ETHOSOMAL GEL FOR ENHANCED TOPICAL DELIVERY: A REVIEW

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Abstract

Ethosomal gels are advanced vesicular drug delivery systems designed to enhance topical and transdermal delivery of therapeutic agents by improving skin permeation, drug retention, and bioavailability. Ethosomes are composed of phospholipids, high concentrations of ethanol, and water, which together create flexible vesicles capable of penetrating the stratum corneum more effectively than conventional liposomes. The presence of ethanol disrupts the skin lipid barrier and increases drug partitioning, while the vesicular structure enables delivery of both hydrophilic and lipophilic drugs into deeper skin layers. Incorporation of ethosomes into gel bases further improves stability, spreadability, patient compliance, and residence time, making them suitable for sustained and localized drug delivery. This review summarizes the structure and barrier function of skin, the concept and composition of ethosomes, preparation methods, characterization and evaluation parameters, and their applications in antifungal, antibacterial, anti-inflammatory, analgesic, transdermal, cosmetic, and herbal drug delivery. Recent advances such as nanoethosomes and transethosomes have further enhanced their performance and broadened their pharmaceutical and cosmeceutical applications, although challenges related to stability, irritation potential, and scale-up still need to be addressed for wider clinical and industrial use.

Keywords: *Ethosomal gel; Ethosomes; Transdermal drug delivery; Vesicular systems; Nanocarriers; Skin permeation enhancement.*

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1. INTRODUCTION

Topical and transdermal drug delivery systems have gained considerable attention in recent years because of their ability to provide localized as well as systemic therapeutic effects with improved patient compliance and reduced systemic adverse reactions. Conventional topical formulations such as creams, ointments, and gels often exhibit limited therapeutic efficacy due to the barrier properties of the skin, particularly the stratum corneum, which restricts drug permeation into deeper skin layers (Barry, 2001). The growing demand for efficient and non-invasive drug delivery systems has led to the development of novel vesicular carriers capable of enhancing skin penetration and improving drug bioavailability.

Among various vesicular systems, ethosomes have emerged as promising carriers for topical and transdermal drug delivery. Ethosomes are soft, flexible phospholipid vesicles containing high concentrations of ethanol and water. The presence of ethanol imparts unique deformability to the vesicles and enhances their ability to penetrate through the highly organized lipid structure of the skin (Touitou et al., 2000). Unlike conventional liposomes, ethosomes exhibit superior permeation characteristics and can efficiently deliver both hydrophilic and lipophilic drugs into deeper skin tissues and systemic circulation.

Incorporation of ethosomes into gel formulations has further improved their pharmaceutical applicability by enhancing viscosity, spreadability, stability, and skin retention. Ethosomal gels combine the penetration-enhancing properties of ethosomes with the patient-friendly characteristics of gel systems, thereby offering prolonged residence time, controlled drug release, and improved therapeutic effectiveness (Benson, 2005). Due to these advantages, ethosomal gels have been extensively investigated for the delivery of antifungal, antibacterial, anti-inflammatory, analgesic, antiviral, cosmetic, and herbal therapeutic agents.

Recent advancements in nanotechnology and vesicular drug delivery have expanded the scope of ethosomal systems through the development of nanoethosomes, transethosomes, and targeted vesicular carriers. These advanced systems exhibit enhanced stability, improved drug loading capacity, and superior skin permeation properties (Moghassemi and Hadjizadeh, 2014). Consequently, ethosomal gels have gained significant importance in pharmaceutical and cosmeceutical research as effective alternatives to conventional topical formulations.

This review focuses on the structure and barrier function of the skin, the concept and composition of ethosomes, preparation methods, characterization parameters, applications of ethosomal gels, and recent advancements in the field of ethosomal drug delivery systems.

2. Skin as a Barrier for Drug Delivery

The skin is the body's main protective barrier, but its outermost layer, the stratum corneum, greatly limits drug penetration, making transdermal delivery challenging (Barry, 2001). Although topical delivery offers benefits such as localized action, avoidance of first-pass metabolism, and improved patient compliance, its effectiveness is restricted by the skin's strong barrier function (Prausnitz and Langer, 2008; Benson, 2005). To overcome this limitation, novel carriers like liposomes, niosomes, transferosomes, and ethosomes have been developed, among which ethosomal gels are especially effective due to their enhanced permeation, improved drug retention, and superior therapeutic performance (Touitou et al., 2000).

2.1 Structure of Skin

The skin is the largest organ of the body with a surface area of about 1.5–2.0 m^2 and consists of three main layers: epidermis, dermis, and hypodermis (Williams and Barry, 2012). The epidermis, especially the stratum corneum, acts as the primary barrier and is composed of keratin-filled corneocytes embedded in a lipid matrix arranged in a "brick and mortar" structure (Elias, 2005), making it the major obstacle for drug permeation. The dermis contains blood vessels, nerves, and connective tissue that facilitate systemic absorption once the drug crosses the epidermis (Hadgraft, 2001), while the hypodermis mainly provides insulation and energy storage (Barry, 2001). Skin appendages such as hair follicles and glands also serve as secondary pathways for drug transport, particularly for vesicular systems like ethosomes (Patel et al., 2012).

2.2 Mechanism of Skin Permeation

Drug permeation occurs mainly by passive diffusion following Fick's law and involves transcellular, intercellular, and transappendageal pathways (Prausnitz et al., 2004). The intercellular route is the most dominant, where drugs diffuse through the lipid matrix of the stratum corneum (Williams and Barry, 2012), while the transcellular pathway involves movement through corneocytes and is less favorable due to repeated partitioning (Benson, 2005). The transappendageal route occurs via hair follicles and glands and is important for delivery of nanoparticles and vesicular systems (Patel et al., 2012). Ethosomes enhance permeation by ethanol-induced lipid fluidization of the stratum corneum combined with vesicular penetration into deeper skin layers (Touitou et al., 2000; Dragicevic-Curic et al., 2008).

2.3 Factors Affecting Percutaneous Absorption

Percutaneous absorption is influenced by physiological factors (skin thickness, hydration, age, site, and blood flow), physicochemical properties of the drug (molecular weight, lipophilicity, solubility, and ionization), formulation characteristics (vehicle type, concentration, viscosity, and penetration enhancers), and environmental conditions such as temperature and humidity (Hadgraft, 2004; Bos and Meinardi, 2000). Hydrated, damaged, or thin skin shows higher permeability, while drugs with MW <500 Da and balanced lipophilicity exhibit better absorption. Penetration enhancers like ethanol and vesicular systems such as ethosomes further improve drug delivery by modifying the stratum corneum barrier (Williams and Barry, 2004; Prausnitz and Langer, 2008).

3. Ethosomes

Ethosomes are soft, flexible lipid vesicles composed of phospholipids, water, and high ethanol content (20–45%) designed for enhanced transdermal drug delivery (Touitou et al., 2000). Ethanol increases membrane fluidity and disrupts stratum corneum lipids, allowing deeper penetration, while vesicular flexibility enables efficient drug transport into skin layers. Compared to conventional liposomes, ethosomes show superior permeation and are widely used for antifungal, anti-inflammatory, antiviral, analgesic, and cosmetic drug delivery due to improved efficacy, retention, and patient compliance (Bhalaria et al., 2009; Paolino et al., 2008).

3.1 Concept and Composition

The concept of ethosomes is based on combining the penetration-enhancing effect of ethanol with the vesicular properties of phospholipids. Ethanol not only acts as a permeation enhancer but also imparts flexibility to the vesicular membrane, allowing the vesicles to penetrate through the narrow intercellular spaces of the stratum corneum (Touitou et al., 2000). The synergistic interaction between ethanol and phospholipids results in efficient drug delivery into deeper skin tissues and systemic circulation.

Ethosomes are generally composed of phospholipids, ethanol, water, and occasionally glycols or other additives. Phospholipids such as phosphatidylcholine, phosphatidylserine, and phosphatidylethanolamine form the bilayer structure of the vesicles and encapsulate both hydrophilic and lipophilic drugs (Godin and Touitou, 2007). Ethanol is considered the key component of ethosomes and is usually present in high concentrations ranging from 20–45%. It enhances vesicle flexibility, increases drug solubility, and disrupts the lipid organization of the stratum corneum, thereby improving skin permeation (Elsayed et al., 2006).

Water serves as the hydration medium and stabilizes the vesicular system. Additional components such as propylene glycol, cholesterol, surfactants, and penetration enhancers may also be incorporated to improve vesicle stability, entrapment efficiency, and drug permeation characteristics (Bhalaria et al., 2009). Depending on the formulation composition and preparation method, ethosomes can vary in size from nanometers to micrometers and may possess unilamellar or multilamellar structures.

3.2 Types of Ethosomes

Ethosomes are broadly classified into classical ethosomes, binary ethosomes, and transethosomes based on their composition and structural characteristics.

Classical Ethosomes

Classical ethosomes are composed mainly of phospholipids, ethanol, and water. These systems possess soft and flexible vesicular membranes capable of penetrating the skin barrier efficiently. Classical ethosomes are widely used for topical and transdermal delivery of various therapeutic agents because of their simple composition and enhanced permeation properties (Touitou et al., 2000).

Binary Ethosomes

Binary ethosomes contain phospholipids, ethanol, water, and an additional alcohol such as isopropyl alcohol or propylene glycol. The inclusion of a second alcohol further enhances vesicle flexibility and skin permeation. Binary ethosomes exhibit improved stability, drug loading capacity, and penetration efficiency compared to classical ethosomes (Song et al., 2012).

Transethosomes

Transethosomes are advanced vesicular systems containing phospholipids, ethanol, water, and surfactants or edge activators such as Tween 80 or Span 60. The addition of surfactants increases vesicle deformability and facilitates deeper penetration into the skin layers. Transethosomes combine the advantages of both transferosomes and ethosomes, resulting in superior permeation and therapeutic performance (Ascenso et al., 2015).

Table 2: Comparison of Ethosomes with Other Vesicular Systems

Feature	Ethosomes	Liposomes	Transfersomes	Nanoethosomes
Main component	Phospholipids + high ethanol	Phospholipids + water	Phospholipids + edge activators	Nano-sized ethosomes
Ethanol content	High (20–45%)	Low/none	Low	High
Flexibility	Very high	Low	Very high	Very high

Skin penetration	Excellent	Limited	Excellent	Superior
Drug delivery depth	Deep dermal/systemic	Mainly superficial	Deep dermal	Deepest penetration
Stability	Moderate	Moderate	Moderate	Improved
Vesicle size	Nano to micro	Micro	Nano	<200 nm
Primary advantage	Strong permeation enhancement	Biocompatibility	High deformability	Enhanced targeting & stability
Limitation	Ethanol irritation risk	Poor penetration	Complex formulation	Scale-up challenges

3.3 Mechanism of Penetration Enhancement

The enhanced skin permeation exhibited by ethosomes is mainly attributed to the synergistic effect of ethanol and flexible phospholipid vesicles. Ethanol acts as a potent penetration enhancer by interacting with the lipid molecules of the stratum corneum and reducing their highly ordered arrangement. This interaction increases membrane fluidity and decreases the density of the lipid bilayers, thereby enhancing skin permeability (Williams and Barry, 2012). In addition to altering skin lipids, ethanol also increases the flexibility and deformability of ethosomal vesicles. The soft vesicles can easily penetrate through the intercellular spaces of the stratum corneum and deliver the encapsulated drug into deeper skin layers (Touitou et al., 2000). Once inside the skin, the vesicles fuse with cellular membranes and release the drug gradually, leading to enhanced drug retention and prolonged therapeutic action.

Another important mechanism involves the increased thermodynamic activity of the drug in the presence of ethanol, which promotes higher drug partitioning into the skin (Godin and Touitou, 2007). Ethosomes can also facilitate follicular delivery through hair follicles and sebaceous glands, making them effective carriers for localized and systemic drug delivery applications (Paolino et al., 2008).

The combined action of ethanol-induced lipid disruption and vesicular transport distinguishes ethosomes from conventional liposomes and contributes to their superior permeation efficiency.

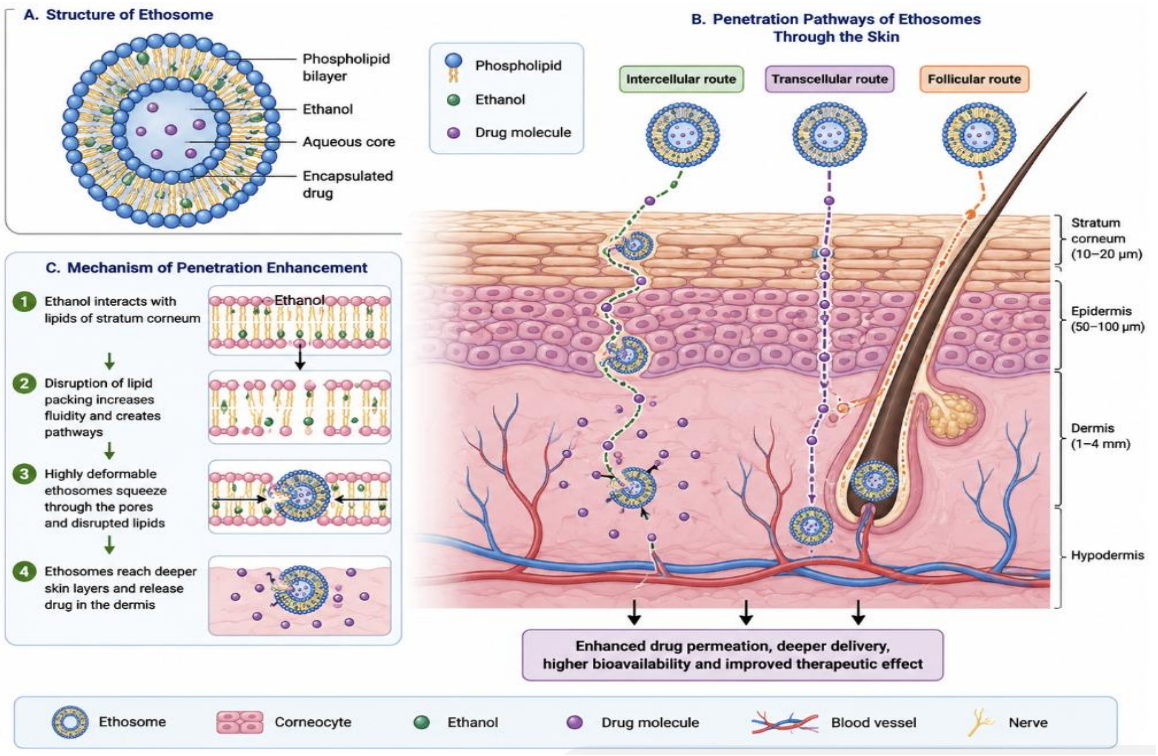

Figure 1: Structure and Mechanism of Ethosomal Penetration

3.4 Advantages and Limitations

Ethosomes offer several advantages over conventional topical and transdermal delivery systems. One of the major advantages is their enhanced penetration capability, which allows efficient delivery of drugs through the skin barrier into deeper tissues and systemic circulation (Touitou et al., 2000). Ethosomes can encapsulate both hydrophilic and lipophilic drugs, thereby expanding their therapeutic applications.

Another important advantage is improved drug bioavailability and therapeutic efficacy due to enhanced skin permeation and prolonged drug retention. Ethosomal formulations are non-invasive, patient-friendly, and capable of reducing dosing frequency and systemic side effects (Bhalaria et al., 2009). Their flexible vesicular structure also enables efficient delivery of peptides, proteins, and macromolecules that normally exhibit poor skin permeability.

Ethosomal systems demonstrate better stability and higher entrapment efficiency compared to conventional liposomes because ethanol imparts negative surface charge and prevents vesicle aggregation (Elsayed et al., 2006). In addition, ethosomal gels provide good spreadability, improved residence time, and enhanced patient acceptability for topical applications.

Despite these advantages, ethosomes also possess certain limitations. High ethanol concentrations may occasionally cause skin irritation, dryness, or erythema, particularly in sensitive individuals (Paolino et al., 2008). Ethosomal formulations may exhibit physical instability such as vesicle fusion, leakage, or drug precipitation during long-term storage.

Moreover, large-scale manufacturing and commercialization of ethosomal systems remain challenging because of formulation complexity and stability concerns (Ascenso et al., 2015). Another limitation is the relatively high production cost associated with phospholipids and specialized formulation techniques. Therefore, further research is necessary to optimize ethosomal formulations and improve their industrial applicability and long-term stability.

4. Ethosomal Gel

4.1 Concept and Rationale

Ethosomal gel is developed by incorporating ethosomal vesicles into a gel base to combine enhanced skin permeation with improved formulation properties. Ethosomes, due to their ethanol-rich flexible phospholipid vesicles, penetrate deeply through the stratum corneum, but their liquid form suffers from low viscosity, poor stability, and short residence time on the skin (Touitou et al., 2000). Incorporation into gels such as Carbopol or HPMC improves viscosity, spreadability, skin adhesion, and contact time, thereby enhancing drug absorption and therapeutic efficacy (Paolino et al., 2008).

This system enables controlled and targeted drug delivery by combining ethanol-induced skin permeation enhancement with vesicular transport into deeper layers, while the gel base provides sustained release, ease of application, and better patient compliance (Elsayed et al., 2006). Ethosomal gels are especially useful for drugs with poor oral bioavailability or significant first-pass metabolism, offering localized action with reduced dosing frequency (Bhalaria et al., 2009).

4.2 Components of Ethosomal Gel

Ethosomal gels consist of ethosomal vesicles and a gel base, both contributing to stability and drug delivery efficiency. Phospholipids such as phosphatidylcholine form the vesicular membrane and encapsulate both hydrophilic and lipophilic drugs (Godin and Touitou, 2007). Ethanol (20–45%) is a key component that increases vesicle flexibility, enhances drug solubility, and disrupts stratum corneum lipids, improving skin permeation while preventing vesicle aggregation.

Water maintains vesicle structure, while additives like propylene glycol, surfactants, and cholesterol may improve stability and entrapment efficiency (Song et al., 2012). The gel base, prepared using polymers such as Carbopol, HPMC, xanthan gum, or CMC, provides viscosity, spreadability, and stability (Benson, 2005). Triethanolamine is commonly used for pH adjustment, and optional excipients like preservatives and humectants may be added depending on formulation needs.

Table 1: Composition and Role of Ethosomal Gel Components

Feature	Ethosomes	Liposomes	Transfersomes	Nanoethosomes
Main component	Phospholipids + high ethanol	Phospholipids + water	Phospholipids + edge activators	Nano-sized ethosomes
Ethanol content	High (20–45%)	Low/none	Low	High
Flexibility	Very high	Low	Very high	Very high
Skin penetration	Excellent	Limited	Excellent	Superior
Drug delivery depth	Deep dermal/systemic	Mainly superficial	Deep dermal	Deepest penetration
Stability	Moderate	Moderate	Moderate	Improved
Vesicle size	Nano to micro	Micro	Nano	<200 nm
Primary advantage	Strong permeation enhancement	Biocompatibility	High deformability	Enhanced targeting & stability
Limitation	Ethanol irritation risk	Poor penetration	Complex formulation	Scale-up challenges

4.3 Methods of Preparation

The preparation of ethosomal gel generally involves two major steps: preparation of ethosomal vesicles followed by incorporation of the vesicular suspension into a suitable gel base. Various formulation and processing parameters influence vesicle size, entrapment efficiency, stability, and drug permeation characteristics.

4.3.1 Preparation of Ethosomes

Ethosomes are commonly prepared by cold method or hot method depending on the physicochemical properties of the drug and formulation components.

In the cold method, phospholipids and the drug are dissolved in ethanol under continuous stirring at room temperature. Polyols such as propylene glycol may also be added during this step. Water is then added slowly to the alcoholic phase under constant stirring, resulting in the spontaneous formation of ethosomal vesicles (Touitou et al., 2000). The obtained vesicular dispersion may be subjected to sonication or extrusion to reduce vesicle size and achieve uniform distribution.

The hot method involves dispersing phospholipids in water and heating the mixture to approximately 40°C. In a separate container, ethanol and the drug are heated to the same temperature and subsequently added to the aqueous phase under continuous stirring. The resulting formulation is then cooled to room temperature to obtain ethosomal vesicles (Elsayed et al., 2006).

Sonication, homogenization, and extrusion techniques are frequently employed to reduce vesicle size and improve homogeneity. The prepared ethosomal suspension is generally stored under refrigerated conditions to maintain stability and prevent vesicle aggregation.

4.3.2 Incorporation into Gel Base

The prepared ethosomal suspension is incorporated into a previously prepared gel base under gentle stirring to obtain the final ethosomal gel formulation. Gelling agents such as Carbopol or HPMC are dispersed in purified water and allowed to hydrate completely. Neutralizing agents like triethanolamine are added to adjust pH and develop appropriate gel consistency (Bhalaria et al., 2009).

The ethosomal suspension is slowly mixed with the gel base using mechanical stirring to ensure uniform distribution of vesicles throughout the formulation. Excessive agitation is avoided because it may disrupt vesicle integrity and reduce entrapment efficiency. The final ethosomal gel is then evaluated for parameters such as pH, viscosity, spreadability, drug content, vesicle size, stability, and in vitro drug permeation (Paolino et al., 2008).

Incorporation of ethosomes into gel systems significantly improves formulation stability, skin retention, and patient acceptability while maintaining the enhanced permeation properties of the vesicular carriers.

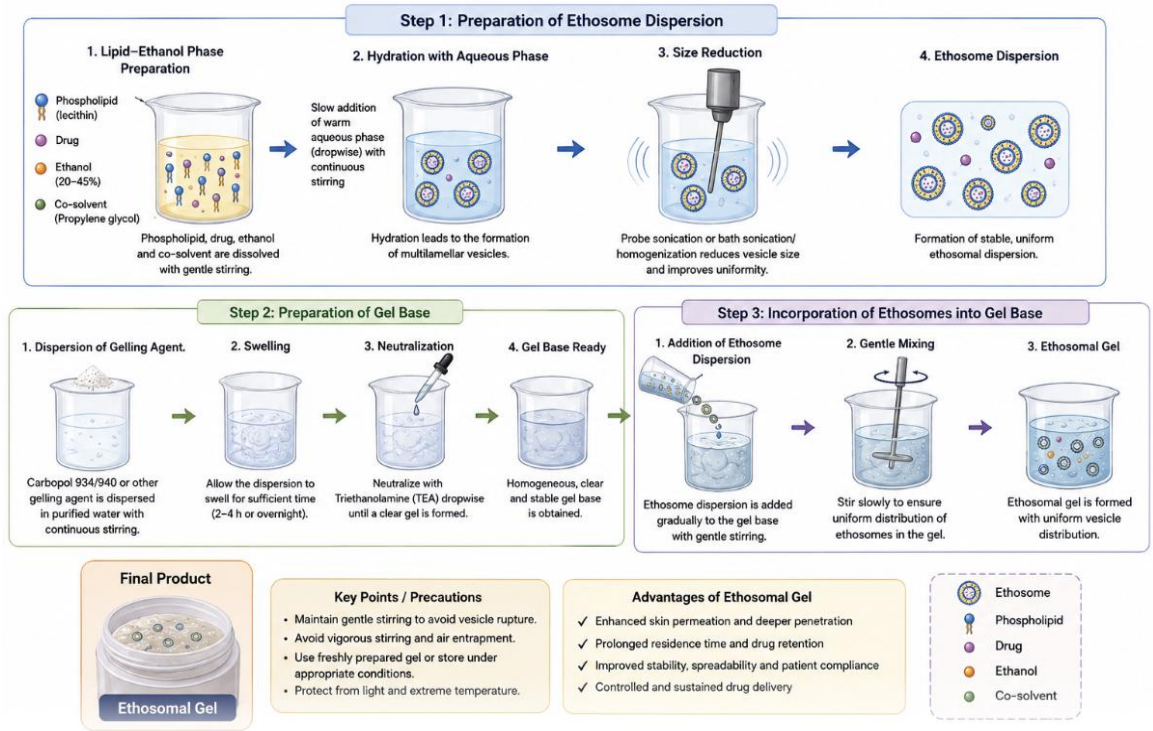

Figure 2: Preparation and Conversion of Ethosomes into Ethosomal Gel

5. Characterization and Evaluation

5.1 Vesicle Size and Zeta Potential

Vesicle size is a key factor influencing skin penetration, drug release, and stability of ethosomal formulations. Smaller vesicles generally show □□□□□ permeation through the stratum corneum due to higher surface area and flexibility (Godin and Touitou, 2007). Size and polydispersity index (PDI) are commonly measured by DLS, where lower PDI indicates a more uniform and stable system (Elsayed et al., 2006).

Zeta potential indicates surface charge and stability; higher absolute values prevent aggregation through electrostatic repulsion. Ethosomal vesicles typically show negative zeta potential due to ethanol and phospholipids. It is measured by electrophoretic light scattering and is influenced by formulation components such as phospholipid and ethanol content (Benson, 2005).

5.2 Entrapment Efficiency

Entrapment efficiency refers to the percentage of drug incorporated within ethosomal vesicles, reflecting drug loading capacity and therapeutic performance (Paolino et al., 2008). It is affected by drug properties, lipid concentration, ethanol content, and vesicle size (Bhalaria et al., 2009). Lipophilic drugs generally show higher entrapment in the lipid bilayer, while hydrophilic drugs are entrapped in the aqueous core. It is determined by separating free drug using centrifugation or dialysis and analyzing it spectrophotometrically or by HPLC.

The percentage entrapment efficiency is generally calculated using the following equation:

$$\textbf{Entrapment Efficiency (\%)} = [(\textbf{Total Drug} - \textbf{Free Drug}) / \textbf{Total Drug}] \times 100$$

Optimized ethosomal formulations usually demonstrate high drug entrapment and improved drug retention within the skin layers, contributing to prolonged therapeutic action.

5.3 In vitro Drug Release and Permeation

In vitro release studies evaluate drug diffusion from ethosomal systems using Franz diffusion cells with dialysis or synthetic membranes. Samples are withdrawn at intervals and analyzed to determine release profile (Elsayed et al., 2006).

Permeation studies use excised skin (rat, porcine, or human) to assess drug transport across the skin barrier, measuring parameters like flux and permeability coefficient (Williams and Barry, 2012). Ethosomal systems show enhanced permeation due to ethanol-induced lipid disruption and vesicle flexibility (Touitou et al., 2000). Release kinetics are often analyzed using models like zero-order, Higuchi, or Korsmeyer–Peppas.

5.4 Evaluation of Ethosomal Gel

pH

The pH of ethosomal gel is an important parameter affecting skin compatibility, stability, and patient acceptability. The pH of topical formulations should generally be close to the physiological skin pH to minimize irritation and discomfort (Benson, 2005). pH is measured using a calibrated digital pH meter by dispersing the gel in distilled water. Ethosomal gels usually exhibit pH values within the acceptable range of 5.0–7.0 suitable for topical application.

Viscosity

Viscosity determines the consistency, spreadability, and ease of application of the gel formulation. Appropriate viscosity is necessary to ensure adequate residence time of the formulation on the skin surface and prevent leakage after application (Bhalaria et al., 2009). Viscosity is commonly measured using Brookfield viscometers at different rotational speeds. The viscosity of ethosomal gels depends on the concentration and type of gelling agent used in the formulation.

Spreadability

Spreadability indicates the ability of the gel to spread uniformly over the skin surface with minimal friction. Good spreadability ensures easy application and uniform drug distribution at the site of administration (Paolino et al., 2008). Spreadability is generally evaluated by measuring the time required for two glass slides to separate under the influence of a specified weight after placing the gel between them.

Drug Content

Drug content determination ensures uniform distribution of the drug throughout the gel formulation. Accurate drug content is essential for consistent therapeutic efficacy and quality control (Godin and Touitou, 2007). Drug content is usually analyzed by dissolving a known quantity of gel in a suitable solvent followed by spectrophotometric or chromatographic analysis.

Stability Studies

Stability studies are performed to evaluate the physical, chemical, and microbiological stability of ethosomal gel formulations during storage. Stability testing helps determine shelf life, storage conditions, and formulation integrity over time (ICH guidelines, 2003). Formulations are generally stored under different temperature and humidity conditions such as refrigerated, room temperature, and accelerated stability conditions.

Parameters including vesicle size, zeta potential, drug content, pH, viscosity, appearance, and entrapment efficiency are periodically evaluated during storage (Elsayed et al., 2006). Stable ethosomal formulations should exhibit minimal vesicle aggregation, drug leakage, and changes in physicochemical properties throughout the storage period.

6. Applications of Ethosomal Gel

Ethosomal gels have gained considerable importance in topical and transdermal drug delivery because of their ability to enhance skin permeation, improve drug localization, and provide sustained therapeutic action. The unique vesicular structure of ethosomes combined with high ethanol concentration facilitates deep penetration of active pharmaceutical ingredients through the stratum corneum. Incorporation of ethosomes into gel systems further improves formulation stability, spreadability, patient compliance, and residence time on the skin surface (Kumar et al., 2018).

Due to these advantages, ethosomal gels have been widely explored for the delivery of antimicrobial, anti-inflammatory, analgesic, cosmetic, transdermal, and herbal therapeutic agents. These systems are particularly beneficial for drugs with poor oral bioavailability, extensive first-pass metabolism, or limited skin penetration (Sharma and Bali, 2018).

6.1 Antifungal and Antibacterial Delivery

Fungal and bacterial infections affecting the skin are among the most common dermatological disorders worldwide. Conventional topical formulations such as creams and ointments often exhibit inadequate penetration into deeper skin layers, resulting in incomplete eradication of microorganisms and frequent recurrence of infections. Ethosomal gels have demonstrated significant potential in improving the topical delivery of antimicrobial agents due to their superior permeation characteristics (Patel et al., 2014).

Several antifungal drugs including fluconazole, clotrimazole, terbinafine, ketoconazole, and voriconazole have been formulated into ethosomal gels for enhanced treatment of fungal infections such as candidiasis, dermatophytosis, and pityriasis versicolor. The high ethanol content present in ethosomes disrupts the lipid arrangement of the stratum corneum and facilitates deeper penetration of antifungal agents into infected tissues (Rizwan et al., 2009). Studies have reported improved skin retention, prolonged drug release, and superior antifungal activity of ethosomal gels compared to conventional formulations.

Ethosomal gels have also been extensively investigated for antibacterial drug delivery. Antibiotics such as erythromycin, clindamycin, tetracycline, and azithromycin incorporated into ethosomal systems have shown enhanced penetration into pilosebaceous units and infected skin tissues, making them effective in the management of acne vulgaris and bacterial

skin infections (Mbah et al., 2014). Improved localization of antibacterial agents at the target site reduces systemic exposure and minimizes adverse effects associated with oral therapy.

Furthermore, ethosomal formulations may help overcome microbial resistance by maintaining higher local drug concentrations within infected tissues. Their ability to improve drug permeation and retention has made them promising carriers for future antimicrobial therapy.

6.2 Anti-inflammatory and Analgesic Delivery

Ethosomal gels are widely utilized for the topical delivery of anti-inflammatory and analgesic agents because they provide enhanced drug permeation, prolonged therapeutic action, and reduced systemic side effects. Nonsteroidal anti-inflammatory drugs (NSAIDs) incorporated into ethosomal systems have shown improved penetration into deeper tissues and joints, thereby increasing therapeutic effectiveness in inflammatory disorders (Puri et al., 2009).

Drugs such as diclofenac sodium, aceclofenac, ketoprofen, meloxicam, and ibuprofen have been successfully formulated into ethosomal gels for the treatment of arthritis, musculoskeletal pain, and localized inflammation. Enhanced skin permeation achieved by ethosomes allows greater accumulation of drugs within inflamed tissues, leading to improved anti-inflammatory response and pain relief (Jain et al., 2014).

Analgesic agents including lidocaine and tramadol have also demonstrated improved efficacy when delivered through ethosomal gels. The flexible vesicular system enables deeper penetration of the drug into pain-sensitive tissues and provides sustained drug release, thereby prolonging analgesic activity (Ruckmani et al., 2012).

Corticosteroids such as hydrocortisone and flurbiprofen loaded into ethosomal formulations have shown improved therapeutic response in dermatological conditions including eczema, psoriasis, and dermatitis. Enhanced dermal retention reduces dosing frequency and minimizes systemic toxicity associated with long-term corticosteroid therapy (Cevc and Blume, 2001).

Overall, ethosomal gels represent an effective alternative to oral anti-inflammatory therapy by providing localized action, enhanced bioavailability, and improved patient compliance.

6.3 Transdermal and Cosmetic Applications

Ethosomal gels have shown remarkable potential in transdermal drug delivery due to their ability to transport drugs across the skin barrier into systemic circulation. Transdermal delivery offers several advantages including sustained drug release, improved bioavailability, reduced gastrointestinal irritation, and avoidance of hepatic first-pass metabolism (Brown et al., 2006).

Various drugs including hormones, antivirals, cardiovascular agents, and central nervous system drugs have been incorporated into ethosomal systems for transdermal administration. Hormones such as testosterone and estradiol formulated into ethosomal gels have demonstrated improved skin permeation and controlled plasma drug levels suitable for hormone replacement therapy (Pierre and Dos Santos Miranda Costa, 2011).

Ethosomal gels have also been explored for transdermal delivery of antiviral drugs such as acyclovir and lamivudine. Enhanced skin penetration achieved by ethosomal carriers improves drug bioavailability and therapeutic efficacy while minimizing systemic toxicity (Fang et al., 2008).

In the cosmetic field, ethosomal gels are increasingly used for delivery of antioxidants, vitamins, anti-aging compounds, depigmenting agents, and moisturizers. Active ingredients such as coenzyme Q10, retinoids, vitamin E, and kojic acid incorporated into ethosomal systems exhibit enhanced penetration into deeper skin layers, thereby improving their cosmetic effectiveness (Verma et al., 2010).

Ethosomal cosmetic formulations are also employed in anti-aging therapies because they enhance collagen stimulation, skin hydration, and protection against oxidative stress. Their non-greasy nature, smooth texture, and improved skin compatibility make them highly suitable for cosmetic and dermatological applications.

6.4 Herbal Drug Delivery

The use of herbal medicines for topical therapy has increased substantially because of their natural origin, therapeutic effectiveness, and relatively low toxicity. However, many phytoconstituents exhibit poor water solubility, limited permeability, and inadequate skin retention, which reduce their therapeutic performance. Ethosomal gels have emerged as promising carriers for enhancing the topical delivery of herbal bioactive compounds (Dubey et al., 2007).

Several herbal compounds including curcumin, quercetin, rutin, aloe vera, green tea extract, neem extract, and resveratrol have been successfully incorporated into ethosomal gels for various therapeutic applications. Ethosomal carriers improve the solubility, stability, and skin permeation of these phytoconstituents, thereby enhancing their bioavailability and pharmacological activity (Manosroi et al., 2011).

Curcumin-loaded ethosomal gels have demonstrated enhanced anti-inflammatory, antioxidant, and wound healing activity compared to conventional herbal formulations. Similarly, quercetin and resveratrol ethosomal systems have shown improved antioxidant and

anti-aging effects due to deeper skin penetration and prolonged retention within skin tissues (Vyas et al., 2015).

Herbal ethosomal gels are also extensively investigated for antimicrobial, anti-acne, anti-psoriatic, and skin rejuvenation therapies. The synergistic combination of natural bioactive compounds with ethosomal vesicles enhances therapeutic efficacy while minimizing skin irritation and adverse effects.

The growing demand for herbal cosmetics and natural therapeutics is expected to further expand the application of ethosomal gels in pharmaceutical and cosmeceutical industries.

7. Recent Advances and Future Perspectives

Rapid advancements in nanotechnology and vesicular drug delivery systems have significantly expanded the applications of ethosomal formulations in topical and transdermal therapy. Continuous research has focused on improving vesicle stability, drug loading capacity, skin penetration efficiency, and therapeutic effectiveness of ethosomal systems. Advanced modifications such as nanoethosomes and transethosomes have emerged as promising approaches for overcoming the limitations associated with conventional topical formulations and classical ethosomes (Nayak et al., 2020).

The growing demand for non-invasive drug delivery systems, targeted therapy, and controlled drug release has accelerated the development of novel ethosomal formulations for pharmaceutical and cosmeceutical applications. Recent studies have demonstrated the potential of advanced ethosomal systems in delivering peptides, proteins, herbal compounds, anticancer agents, vaccines, and gene-based therapeutics (Chaudhary et al., 2021). Despite significant progress, certain challenges related to formulation stability, large-scale production, and regulatory approval still need to be addressed for successful commercialization.

7.1 Nanoethosomes and Transethosomes

Nanoethosomes are modified ethosomal vesicles with particle sizes in the nanometer range, generally below 200 nm. Reduction in vesicle size increases surface area, improves skin interaction, and enhances penetration through the stratum corneum and deeper skin layers (Kaur et al., 2022). Nanoethosomal systems provide superior drug entrapment, controlled release, and enhanced bioavailability compared to conventional ethosomes.

Nanoethosomes have been extensively explored for the delivery of antifungal, anticancer, anti-inflammatory, and cosmetic agents. Studies have shown that nanoethosomal formulations exhibit improved skin deposition and prolonged therapeutic activity due to their smaller vesicle size and greater flexibility (Moghassemi and Hadjizadeh, 2014).

Nanoethosomes are particularly beneficial for drugs with poor water solubility and limited skin permeability.

Transethosomes are another advanced vesicular system developed by incorporating edge activators or surfactants into ethosomal formulations. These systems combine the advantages of transferosomes and ethosomes, resulting in highly deformable vesicles with superior penetration capability (Song et al., 2012). Surfactants such as Tween 80, Span 60, and sodium cholate increase vesicle elasticity and facilitate passage through narrow skin pores without disrupting vesicle integrity.

Transethosomal gels have demonstrated enhanced permeation and therapeutic effectiveness for various drugs including antifungals, corticosteroids, anticancer agents, and hormones. Improved vesicle flexibility allows deeper penetration into skin tissues and enhanced transdermal delivery compared to classical ethosomes (Ascenso et al., 2015).

Recent advancements have also focused on surface-modified ethosomes, ligand-targeted vesicles, and stimuli-responsive vesicular systems capable of controlled drug release under specific physiological conditions. Such innovations are expected to broaden the scope of ethosomal drug delivery in personalized and targeted therapy.

7.2 Current Research Trends

Current research in ethosomal drug delivery is primarily directed toward improving formulation performance, enhancing targeting efficiency, and expanding therapeutic applications. One major area of investigation involves the development of multifunctional vesicular systems capable of delivering multiple drugs simultaneously for synergistic therapeutic effects (Ahmed and Madkan, 2020).

Researchers are increasingly exploring ethosomal systems for delivery of macromolecules such as peptides, proteins, vaccines, and nucleic acids that traditionally exhibit poor skin permeability. The flexibility and penetration-enhancing ability of ethosomes make them suitable carriers for transcutaneous immunization and gene delivery applications (Verma and Pathak, 2012).

Another important trend involves the incorporation of herbal and natural bioactive compounds into ethosomal formulations. Phytoconstituents such as curcumin, quercetin, resveratrol, and essential oils are being investigated extensively for antioxidant, anti-aging, antimicrobial, and anti-inflammatory applications (Rai et al., 2021). Nanoethosomal herbal gels have shown improved bioavailability and therapeutic effectiveness compared to conventional herbal formulations.

The application of ethosomal systems in skin cancer therapy and targeted drug delivery has also attracted considerable attention. Ethosomal carriers can improve localization of anticancer drugs within tumor tissues while minimizing systemic toxicity (Pleguezuelos-Villa et al., 2020). In addition, combination therapy using ethosomal gels containing chemotherapeutic and anti-inflammatory agents is emerging as a promising strategy in dermatological treatment.

Advanced analytical techniques and artificial intelligence-based optimization approaches are increasingly being utilized for formulation design, characterization, and prediction of drug permeation behavior. These technological advancements are expected to improve the precision and reproducibility of ethosomal formulations.

7.3 Challenges and Future Scope

Despite numerous advantages and promising applications, ethosomal systems still face several challenges that limit their large-scale industrial application and commercialization. One of the major concerns is physical and chemical instability during storage. Ethosomal vesicles may undergo aggregation, fusion, drug leakage, or phospholipid oxidation over time, affecting formulation performance and shelf life (Mbah et al., 2014).

High ethanol concentration, although beneficial for skin permeation, may occasionally cause skin irritation, dryness, or erythema in sensitive individuals. Therefore, optimization of ethanol concentration and formulation composition is necessary to balance permeation enhancement and skin safety (Nayak et al., 2020).

Another challenge involves large-scale manufacturing and reproducibility of ethosomal formulations. Maintaining consistent vesicle size, entrapment efficiency, and stability during industrial production remains difficult because ethosomal systems are highly sensitive to formulation and processing parameters (Kaur et al., 2022). The high cost of phospholipids and sophisticated manufacturing equipment may also increase production expenses.

Regulatory approval and standardization of ethosomal formulations represent additional challenges because comprehensive guidelines for evaluation, safety assessment, and quality control of nanovesicular systems are still evolving. Long-term toxicity studies and clinical trials are necessary to establish the safety and efficacy of advanced ethosomal systems for human use.

Future research is expected to focus on the development of more stable, targeted, and patient-friendly ethosomal formulations with improved therapeutic outcomes. Integration of nanotechnology, biotechnology, and smart drug delivery approaches may lead to the

development of stimuli-responsive and site-specific ethosomal systems capable of personalized therapy (Chaudhary et al., 2021).

The future scope of ethosomal gels appears highly promising in areas such as transdermal vaccination, gene delivery, anticancer therapy, regenerative medicine, and cosmeceuticals. With continued advancements in formulation science and nanomedicine, ethosomal systems are expected to become important platforms for next-generation topical and transdermal drug delivery.

8. Conclusion

Ethosomal gels have emerged as advanced and efficient vesicular drug delivery systems for enhanced topical and transdermal therapy due to their ability to improve skin permeation, drug retention, and therapeutic efficacy. The synergistic effect of phospholipid vesicles and high ethanol concentration enables effective penetration through the stratum corneum, making ethosomal formulations suitable for the delivery of antifungal, antibacterial, anti-inflammatory, analgesic, cosmetic, hormonal, and herbal agents. Incorporation of ethosomes into gel bases further enhances formulation stability, spreadability, patient compliance, and controlled drug release. Recent advancements such as nanoethosomes and transethosomes have expanded the scope of ethosomal technology by providing improved deformability, targeted delivery, and enhanced bioavailability. Although challenges related to stability, skin irritation, large-scale production, and regulatory approval still exist, continuous research and technological developments are expected to overcome these limitations. Overall, ethosomal gels represent a promising and versatile platform for future topical and transdermal drug delivery applications in both pharmaceutical and cosmeceutical fields.

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10. Conflict of Interest

The authors declare that there are no conflicts of interest.

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