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ETHOSOMES AS ADVANCED DRUG CARRIERS: INSIGHTS INTO DESIGN AND THERAPEUTIC POTENTIAL

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ABSTRACT

Ethosomes are advanced lipid-based vesicular systems designed to enhance transdermal and topical drug delivery. These nanosized vesicles, composed of phospholipids, ethanol and water, enable deep skin penetration for both hydrophilic and lipophilic drugs. This review highlights key characterization techniques, including vesicle size and zeta potential analysis (DLS), vesicle shape assessment (TEM) and transition temperature evaluation (DSC). Entrapment efficiency is determined via ultracentrifugation, while drug content is analyzed using HPLC. Surface tension measurement, vesicle stability and skin permeation studies (CLSM) provide further insights into ethosomal properties. Ethosomes have significant applications in pilosebaceous targeting, transdermal hormone delivery, DNA and gene delivery, anti-inflammatory therapy and treatment of psoriasis. Their ability to enhance solubility, stability and bioavailability makes them a promising platform for pharmaceutical and cosmeceutical drug delivery. Future research should address formulation stability and targeted delivery strategies to expand clinical applications.

KEYWORDS: Ethosomes, transdermal drug delivery, vesicular systems, skin penetration, entrapment efficiency, cosmeceuticals, lipid-based nanoparticles, pilosebaceous targeting, bioavailability enhancement, pharmaceutical applications.

INTRODUCTION

In recent years, drug delivery has been revolutionized by the development of nanosized vesicular carrier systems. These advanced systems have demonstrated remarkable effectiveness in overcoming the limitations of traditional drug delivery methods.[1]

The transdermal route has become a widely utilized method for delivering chemical drugs and natural compounds to treat various skin conditions, such as skin diseases and premature aging. This approach offers several advantages over oral administration, including bypassing first-pass metabolism, reducing fluctuations in drug plasma levels, and providing localized, targeted delivery. These benefits result in fewer side effects, improved therapeutic outcomes, and enhanced patient compliance.[2]

Transdermal drug delivery systems encompass various dosage forms, including gels, emulgels, nanoemulgels, and patches. However, one of the primary challenges of delivering medications through the skin is the low permeability of drugs across the skin barrier, which can lead to reduced transdermal flux. To address this, enhancing drug penetration has become a critical goal, achievable through various strategies, including the use of penetration enhancers.

Ethanol is among the most widely used penetration enhancers, known for its ability to improve drug transport through the skin and facilitate percutaneous diffusion. More recently, innovative topical drug delivery systems incorporating ethanol, such as ethosomes, have been developed to overcome these limitations and enhance therapeutic efficacy.[3][4]

ETHOSOMES

Ethosomes are lipid vesicles composed of phospholipids, alcohol, and water. The alcohol component, typically ethanol or isopropyl alcohol, is present in higher concentrations compared to water. The inclusion of ethanol within the lipid bilayer enhances the carrier's ability to penetrate the stratum corneum, enabling effective local and systemic delivery of both hydrophilic and lipophilic compounds. The size of ethosomes typically ranges from several nanometre's (nm) to microns (μ).[5]

Ethosomes are non-invasive drug delivery systems designed to facilitate the deep penetration of medications into the epidermal layers and/or the bloodstream. These flexible, soft vesicles are specifically engineered to enhance the delivery of active agents. For many years, the role of vesicles in cellular communication and particle transportation has been well established.

Vesicles also offer the ability to regulate drug release over an extended period, protect medications from immune responses or other elimination mechanisms, and deliver the optimal drug dosage while maintaining a

consistent concentration over time. One of the significant advancements in vesicle research was the discovery of ethosomes, a derivative of traditional vesicles, which further improved drug delivery efficiency.[6][7]

TYPES OF ETHOSOMES

Ethosomes can be categorized based on their composition into various types, including classical ethosomes, binary ethosomes, transethosomes, composite phospholipid ethosomes, and active targeting ethosomes as shown in fig 1. Each type has unique characteristics and benefits.

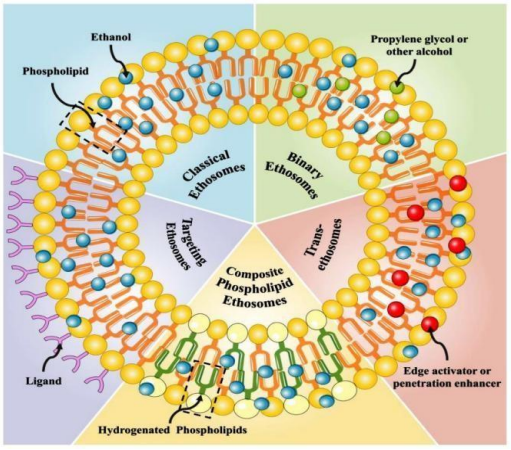

Fig 1: Types of ethosome.

1. Classical Ethosomes

Classical ethosomes are lipid-based vesicles composed of phospholipids, water, and a high concentration of ethanol, typically up to 45% w/w. This unique composition distinguishes them from traditional liposomes and enhances their ability to deliver drugs through the skin.[8] The high ethanol content disrupts the lipid structure of the stratum corneum, increasing its fluidity and permeability, which facilitates deeper penetration of the ethosomal vesicles into the skin layers. Additionally, classical ethosomes are characterized by their smaller size, negative zeta potential, and higher entrapment efficiency compared to conventional liposomes, making them more effective for transdermal drug delivery.[9][10]

2. Binary Ethosomes

Binary ethosomes are an advanced form of ethosomal vesicles designed to enhance transdermal drug delivery. They are composed of phospholipids, ethanol, water, and an additional alcohol, typically propylene glycol or isopropyl alcohol. The inclusion of this secondary alcohol improves the flexibility and stability of the vesicles, facilitating deeper penetration into the skin layers. Studies have demonstrated that binary ethosomes can significantly increase the transdermal flux of various drugs, making them a promising carrier for transdermal drug delivery systems.[11][12]

3. Transethosomes (TEs)

Transethosomes (TEs) represent a more advanced generation of ethosomal systems, combining the benefits of both ethosomes and traditional transdermal delivery systems into a single formulation.[13] The development of TEs involves incorporating a penetration enhancer or surfactant—such as Tween 20, Span 60, sodium cholate, or sodium deoxycholate—into the traditional ethosomal structure.[14] These surfactants are integrated into the phospholipid bilayer, increasing the spacing between phospholipid molecules, disrupting the bilayer's structure, and enhancing its fluidity.

When the skin becomes hydrated, the TEs deform and penetrate the stratum corneum, facilitating improved transdermal drug absorption.[11]

4. Composite phospholipid ethosomes (CE)

Composite phospholipid ethosomes are an advanced form of ethosomal vesicles designed to enhance transdermal drug delivery. These vesicles are composed of a combination of different phospholipids, ethanol, and water, which work synergistically to improve the encapsulation efficiency and stability of the drug within the vesicle. The unique composition of composite phospholipid ethosomes allows for better interaction with the stratum corneum, the outermost layer of the skin, thereby enhancing the penetration of the encapsulated drug. Studies have shown that these composite vesicles can significantly increase the transdermal flux of various drugs, making them a promising carrier for transdermal drug delivery systems.[11][15]

5. Actively targeted ethosomes

Actively targeted ethosomes are specialized vesicular systems designed to enhance the delivery of therapeutic agents to specific skin cells or tissues. By incorporating targeting ligands—such as antibodies, peptides, or other molecules that recognize and bind to specific receptors on target cells—these ethosomes can selectively interact with and deliver their payload to the intended site. This targeted approach not only improves the therapeutic efficacy of the encapsulated drugs but also minimizes potential side effects by reducing off-target interactions. For instance, galactosylated chitosan has been utilized as a targeting ligand to direct ethosomal formulations to specific skin cells, thereby enhancing the treatment of skin-related conditions.[11]

STRUCTURE AND ITS COMPOSITION

Ethosomes are vesicular carriers composed of hydroalcoholic mixtures with relatively high concentrations of alcohols or their combinations. They are typically formulated using phospholipids with diverse chemical structures, such as hydrogenated phosphatidylcholine (PC), phosphatidylcholine (PC), phosphatidic acid (PA), phosphatidylserine (PS), phosphatidylethanolamine (PE), phosphatidylglycerol (PPG), and phosphatidylinositol (PI). Additional components include alcohol (ethanol or isopropyl alcohol), water, and glycols such as propylene glycol.

These formulations allow for the efficient delivery of high concentrations of active substances through the skin. The ratio of alcohol to water, or alcohol-polyol to water, can be adjusted to control drug delivery. Soya-based phospholipids, such as Phospholipon 90 (PL- 90), are commonly used within a concentration range of 0.5–10% w/w. Cholesterol may also be incorporated into the mixture in amounts ranging from 0.1–1%.

Alcohols like ethanol and isopropyl alcohol are typically employed, and phospholipids may be combined with non-ionic surfactants (e.g., PEG-alkyl ethers). The alcohol content in ethosomal formulations generally ranges between 20–50%, while the non-aqueous phase (a mixture of alcohol and glycol) can range from 22–70%.[6][16]

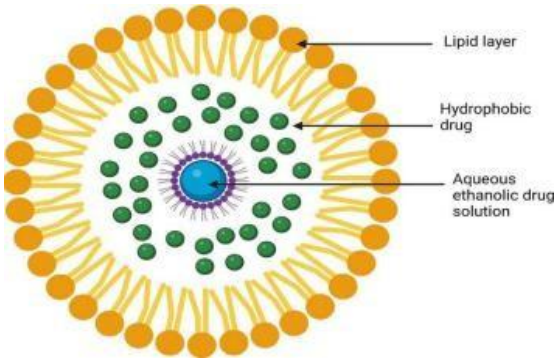

Fig 2: structure of ethosome.

ADVANTAGES

- Degradation in the gastrointestinal tract, poor oral absorption, and low bioavailability.
- Enhanced drug penetration and systemic effects.
- Formulation includes nontoxic raw materials.
- High patient compliance due to administration in semisolid forms like gels or creams.
- Passive, non-invasive ethosomal system ready for immediate commercialization.
- Increased drug entrapment efficiency, reduced side effects, and stable systemic drug levels.
- Significant drug accumulation in the skin.
- Enhanced drug permeation through the skin for transdermal and dermal delivery.[17][18]

DISADVANTAGES

- Drugs requiring high blood concentrations cannot be administered, limiting the approach to potent molecules with a daily dose of 10 mg or less.
- The drug must have adequate solubility in both lipophilic and aqueous environments to reach dermal microcirculation and access systemic circulation.
- The molecular size of the drug must be suitable for percutaneous absorption.
- May not be cost-effective due to poor yield.
- Risk of skin irritation or dermatitis caused by excipients and enhancers used in drug delivery systems.
- The primary advantage of ethosomes over liposomes is the enhanced drug permeation.
- Potential loss of product during the transfer from organic to aqueous media.[18][19]

MECHANISM OF SKIN PENETRATION

Ethosomes provide a significant advantage over liposomes in terms of drug permeability. However, the precise mechanism of drug absorption from ethosomes is not yet fully understood.[20] The absorption process is believed to occur in two key phases.

1. **Ethanol Effect**
2. **Ethosome Effect**

1. Ethanol effect

Ethanol plays a crucial role in ethosomes by enhancing their ability to deliver drugs through the skin. It disrupts the lipid structure of the stratum corneum, increasing membrane fluidity and permeability. Additionally, ethanol integrates into the ethosomal lipid bilayer, reducing the tight packing of lipids and imparting flexibility to the vesicles, which facilitates deeper skin penetration. This combination of effects allows ethosomes to effectively transport encapsulated drugs into deeper skin layers and potentially into systemic circulation as shown in fig 3.[21][22][23]

2. Ethosome effect

Ethosomes are advanced lipid-based vesicles designed to enhance transdermal drug delivery. Their mechanism, often referred to as the "ethosome effect," involves the high ethanol content disrupting the lipid structure of the stratum corneum, increasing its fluidity and permeability. This disruption allows ethosomal vesicles to penetrate deeper into the skin layers. Once within the skin, ethosomes can fuse with the lipid components of skin cells, facilitating the direct release of encapsulated drugs into the cells as shown in fig 3. Additionally, the flexible and malleable nature of ethosomal vesicles enables a controlled and sustained release of active substances over time, maintaining therapeutic levels and reducing the frequency of application.[24][25]

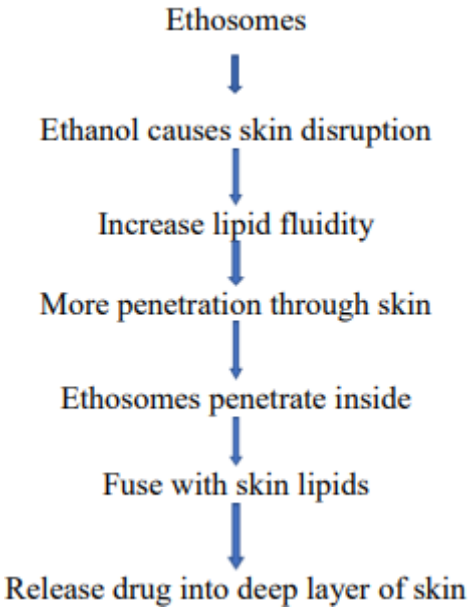

Fig 3: Mechanism of penetration.

METHOD OF PREPARATION

Traditionally, ethosomal vesicles can be prepared using three main methods: the hot method, the cold method, and the dispersion method.

1. Hot method

As shown in the fig 4, the hot method involves two main steps. First, the phospholipid is dispersed in water, and the mixture is heated in a water bath to 40°C until a colloidal solution forms. In a separate container, ethanol and PG are mixed, heated to 40°C, and then added to the aqueous phase. The vesicle size can be reduced by using sonication or extrusion.[26][27]

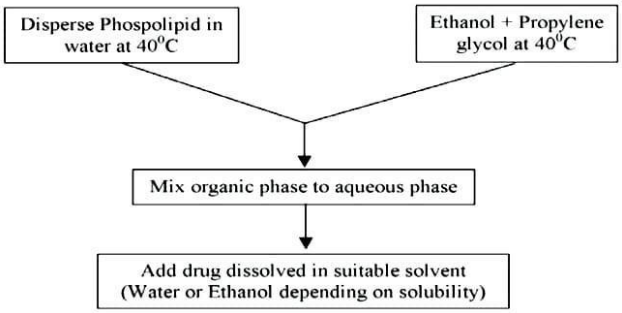

Fig 4: Hot method.

2. Cold Method

The cold method is the most commonly used technique for synthesizing ethosomes. In this method, phospholipids and the drug are dissolved in ethanol and glycol at room temperature. Sometimes, other lipids like cholesterol are added to stabilize the formulation. The mixture is stirred at 700 rpm at 30°C. After 5 minutes, distilled water, previously heated to 30°C, is added to the ethanolic solution using a syringe while continuing to stir at 700 rpm for 30 minutes. The vesicle size of ethosomes can be reduced using extrusion or sonication. During the process, the vessel containing ethanol should be well-covered to prevent ethanol evaporation. The final product should be stored in a refrigerator as shown in fig 5.[28][29]

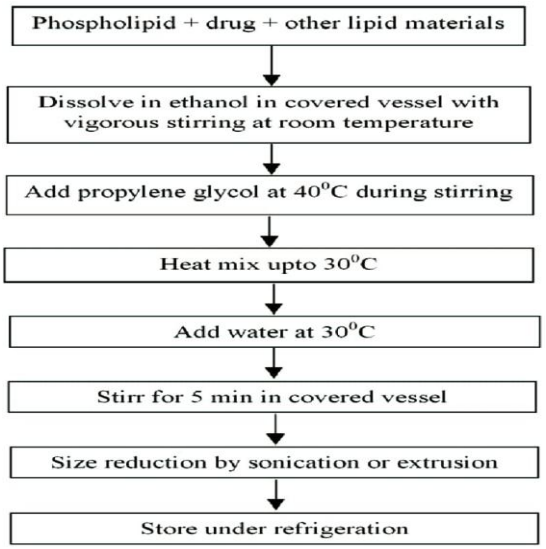

Fig 5: Cold method.

3. Mechanical dispersion method

In this method, Soya phosphatidylcholine is dissolved in a chloroform: methanol mixture (3:1) in a round-bottom flask. The organic solvents are then removed using a rotary vacuum evaporator at a temperature above the lipid transition point, forming a thin lipid film on the flask's walls. Any remaining traces of the solvent mixture are eliminated by leaving the flask under vacuum overnight. Hydration is carried out using different concentrations of a hydroethanolic mixture containing the drug, with the flask being rotated at an appropriate temperature.[30][31]

4. Classic Method

In this method, the drug and phospholipid are dissolved in ethanol and heated to 30°C ± 1°C in a water bath. Double-distilled water is then added in a fine stream with a syringe to the lipid mixture, while stirring continuously at 700 rpm in a closed vessel to prevent ethanol evaporation. The vesicle suspension is subsequently homogenized by passing it through a polycarbonate membrane using a hand extruder for three cycles.[31][32]

5. Thin film hydration method

In this method, the drug and phospholipids are dissolved in a chloroform: methanol mixture in a 3:1 ratio and placed in a round-bottom flask. The mixture is then evaporated using a rotary evaporator at a temperature above the lipid transition point (above 60°C) to remove all the methanol and chloroform, forming a thin film in the flask. The thin film is then hydrated with phosphate-buffered saline (pH 7.4) containing ethanol. The formulation is sonicated for 5 minutes to reduce the particle size, resulting in the formation of ethosomes. Finally, the ethosomes are stored in a refrigerator.[5]

CHARACTERIZATION OF ETHOSOMES

1. Vesicle size and zeta potential

The particle size and zeta potential of ethosomes can be measured using dynamic light scattering (DLS) with a computerized inspection system and photon correlation spectroscopy (PCS). Ethosome size typically ranges from tens of nanometers to microns, depending on the formulation's composition. Zeta potential serves as a key indicator of particle surface charge and is essential for predicting and controlling stability. Generally, particles can achieve stable dispersion when the absolute value of their zeta potential exceeds 30 mV, due to the electric repulsion between particles.[33]

2. Vesicle shape

Characterizing the vesicle shape of ethosomes is essential for understanding their morphology, stability, and suitability as drug delivery systems. Transmission Electron Microscopy (TEM) is a primary technique employed for this purpose. TEM provides high-resolution images that allow for the detailed visualization of ethosomal vesicles, enabling the assessment of their shape, size, and surface characteristics. Studies utilizing TEM have reported that ethosomes typically exhibit spherical shapes with smooth surfaces.[34][35]

In addition to TEM, other microscopic techniques such as Scanning Electron Microscopy (SEM) and Cryogenic Transmission Electron Microscopy (Cryo-TEM) are also utilized to characterize ethosome vesicles. SEM offers detailed surface morphology images, while Cryo-TEM allows for the observation of vesicles in their near-native hydrated state, providing insights into their structural integrity and lamellarity. [36]

3. Transition temperature

The transition temperature (T_m) of ethosomes is a critical parameter that influences their fluidity, stability, and drug delivery performance. Differential Scanning Calorimetry (DSC) is commonly employed to determine the T_m of the lipids used in ethosomal formulations. This technique provides insights into the thermal behaviour of the lipid bilayers, which is essential for understanding the interaction between ethanol and phospholipids in the vesicles.[37][38]

Incorporating ethanol into ethosomal formulations significantly impacts the T_m of the lipid bilayers. Ethanol interacts with the lipid molecules in the polar head group region, decreasing the transition temperature of the lipids in the stratum corneum. This reduction in T_m increases the fluidity of the lipid bilayers, enhancing the ethosomes' ability to penetrate the skin's deeper layers.[12]

4. Entrapment efficiency

The entrapment efficiency of ethosomal vesicles can be assessed using the ultracentrifugation method. The vesicles are separated in a high-speed cooling centrifuge at 20,000 rpm for 90 minutes, with the temperature kept at 4°C. After centrifugation, the sediment and supernatant are separated. The drug content in the sediment is determined by lysing the vesicles with methanol. The entrapment efficiency is then calculated using the following equation.

Entrapment efficiency = DE / DT x 100

Where, DE - Amount of drug in the ethosomal sediment

DT - Theoretical amount of drug used to prepare the formulation (Equal to amount of drug in supernatant liquid and in the sediment.[39]

5. Drug Content

Determining the drug content in ethosomal formulations is essential for assessing their efficacy and ensuring accurate dosing. High-Performance Liquid Chromatography (HPLC) is a widely used analytical technique for this purpose. In practice, a specific amount of the ethosomal formulation is dissolved in an appropriate solvent to extract the encapsulated drug. The resulting solution is then analyzed using HPLC to quantify the drug concentration. For instance, in a study involving ligustrazine-loaded ethosomes, the drug content was determined by dissolving the ethosomal preparation in a solvent and analyzing it via HPLC.[40][41]

6. Surface tension measurement

A common method for assessing the surface tension of ethosomes is the Du Nouy ring tensiometer technique. This method involves immersing a platinum or gold ring into the ethosomal dispersion and measuring the force required to detach the ring from the liquid surface. The measured force is then used to calculate the surface tension of the dispersion. This technique is effective for evaluating both surface and interfacial tensions, providing valuable information about the formulation's characteristics.[37][38]

7. Vesicle stability

The stability of vesicles can be evaluated by monitoring the size and structure of the vesicles over time. The mean size is measured using DLS, while structural changes are observed through TEM.[42]

8. Skin permeation studies

The ability of the ethosomal preparation to penetrate the skin layers can be assessed using confocal laser scanning microscopy (CLSM). The Ethosomes exhibit significantly higher skin deposition, likely due to the combined effect of ethanol and phospholipids, which enhances dermal and transdermal delivery.[39][43]

APPLICATIONS OF ETHOSOMES

Ethosomes can be used for various purposes for drug delivery system. Various studies using ethosomal formulations have demonstrated improved skin permeability for drugs. The applications of ethosomes as a carrier system for transdermal or topical drug delivery are summarized below,

1. Pilosebaceous targeting

Pilosebaceous units have been utilized for localized

therapy, especially in the treatment of follicle-related conditions such as acne or alopecia. Sebaceous glands and hair follicles are increasingly recognized as important pathways for percutaneous drug delivery. Many studies focus on exploring these follicles as routes for systemic drug delivery. Minoxidil, a lipid-soluble drug, is topically applied to the scalp for the treatment of baldness through pilosebaceous delivery.[5][44]

2. Transdermal Delivery of Hormones

Oral administration of hormones is linked to challenges such as significant first-pass metabolism, low oral bioavailability, and various dose-dependent side effects. It was found that testosterone from an ethosomal formulation penetrated the skin approximately 30 times more effectively than from a commercial formulation.[23][45]

3. Topical delivery of DNA

The skin serves as a highly effective protective barrier while also being permeable and capable of expressing genes and exhibiting immunological activity. Based on this, ethosomes have been explored as a delivery system for DNA molecules into skin cells to facilitate gene expression. Touitou et al. encapsulated a GFP-CMV-driven transfecting construct within ethosomal DNA for their study. This formulation was applied to the dorsal skin of 5-week-old male CD-1 nude mice for 48 hours. After the treatment, the skin was removed, and confocal laser scanning microscopy (CLSM) was used to observe the penetration of the green fluorescent protein (GFP) formulation. Recently, Gupta and colleagues described a transfersomal formulation with immunogenic potential. The enhanced skin penetration ability of ethosomes presents a promising opportunity to use these formulations for delivering immunizing drugs.[16][37]

4. Anti-inflammatory ethosomal systems

Paolino and colleagues investigated the use of ammonium glycyrrhizinate (AG) ethosomes for treating inflammatory-based skin diseases in human volunteers with methyl-nicotinate-induced erythema. The anti-inflammatory effects of the AG ethosomal system were assessed for both pre-treatment and treatment of skin erythema and compared to aqueous and hydroethanolic drug solutions. A reflectance visible spectrophotometer was used to measure the erythema index. The results demonstrated that AG ethosomes significantly reduced the intensity and duration of erythema compared to the other formulations.[46]

5. Analgesic and Antipyretic Ethosomal Systems

A recent study examined the in vivo analgesic and antipyretic effects of transdermal ethosomal ibuprofen using two animal models: Brewer's yeast-induced fever in rats and the tail flick nociception test in mice. Application of ibuprofen gel to the skin of fevered rats led to a gradual reduction in body temperature. The analgesic efficacy of ethosomal ibuprofen gel was evaluated in comparison to oral administration using the tail flick test in mice. Results showed a significantly greater effect for the ethosomal ibuprofen system at 120 and 360 minutes post-administration, with a duration of action lasting at least six hours.[47]

6. Delivery of Anti-Psoriasis Drug:

Psoriasis is a chronic, non-infectious autoimmune skin disease characterized by red, scaly plaques. Ethosomes have the potential to enhance treatment efficacy while minimizing side effects. Fathalla et al. developed liposomal and ethosomal Pluronic® F-127 gels containing anthralin and evaluated their efficacy and safety in psoriasis treatment. The study, registered under ClinicalTrials.gov ID NCT03348462, reported PASI reductions of −68.66% for liposomes and −81.84% for ethosomes. The findings indicated that ethosomes were more effective than liposomes, with no adverse effects observed in either group. These results suggest that anthralin-loaded ethosomes may be a promising approach for psoriasis treatment.[11][48]

7. Cosmeceutical Applications of Ethosomes

In the cosmetic industry, ethosomes offer the advantage of enhancing the stability of cosmetic ingredients while reducing skin irritation caused by harsh chemicals. Additionally, they improve transdermal permeability, particularly in their elastic forms. However, the composition and size of ethosomal vesicles are crucial factors to consider during formulation.[23][49]

8. Gene Delivery

The topical delivery of DNA molecules to skin and hair follicle cells is gaining popularity for various applications, including alopecia treatment and vaccination. Various carriers have been explored to transport DNA molecules, which, when expressed in follicular and dermal stem cells, can produce local or systemic effects. However, the dermal delivery of genetic material remains significantly limited due to the strong negative charge and high molecular weight of DNA molecules.

In-vivo studies demonstrated the formation of green fluorescent protein (GFP) following the dermal application of GFP-CMV-driven transfecting constructs via ethosomes. This study observed the ability of ethosomal carriers to deliver CMV-GFP cDNA to the dorsal skin of five-week-old male CD-1 nude mice after a 48-hour application. The treated skin was then excised, and GFP expression was confirmed using confocal laser scanning microscopy (CLSM). These findings suggest that ethosome–DNA formulations enable efficient gene delivery and expression in skin cells, indicating their potential as suitable carriers for various gene therapy applications requiring transient gene expression.[50]

CONCLUSION

Ethosomes represent a significant advancement in transdermal and topical drug delivery, offering enhanced permeability, improved bioavailability, and increased

therapeutic efficacy. Their unique composition, incorporating ethanol and phospholipids, facilitates deeper skin penetration, making them effective for delivering both hydrophilic and lipophilic drugs. Various characterization techniques, including DLS, TEM, DSC, and HPLC, help assess their structural and physicochemical properties, ensuring formulation stability and efficiency.

Ethosomal formulations have shown great potential in pilosebaceous targeting, transdermal hormone delivery, gene therapy, anti-inflammatory treatments, analgesic applications, and cosmeceuticals. Their high ethanol content disrupts the skin barrier, allowing for improved drug absorption while maintaining controlled and sustained release. Despite their advantages, challenges such as formulation stability, potential skin irritation, and cost need to be addressed for widespread clinical applications.

Future research should focus on optimizing ethosomal formulations, enhancing stability, and developing targeted delivery approaches for better therapeutic outcomes. With continued advancements, ethosomes are poised to become a key technology in modern drug delivery systems, offering a versatile and efficient alternative to conventional transdermal methods.

REFERENCE

1. Akhtar N, Menaa F, Akhtar N, Javed N, Sethi A, Khan MS. Tocopherol succinate- loaded ethosomal gel synthesized by cold method technique: Deeper biophysical characterizations for translational application on human skin. J. Cosmet. Dermatol, 2024; 23(3): 1015-28.
2. Madni A, Rahim MA, Mahmood MA, Jabar A, Rehman M, Shah H, Khan A, Tahir N, Shah A. Enhancement of dissolution and skin permeability of pentazocine by proniosomes and niosomal gel. AAPS PharmSciTech, 2018; 19: 1544-53.
3. Ismail TA, Shehata TM, Mohamed DI, Elsewedy HS, Soliman WE. Quality by design for development, optimization and characterization of brucine ethosomal gel for skin cancer delivery. Molecules, 2021; 26(11): 1-17.
4. Cosco D, Celia C, Cilurzo F, Trapasso E, Paolino D. Colloidal carriers for the enhanced delivery through the skin. Expert Opin Drug Deliv, 2008; 5(7): 737-55.
5. Mohite Mukesh T, Ahire Saurabh N, Shinde Supriya S, Revan K, Shubham K. An overview on ethosomes: need of future. IJCRT, 2021; 9(8): 796-811.
6. Roshini R, Saraswathi TS, Damodharan M. Ethosomes: novel lipid vesicular and non- invasive delivery carrier–a review. J Posit School Psychol, 2022; 6(8): 4099-111.
7. Manosroi A, Jantrawut P, Khositsuntiwong N, Manosroi W, Manosroi J. Novel elastic nanovesicles for cosmeceutical and pharmaceutical applications. Chiang Mai J Sci, 2009; 36(2): 168-78.
8. Zhang JP, Wei YH, Zhou Y, Li YQ, Wu XA. Ethosomes, binary ethosomes and transfersomes of Terbinafine hydrochloride: A comparative study. Arch Pharm Res, 2012; 35(1): 109-17.
9. Yucel C, Seker Karatoprak G, Degim IT. Anti-aging formulation of rosmarinic acid- loaded ethosomes and liposomes. J. Microencapsul, 2019; 36(2): 180-91.
10. Abdulbaqi IM, Darwis Y, Khan NA, Assi RA, Khan AA. Ethosomal nanocarriers: the impact of constituents and formulation techniques on ethosomal properties, in vivo studies, and clinical trials. Int J Nanomedicine, 2016; 11(5): 2279-304.
11. Zhan B, Wang J, Li H, Xiao K, Fang X, Shi Y, Jia Y. Ethosomes: A Promising Drug Delivery Platform for Transdermal Application. Chemistry, 2024; 6(5): 993-1019.
12. Chauhan N, Vasava P, Khan SL, Siddiqui FA, Islam F, Chopra H, Emran TB. Ethosomes: A novel drug carrier. Ann. Med. Surg, 2022; 82(10): 1-4.
13. Carita AC, Eloy JO, Chorilli M, Lee RJ, Leonardi GR. Recent advances and perspectives in liposomes for cutaneous drug delivery. Curr. Med. Chem, 2018; 25(5): 606-35.
14. Ascenso A, Raposo S, Batista C, Cardoso P, Mendes T, Praca FG, Bentley MV, Simoes S. Development, characterization, and skin delivery studies of related ultradeformable vesicles: transfersomes, ethosomes, and transethosomes. Int J Nanomedicine, 2015; 10(15): 5837-51.
15. Li Y, Xu F, Li X, Chen SY, Huang LY, Bian YY, Wang J, Shu YT, Yan GJ, Dong J, Yin SP. Development of curcumin-loaded composite phospholipid ethosomes for enhanced skin permeability and vesicle stability. Int. J. Pharm, 2021; 592(9): 1-37.
16. Patrekar PV, Inamdar SJ, Mali SS, Mujib MT, Ahir AA, Hosmani AH. Ethosomes as novel drug delivery system: A review. Pharm. Innov, 2015; 4(9): 10-21.
17. Nandure HP, Puranik P, Giram P, Lone V. Ethosome: A Novel Drug Carrier. IJPRAS, 2013; 2(3): 18-30.
18. Pakhale NV, Gondkar SB, Saudagar RB. Ethosomes: transdermal drug delivery system. JDDT, 2019; 9(3): 729-33.
19. Shahidulla S. Ethosomes as novel vesicular carrier: an overview. Curr. Drug Deliv, 2021; 15(6): 795-817.
20. Raut S, Koli P, Desai H, Shelake S, Chougule N. An overview of ethosomes as novel vesicular carrier: its principle, preparation and applications. Int J Pharm Sci Rev Res, 2023; 79(1): 50-55.
21. Paiva-Santos AC, Silva AL, Guerra C, Peixoto D, Pereira-Silva M, Zeinali M, Mascarenhas-Melo F, Castro R, Veiga F. Ethosomes as nanocarriers for the development of skin delivery formulations. Pharm. Res, 2021; 38(6): 947-70.
22. Sala M, Diab R, Elaissari A, Fessi H. Lipid

nanocarriers as skin drug delivery systems: Properties, mechanisms of skin interactions and medical applications. Int. J. Pharm, 2018; 535(1-2): 1-7.
23. Verma P, Pathak K. Therapeutic and cosmeceutical potential of ethosomes: An overview. JAPTR, 2010; 1(3): 274-82.
24. Musielak E, Krajka-Kuzniak V. Liposomes and Ethosomes: Comparative Potential in Enhancing Skin Permeability for Therapeutic and Cosmetic Applications. Cosmetics. 2024; 11(6): 1-18.
25. Chunchuwar Mandlik Y, Kasliwal RH, Gholse YN, Chaple DR. AN UPDATED REVIEW ON NANOVESICLES-ETHOSOMES, AS A NOVEL DRUG DELIVERY SYSTEM. World J. Pharm. Res, 2024; 13(13): 1689-702.
26. Yadav KK, Verma NK. Formulation and evaluation of ethosome of mefenamic acid using hot method. J. Chem. Pharm. Res, 2018; 10(5): 4-15.
27. Kumar N, Dubey A, Mishra A, Tiwari P. Ethosomes: A Novel Approach in Transdermal Drug Delivery System. IJPLS, 2020; 11(5): 6598-608.
28. Supraja R, Sailaja AK. Formulation of Mefenamic acid loaded ethosomal gel by hot and cold methods. Nano Biomed. Eng, 2017; 9(1): 27-35.
29. Agarwal S, Gautam G. Formulation, development and characterization of ethosomes of Atorvastatin. Int. J. Pharm. Investig, 2020; 10(02): 156-159.
30. Parmar P, Mishra A, Pathak A. Preparation and evaluation of ethosomal gel of clotrimazole for fungal infection by mechanical dispersion method. Curr. Res. Pharm. Sci, 2016; 6(2): 45-9.
31. Hariharanb S, Justinc A. Topical delivery of drugs using ethosomes: A review. Indian Drugs, 2019; 56(08): 7-20.
32. Ramakrishna GA, Manohar SD, Bhanudas SR. Ethosomes: carrier for enhanced transdermal drug delivery system. JAPER, 2014; 4(4): 380-7.
33. Dhurve R, Kashyap N, Mishra A, Pathak AK. A holistic review on ethosome: a promising drug delivery system for topical fungal disease. Int J Pharm Biol Arch, 2014; 5(05): 13-26.
34. Kalra N, Choudhary S, Arora P, Arora N. Ethosomal drug delivery system: A newer approach. AJPRD. 2020; 8(5): 158-62.
35. Barupal AK, Gupta V, Ramteke S. Preparation and characterization of ethosomes for topical delivery of aceclofenac. Indian J. Pharm. Sci, 2010; 72(5): 582-86.
36. Hallan SS, Sguizzato M, Mariani P, Cortesi R, Huang N, Simeliere F, Marchetti N, Drechsler M, Ruzgas T, Esposito E. Design and characterization of ethosomes for transdermal delivery of caffeic acid. Pharmaceutics, 2020; 12(8): 1-19.
37. Parashar T, Sachan R, Singh V, Singh G, Tyagi S, Patel C, Gupta A. Ethosomes: a recent vesicle of transdermal drug delivery system. Int. J. Res. Dev. Pharm. Life Sci, 2013; 2(2): 285-92.
38. Abu Huwaij R, Zidan AN. Unlocking the potential of cosmetic dermal delivery with ethosomes: A comprehensive review. J. Cosmet. Dermatol, 2024; 23(1): 17-26.
39. Aute PP, Kamble MS, Chaudhari PD, Bhosale AV. A comprehensive review on ethosomes. IJRDPL, 2012; 2(1): 218-24.
40. Gupta NB, Loona S, Khan MU. Ethosomes as elastic vesicles in transdermal drug delivery: An overview. Int. J. Pharm. Sci. Res, 2012; 3(3): 682-87.
41. Liu X, Liu H, Liu J, He Z, Ding C, Huang G, Zhou W, Zhou L. Preparation of a ligustrazine ethosome patch and its evaluation in vitro and in vivo. Int J Nanomedicine, 2011; 6(1): 241-7.
42. Dayan N, Touitou E. Carriers for skin delivery of trihexyphenidyl HCl: ethosomes vs. liposomes. Biomaterials, 2000; 21(18): 1879-85.
43. Ahad A, Aqil M, Kohli K, Sultana Y, Mujeeb M. Enhanced transdermal delivery of an anti-hypertensive agent via nanoethosomes: statistical optimization, characterization and pharmacokinetic assessment. Int. J. Pharm, 2013; 443(1-2): 26-38.
44. Biju S, Talegaonkar S, Mishra P, Khar R. Vesicular systems: an overview. Indian J. Pharm. Sci, 2006; 68(2): 141-53.
45. Pandey V, Golhani D, Shukla R. Ethosomes: versatile vesicular carriers for efficient transdermal delivery of therapeutic agents. Drug delivery, 2015; 22(8): 988-1002.
46. Mohanty D, Mounika A, Bakshi V, Haque MA, Sahoo CK. Ethosomes: a novel approach for transdermal drug delivery. Int. J. ChemTech Res, 2018; 11(8): 219-26.
47. Ainbinder D, Paolino D, Fresia M, Touitou E. Drug delivery applications with ethosomes. J. Biomed. Nanotechnol, 2010; 6(5): 558-68.
48. Fathalla D, Youssef EM, Soliman GM. Liposomal and ethosomal gels for the topical delivery of anthralin: preparation, comparative evaluation and clinical assessment in psoriatic patients. Pharmaceutics, 2020; 12(5): 1-24.
49. Shitole MM, Nangare SN, Patil U, Jadhav N. Review on drug delivery applications of ethosomes: Current developments and prospects: (TJPS-2021-0031. R1). TJPS, 2022; 46(3): 251-65.
50. Godin B, Touitou E. Ethosomes: new prospects in transdermal delivery. Critical reviews in therapeutic drug carrier systems, 2003; 20(1): 63-102.