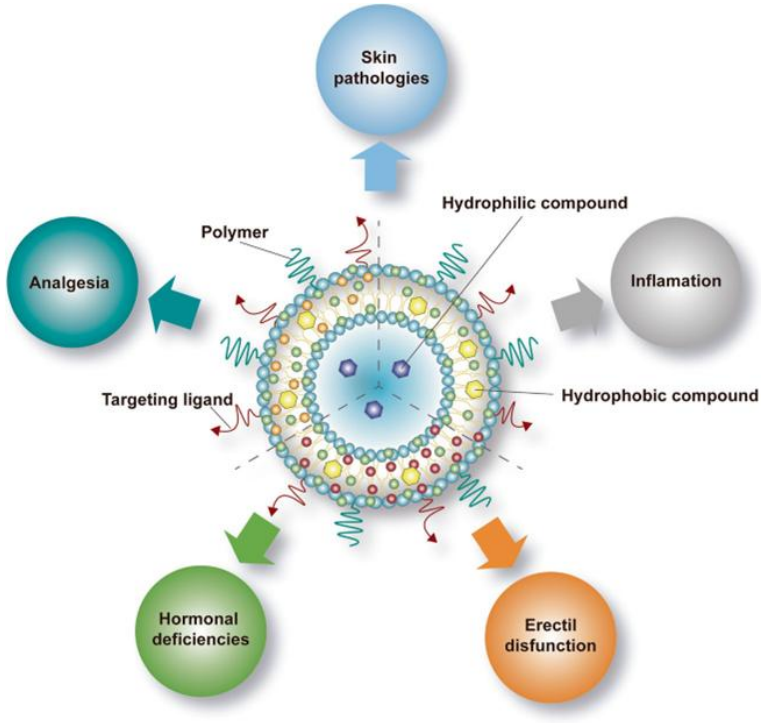

Figure 5. Schematic representation of the application of surface functionalized ethosome-based formulations in a wide variety of pathologies for the entrapment of hydrophobic and hydrophilic compounds and of the functionalizing agents **[20]**.

I. Ethosome-Based Formulations for Inflammation and Analgesy

Inflammation is an essential defensive mechanism induced by the immune system, in response to any stimuli (e.g. tissue injury or pathogen), which involves the release of pro- inflammatory mediators, recruitment of innate immune cells, and tissue damage **[21]**. In some cases, the inflammatory process is temporary, and the homeostasis is re-established, yet occasionally it can become persistent and evolve into a chronic disease. Non-steroidal anti-inflammatory drugs (NSAID) are one of the most commonly used anti-inflammatory agents in the treatment of chronic musculoskeletal disorders, osteoarthritis and acute or chronic rheumatoid arthritis. However, their oral administration is associated with severe side effects, including injury of the gastric epithelium, development of gastric ulcers and renal impairment, so their pro- longed use is highly unadvised **[22]**.

Therefore, topical administration is a promising alternative to the delivery of active ingredients in the treatment of inflammation **[23]**.

- **Ammonium Glycyrrhizinate :**Research by Paolino et al. (2005) showed that ethosomal suspensions (ethanol/lecithin/water) significantly outperformed standard solutions in treating skin redness (erythema). They provided better skin tolerance, deeper penetration, and sustained release of the drug. **[21]**

- **Apigenin :**This antioxidant flavonoid is effective against radiation-induced inflammation by inhibiting the COX-2 enzyme. Shen et al. (2014) found that an optimized ethosomal mix (1:10 ratio of PG to ethanol) allowed apigenin to bypass the skin's outer layers and reach the bloodstream, showing much higher efficiency than traditional liposomes **[23]**.

- **Ketoprofen :**As a potent NSAID, ketoprofen's delivery via ethosomes was evaluated in pre-clinical studies to harness its analgesic and anti-inflammatory properties through the skin, avoiding the digestive tract **[22]**.

- **A recent study developed a transdermal drug delivery system composed of an ethosomal gel containing Thymosin β-4 (Tβ-4) :** this protein is excellent for tissue repair and wound healing, its large molecular size makes it hard to absorb. Developing an ethosomal gel with added surfactants (like sodium deoxycholate) improved the protein's stability and significantly accelerated the wound healing process **[21]**.

- **The ethosomal formulation included soya PC, a surfactant (sodium deoxycholate), and cholesterol.** The surfactant's inclusion

resulted in higher deformability, reduced par- ticle size and improved negative charge, which favoured the system's stability. This formulation revealed a superior drug transdermal rate, compared to the free drug group, and reduced wound healing time, as presented in Figure 6.

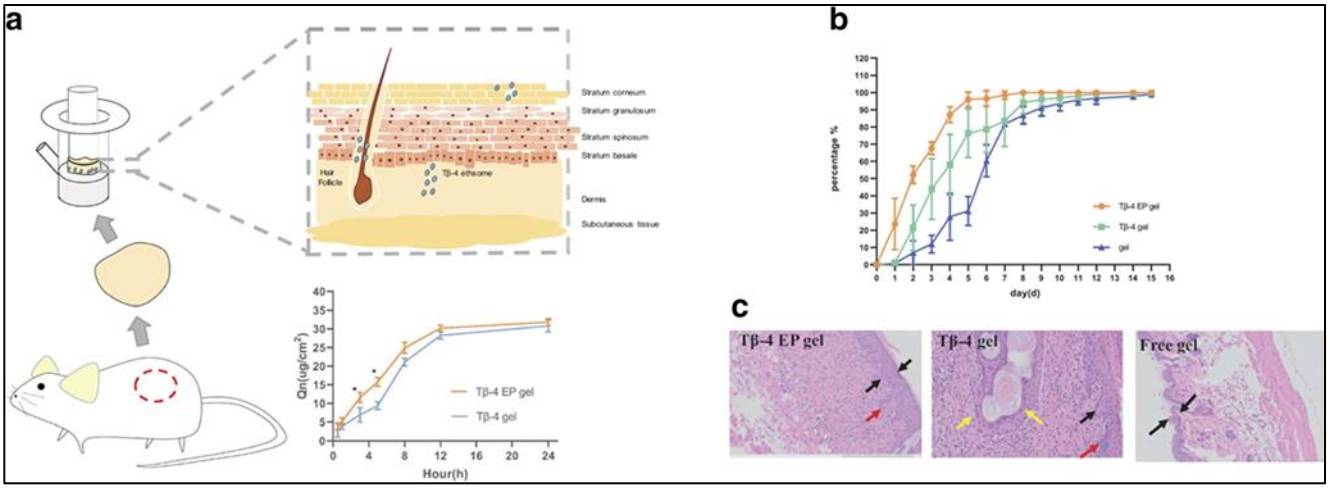

Figure 6: (a) In vitro drug-release study, Tβ-4 ethsomes pass through the stratum corneum into the deeper layers of the skin fixed in Franz diffusion cells and the cumulative permeation amount in unit area of the Tβ-4 ethosomes and Tβ-4 gel varies with time. Statistical significance was noted as follows: *p < 0.05. Kunming mice administrated with different gel for 15 days have different degrees of wound healing (b) and the photomicrographs of the healed skin structure of using different preparations (c). In Fig. 6C, the black arow indicated the degree of skin thickening, the red arow indicated new capillaries and the yellow arrow showed embolization and localized parakeratosis . Originally published by **[22]** and used with permission from Dove Medical Press Ltd.

II. Ethosome-Based Formulations for Skin Disorders

1. Acne Vulgaris

The Role of Ethosomal Carriers in Enhancing Acne Therapy

a. Pathophysiology and Conventional Treatment

Acne vulgaris is a chronic inflammatory disorder primarily affecting the pilosebaceous unit. Its pathogenesis involves four interconnected mechanisms: follicular hyperkeratosis, excessive sebum production, inflammatory responses, and the proliferation of *Cutibacterium (formerly Propionibacterium) acnes* . While topical antibiotics (e.g., clindamycin) and retinoids (e.g., tretinoin) remain first-line therapies, their efficacy is often limited by poor skin penetration and localized irritation **[24]**.

b. Ethosomes as Advanced Delivery Systems

To overcome the skin's barrier function, ethosomes-lipid vesicles characterized by high ethanol content have been investigated for their superior deformability and penetrative capabilities **[25]**.

- **Polypeptide Delivery:** Godin and Touitou (2004) demonstrated that bacitracin-loaded ethosomes (114.9–96.4 nm) achieved deep dermal delivery (up to 200 μm). Fluorescent tracking suggested these carriers fuse directly with cellular membranes, facilitating the intracellular release of the drug **[24]**.

- **Clinical Efficacy:** In clinical trials, an ethosomal gel combining clindamycin phosphate and salicylic acid (CLSA) showed superior therapeutic outcomes over placebo. Patients reported a significant reduction in inflammatory lesions (comedones and pustules) with high skin tolerability **[26]**.

c. Comparative Performance and Limitations

The application of ethosomes varies depending on the active pharmaceutical ingredient (API) and the target depth:

- **Retinoids:** While ethosomal tretinoin significantly enhances drug permeation and entrapment (76%), the presence of ethanol may exacerbate skin irritancy. Consequently, these carriers are recommended for deep-seated acne rather than superficial skin disorders **[26]**.

- **Azelaic Acid:** Research indicates that ethosomal formulations of azelaic acid (179 nm) exhibit higher antibacterial potency compared to commercial products like Zelface®. This is attributed to the synergistic effect of ethanol and phospholipids, which disrupt the bacterial cell wall of *P. acnes*, allowing for higher intracellular drug concentrations **[24]**.

2. Psoriasis and Atopic Dermatitis

Psoriasis is a chronic autoimmune inflammatory skin condition marked by epidermal proliferation, hyperkeratosis, and angiogenesis. While it primarily affects the skin, it is a systemic risk factor for comorbidities like Type 2 diabetes, hypertension, and depression. Psoriasis systemic therapy consists of oral or intravenous administration of methotrexate, cyclosporine, hydroxycarba- mide, among others, usually accompanied by immunosuppression, subtherapeutic effects and severe toxicity **[27]**. Currently, there is no cure, leaving management through topical or systemic therapies as the only option **[25]**.

Topical delivery is preferred for moderate cases because it targets the affected area directly, minimizing the severe adverse effects associated with systemic administration. However, conventional topicals often suffer from poor skin penetration and low patient compliance **[28]**.

Advancements in Ethosomal Delivery Systems

To overcome penetration barriers, researchers have utilized ethosomes (lipid-based nanocarriers containing high ethanol concentrations).

- **Psoralen:** Zhang et al. (2014) demonstrated that psoralen-loaded ethosomes (approx. 120 nm) achieved a 6.56-fold increase in skin deposition compared to standard tinctures. Furthermore, ethosomal systems outperformed traditional liposomes by 3.5 times in transdermal flux, offering a safer and more biocompatible delivery method **[27]**.

- **5-Aminolevulinic Acid (ALA):** In Photodynamic Therapy (PDT), ALA is often limited by its hydrophilic nature. Fang et al. (2009) found that ethosomal ALA increased the intensity of the active photosensitizer (PpIX) by 3.64-fold in murine models, significantly reducing inflammatory markers like TNF-α **[25]**.

- **Methotrexate (MTX):** Although MTX is a gold-standard systemic treatment, it carries high toxicity. Studies show that MTX-loaded ethosomes provide superior transdermal flux compared to hydroethanolic solutions. Recent innovations involve combining MTX-ethosomes with salicylic acid in a gel form; this combination acts as a penetration enhancer and pH adjuster, resulting in sustained drug release and the successful elimination of psoriatic lesions **[25]**.

- **A recent study developed a new strategy to target inflam- matory skin diseases**, namely psoriasis. CD44 receptor is a highly expressed protein in psoriatic inflamed skin, indicating that CD44 is a potential target for topical nanocarriers **[29]**. Hyaluronic acid, an extensively used molecule in targeted drug delivery systems, is a biological ligand to this protein. Therefore, a modified formulation of ethosomes was prepared with PG (in replacement of ethanol), a combination of phos- pholipids, cholesterol, curcumin, and hyaluronic acid. Hyaluronic acid was also added to the surface of ethosomes, as a functionalization surface agent, via covalent bond ar- rangement between this hydrophilic polymer and dioleoyl phosphor ethanolamine (DOPE). Curcumin-loaded ethosomes functionalized with hyaluronic acid enhanced topical and transdermal drug delivery **[27]**. In fact, the cumulative transdermal amount of curcumin and skin retention of curcumin were significantly higher than the other tested formulations without hyaluronic acid **[30]**. This may be explained by the hydrating ef- fect caused by the hyaluronic acid on the SC barrier, which expands and relaxes with increased water amounts and thus improves drug permeability and accumulation on the skin. Topical delivery experiments were conducted in vivo in imiquimod-induced psoriasis-like inflamed skin. The CD44 targeted hyaluronic acid-ethosomes formulation produced a strong inhibitory effect on psoriatic inflamed skin and a sub- stantial downregulation of several cytokines **[27]**.

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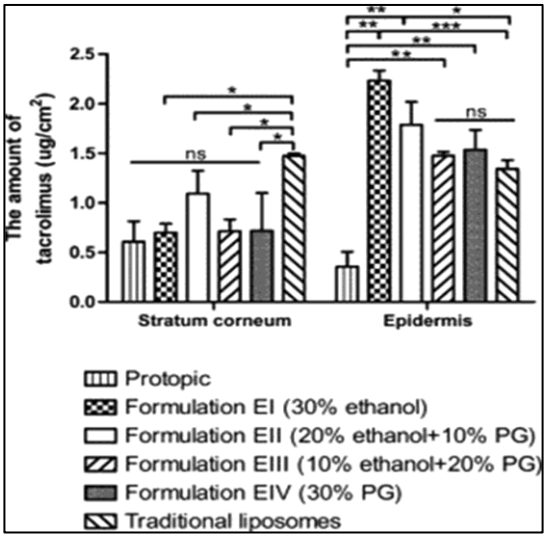

Figure 7: The amount of drug at the stratum corneum and epidermis for tacrolimus formulations. ns $p > 0.05$ between any of two group **[31]**.

III.Ethosomes-Based Formulations for Alopecia

Minoxidil, originally a systemic vasodilator, is the primary FDA-approved topical treatment for androgenetic alopecia, acting by stimulating microcirculation and opening potassium channels, though conventional application causes adverse dermatological effects **[30]**. To address these, studies have developed minoxidil-loaded ethosomal systems using α-DPPC and ethanol, which create smaller, more efficient vesicles than liposomes that significantly improve skin penetration to the pilosebaceous follicles. The presence of cholesterol and ethanol generated higher fluorescence intensity and increased penetration depth. Additionally, increased concentrations of cholesterol and ethanol allowed the drug to reach deeper skin structures, includ- ing the pilosebaceous follicles **[32]**.

IV. Ethosomes-Based Formulations for Skin Cancer

Recent research has highlighted the potential of ethosomes-ultraflexible lipid vesicles-as a superior non-invasive alternative to traditional surgery and systemic chemotherapy for managing skin malignancies, including basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and malignant melanoma **[30]**.

a. Fisetin-Loaded Binary Ethosomes

Ethosomal formulations of the flavonoid fisetin have demonstrated significant efficacy in managing UV-induced skin carcinogenesis. By incorporating fisetin into a binary ethosomal gel (phospholipid 90G, ethanol, and propylene glycol), researchers achieved a penetration depth of 70 µm in skin tissues. In vivo studies showed that this formulation **[32]**:

- Reduced tumor incidence from 96% to 49%.
- Suppressed pro-inflammatory cytokines (TNF-α and IL-1β).
- Decreased lipid peroxidation by 45% through enhanced antioxidant delivery **[30]**.

b. Mitoxantrone Ethosomes for Melanoma

The delivery of mitoxantrone, a potent DNA-intercalating agent, is often hindered by poor skin permeability. However, ethosomal gels have overcome this barrier due to their high deformability. While standard mitoxantrone solutions show negligible therapeutic effects on melanoma-bearing models, ethosomal preparations achieved a 68.44% tumor inhibition rate, underscoring the necessity of specialized transdermal carriers for effective melanoma treatment **[30]**.

c. Synergistic Approaches: 5-Fluorouracil and Microwave Technology

To enhance the localized treatment of melanoma while minimizing systemic toxicity, studies explored combining 5-fluorouracil (5-FU) ethosomes with microwave radiation (2450 MHz) **[33]**.

- **Ethanol** acts as a permeation enhancer by fluidizing epidermal lipids.
- **Microwave pre-treatment** significantly increased drug retention within the skin (395.4 µg) compared to ethosomes alone.
- This synergy creates a "dermal barrier" effect, optimizing local drug concentration while reducing systemic absorption **[30]**.

d. Photodynamic Therapy (PDT) via Ethosomal Carriers

Ethosomes have also been utilized to deliver photosensitizers like ferrous chlorophyllin (Fe-CHL). Compared to chitosan-based nanocarriers, ethosomes provide deeper penetration into both the epidermis and dermis. This superior fluidity is attributed to the presence of ethanol and edge activators, which allow the vesicles to navigate the intercellular pathways of the skin more effectively**[32]**.

V. Ethosomes-Based Formulations for Skin Infections

Traditional antimicrobial therapies often face challenges such as drug resistance, poor site-specific targeting, and inefficient release kinetics.

To overcome these barriers, ethosomes lipid-based nanocarriers have emerged as a superior delivery system for treating bacterial, viral, and fungal skin pathologies **[34]**.

1. Antibacterial Applications

Research by Godin et al. (2005) demonstrated that erythromycin-loaded ethosomes significantly enhance antibacterial efficacy compared to standard hydroethanolic solutions. In both *in vitro* and *in vivo* models, these carriers proved effective against *Bacillus subtilis* and *Staphylococcus aureus*. Notably, ethosomal delivery reduced the Minimum Inhibitory Concentration (MIC) for erythromycin-resistant *S. aureus* by 2.5-fold. Animal studies confirmed that ethosomal treatment prevented skin necrosis and inflammatory infiltration (neutrophils/macrophages), which were prevalent in untreated or conventionally treated groups **[35]**.

2. Antiviral Efficacy

Ethosomes have also optimized the delivery of Acyclovir, a drug typically hindered by poor solubility. A randomized double-blind clinical study revealed that a 5% acyclovir ethosomal formulation outperformed commercial creams (e.g., Zovirax®) in treating recurrent herpes labialis. This research paved the way for the commercialization of Supravir®, a topical ethosomal-based antiviral **[36]**.

3. Antifungal Advancements

Ethosomes have shown remarkable potential in managing cutaneous candidiasis and dermatophytosis **[35]**:

- **Clotrimazole:** Comparative studies indicate that ethosomes achieve a higher transdermal flux and a shorter lag time than ultra deformable liposomes. Their superior antifungal activity against *C. albicans* is attributed to the synergistic effect of ethanol, which denatures fungal proteins and fluidizes the Stratum Corneum (SC) **[35]**.
- **Sertaconazole Nitrate:** Ethosomal gels facilitate drug penetration into deeper skin layers by lowering the phase transition temperature of the lipid bilayer, thereby increasing membrane fluidity **[37]**.
- **Griseofulvin (GRF):** To treat pediatric dermatophytosis, ethosomes have been used to increase drug retention in the SC by approximately 40% over 24 hours **[38]**. Fluorescence assays confirmed that these carriers specifically target hair follicles, ensuring the drug remains at the primary site of fungal colonization rather than leaching into the systemic circulation **[39]**, as presented in Figure 8.

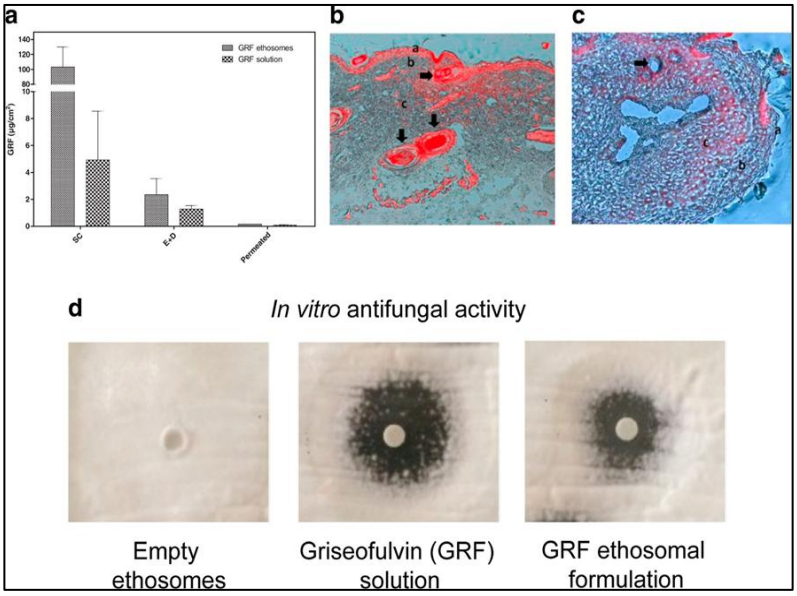

Figure 8: (a) GRF retention in different skin layers, SC (stratum corneum); E + D (viable epidermis and dermis) and GRF permeated within 24 h solution and ethosomes (results expressed as mean ± standard deviation; n = 3, independent batches). (b) Penetration of Nile red from ethosomes, after 24 h. (c) Penetration of Nile red from ethanol:water solution 45:55 (v/v), after 24 h. The sections depict the SC (a), the epidermis (b), and the dermis (c). Pictures are obtained by superposing normal light and fluorescence images of the same area (magnification, 100×). Black arrows are pointing to hair follicles were retention also occurred. (d) In vitro antifungal activity of 0.1% GRF solution, 0.1% GRF ethosomes and empty ethosomes. Reprinted from **[38]**.

VI. Ethosomes-Based Formulations for Erectile Dysfunction

Erectile dysfunction (ED) is a prevalent condition, particularly among the aging population, and is often linked to comorbidities such as diabetes, obesity, and sedentary lifestyles. While Phosphodiesterase-5 (PDE5) inhibitors are the primary clinical intervention, their efficacy is significantly diminished in patients with cavernous nerve damage **[40]**.

Among these inhibitors, vardenafil is noted for its superior potency and selectivity compared to sildenafil and tadalafil. Despite these advantages, vardenafil's clinical utility is limited by its classification as a BCS Class II drug, resulting in poor oral bioavailability **[41]**. To address these pharmacokinetic limitations, recent research has pivoted toward transdermal delivery systems to bypass first-pass metabolism and extend the drug's duration of action.

A pivotal study by Fahmy et al. (2015) explored the use of ethosomes as a carrier for vardenafil. Key findings from this investigation include **[40]**:

- **Physicochemical Properties:** The optimized ethosomal vesicles were characterized by a small particle size (~128 nm) and high entrapment efficiency (76.23%), facilitating deep skin penetration **[41]**.

- **Enhanced Permeability:** Confocal laser scanning microscopy (CLSM) confirmed that the formulation successfully reached the dermis and hypodermis, creating a "drug reservoir" within the skin layers **[41]**.

- **Pharmacokinetic Superiority:** In vivo rat models demonstrated that the ethosomal formulation achieved twice the bioavailability of oral suspensions.

- **Sustained Release:** The mean residence time was recorded at approximately 16.84 hours, suggesting that ethosomes allow for a more prolonged therapeutic effect and a reduction in required dosage **[40]**.

VII. Ethosomes-Based Formulations for Hormonal Deficiencies

To overcome the challenges of traditional androgen replacement therapy-such as painful intramuscular injections and the poor oral bioavailability caused by extensive first-pass metabolism- researchers have focused on ethosomal delivery systems **[42]**.

- **Superior Permeation:** A transdermal testosterone ethosomal patch (Testosome) demonstrated a 30-fold increase in skin permeation compared to the commercial patch (Testoderm®) in animal models **[43]**.

- Enhanced Pharmacokinetics: In vivo applications of ethosomal gels achieved significantly higher peak plasma concentrations (C_{max}) and systemic absorption (AUC) than conventional products like AndroGel®. Specifically, the ethosomal formulation reached a C_{max} of1970 ng/dL, nearly triple that of the commercial gel (601 ng/dL) **[43]**.

- **Human Skin Efficacy:** In vitro experiments on human skin revealed a six-fold enhancement in testosterone flux when delivered via an ethosomal vehicle.

- **Structural Optimization:** The addition of surfactants (such as Cremophor EL-35) to testosterone propionate ethosomes resulted in spherical, unilamellar vesicles with high entrapment efficiency (92.7%). These modified ethosomes penetrated deeper into skin layers (260 µm) compared to standard liposomes (120 µm), providing more stable plasma levels and a prolonged elimination half-life **[42]**.

Buspirone Ethosomes in Menopausal Management

Beyond hormone replacement, ethosomes have been investigated for managing menopausal symptoms like hot flashes and anxiety**[43]**.

- **Overcoming Metabolic Barriers:** While oral buspirone suffers from a short half-life and heavy metabolism, ethosomal transdermal delivery maintains higher therapeutic levels over a 12-hour period **[43]**.

- **Therapeutic Outcomes:** In pharmacodynamic studies using ovariectomized rats, the ethosomal application successfully reduced tail skin temperature (a proxy for hot flashes) within 3 hours, with the effect persisting for 6 hours **[42]**.

Cosmetic/ Skin Care Applications of Ethosomes

The Role of Ethosomes in Enhancing Antioxidant Delivery for Cosmetics

1. Overcoming Physicochemical Limitations

While antioxidants are vital for neutralizing reactive oxygen species (ROS) and preventing skin disorders like premature aging and melanoma, their clinical application is hindered by extreme instability. They are highly sensitive to pH, light, and temperature, and their poor water solubility often results in low skin permeability. To address these challenges, nanocarriers specifically ethosomes, have emerged as a superior delivery system **[44]**.

2. Mechanisms of Enhanced Permeation

Research indicates that ethosomes significantly outperform traditional formulations in drug deposition. The high ethanol content plays a dual role: it fluidizes both the vesicular lipid bilayer and the stratum corneum (SC) lipids. This increased fluidity, combined with the "edge activation" effect, allows the vesicles to deform and penetrate through small openings in the skin barrier, reaching the deeper dermal layers **[44]**.

3. Case Study: Resveratrol and Polyphenols

- **Resveratrol:** Studies by Scognamiglio et al. and Arora et al. demonstrated that ethosomal systems prevent the conversion of *trans-resveratrol* into its less active *cis* form. Compared to standard creams, ethosomal hydrogels showed significantly higher flux and deeper skin distribution, effectively inhibiting ROS production in human keratinocytes **[45]**.

- **Botanical Extracts:** Ethosomes loaded with *Fraxinus angustifolia* (Bark/Leaf extract) proved more effective than ethanolic solutions in reducing myeloperoxidase activity and accelerating the healing process in inflammatory skin models.

4. Clinical Implications for Anti-Aging

The incorporation of bioactive compounds like Curcumin into ethosomes addresses the need for dermal targeting **[46]**. By reaching the dermis, these antioxidants can inhibit metalloproteinases (such as collagenase), which are responsible for degrading collagen

and elastin. Consequently, ethosomal delivery provides a potent strategy for mitigating wrinkle formation and extracellular matrix degradation **[45]**.

Conclusion

This study explores the transition from traditional ethosomal design to this sustainable framework, evaluating how "green" parameters influence the stability, penetration, and overall performance of next-generation transdermal carriers. In recent years, the application of ethosomes in the fields of dermatology and cosmetics has gained growing interest among the scientific community, owing to their high deform- ability, high encapsulation efficiency and enhanced penetra- tion through deeper skin layers. This review presents numer- ous ethosomal formulations developed and investigated so far for the treatment of several diseases, including acne, psoriasis, alopecia, skin infections, hormonal deficiencies, among others.

Conflict of interest: The authors declare that there is no conflict of interests.

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