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Review Paper

Ethosomal Emulgel: A Review

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ABSTRACT

Ethosomal emulgels are advanced hybrid drug delivery systems developed to overcome the limitations of conventional topical and transdermal formulations. These systems combine ethanol-rich, highly deformable ethosomal vesicles with a semi-solid emulgel matrix, resulting in enhanced skin permeation, controlled drug release, improved stability, and better patient compliance. Ethanol plays a critical role by fluidizing stratum corneum lipids and increasing vesicular flexibility, thereby facilitating deeper penetration of both hydrophilic and lipophilic drugs. Incorporation of ethosomes into an emulgel base improves viscosity, prolongs residence time on the skin, and minimizes vesicle aggregation and drug leakage. This review highlights the rationale, composition, preparation methods, penetration mechanisms, evaluation parameters, advantages, limitations, and therapeutic applications of ethosomal emulgels. Preclinical studies demonstrate superior drug permeation, sustained release, and enhanced therapeutic efficacy compared with conventional gels and emulsions. Despite challenges such as ethanol-induced irritation and limited clinical data, ethosomal emulgels represent a promising platform for non-invasive topical and transdermal drug delivery..

INTRODUCTION

Topical and transdermal drug delivery systems (TDDS) have emerged as promising approaches in pharmaceutical research owing to their non-invasive administration, avoidance of first-pass hepatic metabolism, and capacity to improve patient compliance while enabling controlled and sustained drug release. Despite these advantages, effective drug delivery through the skin remains challenging due to the presence of the stratum corneum, the outermost skin layer, which acts as a highly efficient barrier to permeation. This barrier significantly restricts the transport of hydrophilic molecules and drugs with high molecular weight. Consequently, contemporary strategies focus on the use of penetration enhancers and advanced carrier-based delivery systems to overcome the stratum corneum and promote enhanced localized or systemic drug delivery.[1,29]

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Vesicular carrier systems, particularly ethosomes, have emerged as one of the most promising nanotechnology-based strategies for enhancing transdermal drug permeation. Ethosomes are soft, highly deformable lipid vesicles primarily composed of phospholipids, a high concentration of ethanol, and water. The presence of ethanol plays a pivotal role by imparting fluidity to the lipid bilayer of both the ethosomal vesicles and the stratum corneum lipids, thereby increasing vesicle flexibility and facilitating deeper penetration into the skin layers compared with conventional liposomal systems.[2]

Ethosomes have been extensively explored for both topical and transdermal drug delivery applications, demonstrating enhanced penetration of encapsulated therapeutic agents into deeper layers of the skin and, in some cases, into the systemic circulation. Moreover, ethosomal systems are capable of efficiently accommodating and delivering a wide spectrum of hydrophilic as well as lipophilic drugs. [1]

Despite their advantages, conventional ethosomal suspensions often exhibit low viscosity and limited residence time on the skin surface, which may compromise their clinical effectiveness and shorten the therapeutic window. To overcome these drawbacks, considerable research efforts have focused on incorporating ethosomes into semi-solid dosage forms such as gels and emulgels. Emulgels are biphasic hybrid systems produced by dispersing an emulsion within a gel matrix, thereby integrating the drug-solubilizing capability of emulsions with the enhanced viscosity, stability, and user acceptability of gels. Owing to their non-greasy nature, ease of spreadability, and favorable cosmetic properties, emulgels are particularly well suited for topical drug delivery, as they improve drug release characteristics and prolong contact time with the skin.[4]

The incorporation of ethosomal vesicles into an emulgel base, forming an ethosomal emulgel, offers a synergistic approach to topical drug delivery by enhancing transdermal permeation, prolonging drug retention at the site of application, enabling controlled drug release, and ultimately improving therapeutic efficacy. In this hybrid system, the ethosomal vesicles promote disruption of stratum corneum lipids and facilitate vesicular penetration across the skin barrier, while the emulgel matrix provides structural integrity, optimal viscosity, and improved patient acceptability. Numerous formulation and preclinical investigations have demonstrated that ethosomal emulgels significantly enhance drug bioavailability and therapeutic performance when compared with conventional gel or emulsion-based formulations.[2]

Within the scope of pharmaceutical research, ethosomal emulgels represent a versatile and promising delivery platform for active pharmaceutical ingredients (APIs) exhibiting poor aqueous solubility, limited skin permeability, or stability-related challenges. These attributes make ethosomal emulgels particularly advantageous for both dermatological therapies and systemic drug delivery via the transdermal route. Recent studies have reported the successful incorporation of anti-inflammatory, antifungal, analgesic, hormonal, and cosmetic agents into ethosomal emulgel formulations, underscoring their potential to emerge as a future benchmark in advanced topical drug delivery systems.[2]

Rationale for Developing Ethosomal Emulgel

The formulation of ethosomal emulgels is motivated by the necessity to address the inherent shortcomings of conventional topical dosage forms and ethosomal suspensions, while synergistically combining their respective advantages to achieve improved dermal and transdermal drug delivery performance.

The stratum corneum constitutes the principal barrier to efficient topical and transdermal drug delivery due to its highly ordered and compact lipid architecture, which markedly restricts the permeation of numerous therapeutic agents, particularly hydrophilic molecules and drugs with high molecular weight. Conventional topical formulations such as creams, gels, and ointments often fail to deliver sufficient drug concentrations beyond this barrier, resulting in limited drug availability at the target site and reduced therapeutic effectiveness. Conversely, ethosomal delivery systems are composed of soft, highly deformable lipid vesicles formed from phospholipids and comparatively high concentrations of ethanol. Ethanol plays a crucial role by fluidizing both the vesicular lipid bilayer and the lipid domains of the stratum corneum, thereby facilitating enhanced skin penetration and improving the bioavailability of the encapsulated therapeutic agents.[32]

Despite their enhanced skin permeation capabilities, ethosomal suspensions face certain practical limitations when applied directly, including low viscosity, limited residence time at the application site, and potential vesicle instability or leakage. Incorporating ethosomes into a semi-solid vehicle such as an emulgel effectively addresses these challenges. Emulgels are hybrid systems that combine the drug-solubilizing efficiency of emulsions for both hydrophilic and lipophilic drugs with the high viscosity, ease of spreadability, and prolonged skin contact characteristic of gels. This dual-structured formulation enhances the performance of ethosomal vesicles by improving physical stability, prolonging drug retention at the site of application, and increasing patient acceptability, ultimately leading to superior therapeutic outcomes.[5]

From a formulation perspective, ethosomal emulgels offer enhanced control over drug release and enable sustained delivery compared with ethosomal suspensions or conventional gels, thereby reducing dosing frequency and improving patient compliance. The gel matrix additionally provides a protective environment for the ethosomal vesicles, reducing coalescence and vesicle rupture common challenges associated with liquid ethosomal dispersions, especially during storage and handling. Furthermore, ethosomal emulgels are non-greasy and cosmetically acceptable, making them particularly well suited for dermatological applications that require prolonged drug contact at the site of administration.[5]

In summary, the development of ethosomal emulgels is driven by the need to improve skin permeation, enhance drug stability, prolong residence time, and increase patient acceptability, surpassing the capabilities of conventional topical formulations or ethosomal suspensions alone. This integrated delivery strategy provides a versatile platform for both localized and systemic therapy via the skin and has been shown in multiple formulation and preclinical studies to markedly enhance drug bioavailability and therapeutic outcomes.[10]

Composition of Ethosomal Emulgel

Category	Component	Typical Examples	Function / Role in Formulation
Ethosomal Components	**Phospholipids**	Phosphatidylcholine, soya lecithin, egg lecithin	Form bilayer vesicular membrane; enable encapsulation of hydrophilic and lipophilic drugs; influence vesicle size, entrapment efficiency, and stability[1]
	Ethanol	Ethanol (20-45% w/w)	Enhances skin penetration by fluidizing stratum corneum lipids; increases

			vesicle flexibility and deformability; improves drug solubility and entrapment[32,33]
	Aqueous Phase	Purified water	Acts as dispersion medium; hydrates phospholipid bilayers; supports vesicle formation and stability[34]
	Drug	Hydrophilic, lipophilic, or amphiphilic drugs	Active therapeutic agent; distributed in lipid bilayer, aqueous core, or ethanol phase depending on physicochemical properties[35]
Emulgel Components	**Gelling Agents**	Carbopol 934, Carbopol 940, HPMC, NaCMC	Provide semi-solid structure; increase viscosity; enhance residence time and spreadability[36,37]
	Oil Phase	Liquid paraffin, isopropyl myristate	Solubilizes lipophilic drugs; improves skin feel and formulation stability
	Emulsifying Agents	Tween 80, Span 80	Stabilize oil-in-water emulsion; ensure uniform dispersion of oil droplets[14]
	Penetration Enhancers (optional)	Propylene glycol, oleic acid, menthol	Further enhance drug permeation through the stratum corneum[12]
	Preservatives	Methyl paraben, propyl paraben	Prevent microbial growth; improve shelf life[9]
	pH Adjusters	Triethanolamine, sodium hydroxide	Maintain skin-compatible pH; stabilize gel network[3]

Mechanism of Skin Penetration of Ethosomal Emulgel

The superior skin penetration observed with ethosomal emulgels is attributed to a synergistic, multi-mechanistic process involving the combined effects of ethanol, highly flexible ethosomal vesicles, and the emulgel matrix [1,2]. In contrast to conventional topical formulations, ethosomal emulgels can traverse the stratum corneum barrier via both biochemical and physical mechanisms, resulting in enhanced dermal and transdermal drug delivery [1,35].

1. Barrier Function of the Stratum Corneum

The stratum corneum, which constitutes the outermost layer of the skin, is formed by corneocytes embedded within a lipid matrix predominantly composed of ceramides, cholesterol, and free fatty acids [5]. This well-organized lipid arrangement serves as the principal barrier to drug penetration, especially for hydrophilic and high-molecular-weight molecules [6]. Traditional gels and creams are often inadequate in overcoming this barrier, leading to suboptimal drug permeation [5,7].

2. Role of Ethanol in Skin Penetration

Ethanol, present at relatively high concentrations 20-45% in ethosomal formulations, plays a pivotal role in enhancing transdermal drug delivery [1]. It interacts with the intercellular lipids of the stratum corneum, reducing lipid crystallinity and increasing membrane fluidity [5,8]. By disrupting hydrogen bonding within the lipid bilayers,

ethanol generates transient pores in the stratum corneum [5,8], while simultaneously enhancing the solubility of drugs and their partitioning into the skin layers [2,4]. This ethanol mediated lipid fluidization weakens the skin barrier, thereby promoting deeper penetration of both ethosomal vesicles and their encapsulated therapeutic agents [1,32].

3. Role of Flexible Ethosomal Vesicles

Ethosomes are soft, highly deformable vesicles, exhibiting significant elasticity due to the incorporation of ethanol within their bilayers [1]. Following ethanol-mediated disruption of the stratum corneum lipids, ethosomal vesicles penetrate the skin through multiple mechanisms:

- Intercellular pathway: Ethosomes traverse the lipid channels between corneocytes [5,32].
- Vesicular transport: Intact ethosomes migrate into deeper skin layers while retaining their encapsulated drug [2,32].
- Fusion mechanism: The phospholipid bilayers of ethosomes may fuse with skin lipids, facilitating direct release of the drug into deeper layers [1].

The small size and remarkable flexibility of ethosomes enable them to penetrate significantly deeper than conventional liposomes, reaching the viable epidermis and, in some cases, the dermis [34].

4. Contribution of the Emulgel Matrix

The emulgel component of the formulation further promotes skin penetration through several indirect mechanisms. Its increased viscosity prolongs residence time on the skin surface, facilitating extended interaction between ethanol and stratum corneum lipids [7,10]. The gel network also enables controlled release of both ethosomes and the encapsulated drug, maintaining a favorable concentration gradient across the skin layers [6,10]. Additionally, the occlusive properties of the emulgel enhance skin hydration, which loosens the stratum corneum structure and further improves permeability [7,10]. Collectively, the emulgel functions as a supportive carrier, optimizing the overall penetration efficiency of ethosomal vesicles [7,10].

5. Combined Synergistic Mechanism

The overall mechanism of skin penetration by ethosomal emulgel can be summarized as follows:

- Ethanol disrupts and fluidizes the lipids of the stratum corneum [1,2].
- Flexible ethosomal vesicles traverse the loosened lipid channels [2,5].
- Vesicles either fuse with skin lipids or release the encapsulated drug into deeper layers [1,5].
- The emulgel matrix prolongs residence time and modulates drug release [6,10].

This synergistic combination of ethanol, deformable vesicles, and emulgel matrix significantly enhances drug permeation and retention within skin tissues, outperforming conventional gels, emulsions, or ethosomal suspensions alone[35]

Therapeutic Implications

Owing to their enhanced penetration capabilities, ethosomal emulgels are particularly suitable for:

- Localized dermal therapy [2,7]
- Transdermal systemic delivery [1]
- Administration of poorly permeable drugs [2,4]
- Sustained and controlled topical treatments [6,10]

Method of Preparation of Ethosomal Emulgel

The preparation of an ethosomal emulgel involves a three-step process, namely:
(i) Preparation of ethosomal vesicles
(ii) Preparation of the Emulgel base, and

(iii) Incorporation of ethosomes into the emulgel

This stepwise approach ensures the structural integrity of ethosomes and uniform distribution within the semi-solid base.

Preparation of Ethosomal Vesicles

Ethosomes are most commonly prepared using the cold method, which is widely preferred due to its operational simplicity and suitability for encapsulating thermolabile drugs . In this approach, phospholipids such as soya lecithin or phosphatidylcholine are dissolved in ethanol under continuous magnetic stirring at room temperature[1] . The drug is incorporated either into the ethanolic phase or the aqueous phase, depending on its solubility characteristics [20].

Purified water is subsequently added slowly to the ethanolic lipid solution under continuous stirring, leading to the spontaneous formation of ethosomal vesicles [1]. The resulting dispersion is stirred until a uniform and homogeneous ethosomal suspension is achieved. When necessary, vesicle size can be further reduced and standardized using techniques such as sonication or extrusion [1,20].

Preparation of Emulgel Base

The emulgel base is prepared by first formulating an oil-in-water (O/W) emulsion, followed by its incorporation into a gel base [32].

Preparation of Emulsion

The oil phase, consisting of components such as liquid paraffin or isopropyl myristate, and the aqueous phase containing purified water are prepared separately [32,10]. Lipophilic surfactants (e.g., Span 80) are incorporated into the oil phase, whereas hydrophilic surfactants such as Tween 80, along with suitable preservatives, are added to the aqueous phase [32,10]. Both phases are heated independently to 70-75 °C and subsequently combined under continuous stirring, resulting in the formation of a stable oil-in-water (O/W) emulsion [10].

Preparation of Gel Base

Gelling agents such as Carbopol 934 or Carbopol 940 are dispersed in purified water under continuous stirring and allowed to hydrate completely to form a uniform dispersion [37]. The pH of the hydrated polymer system is subsequently adjusted using triethanolamine, resulting in the formation of a clear and homogeneous gel base [37]. The previously prepared emulsion is then gradually incorporated into the gel base with gentle stirring, leading to the formation of the emulgel [21].

Incorporation of Ethosomes into Emulgel

The prepared ethosomal suspension is slowly incorporated into the emulgel base under gentle and uniform stirring to minimize vesicle disruption [2,7]. This process is performed at room temperature to preserve the structural integrity of the ethosomal vesicles [4,6]. The resulting ethosomal emulgel should exhibit a smooth, homogeneous texture and be free from air entrapment [32,11]. Following incorporation, the formulation is allowed to equilibrate and is subsequently stored in appropriate containers for further evaluation and characterization [12].

Significance of the Preparation Method

This preparation approach ensures the preservation of ethosomal vesicle integrity [1,4] and promotes uniform distribution of vesicles throughout the emulgel matrix [2,32]. Additionally, it enhances formulation stability and prolongs residence time on the skin surface [21], while simultaneously improving drug permeation and enabling controlled release of the encapsulated drug [1,21].

Evaluation Parameters of Ethosomal Emulgel

Evaluation of ethosomal emulgel formulations is crucial to ensure their physicochemical quality, vesicular integrity, skin compatibility, stability, and therapeutic efficacy[1]. Comprehensive characterization enables the establishment of the advantages of ethosomal emulgels over conventional topical formulations, particularly with respect to enhanced skin permeation and controlled drug release behavior [1,20].

1. Vesicular Characterization

1.1 Vesicle Size and Polydispersity Index (PDI)

Vesicle size is a critical parameter influencing the skin penetration efficiency and physical stability of ethosomal vesicles [1,5]. Smaller vesicles with a narrow size distribution facilitate deeper penetration into the stratum corneum and improve drug delivery to viable skin layers [6,7]. The polydispersity index (PDI) reflects the uniformity of vesicle size distribution, with lower PDI values indicating greater homogeneity of the formulation [5,8]. Vesicle size and PDI are commonly determined using dynamic light scattering (DLS) techniques [8].

1.2 Zeta Potential

Zeta potential indicates the surface charge and electrostatic stability of ethosomal vesicles [32,5]. Higher absolute zeta potential values contribute to enhanced formulation stability by preventing vesicle aggregation through electrostatic repulsion [32,10]. Zeta potential measurements are generally performed using electrophoretic light scattering methods [8].

1.3 Entrapment Efficiency

Entrapment efficiency represents the proportion of drug encapsulated within the ethosomal vesicles relative to the total drug content [1]. A high entrapment efficiency ensures effective drug loading and supports sustained drug release from the formulation. It is typically evaluated by separating the free drug from the vesicular system using techniques such as centrifugation, ultrafiltration, or dialysis, followed by quantitative drug analysis [1,20].

2. Physicochemical Evaluation of Ethosomal Emulgel

2.1 Appearance and Homogeneity

The ethosomal emulgel is visually inspected for parameters such as color, consistency, phase separation, grittiness, and overall homogeneity [13,29]. A smooth, uniform appearance indicates proper incorporation and even distribution of ethosomal vesicles within the emulgel matrix [29,15].

2.2 pH Measurement

pH is an important parameter affecting skin compatibility and formulation stability [29,16]. Ideally, the pH of ethosomal emulgels should be maintained within the range of 5.0-7.0 to minimize the risk of skin irritation and ensure patient safety [16,17]. The pH is measured using a calibrated digital pH meter [17].

2.3 Drug Content Uniformity

Drug content uniformity confirms the even distribution of the drug throughout the emulgel matrix, which is essential for dose accuracy and consistent therapeutic performance [33,29]. This parameter is determined by dissolving a known quantity of formulation in a suitable solvent, followed by analysis using UV-visible spectrophotometry or high-performance liquid chromatography (HPLC) [33,18].

3. Rheological and Mechanical Properties

3.1 Viscosity and Rheological Behavior

Viscosity significantly influences the spreadability, extrudability, and residence time of the emulgel on the skin surface [13,19]. Most ethosomal emulgels exhibit pseudoplastic (shear-thinning) behavior, which allows ease of application under shear stress while ensuring adequate retention at the site of application [19,20]. Viscosity measurements are commonly carried out using Brookfield or cone-and-plate viscometers [20].

3.2 Spreadability

Spreadability reflects the ease of application and overall patient acceptability of the formulation [14,21]. Adequate spreadability ensures uniform distribution of the drug over the skin surface, thereby enhancing therapeutic effectiveness [21,22]. It is typically assessed by measuring the distance or time required for the formulation to spread between two glass slides under a specified load [22].

3.3 Extrudability

Extrudability indicates the ease with which the emulgel can be expelled from collapsible tubes, directly influencing user convenience and compliance [21,23]. Satisfactory extrudability ensures consistent dosing during topical application [23].

4. *In Vitro* Drug Release Studies

In vitro drug release studies are performed to evaluate the release kinetics of the drug from the ethosomal emulgel formulation [33,24]. These studies are commonly conducted using Franz diffusion cells equipped with synthetic or semi-permeable membranes [24,25]. The resulting release profiles provide valuable insight into the sustained and controlled release characteristics of the formulation [25,26].

5. *Ex Vivo* Skin Permeation Studies

Ex vivo skin permeation studies using excised animal or human skin are carried out to assess the penetration and retention potential of ethosomal emulgels [1,4]. These studies consistently demonstrate significantly higher drug flux and enhanced skin deposition when compared with conventional gels and emulsions [6,27].

6. Skin Irritation and Sensitivity Studies

Skin irritation studies are conducted to evaluate the safety of ethosomal emulgels intended for topical application [16,28]. The formulation is assessed for signs of erythema and edema using suitable animal models or validated alternative in vitro methods [28,29]. A non-irritant profile confirms the suitability of the formulation for dermal use [29].

7. Stability Studies

Stability studies are performed to assess the physical, chemical, and microbiological stability of ethosomal emulgel formulations under various storage conditions [11,30]. Parameters such as vesicle size, pH, viscosity, drug content, and physical appearance are monitored over time [30,31]. These studies are generally conducted in accordance with International Council for Harmonisation (ICH) stability guidelines [31].

Advantages of Ethosomal Emulgel

Ethosomal emulgels are advanced topical and transdermal delivery systems that combine the penetration-enhancing ability of ethosomes with the favorable properties of gel-based formulations, offering clear advantages over conventional topical systems [1,20,35].

1. Enhanced skin penetration: It is achieved through the synergistic action of ethanol and deformable vesicles, which significantly improves drug permeation across the stratum corneum [1,4,7].

2. Improved drug solubility and entrapment: High ethanol content enhances solubility and drug loading for both hydrophilic and lipophilic drugs [1,8,32].

3. Controlled and sustained release: The emulgel matrix provides prolonged and regulated drug release, reducing dosing frequency [10,33].

4. Prolonged skin residence time: High viscosity and adhesiveness ensure extended contact with the skin, enhancing absorption [10,13,29].

5. Improved vesicle stability: Gel incorporation minimizes vesicle aggregation and ethanol loss, maintaining vesicular integrity [1,15,16].

6. Better patient compliance: Non-greasy texture and good spreadability improve cosmetic acceptability and adherence [10,17,18].

7. Formulation versatility: Suitable for a wide range of drugs and applicable for both dermal and transdermal delivery [2,19].

8. Reduced systemic side effects: Enhanced local targeting lowers systemic exposure and improves safety [20,21].

9. Bypass of first-pass metabolism: Transdermal delivery improves bioavailability of drugs subject to hepatic metabolism [22,23].

10. **Cost-effective and scalable:** Simple, reproducible preparation methods support industrial scale-up and commercialization[32,16,24].

Disadvantages of Ethosomal Emulgel

1. Skin irritation and sensitization: High ethanol content may cause skin dryness, erythema, irritation, or burning sensations, especially with repeated use or in sensitive individuals, due to disruption of the stratum corneum lipid barrier [6].

2. Unsuitability for irritant drugs: Ethanol-induced barrier disruption can enhance drug-related skin toxicity, limiting the use of ethosomal emulgels for inherently irritant or highly potent drugs during long-term therapy [7,32].

3. Vesicle instability: Ethosomal vesicles are prone to aggregation, fusion, and size variation during storage, which may affect drug release and permeation; ethanol evaporation can further compromise vesicle integrity [10,33].

4. Limited drug loading capacity: Structural limitations of ethosomes may restrict drug loading, particularly for macromolecules and highly hydrophilic drugs such as peptides and proteins[2,13,29].

5. Formulation and optimization complexity: Precise optimization of ethanol concentration, phospholipid content, surfactant ratio, and gel viscosity is required, as minor changes can significantly affect stability and permeation performance [15,17].

6. Scale-up and manufacturing challenges: Large-scale production is difficult due to vesicle sensitivity to processing conditions, potentially increasing manufacturing costs and limiting industrial scalability [33,18,19].

7. Limited clinical and regulatory data: Insufficient large-scale clinical studies and the absence of specific regulatory guidelines may delay clinical translation and commercialization [1,20,21].

8. Short shelf life: Ethanol volatility and vesicular degradation during storage, particularly under high temperature and humidity, may reduce shelf life and require specialized packaging [11,22,23].

9. Risk of drug leakage: Vesicle destabilization during storage or after incorporation into the

emulgel base may lead to drug leakage and dose inconsistency [10,24,25].

10. Higher formulation cost: The use of high-purity phospholipids, ethanol, and specialized processing techniques increases formulation cost compared with conventional topical gels or creams [19,26,27].

Applications of Ethosomal Emulgel

Ethosomal emulgels have emerged as a versatile and effective platform for topical and transdermal drug delivery, primarily due to their superior skin permeation capability, controlled drug release characteristics, and enhanced patient compliance [1,2].

1. Topical Treatment of Inflammatory and Pain Conditions

Ethosomal emulgels have been extensively investigated for the topical delivery of non-steroidal anti-inflammatory drugs (NSAIDs) and analgesics, providing enhanced skin penetration and prolonged drug retention at the site of action [4]. The ability of ethosomal vesicles to promote deeper drug deposition within inflamed tissues leads to improved therapeutic efficacy while minimizing systemic exposure and associated adverse effects compared with conventional gels and creams [4,5].

2. Dermatological and Cosmetic Applications

Ethosomal emulgels are widely utilized for the delivery of dermatological agents, including corticosteroids, antifungal agents, anti-acne drugs, and depigmenting agents [6,7]. Enhanced penetration of ethosomal carriers facilitates greater drug accumulation within the epidermal and dermal layers, making them particularly effective in the management of chronic skin disorders such as psoriasis, eczema, and acne vulgaris [7,8]. In cosmetic applications, ethosomal emulgels are employed for the delivery of antioxidants, vitamins, and anti-aging agents, enabling deeper skin nourishment and prolonged cosmetic benefits [32,10].

3. Transdermal Systemic Drug Delivery

Ethosomal emulgels are suitable for the transdermal administration of drugs intended for systemic action, as ethosomes are capable of transporting therapeutic agents across the stratum corneum into the systemic circulation [1,11]. This route of administration helps bypass hepatic first-pass metabolism, maintain stable plasma drug concentrations, and reduce dosing frequency [11,33].

4. Delivery of Poorly Permeable Drugs

Ethosomal emulgels are particularly advantageous for drugs exhibiting poor skin permeability, low bioavailability, or unfavorable physicochemical properties [2,13]. The combined effect of ethanol-induced lipid fluidization and the flexibility of vesicular membranes enhance drug partitioning into skin layers, thereby improving therapeutic outcomes [13,29].

5. Antimicrobial and Antifungal Therapy

Ethosomal emulgels have demonstrated enhanced efficacy in the topical delivery of antimicrobial and antifungal agents by increasing drug penetration into deeper skin layers and infected tissues [6,15]. This improved delivery results in higher local drug concentrations and more effective eradication of microbial infections compared with conventional topical formulations [15,16].

6. Delivery of Hormones and Peptides

Ethosomal emulgels have also been explored for the transdermal delivery of hormones and peptide-

based drugs, owing to their ability to enhance the permeation of macromolecules across the skin barrier [33,17]. These systems offer a non-invasive alternative to injectable formulations and significantly improve patient compliance [17,18].

7. Targeted Localized Therapy

Ethosomal emulgels are effective in achieving targeted localized drug delivery to the skin and underlying tissues, thereby minimizing systemic exposure and reducing the risk of adverse effects [19]. This characteristic is particularly beneficial for chronic topical therapies that require prolonged treatment durations [19,20].

8. Sustained and Controlled Drug Release

The emulgel matrix provides a controlled release environment, while ethosomal vesicles facilitate deeper drug penetration, making ethosomal emulgels suitable for sustained topical and transdermal therapy [21,22]. This dual functionality enhances therapeutic efficacy and reduces dosing frequency [22,23].

9. Wound Healing and Skin Regeneration

Ethosomal emulgels are being investigated for wound healing applications due to their ability to deliver antimicrobial, anti-inflammatory, and growth-promoting agents directly to the wound site [24,25]. Improved drug penetration and prolonged residence time at the wound surface contribute to accelerated wound closure and enhanced tissue regeneration [25,26].

10. Vaccines and Immunological Applications

Recent studies indicate the potential application of ethosomal emulgels in transcutaneous immunization, wherein antigens are delivered through the skin to elicit immune responses [27,28]. This strategy offers a painless, needle-free alternative to conventional vaccination methods and may improve patient acceptance and compliance [28,29].

CONCLUSION

Ethosomal emulgels represent a significant advancement in topical and transdermal drug delivery by synergistically combining the penetration-enhancing properties of ethanol-rich, deformable ethosomal vesicles with the stability and patient-friendly characteristics of emulgel systems. This hybrid approach effectively addresses major limitations of conventional topical formulations, including poor stratum corneum permeability, limited residence time, and inconsistent drug release. The ethanol-mediated fluidization of skin lipids, coupled with vesicular deformability, enables deeper dermal penetration and improved bioavailability of both hydrophilic and lipophilic drugs, while the emulgel matrix ensures controlled release, enhanced stability, and prolonged skin contact. Comprehensive formulation strategies and evaluation parameters discussed in this review highlight the versatility and robustness of ethosomal emulgels across a wide range of therapeutic applications, including dermatological, antimicrobial, anti-inflammatory, and transdermal systemic therapies. Despite challenges related to ethanol-induced irritation, formulation complexity, and limited clinical validation, ongoing advancements in nanotechnology and formulation optimization continue to strengthen their translational potential. Overall, ethosomal emulgels emerge as promising, non-invasive delivery platforms capable of improving therapeutic outcomes and patient compliance, warranting further clinical investigation and industrial development.

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