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ETHOSOMES IN TRANSDERMAL DRUG DELIVERY: FORMULATION STRATEGIES, SKIN-PENETRATION MECHANISMS, CHARACTERIZATION AND RECENT THERAPEUTIC APPLICATIONS

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ABSTRACT

Transdermal drug delivery systems (TDDS) have emerged as an attractive alternative to conventional oral and parenteral routes because they can provide sustained drug delivery, improve patient compliance, and, for suitable drugs, reduce gastrointestinal degradation and first-pass hepatic metabolism. However, the stratum corneum, the outermost layer of the skin, represents a major barrier to the penetration of most therapeutic molecules. Vesicular nanocarriers have therefore been extensively investigated to improve drug transport across the skin. Ethosomes are deformable phospholipid-based vesicles containing a relatively high concentration of ethanol, which distinguishes them from conventional liposomes. Ethanol modifies the organization and fluidity of skin lipids and contributes to the flexibility of the vesicular membrane, facilitating penetration into deeper skin layers. Ethosomes can accommodate both hydrophilic and lipophilic active pharmaceutical ingredients and have been investigated for topical, dermal and systemic delivery. Their composition generally includes phospholipids, ethanol, water and the drug, while cholesterol, edge activators and other functional excipients may be incorporated depending on the formulation objective. Various preparation techniques, including cold method, hot method, ethanol injection and thin-film hydration, have been reported. Critical quality attributes include vesicle size, polydispersity index, zeta potential, morphology, entrapment efficiency, drug loading, in-vitro release, ex-vivo permeation and stability. Recent research has expanded ethosomal applications into anti-inflammatory, antimicrobial, antifungal, anticancer, cardiovascular, metabolic, neurological and cosmetic delivery. Nevertheless, challenges associated with long-term stability, ethanol concentration, formulation reproducibility, scale-up, skin irritation, regulatory requirements and clinical translation remain. This review discusses the composition, types, preparation methods, mechanism of skin penetration, characterization, advantages, limitations, therapeutic applications and future prospects of ethosomes as advanced transdermal drug delivery carriers.

KEYWORDS: Ethosomes, transdermal drug delivery, phospholipid vesicles, skin penetration, nanocarriers, vesicular drug delivery, dermal delivery.

1. INTRODUCTION

Drug delivery through the skin has attracted considerable interest because the skin is easily accessible and can provide both local and systemic delivery. Transdermal delivery can offer several advantages over conventional oral administration, including avoidance of gastrointestinal degradation, reduced exposure to first-pass metabolism, prolonged drug input and improved patient convenience. However, the successful development of transdermal formulations is restricted by the protective barrier function of the skin, particularly the stratum corneum.[1]

The stratum corneum consists mainly of corneocytes embedded in an organized lipid matrix and is frequently described as the principal barrier to percutaneous drug transport. Many therapeutic molecules, especially hydrophilic compounds, macromolecules and drugs with unsuitable physicochemical properties, exhibit inadequate skin permeability. Consequently, several approaches have been developed to improve transdermal transport, including chemical permeation enhancers, iontophoresis, microneedles, chemical modification and vesicular drug delivery systems.[2]

Lipid-based vesicles have become particularly important because they can encapsulate drugs with different physicochemical properties and can interact with biological membranes. Conventional liposomes, although useful for topical delivery, may have limited ability to penetrate intact stratum corneum. This limitation encouraged the development of more flexible vesicular systems such as transfersomes and ethosomes.[3]

Ethosomes were introduced as soft, deformable vesicles containing phospholipids, ethanol and water. The high ethanol content is a defining characteristic of the system and contributes to improved skin permeability. Ethanol can interact with the lipid components of the stratum corneum, increase lipid fluidity and facilitate drug transport. At the same time, ethanol contributes to the flexibility of the vesicular membrane, allowing the vesicles to deform and penetrate narrow intercellular pathways.[4]

The potential of ethosomes has been demonstrated for a wide variety of therapeutic agents. Early investigations reported delivery of molecules including acyclovir, minoxidil, testosterone, propranolol and other compounds. Subsequent research has explored ethosomal delivery for anti-inflammatory, antimicrobial, antifungal, anticancer and other therapeutic applications.[5]

Recent reviews have further emphasized the potential of ethosomes for chronic and systemic disorders, while also identifying stability, scale-up and clinical translation as important challenges. Therefore, continued optimization of composition, manufacturing and performance evaluation is necessary for broader pharmaceutical application.[6]

2. Ethosomes: Concept and Definition

Ethosomes are lipid-based, soft and deformable vesicular carriers designed primarily to enhance the dermal and transdermal delivery of therapeutic agents. They are characterized by the presence of phospholipids, water and a relatively high concentration of ethanol. Depending on the formulation, additional components such as cholesterol, surfactants or edge activators may be incorporated.

The distinctive feature of ethosomes is their ethanol-rich environment. Conventional liposomes generally contain phospholipids and aqueous phases, whereas ethosomes contain substantially more ethanol. Classical descriptions of ethosomal systems commonly report ethanol concentrations in the approximate range of 20–45%, although the optimal concentration depends on formulation composition and intended application.[7]

The incorporation of ethanol serves several functions. First, it acts as a penetration-enhancing component by modifying the lipid organization of the stratum corneum. Second, it contributes to the flexibility and deformability of ethosomal vesicles. Third, it can influence vesicle size, surface charge, drug entrapment and release characteristics.

The combination of these properties allows ethosomes to function as carriers rather than simply acting as hydroalcoholic drug solutions. Their ability to carry both hydrophilic and lipophilic compounds makes them attractive for the delivery of a broad range of therapeutic agents.[8]

3. Composition of Ethosomes

The composition of an ethosomal formulation is a critical determinant of its physicochemical characteristics, drug encapsulation and skin permeability.

3.1 Phospholipids

Phospholipids form the primary structural component of ethosomal vesicles. Commonly investigated phospholipids include phosphatidylcholine and related phospholipid materials. They arrange themselves into bilayer structures around the aqueous phase.

The type, purity and concentration of phospholipid can influence vesicle formation, size, membrane rigidity, drug entrapment and stability. Higher phospholipid concentrations may increase the amount of drug incorporated into vesicles but can also affect viscosity and particle size.

3.2 Ethanol

Ethanol is the defining component of ethosomes. It acts as both a formulation component and a penetration enhancer. Ethanol can increase the fluidity of the stratum-corneum lipid domains and may reduce the resistance encountered by drug molecules during skin penetration.

Ethanol also influences the physical properties of the vesicle. Increasing ethanol concentration may alter vesicle size, surface charge, membrane fluidity and deformability. However, excessively high concentrations may destabilize vesicles or cause undesirable skin effects. Consequently, ethanol concentration must be optimized rather than maximized.[9]

3.3 Water

Water constitutes the aqueous phase of the system and participates in vesicle formation. Its concentration influences the overall solvent environment and can affect vesicle structure and drug distribution.

3.4 Cholesterol

Cholesterol may be incorporated into selected formulations to modify membrane rigidity and stability. It can reduce excessive membrane fluidity and influence drug leakage. However, an excessive amount may reduce vesicle deformability and consequently alter skin penetration.

3.5 Edge Activators and Surfactants

Some advanced ethosomal systems incorporate surfactants or edge activators to increase deformability. These components are particularly important in systems such as transethosomes, in which ethanol is combined with an edge activator.[10]

3.6 Active Pharmaceutical Ingredient

The drug can be hydrophilic, lipophilic or amphiphilic depending on the characteristics of the vesicular system. Drug physicochemical properties influence entrapment efficiency, release, partitioning and skin permeation.

Table 1: Major components of ethosomes and their functions.

Component	Major function	Influence on formulation
Phospholipid	Forms vesicular bilayer	Influences size, stability and drug entrapment
Ethanol	Penetration enhancer and membrane fluidizer	Improves skin permeation and vesicle flexibility
Water	Aqueous phase	Supports vesicle formation
Cholesterol	Membrane-modifying agent	Can improve membrane stability and reduce leakage
Edge activator	Enhances deformability	Improves flexibility and membrane passage
Drug	Therapeutic active	Determines loading, release and therapeutic performance
Buffer/other excipients	pH and formulation control	Supports stability and compatibility

4. Types of Ethosomal Systems

Several ethanol-containing vesicular systems have been developed.

4.1 Classical Ethosomes

Classical ethosomes generally consist of phospholipids, ethanol, water and the active drug. They are primarily designed to enhance dermal or transdermal drug delivery.

4.2 Binary Ethosomes

Binary ethosomes contain ethanol along with another alcohol or related component. The additional component can modify vesicle properties and potentially improve drug delivery.

4.3 Transethosomes

Transethosomes combine the characteristics of ethosomes and transfersomes. They generally contain phospholipids, ethanol and an edge activator. The combination can provide enhanced deformability and skin penetration.[11]

4.4 Other Modified Ethosomal Systems

Researchers have explored surface modification, incorporation of polymers, incorporation into hydrogels and combination with other nanocarriers. Such modifications are intended to improve residence time, stability, targeting or controlled release.

5. Mechanism of Skin Penetration

The effectiveness of ethosomes is closely associated with their interaction with the stratum corneum.

5.1 Modification of Stratum-Corneum Lipids

Ethanol can interact with lipid components in the stratum corneum and increase their fluidity. This can temporarily reduce the barrier resistance of the skin and facilitate movement of the drug and vesicles through the superficial skin layers.[12]

5.2 Increased Vesicle Deformability

Ethosomal membranes are relatively flexible because of their ethanol-rich composition. The vesicles can undergo deformation when exposed to narrow skin pathways. This property distinguishes them from many conventional rigid vesicles.

5.3 Intercellular Penetration

Drug and vesicular components may move through pathways between corneocytes. Modification of the lipid matrix by ethanol can facilitate movement through these intercellular regions.

5.4 Transcellular Transport

Some drug molecules may partition into and move across corneocytes. The relative contribution of this route depends on the physicochemical properties of the drug and formulation.[13]

5.5 Transfollicular Transport

Hair follicles and associated structures may provide additional pathways for penetration, particularly for appropriately sized particulate systems. However, the contribution of the follicular route varies with formulation and experimental conditions.

5.6 Drug Deposition and Reservoir Formation

Ethosomal formulations can increase drug deposition within skin layers. Depending on the drug and formulation, this may provide a local reservoir and prolonged exposure.

6. Methods of Preparation

The preparation method can significantly influence vesicle size, drug entrapment, morphology, stability and reproducibility.

6.1 Cold Method

The cold method is one of the commonly described techniques for preparing ethosomes. In general, phospholipid is dissolved or dispersed in ethanol, followed by gradual addition of the aqueous phase under controlled stirring. The drug may be incorporated depending on its solubility and formulation design.

The method is attractive because it does not require prolonged exposure to elevated temperatures and is relatively simple for laboratory-scale preparation.[14]

6.2 Hot Method

In the hot method, the aqueous and lipid phases are separately heated to a controlled temperature before mixing. The method can facilitate dispersion of lipid components but may not be suitable for thermolabile drugs.

6.3 Ethanol Injection Method

In ethanol injection, the lipid components are dissolved in ethanol and injected into an aqueous phase under controlled stirring. Rapid mixing results in spontaneous formation of vesicles.

6.4 Thin-Film Hydration

In thin-film hydration, phospholipids and other lipid components are dissolved in an organic solvent and subsequently deposited as a thin film after solvent evaporation. The film is then hydrated with an appropriate aqueous/ethanolic phase containing the drug or other components.

6.5 Sonication and Extrusion

Post-preparation processing such as sonication or membrane extrusion can be used to reduce vesicle size and improve size distribution. However, excessive mechanical energy may influence drug stability or vesicle integrity.[15]

Table 2: Preparation methods of ethosomes.

Method	Basic principle	Advantages	Limitations
Cold method	Mixing lipid/ethanol phase with aqueous phase at controlled temperature	Simple, suitable for many laboratory formulations	Requires optimization of mixing
Hot method	Heated lipid and aqueous phases are combined	Useful for improved lipid dispersion	Not ideal for thermolabile drugs
Ethanol injection	Ethanolic lipid phase injected into aqueous phase	Relatively simple and rapid	Particle-size control can require optimization
Thin-film hydration	Lipid film is formed and subsequently hydrated	Widely applicable to vesicular systems	Multiple processing steps
Sonication	Mechanical energy reduces vesicle size	Can reduce particle size	Excessive energy may cause instability
Extrusion	Vesicles passed through membranes	Improved size uniformity	Requires specialized equipment

7. Factors Affecting Ethosomal Formulation

7.1 Ethanol Concentration

Ethanol concentration is one of the most important formulation variables. Increasing ethanol may enhance membrane flexibility and skin penetration up to an optimum concentration. Excessive ethanol, however, may destabilize the vesicles or increase irritation.[16]

7.2 Phospholipid Concentration

Phospholipid concentration affects vesicle formation, membrane structure, drug entrapment and particle size. Optimization is therefore necessary to obtain a stable and efficient formulation.

7.3 Drug Concentration

Increasing drug concentration may improve loading up to the solubility and encapsulation limit. Beyond this level, precipitation or drug leakage may occur.

7.4 Cholesterol Concentration

Cholesterol can modify membrane packing and reduce leakage. However, high concentrations may decrease membrane flexibility.

7.5 Preparation Conditions

Mixing speed, hydration time, temperature, sonication energy and processing time can all affect the final vesicular properties.[17]

7.6 Drug Physicochemical Properties

Molecular weight, log P, aqueous solubility, ionization and melting point can influence the ability of a drug to partition into the vesicle and subsequently cross the skin.

8. Characterization of Ethosomes

Comprehensive characterization is necessary to establish formulation quality and predict performance.

8.1 Vesicle Size

Particle size is commonly determined using dynamic light scattering. Vesicle size can influence skin deposition, physical stability and drug release.

8.2 Polydispersity Index

PDI describes the distribution of particle sizes. A lower PDI generally indicates a more uniform vesicle population.

8.3 Zeta Potential

Zeta potential provides information about surface electrical characteristics and can provide an indication of electrostatic stability. However, zeta potential alone should not be considered a complete predictor of long-term physical stability.[18]

8.4 Morphology

Transmission electron microscopy, scanning electron microscopy or atomic force microscopy can be used to evaluate vesicle shape and morphology.

8.5 Entrapment Efficiency

Entrapment efficiency represents the proportion of drug associated with the vesicular system relative to the total amount of drug used.

A commonly used expression is:

Entrapment efficiency (%) = (Entrapped drug / Total drug added) × 100

8.6 Drug Loading

Drug loading indicates the quantity of drug associated with a given amount of formulation or lipid material.

8.7 In-Vitro Drug Release

Drug release can be studied using appropriate diffusion or membrane-based techniques. Release profiles can subsequently be fitted to mathematical models such as zero-order, first-order, Higuchi and Korsmeyer–Peppas models where appropriate.

8.8 Ex-Vivo Skin Permeation

Ex-vivo studies using animal or human skin models can evaluate cumulative drug permeation, flux, permeability coefficient and skin retention.

8.9 Skin Deposition

Drug retained in different skin layers can be quantified to determine whether the formulation promotes local deposition or transdermal transport.[19]

8.10 Stability Studies

Stability studies should evaluate changes in particle size, PDI, zeta potential, drug content, entrapment efficiency, appearance and leakage under appropriate storage conditions.

Table 3: Characterization parameters of ethosomes.

Parameter	Common technique	Importance
Vesicle size	Dynamic light scattering	Determines size distribution and influences delivery
PDI	Dynamic light scattering	Indicates size uniformity
Zeta potential	Electrophoretic light scattering	Provides surface-charge information
Morphology	TEM/SEM/AFM	Determines vesicle shape and structure
Entrapment efficiency	Centrifugation + analytical assay	Measures incorporated drug
Drug content	UV/Vis/HPLC	Confirms dose and content uniformity
In-vitro release	Dialysis/diffusion methods	Evaluates drug-release behavior
Ex-vivo permeation	Franz diffusion cell	Determines skin permeation
Skin deposition	Extraction + analytical assay	Determines drug retained in skin
Stability	Storage studies	Determines physical and chemical stability

9. Advantages of Ethosomes[20]

Ethosomes offer several potential advantages over conventional vesicular and transdermal systems:

1. Enhanced skin penetration.
2. Ability to deliver hydrophilic and lipophilic drugs.
3. High flexibility and deformability.
4. Potential for local and systemic drug delivery.
5. Relatively simple preparation methods.
6. Potential improvement in drug bioavailability.
7. Ability to increase drug deposition in skin.
8. Potential reduction in dosing frequency for suitable drugs.
9. Compatibility with gels, creams and other topical dosage forms.
10. Potential application to a wide range of therapeutic classes.

10. Limitations and Challenges[21]

Despite their advantages, ethosomes have several limitations.

10.1 Stability

Physical instability, vesicle aggregation, drug leakage and changes in particle size can occur during storage. Ethanol concentration and phospholipid composition must therefore be carefully optimized.

10.2 Skin Irritation

Because ethanol acts as a strong penetration enhancer, high concentrations may cause dryness, irritation or discomfort in susceptible individuals.

10.3 Formulation Optimization

Small changes in phospholipid, ethanol, cholesterol and drug concentration can significantly modify formulation performance. Consequently, systematic optimization is essential.

10.4 Scale-Up

Laboratory-scale preparation may not directly translate to industrial production. Mixing, temperature control, particle-size reduction and solvent management require reproducible large-scale processes.

10.5 Reproducibility

Differences in phospholipid source, ethanol concentration, preparation equipment and characterization methodology can make comparison between studies difficult.

10.6 Limited Clinical Evidence

Although numerous preclinical studies demonstrate enhanced permeation, comparatively fewer ethosomal systems have progressed to well-established clinical products. Reviews have therefore emphasized the need for stronger clinical and translational evidence.

11. Pharmaceutical and Therapeutic Applications

11.1 Anti-Inflammatory Drugs

Ethosomes have been investigated for delivery of anti-inflammatory drugs because improved penetration may increase drug concentration at the site of inflammation. Local delivery may also reduce the need for high systemic exposure.

11.2 Antifungal Therapy

Antifungal drug delivery is an important area of ethosomal research. Improved penetration and drug retention in skin may be useful for treating superficial fungal infections. A 2026 systematic review specifically highlighted the potential of ethosomal nanocarriers for transdermal antifungal delivery and noted improvements in permeation and antifungal performance across the evaluated literature.

11.3 Antiviral Drugs[22]

Acyclovir is one of the historically investigated drugs in ethosomal delivery. Early clinical work reported improved therapeutic outcomes with an ethosomal acyclovir formulation compared with conventional treatment in the investigated setting.

11.4 Anticancer Drug Delivery

Ethosomal systems have been investigated for delivering anticancer agents through the skin. Although transdermal cancer therapy is challenging, local delivery may be relevant for selected superficial tumors or for drugs requiring localized action. More clinical research is necessary before broad therapeutic application.

11.5 Cardiovascular Drugs[23]

Drugs used for cardiovascular conditions have been explored using ethosomal systems to potentially provide sustained systemic delivery and reduce fluctuations in plasma drug concentration.

11.6 Antidiabetic and Metabolic Applications

Recent literature has expanded ethosomal research toward diabetes and other metabolic diseases. The objective is to explore non-invasive delivery and improve drug exposure while potentially reducing limitations associated with oral administration.

11.7 Neurological Applications

The possibility of systemic delivery through the skin has generated interest in drugs used for neurological disorders. However, the ability to achieve therapeutically relevant systemic concentrations remains drug-specific and requires rigorous pharmacokinetic evaluation.

11.8 Analgesic and Anti-Arthritic Delivery[24]

Ethosomes have been investigated for localized delivery of analgesic and anti-inflammatory drugs to painful joints and tissues.

11.9 Peptides and Macromolecules

The skin is a particularly challenging route for macromolecules. Although ethosomes may improve delivery of selected larger molecules, substantial barriers remain and combination technologies may be required.

11.10 Cosmetic Applications

Ethosomes have also been explored for delivery of cosmetic and cosmeceutical ingredients, including antioxidants and botanical compounds. Enhanced deposition in skin can potentially improve the effectiveness of selected cosmetic actives.

Table 4: Representative therapeutic applications of ethosomal systems.

Therapeutic area	Representative drug/active investigated	Potential benefit
Antiviral	Acyclovir	Enhanced dermal delivery and local antiviral activity
Anti-inflammatory	NSAIDs and other anti-inflammatory agents	Improved local penetration
Antifungal	Various antifungal agents	Enhanced skin permeation and retention
Anticancer	Selected anticancer agents	Potential localized or systemic delivery
Cardiovascular	Selected cardiovascular drugs	Potential sustained systemic delivery
Antidiabetic	Selected antidiabetic agents	Exploration of non-invasive systemic delivery
Neurological	CNS-active drugs	Potential systemic delivery through skin
Analgesic	Analgesic agents	Local drug deposition and prolonged action
Herbal/cosmeceutical	Phytoconstituents	Improved skin deposition and bioavailability

12. Ethosomal Gels and Other Dosage Forms[25]

Although ethosomes can be administered as vesicular dispersions, incorporation into secondary dosage forms may improve practical usability.

12.1 Ethosomal Gel

Ethosomal dispersions can be incorporated into suitable hydrophilic or hydroalcoholic gels. The gel can improve viscosity, residence time and ease of application while maintaining the vesicular delivery mechanism.

12.2 Ethosomal Cream

Cream-based systems may be useful for dermatological and cosmetic applications. However, compatibility between the vesicles and cream components must be carefully evaluated.

12.3 Ethosomal Patch[26]

Integration of ethosomes with transdermal patches may provide controlled application and improve handling. The interaction between vesicles, adhesive and backing layers must be investigated.

12.4 Hydrogel-Integrated Ethosomes

Combination of ethosomes with hydrogels is increasingly attractive because the vesicle can provide enhanced penetration while the hydrogel can act as a local reservoir.

13. Ethosomes Compared with Other Vesicular Systems

Conventional liposomes, transfersomes and ethosomes are related lipid-based delivery systems but differ in their composition and mechanism.

Liposomes

Liposomes are phospholipid vesicles that can encapsulate hydrophilic and lipophilic compounds. However, conventional liposomes may have limited penetration across intact stratum corneum.[27]

Transfersomes

Transfersomes contain phospholipids and edge activators that impart high deformability. Their penetration is strongly associated with membrane flexibility and the ability to deform under a hydration gradient.

Ethosomes

Ethosomes use high ethanol content to increase skin permeability and vesicle flexibility. Ethanol is therefore a key functional component.

Transethosomes

Transethosomes combine ethanol with an edge activator and may provide greater deformability than conventional ethosomes.[28]

Table 5: Comparison of major vesicular systems for transdermal delivery.

Characteristic	Conventional liposomes	Transfersomes	Ethosomes	Transethosomes
Phospholipids	Yes	Yes	Yes	Yes
High ethanol content	No	Usually no	Yes	Yes
Edge activator	No	Yes	Usually no	Yes
Deformability	Low–moderate	High	High	Very high
Skin penetration	Limited–moderate	High	High	Potentially very high
Major mechanism	Vesicular deposition	Elastic deformation	Ethanol-mediated penetration + deformation	Ethanol + elastic deformation
Main advantage	Versatile encapsulation	High deformability	Enhanced skin penetration	Combined penetration mechanisms
Major challenge	Limited deep penetration	Formulation stability	Ethanol-related stability/irritation	Greater formulation complexity

14. Recent Advances in Ethosomal Drug Delivery

The field has moved beyond conventional ethosomes toward multifunctional and optimized systems.

14.1 Phytochemical-Loaded Ethosomes

Poor aqueous solubility and limited skin permeability of many phytoconstituents make them attractive candidates for ethosomal delivery. Encapsulation may improve dispersion and skin deposition.

14.2 Combination Therapy

Ethosomes can potentially accommodate more than one active component, allowing combination treatment where appropriate. Such systems require careful evaluation of drug compatibility and release.

14.3 Surface-Modified Ethosomes[29]

Surface modification may be used to alter interaction with skin or biological tissues. Functionalization strategies could potentially improve targeting, although their clinical relevance requires validation.

14.4 Ethosomes for Chronic Diseases

Recent work has investigated ethosomal delivery for chronic diseases such as diabetes, cardiovascular disorders, arthritis and neurological disorders. This represents a shift from conventional topical applications toward systemic therapeutic applications.

14.5 Antifungal Resistance[30]

The 2026 literature has specifically highlighted ethosomal delivery as a potential strategy for improving antifungal penetration and activity, while emphasizing the need for standardized experimental protocols and clinical validation.

14.6 Quality-by-Design Approach[31]

Quality-by-Design and Design of Experiments approaches can be used to systematically investigate formulation variables such as ethanol concentration, phospholipid concentration, drug concentration and processing conditions. This can improve formulation robustness and facilitate scale-up.

14.7 Combination with Hydrogels

Ethosome-hydrogel systems combine the penetration-enhancing properties of vesicles with the residence and application advantages of hydrogels.

15. Safety Considerations[32]

Safety evaluation is essential before clinical translation. Although ethosomes are generally constructed from materials that have extensive pharmaceutical and cosmetic use, the complete formulation must be evaluated rather than assuming safety based only on individual excipients.

Important safety assessments include:

- Skin irritation studies.
- Skin sensitization studies.
- Cytotoxicity studies.
- Histopathological evaluation.
- Repeated-dose dermal exposure.

- Systemic toxicity where systemic delivery is intended.
- Evaluation of ethanol-related irritation.
- Assessment of long-term formulation stability.

The amount of ethanol, drug concentration, phospholipid composition and application frequency can influence tolerability.[33]

16. Future Perspectives

Ethosomes have considerable potential as advanced transdermal carriers, but their future development depends on overcoming several formulation and translational barriers.

Future research should focus on developing more stable formulations with reproducible manufacturing characteristics. Standardized methods for evaluating skin permeation and drug deposition would allow more meaningful comparison between studies.[34]

The application of Quality-by-Design principles can help identify critical formulation and process variables. Advanced analytical techniques may also provide better understanding of vesicle structure, drug localization and interactions with the skin barrier.[35]

The combination of ethosomes with hydrogels, microneedles, patches or other nanocarriers may provide additional opportunities for controlled and targeted delivery. However, combining technologies also increases formulation complexity and regulatory requirements.[36]

Artificial intelligence and computational formulation optimization could potentially assist in predicting the relationship between composition and vesicle properties. Machine-learning approaches may eventually help identify optimal combinations of phospholipid, ethanol and drug concentrations.

For systemic applications, future research should increasingly emphasize pharmacokinetic and pharmacodynamic studies rather than relying only on in-vitro permeation results. Similarly, clinical studies should evaluate not only enhanced skin permeation but also clinically meaningful therapeutic outcomes.[37]

CONCLUSION

Ethosomes represent an important class of flexible phospholipid-based vesicular carriers for dermal and transdermal drug delivery. Their characteristic high ethanol content provides a dual advantage by modifying the lipid organization of the stratum corneum and increasing vesicle flexibility. These properties can improve drug penetration, skin deposition and, for appropriate drugs, systemic delivery. Ethosomes can accommodate diverse therapeutic agents and have been investigated in antiviral, antifungal, anti-inflammatory, analgesic, anticancer, cardiovascular, metabolic, neurological and cosmetic applications.

Despite promising laboratory and preclinical findings, ethosomal delivery remains associated with challenges including formulation stability, ethanol-related irritation, manufacturing reproducibility, scale-up and limited clinical translation. The recent expansion of research into chronic diseases, antifungal therapy and multifunctional nanocarriers demonstrates continuing interest in the technology. Future development should emphasize standardized

characterization, Quality-by-Design approaches, robust stability studies, industrial-scale manufacturing and well-designed clinical investigations. With appropriate optimization and regulatory development, ethosomes may contribute significantly to the next generation of non-invasive drug delivery systems.

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