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ETHOSOMES: modern drug delivery systems – a review

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ABSTRACT :

Ethosomes are advanced lipid-based nanocarriers that enhance transdermal and dermal drug delivery by improving drug penetration through the stratum corneum. They are composed of phospholipids, high concentrations of ethanol, and water, which give them high flexibility and permeability. Ethanol disrupts the lipid structure of the skin, increasing vesicle fluidity and enhancing drug absorption. Ethosomes can encapsulate hydrophilic, lipophilic, and amphiphilic drugs, delivering them deep into the skin or systemically. Compared to conventional liposomes, ethosomes offer improved drug entrapment, better skin permeation, controlled release, and fewer side effects. They have been used in the treatment of various conditions such as acne, psoriasis, pain, hormone-related disorders, cancer, and for transdermal vaccine delivery. In cosmetics, they are widely used to deliver bioactive compounds effectively. Despite their advantages, challenges like formulation stability, drug leakage, and difficulty in large-scale production remain. However, ongoing research and advances in nanotechnology are addressing these issues, enhancing the potential of ethosomes as a reliable and efficient drug delivery system. This review highlights the composition, drug delivery mechanism, preparation methods, advantages, limitations, and future scope of ethosomal formulations in pharmaceutical and cosmetic applications.

Key words: Ethosomes, Psoriasis, Ethanol, Nanocarriers, Permeation.

INTRODUCTION:

Advancements in drug delivery have led to innovative formulations to overcome challenges like poor solubility and biological barriers (e.g., skin, organ membranes), which limit drug bioavailability. Effective therapy depends not only on drug activity but also on its availability at the target site. Nanotechnology has enabled the use of biodegradable polymers to develop nanoparticles like nanospheres and Nano capsules that can cross barriers and deliver drugs to organs such as the eyes, brain, GIT, and bladder.[1]

The oral route is common for drug administration but faces challenges like first-pass metabolism, frequent dosing, and high costs.[2] To address limitations of oral drug delivery, a new approach is needed to enhance therapeutic effectiveness, safety, and stability. Transdermal drug delivery systems (TDDS) offer a solution by bypassing absorption barriers, providing stable plasma levels, reducing dosing frequency, and improving patient compliance. The concept of percutaneous absorption, introduced by Stoughton in 1965, laid the groundwork for TDDS development.[3]

Despite advancements in dermal and transdermal drug delivery, effective topical drug administration remains challenging due to the skin's barrier. To enhance drug penetration and broaden applicability, strategies like micro-invasive devices, electrical techniques (e.g., iontophoresis, electrophoresis, sonophoresis), chemical enhancers, and vesicular systems have been explored.[4] Ethosomes, developed by Touitou, are specialized vesicular carriers designed for effective topical drug delivery.[5]

SKIN AND DRUG PERMEATION

The skin, the body's largest organ, serves as a barrier against water loss and offers a convenient, accessible route for drug delivery due to its large surface area.[6] Topical products are applied to the skin or mucous membranes to support natural functions or modify underlying tissue activity.[7] Effective percutaneous absorption requires understanding the skin's anatomy and properties. In adults, the skin spans about 2 m^2 and receives nearly one-third of the body's blood flow.[8]

The effectiveness of treatment relies on the drug's ability to penetrate the target skin layers at therapeutic concentrations. There are three primary pathways for drug penetration:

A. The intercellular pathway, where the drug diffuses through the lipid matrix between keratinocytes, making it the preferred route for lipophilic molecules.

B. The transcellular (intracellular) pathway, in which the drug passes directly through corneocytes.
C. The trans appendageal pathway, which involves drug transport through hair follicles, sebaceous glands, and sweat glands.[9,10]

ETHOSOMES

In 1997, Touitou *et al*., developed ethosomes flexible, lipid-based vesicles composed of ethanol, phospholipids, and water to enhance drug delivery. Ethanol (20–50%) acts as a permeation enhancer by disrupting the stratum corneum's lipid bilayer, improving drug release, hydration, and the physical and chemical properties of transdermal therapies.[11]

Ethosomes are favoured for drug delivery as they bypass gastrointestinal irritation and first-pass metabolism. While TDDS offer benefits over oral routes, skin penetration—especially for drugs >500 Da—remains a hurdle. Enhancers like iontophoresis, sonophoresis, and ethanol improve absorption. Among vesicular carriers, ethosomes outperform others in skin penetration and transdermal delivery. They are room-temperature stable, highly efficient in drug entrapment, and suitable for both lipophilic and hydrophilic drugs. Despite an unclear mechanism, ethosomes mark a significant advance in targeted transdermal delivery.[12]

ADVANTAGES OF ETHOSOMES

- Ethosomes enhance drug permeation through skin corneocytes efficiently due to the combined effects of ethanol on lipid fluidity and the flexible nature of the vesicles.
- They provide drug solubility in both lipophilic and hydrophilic phases, ensuring effective microcirculation in the dermis and facilitating systemic absorption.
- Ethosomes enable the delivery of various molecules with different physicochemical properties, including hydrophilic and lipophilic molecules, peptides, proteins, and other macromolecules.
- Their composition is generally recognized as safe, non-toxic, and approved for use in pharmaceutical, biotechnology, veterinary, cosmetic, and nutraceutical applications.
- High patient compliance is achieved since the drug is delivered in a semi-solid form (gel or cream), making it convenient for users.
- Ethosomes provide a simpler and more cost-effective method for drug delivery compared to techniques like iontophoresis and sonophoresis.
- They offer ease of industrial-scale production without requiring significant technical investments.
- Ethosomes exhibit higher drug entrapment efficiencies compared to liposomes, for both hydrophilic and hydrophobic drugs.
- They demonstrate excellent stability over prolonged periods.
- The presence of alcohol in ethosomes acts as a natural preservative, eliminating the need for additional preservatives.[11,13]

DISADVANTAGES OF ETHOSOMES

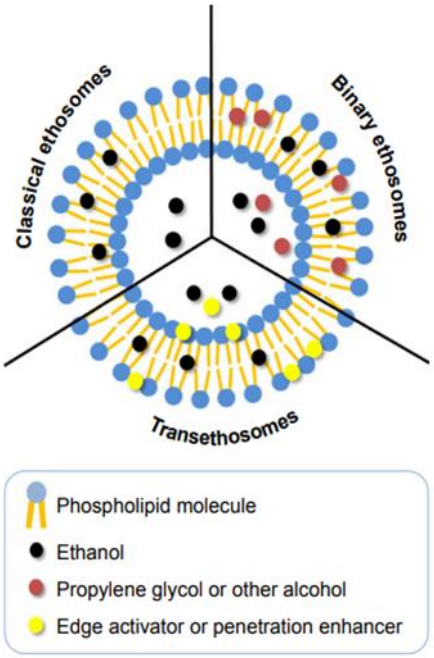
- There is a risk of allergic reactions in patients sensitive to ethanol or other ethosomal components.
- Unlike other carriers (such as solid lipid nanoparticles and polymeric nanoparticles) that support multiple routes of administration, ethosomal carriers are primarily suitable for transdermal delivery.
- Due to ethanol's flammability, careful planning, handling, transportation, and storage are required.
- Ethosomes are mainly confined to potent drug molecules, whether long-acting or short-acting, that require daily dosage.
- The molecular size of the drug must be appropriate for percutaneous absorption.
- Excipients and penetration enhancers used in ethosomal drug delivery systems may cause dermatitis or skin irritation[11,13]

TypeS of Ethosomes

Ethosomes can be classified according to their composition into several categories, including classical ethosomes, binary ethosomes, transethosomes.

classical ethosomeS

Classical ethosomes, derived from liposomes, consist of phospholipids, water, and up to 45% ethanol. They outperform liposomes in transdermal delivery due to smaller size, negative zeta potential, higher entrapment efficiency, and improved skin permeation and stability. They can encapsulate drugs ranging from 130.077 Da to 24 kDa.[14] Yucel et al. developed ethosomes and liposomes loaded with rosmarinic acid. Their study demonstrated that ethosomal formulations enhanced drug permeation across human skin and exhibited a higher transdermal flux compared to liposomes.[15]



Binary ethosomes

Binary ethosomes were introduced by Zhou et al[16]. Basically, they were developed by adding another type of alcohol to the classical ethosomes. The most commonly used alcohols in binary ethosomes are propylene glycol (PG) and isopropyl alcohol (IPA).[17]

Transethosomes (TE):

TEs are ethosomal systems that were discovered by Song et al[18] Transethosomes (TEs) consist of phospholipids, permeation enhancers or edge activators, 30–40% ethanol, and water. Combining features of transfersomes and ethosomes, TEs offer enhanced stratum corneum penetration. Their size ranges from 40 to 200 nm, depending on the drug. Transethosomes (TEs) combine traditional ethosomal components with added permeation enhancers or surfactants to improve delivery. Various enhancers have been used to optimize TE systems, which can encapsulate drugs with molecular weights from 130.077 to 200–325 kDa.

Table 1. Comparison of classical ethosomes, binary ethosomes, and transethosomes in their initial suspension form[17]

Parameter	Classical ethosomes	Binary ethosomes	Transethosomes
composition	1. Phospholipids 2. Ethanol 3. Stabilizer 4. Charge inducer 5. Water 6. Drug/agent	1. Phospholipids 2. Ethanol 3. Propylene glycol 4. Charge inducer 5. Water 6. Drug/agent	1. Phospholipids 2. Ethanol 3. Edge activator (surfactant) or penetration enhancer 4. Charge inducer 5. Water 6. Drug/agent
Morphology	Spherical	spherical	Regular or irregular spherical shapes
size	Smaller than liposomes	Equal to liposomes	Size based on type and concentration of penetration enhancer or edge activator used
ζ-Potentia	Negatively charged	Negatively charged	Positively or negatively charged
Entrapment efficiency	Higher than classical liposomes	Typically, higher than classical ethosomes	Typically, higher than classical ethosomes
Skin permeation	Typically, higher than classical liposomes	Typically, equal to or higher than classical ethosomes	Typically, higher than classical ethosomes
Stability	Stabler than classical liposomes	Stabler than classical ethosomes	No particular trend determined

Composition of ethosomes

Table 2. Different Additives Employed in Formulation of Ethosomes.[19]

Class	Example	Uses
Phospholipid	Soya phosphatidyl choline Egg phosphatidyl choline Dipalmityl phosphatidyl choline Distearyl phosphatidyl choline	Vesicles forming component
Polyglycol	Propylene glycol Transcutol RTM	As a skin penetration enhancer
Alcohol	Ethanol Isopropyl alcohol	For providing the softness for vesicle membrane as a penetration enhancer
Cholesterol	Cholesterol	For providing the stability to vesicle membrane
Dye	Rhodamine-123 Rhodamine red Fluorescen Isothiocynate (FITC) 6- Carboxy fluorescence	For chareterization study
Vehicle	Carbopol 934	As a gel former

Ethanol

Ethanol is a highly effective penetration enhancer.[20] It plays a critical role in ethosomal systems by influencing vesicle properties such as size, ζ-potential, stability, entrapment efficiency, and skin permeability. Ethosomal formulations typically contain ethanol in concentrations ranging from approximately 10% to 50%.[21] Studies indicate that increasing ethanol concentration generally leads to a decrease in ethosome size.[22] For example, Bendas and Tadros reported that an ethosomal formulation with 40% ethanol exhibited a vesicle diameter 44.6% smaller than a conventional liposomal formulation without ethanol.[23]

Excessive ethanol concentrations can compromise vesicle integrity, increasing membrane permeability and vesicle size while reducing entrapment efficiency. High ethanol levels may even cause vesicle dissolution. Studies indicate that ethanol reduces membrane thickness and alters system charge, promoting steric stabilization and smaller vesicle size.[24]

PHOSPOLIPIDS

The formulation of ethosomal systems relies on phospholipids from various sources, which significantly affect vesicle size, stability, zeta potential, entrapment efficiency, and skin penetration.[17] Commonly used phospholipids include PC, PS, PA, PE, PPG, hydrogenated PC, with soya-based options like Phospholipon 90 (PL-90) being preferred. Their concentration typically ranges from 0.5–10% w/w.[25] Phospholipids, combined with non-ionic surfactants, help transport drugs across the skin, acting as nontoxic penetration enhancers due to their amphiphilic nature.[25] Increasing phospholipid concentration slightly enlarges vesicles; entrapment efficiency rises initially but declines at higher concentrations.[26] These lipids can also fuse with stratum corneum lipids, disrupting the skin barrier to enhance drug delivery.[27]

Cholesterol

Cholesterol, a rigid steroid molecule, enhances the stability of ethosomal systems and improves the entrapment efficiency of active ingredients. It reduces vesicular fusion and permeability, thereby preventing leakage. Additionally, cholesterol regulates membrane fluidity by decreasing flexibility and permeability. When incorporated into ethosomes, it increases their rigidity, which limits the permeation of the active substance. However, due to its stabilizing properties, higher cholesterol concentrations enhance drug entrapment efficiency.[17]

Dicetyl phosphate

Dicetyl phosphate is indeed a charge inducer used in ethosomes, but its role is somewhat nuanced. While Dicetyl phosphate is incorporated into the formulation to enhance stability and prevent aggregation of ethosomes, it has minimal influence on the overall charge characteristics of the vesicles. In the ethosomal formulation, it is utilized at concentrations ranging from 8% to 20% of the total phospholipid concentration. Dicetyl phosphate's impacts on other ethosomal system unknown.[14,17]

propylene glycol (pg)

PG is a commonly used penetration enhancer, frequently incorporated into binary ethosomes at concentrations ranging from 5% to 20%. It plays a crucial role in influencing key ethosomal characteristics, including particle size, entrapment efficiency, permeation, and stability. The addition of PG to ethosomal systems results in a further reduction in particle size compared to formulations without PG. Notably, an increase in PG concentration from 0% to 20% v/v led to a significant decrease in particle size, from 103.7±0.9 nm to 76.3±0.5 nm[17,28]

Isopropyl alcohol (IPA)

Dave et al.[29] studied the impact of isopropyl alcohol (IPA) on entrapment efficiency and skin permeation in diclofenac-loaded ethosomes. Three formulations were tested: classical ethosomes (40% ethanol), binary ethosomes (20% IPA + 20% ethanol), and a vesicular system with 40% IPA. The 40% IPA system showed the highest entrapment efficiency (95%) but the lowest drug release (83.2%) and transdermal flux (146 µg/cm²/h). Classical ethosomes had the highest flux (226.1 µg/cm²/h). The study concluded that IPA improves entrapment efficiency but has limited effect on drug release. Further research is needed to evaluate the broader effects of IPA and other alcohols on ethosomal properties.

Edge activators and Penetration enhancers

The selection of an appropriate edge activator or penetration enhancer is a critical aspect of ethosome formulation, as it plays a significant role in determining the physicochemical properties of the ethosomal system. Once incorporated into the phospholipid bilayer, the edge activator increases the intermolecular spacing between phospholipid molecules, disrupts the orderly arrangement of phospholipid phthalide chains, and enhances the overall fluidity of the ethosomes. Upon exposure to skin hydration, ethosomes undergo structural deformation, enabling them to penetrate the stratum corneum and enhance transdermal drug absorption.[17]
examples**:** tween 80, span 80, ethanol, propylene glycol.[30]

Tweens and Spans

In ethosomal systems, Tween 80 is incorporated at concentrations ranging from 10% to 50% of the total phospholipid content. Shen et al.[31] reported that the inclusion of Tween 80 in lipid vesicles enhances membrane fluidity and reduces membrane rigidity. This increase in fluidity leads to a natural decrease in particle size and entrapment efficiency (EE). However, the incorporation of Tween 60 and Tween 20 in ethosomal formulations resulted in the formation of unstable vesicles. Additionally, the production of homogeneous and stable transethosomes was not achievable when using Spans 80, 60, and 40.[17]

SKIN PERMEATION MECHANISM OF ETHOSOMES:

Ethosomes serve as an advanced drug delivery system, providing alternative pathways for drug transport into underlying tissues. Their distinctive composition enhances drug penetration through the skin via multiple mechanisms, leading to improved therapeutic efficacy. The specific route of penetration is influenced by the formulation and composition of ethosomes, as well as the physicochemical properties of the drug being delivered. Ethosomes may integrate with the skin's natural lipid matrix, undergo vesicle fusion with skin cells, penetrate through hair follicles via the transfollicular route, or traverse the skin using the transcellular pathway. Additionally, the presence of ethanol and phospholipids within ethosomes increases the fluidity and permeability of the stratum corneum by modifying its interfacial properties, thereby facilitating efficient drug absorption.[13]

Effect of Ethanol on Ethosome Penetration

The initial step in ethosome penetration is the effect of ethanol, which alters the structural arrangement of the stratum corneum lipids that are typically tightly packed. Ethanol interacts with the hydrophilic (polar) head groups of the lipid bilayers, leading to an increase in lipid fluidity and a reduction in the structural rigidity of the lipid layers. This modification enhances the flexibility of the vesicles, facilitating their penetration into deeper layers of the skin.[13]

Mechanism of Ethosome Penetration

Ethosomes penetrate the skin through both the hair follicle pathway and the stratum corneum. As the vesicles break apart, they release the drug, allowing it to diffuse further into the deeper skin layers. Their superior ability to enhance percutaneous penetration is attributed to the combined effects of their key components, particularly ethanol and phospholipids, which work together to increase skin permeability and improve drug absorption.[13]

Table 3. Methods for the Characterization of Ethosomal Formulation[32]

PARAMETERS	INSTRUMENTS/METHODS USED	IMPORTANCE
Vesicle Shape	Transmission Electron Microscopy (TEM) Scanning Electron Microscopy (SEM)	Determines skin penetration
Vesicle Size and Zeta Potential	Dynamic Light Scattering (DLS), Photon Correlation Spectroscopy (PCS) and Zeta Meter	Determines skin penetration and stability of vesicles
Transition Temperature	Differential Scanning Calorimetry (DSC)	Determines transition temperature of lipid vesicles
Drug Entrapment	Ultracentrifugation Technique	Suitability of method
Drug Content	UV Spectrophotometer, High Performance Liquid Chromatographic Method (HPLC)	Important in deciding the amount of vesicle preparation to be used
Surface Tension Measurement	Ring Method in a Du Nouy ring tensiometer	Determines surface tension activity of drug in aqueous solution
Stability Studies	Dynamic Light Scattering (DLS), Transmission Electron Microscopy (TEM)	To determine the shelf-life of vesicle formulation
Skin Permeation Studies	Confocal Laser Scanning Microscopy (CLSM)	Determines rate of drug transport through skin
In-vitro dissolution	Franz diffusion cell	Determines the drug release rate from vesicle

THERAPEUTIC APPLICATIONS

Pilosebaceous Targeting

Hair follicles and sebaceous glands are key pathways for percutaneous drug delivery, acting as reservoirs for localized treatments of conditions like acne and alopecia. They also show potential as routes for systemic delivery. To target pilosebaceous units, Maiden et al. developed an ethosomal minoxidil formulation, aiming to improve delivery of this lipophilic drug used for baldness. In vivo studies in nude mice showed the ethosomal form achieved 2.0, 7.0, and 5.0 times more drug accumulation than ethanolic phospholipid dispersion, hydroethanolic solution, and ethanolic minoxidil solution, respectively (all with 0.5% drug). These results suggest ethosomal formulations may enhance minoxidil's efficacy in treating hair loss.[33]

Delivery of Anti-Psoriasis Drugs

Psoriasis is a chronic autoimmune skin disorder marked by red, scaly plaques. To improve treatment and reduce side effects, Fathalla et al. developed Pluronic® F-127-based liposomal and ethosomal gels containing anthralin. In clinical trials (NCT03348462), PASI scores dropped by 68.66% with liposomes and 81.84% with ethosomes, with no reported side effects. These results suggest ethosomal anthralin formulations may offer a more effective and safe treatment option for psoriasis.[34]

Delivery of Antifungal and Antibacterial Drug

Pathogenic fungi causing angioinvasive infections are common in the environment but rarely affect immunocompetent individuals. Ethosomal formulations of antifungal and antibacterial drugs enhance transdermal permeation, maintaining stable plasma levels and reducing dosing frequency, thereby improving efficacy and patient compliance.[21] Maheshwari et al. found clotrimazole-loaded ethosomes offered superior skin penetration and antifungal activity against *Candida* species compared to liposomes.[35]

Delivery of anti-parkinsonism agent

In 2000, Dayan and Touitou developed an ethosomal formulation of trihexyphenidyl hydrochloride (THP), a psychoactive drug used to treat Parkinson's disease, and compared it with a conventional liposomal formulation. THP, an M1 muscarinic receptor antagonist, has a short half-life (~3 hours) and is difficult to administer orally due to Parkinson's-related motor issues. Electron microscopy showed the ethosomes as small phospholipid vesicles. Transdermal delivery via ethosomes increased THP flux through nude mouse skin by 87 times over liposomes, 51 times over phosphate buffer, and 4.5 times over a hydroethanolic solution. After 18 hours, skin retention of THP was also highest with ethosomes. These results highlight ethosomal delivery as a promising transdermal approach for Parkinson's management.[36]

Delivery of Antibiotics

Godin and Touitou developed an ethosomal formulation of bacitracin and erythromycin for improved dermal and intracellular delivery. Confocal microscopy showed enhanced penetration of both antibiotics and phospholipids into 3T3 Swiss albino fibroblasts, with flow cytometry confirming intracellular drug release. These results suggest ethosomal antibiotics may offer a more effective alternative to conventional treatments.[37,38]

CONCLUSION

Ethosomes represent a significant advancement in modern drug delivery systems, offering enhanced transdermal and targeted drug delivery capabilities. Their unique structure, composed of phospholipids, ethanol, and water, allows them to penetrate deep into the skin, improving drug bioavailability and therapeutic efficacy. Ethosomes have demonstrated promising applications in the delivery of various drugs, including anti-inflammatory, antifungal, antiviral, and anticancer agents. Despite their numerous advantages, challenges such as stability issues, large-scale production, and cost-effectiveness must be addressed to facilitate widespread clinical use. Continued research and technological advancements in ethosomal formulations will further optimize their efficiency and expand their potential applications in pharmaceuticals and cosmetics. Thus, ethosomes stand as a novel and promising approach for drug delivery, paving the way for more effective and patient-friendly therapeutic solutions.

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