ETHOSOMES: ADVANCING THE FRONTIERS OF TRANSDERMAL DRUG DELIVERY

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Abstract
As the largest organ in the body, the skin represents a convenient route for providing therapeutic substances to either a localized area or throughout the body. However, the outermost layer of the skin, known as the stratum corneum presents a significant barrier to the entry of water-soluble drugs and large molecules. As a result, many topical formulations fail to deliver sufficient amounts of active drug. In order to circumvent this barrier, researchers have recently synthesized ethosomes which are soft, lipid based carrier vesicles constructed from phospholipids, considerable quantities of alcohol and water. Alcohol serves as the primary functional component within this delivery system. By disrupting the closely packed structure of the lipids of the stratum corneum and concurrently increasing the malleability of the vesicle wall, the presence of alcohol allows the carrier to diffuse deeper into the skin than would be possible using traditional liposome technology. Due to this unique dual function property, ethosomal carriers can accommodate both polar and apolar drug molecules and generally exhibit superior loading capacity, permeation ability and bioavailability compared to typical liposomes. Additionally, ethosomes display controlled and prolonged drug release profiles resulting in less frequent administration and reduced side effects outside of the targeted region. The ease of preparation and gentle application characteristics exhibited by ethosomes contribute to their current position as a central focus of dermatological formulation research. Therefore, this article reviews the composition of ethosomes, various types that currently exist, methods used to prepare them, mechanisms involved in transporting drugs through the skin, stability and shelf life concerns, potential toxicity issues and applications for treating disease conditions.

Keywords
Ethosomes, vesicular drug delivery, transdermal delivery, skin permeation enhancement, Phospholipids, controlled drug release.
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Introduction

Skin represents approximately 15-20% of total body mass.Due to its large surface area and structural complexity, is among the most intricate and largest organs in the human body. While protecting underlying tissues from external insult including chemicals, microorganisms and environmental factors, skin also plays roles in regulating body temperature maintaining moisture levels and sensing stimuli [1]. The same attributes of skin (i.e., large surface area and accessability) make it a logical route for drug administration regardless if the desired outcome is localized or systemic [2]. Compared to oral formulations for drug administration topical and transdermal formulations offer practical benefits including avoiding hepatic first pass metabolism, slower drug release rates, decreased risk of systemic adverse effects and improved compliance by patients over extended periods [3].

Structure of the Skin

From anatomical perspective, skin consists of three distinct layers each contributing to the barrier function of skin [4]. The outermost layer is the epidermis which contains the stratum corneum, the layer most resistant to drug penetration [5,6]. Beneath the epidermis lies the dermis consisting of vascularized connective tissue with lymphatic vessels and nerve endings, this is primarily where most absorption into systemic circulation occurs [2,3]. The innermost layer is the hypodermis which consists almost exclusively of adipose tissue providing insulation functions as well as a reservoir for lipophilic drug molecules [2,4].

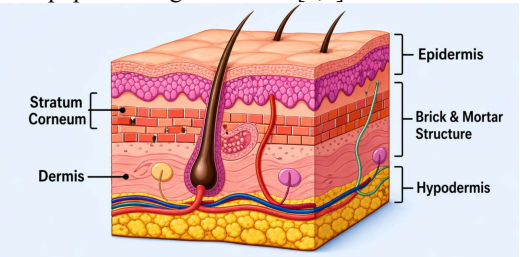

Fig. 1 Structure of skin

Amongst all three layers, it is the stratum corneum which imposes the highest restriction on how much drug actually enters into the skin [6].

Barrier Function of the Stratum Corneum

In terms of structure, the stratum corneum is formed from flat cells called corneocytes arranged in close proximity within an organized lipid bilayer matrix composed of ceramides, cholesterol and free fatty acids. This organization is comparable to bricks bound by mortar [7]. This tightly packed architecture creates a strong barrier against hydrophilic compounds, large molecule size and those possessing high molecular weights [8].

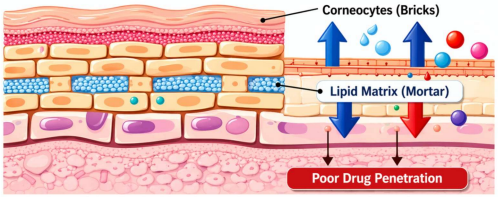

Fig. 2 Barrier Function of Stratum Corneum

Due to this tight packing of corneocyte structures in the stratum corneum, traditional topical formulations such as creams, ointments, lotions and gels generally cannot adequately penetrate into deeper areas of skin thus failing to deliver effective therapeutic concentrations at target sites [9].

To overcome this specific barrier, researchers coines ethosomes the lipid based vesicles specifically designed to overcome stratum corneum barriers to enhance both topical and transdermal delivery [10]. Ethosomes are prepared from phospholipid combinations mixed with ethanol (20-45%) and water. Ethanol performs two separate functions within ethosomes. Ethanol causes disruption in lipid-packing within stratum corneum thus creating pathways for enhanced diffusion. Simultaneously, ethanol increases flexibility of ethosomal walls allowing for greater deformation under mechanical stress, thereby enhancing overall depth of penetration into skin relative to other delivery vehicles [11].

Relative to standard liposomes and all other types of vesicle-based drug delivery systems, ethosomes exhibit superior skin penetration; carry a larger amount of drug, yield a greater degree of bioavailability and release their payload in a manner that is more controlled [12]. The ability to transport both hydrophilic and lipophilic active pharmaceuticals has rendered ethosomes a viable vehicle for treating numerous cutaneous disorders as well as some systemic diseases accessible via the topical route [13].

In summary, ethosomes represent a more advanced version of the vesicular systems that preceded them. Their principal differentiator i.e., the relatively high ethanol load in the membrane provides the membrane increased extensibility and facilitates improved interactions with skin lipids which ultimately allow the ethosome to pass more rapidly through the thickened stratum corneum matrix and penetrate more deeply into the skin than do typical lipid carriers [10]. Ethosomes also have a reputation for retaining both classes of active pharmaceuticals (i.e., hydrophilic and lipophilic) with a high degree of efficiency, thus expanding the scope of therapeutic agents that can be carried in the formulation. Their propensity to retain significant amounts of drug locally in the skin and limit escape into systemic circulation are two characteristics that make ethosomes so desirable for dermatologic and transdermal applications [11].

Ethosomes

Ethosomes originated in 1996 when they were first reported in the scientific literature [14]. Simply stated, they are a class of liposomal drug delivery systems based on ethanol developed as non-invasive vehicles to convey drug molecules into the dermis or into systemic circulation [10,16]. Ethosome's pliable nature enables therapeutic agent to be delivered more effectively than using rigid carrier systems [14,15]. Due to the elevated levels of both ethanol and lipid present in ethosomes compared to conventional systems, considerable attention has been directed towards understanding the skin effects of these vesicles. Researchers have determined that the alcohol is involved in dissolution of the drug while producing softer lipid structures that enhance permeability [10,16]. These vesicles can vary greatly in terms of size from the nano- to micron-scale and their primary characteristic is a soft vesicle wall [14,15].

To put it simply, an ethosome represents a soft vesicle consisting of hydroalcoholic or hydro/glycolic phospholipids dispersed in water with a significantly higher proportion of alcohol (ethanol or isopropanol) than that typically seen in other vesicular carriers [17]. The large volume percentage of alcohol is what distinguishes the ethosome system from other vesicular systems. As completed formulations, the ethanol content is normally between 20% – 30% and the sizes of the resultant vesicles can range from tens of nanometers to micrometers [18].

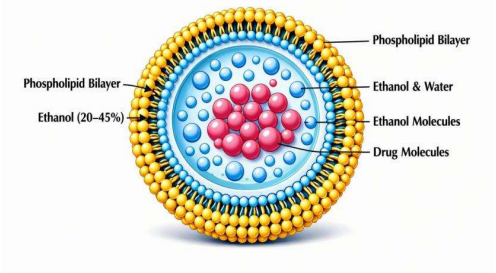

Fig. 3 Structure of Ethosomes

Composition of Ethosomes

Specialized lipid-based vesicular systems called ethosomes are essentially composed of phospholipids, water and a high proportion of

ethanol. Each component plays a distinctive role in vesicle formation, stability, drug loading capacity and skin permeability performance [19].

1. Phospholipids

The phospholipid bilayer membrane forming the structural basis of the ethosome is constructed from phospholipids [20]. Among others commonly employed include phosphatidylcholine derived from soybeans or eggs, as well as hydrogenated phospholipids [21]. Phospholipids provide biocompatibility to ethosomes and enable encapsulation of hydrophilic drugs within the aqueous core of the ethosome and lipophilic drugs within the lipid bilayer [22]. The phospholipid composition and quantity therefore determine aspects of vesicle morphology, drug entrapment efficacy and drug release profile [20].

2.Ethanol

Ethanol is the essential distinguishing factor in ethosomes and generally constitutes approximately 20% - 45% of the system. High levels of ethanol impart additional pliability and extensibility to the vesicle membrane thereby facilitating movement therethrough of the densely-packed lipid layers present in the stratum corneum [23]. Ethanol serves as a penetration enhancer due to its ability to disrupt crystallinity in skin lipids and fluidize them [24]. Additionally, ethanol enhances drug solubilization and increases drug entrapment efficiency, especially for lipophilic agents [25].

3. Aqueous Phase

The aqueous phase acts as a dispersant phase in ethosomal formulations and is necessary for the formation of vesicles by hydrating phospholipid molecules allowing them to spontaneously assemble into vesicular structures [23]. The aqueous phase also accommodates hydrophilic drug molecules and supports overall system stability. However, the quality and pH of the water utilized will influence both vesicle integrity and subsequently drug release [26].

4. Drug Substance

The main advantages of ethosomal platforms are their potential to carry virtually all types of drug molecules - lipophilic, hydrophilic and amphoteric. Drugs of different natures are accommodated in the same vehicle. Lipophilic drugs tend to partition into the phospholipid bilayer, whereas hydrophilic drugs tend to be trapped inside the aqueous center of the ethosome [27]. As a result, the ethosomal technology is applicable to dermatology, anti-inflammatory therapy, antifungals and immunosuppression [28].

Table 1: Components of Ethosomal Gel Formulation and Their Functions

Class	Example	Use	Reference
Phospholipid	Soya phosphatidyl choline, egg phosphatidyl choline, dipalmitoyl phosphatidyl choline, distearoyl phosphatidyl choline	Forms the vesicle wall	29
Polyglycol	Propylene glycol	Acts as a skin penetration enhancer	29
Alcohol	Ethanol, isopropyl alcohol	Lends softness/flexibility to the vesicle membrane and enhances penetration	29-30
Cholesterol	Cholesterol	Stabilizes the vesicle membrane	30-31
Gelling agent	Carbopol 934	Gel former, increases viscosity and provides consistency	31

Types of ethosomes

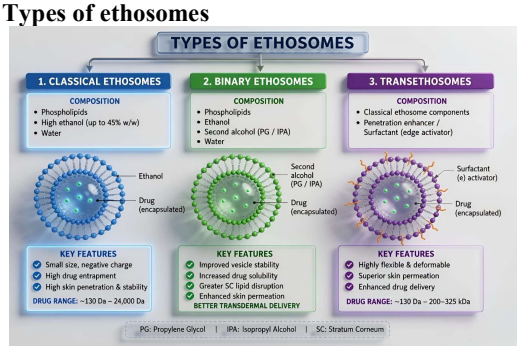

Fig.4 Types of Ethosomes

1) Classical ethosomes

Ethosomes based on classical formulations of phospholipids, water and ethanol were developed from conventional liposomes. Ethosomes have characteristics such as a small particle size, a negative surface charge and an increased entrapment efficiency compared to classical liposomes. These characteristics allow them to penetrate the skin better. Ethanol content is higher in ethosomes than in classical liposomes. High ethanol content in

ethosomes increases vesicle flexibility and permeability throughout the skin. High ethanol content contributes to a good stability profile for ethosomes. Due to their higher permeability and longer duration of stay in the skin, ethosomes are more effective in delivering drugs through topical and transdermal routes compared to classical liposomes. The ability to encapsulate a wider range of molecular weights (from 130.077 Da to 24,000 Da) highlights their versatility for topical and transdermal application [34].

2) Binary ethosomes

Binary ethosomes represent another variation of classical ethosomes. A secondary alcohol, typically propylene glycol (PG) or isopropanol (IPA) are added to the composition to work synergistically with ethanol and increase the performance of the vesicles. The additional alcohol helps stabilize and extend the shelf life of the vesicles as well as increase drug solubility within the lipid bilayer [35]. Additionally, the second alcohol disrupts the organization of the SC lipids more effectively than classical ethosomes alone. Therefore, binary ethosomes are considered more effective transdermal carriers and suitable for both hydrophilic and lipophilic drugs [36].

3) Transethosomes

Transethosomes are the latest generation of ethosomal systems designed to enhance the efficacy of transdermal drug delivery. They incorporate the basic ingredients of classical ethosomes with a surfactant or edge activator to create extremely deformable vesicles. These properties make transethomes capable of achieving even greater deformation and permeation than conventional ethosomes along with a significant enhancement of total drug delivery. The reported entrapment capabilities span a very broad molecular weight range (approximately 130 Da - up to 200 – 325 kDa). Therefore, they offer an opportunity for various therapeutic agents [38].

Mechanism of Action of Ethosomes

The primary function of ethosomes is to improve dermal and transdermal delivery of drugs through enhanced drug penetration through the skin. Systemic side effects are minimized. The targeted and sustained drug delivery is facilitated [37].

Drug permeation from ethosomal vesicles is primarily governed by two interconnected mechanisms:[38]

1) Ethanol effect
2) Ethosome effect

1) Ethanol effect

- As a powerful penetration enhancer, ethanol is one of the main components of ethosomes. There are several studies that describe the mechanism of action of ethanol.
- Ethanol enters the intercellular lipid spaces of the stratum corneum (SC).
- Ethanol reduces lipid packing density by disturbing the highly ordered lipid bilayers in SC. The lipids in SC become more fluid and permeable as a result.
- Ethanol creates temporary defects in the SC barrier by modifying the phase behavior of skin lipids. Improved drug transport across the skin is achieved by disrupting the lipid array which decreases diffusional resistance.
- Ethanol also increases flexibility of the ethosomal vesicle membrane, thereby improving penetration [39]

2) Ethosome Effect

- Because ethanol significantly increases fluidity of phospholipid bilayers, it directly leads to ethosome effect.
- Because of increased fluidity at high ethanol concentrations phospholipid bilayer of ethosome becomes soft, elastic and deformed.
- Soft and deformable vesicles easily go through damaged intercellular lipid channels in SC verses that arrive at deeper epidermal and dermal layers join with skin cell membranes and lipid domains.
- Fusion between vesicles and skin layer is what finally generates localized, controlled drug release in target location [40].

Collectively, the effects of ethanol and phospholipid bilayers account for enhanced skin penetration exhibited by ethosomes. Ethanol fluidizes SC lipids and increases flexibility of phospholipid bilayer, temporarily breaking down the skin barrier [41]. Soft and deformable vesicles generated as a result can subsequently migrate through the disrupted lipid matrix form transient paths and merge with deeper skin layers where they will deliver their contents into viable epidermis or dermis for a passive, targeted and prolonged therapeutic effect [42].

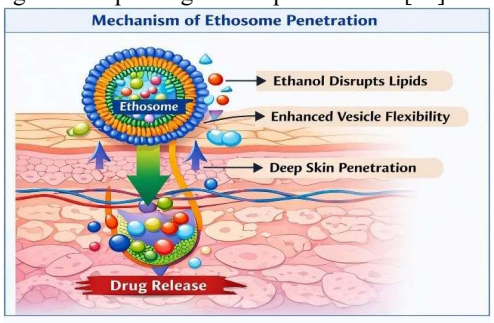

Fig.5 Mechanism of Ethosome Penetration

Advantages of Ethosomes:

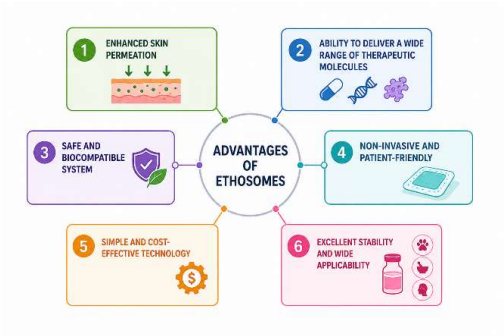

Fig.6 Advantages of ethosomes

1. Enhanced skin permeation: Drugs are transported efficiently across the skin, supporting both localized and systemic delivery regardless of concentration gradients.
2. Broad drug-carrying capacity: Hydrophilic and lipophilic drugs, peptides and macromolecules can all be encapsulated and delivered with entrapment efficiencies exceeding those of conventional liposomes.
3. Favourable safety profile: Formulation is based on GRAS-approved, non-toxic components and ethanol itself contributes a preservative action.
4. Patient-friendly, non-invasive administration: Because delivery is transdermal, pain and needle-related risks are avoided which supports better patient compliance.
5. Simplicity and cost-effectiveness: Preparation does not demand sophisticated equipment or complex methods such as iontophoresis, making the technology amenable to large-scale manufacture.
6. Good stability and broad applicability: Long-term formulation stability supports use across pharmaceutical, veterinary and cosmetic fields. [43,44]

Methods of Preparation of Ethosomes

Ethosomes are prepared by following methods:

1. The classical cold method
2. The ethanol injection-sonication method
3. The hot method
4. The thin-film hydration method
5. The reverse-phase evaporation method [45]

1. Cold method

1. Cold method is considered to be the easiest way to formulate ethosomes and it could be done under nitrogen in order to minimize oxidation.
2. Organic and aqueous phases are formulated separately.
3. For the Organic phase, the drug substance along with surfactant or penetration enhancer (if transethosomes are being formulated), lipid components and phospholipids are dissolved vigorously with mixing in ethanol or an ethanol-propylene glycol combination at 25-30°c.
4. At the same time, the aqueous phase (normal saline, water or buffer) is heated up to 25-30°c. Then, it is added very slowly into the Organic phase as a small jet of liquid or by adding drop wise via a syringe pump at a speed of approximately 175-200 µl/min.
5. Continuous mixing with magnetic or overhead stirrer at 700-2,000 rpm for 5-30 minutes allow the ethosomal vesicles to be formed.
6. Depending upon the drug's physical/chemical characteristics, it should be dissolved in one of the phases or both.
7. If smaller Vesicle sizes are wanted, sonication or extrusion may be employed afterwards. Once made, the final formulations are stored under refrigeration conditions. [46].

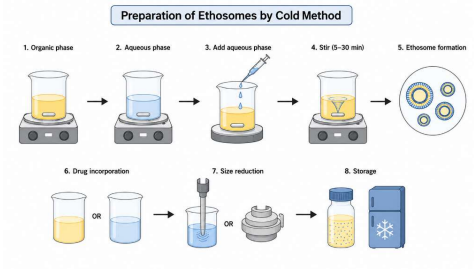

Fig.7 Cold Method for Ethosomes preparation

2.Hot method

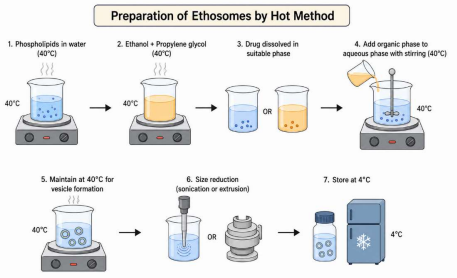

Fig.8 Hot method for ethosomes preparation

1. In contrast to the cold method in the hot method, phospholipids are dispersed first in distilled water and placed in a 40 °c water bath until they become uniformly distributed as a colloidal suspension.
2. In another vessel, ethanol and propylene glycol are mixed and also brought to 40 °c.

3. The drug is then dissolved in whatever phase provides the greatest similarity to its solubility. The two phases are allowed to come to equilibrium at 40 °c and then the Organic phase is slowly added to the aqueous phase while continuously stirring.
4. Following addition of the organic phase to the aqueous phase at 40 °c, the mixture is maintained at this temperature for completion of vesicle formation.
5. Subsequent application of sonication or extrusion techniques brings the Vesicle size to the desired range.
6. Finally, the prepared Formulation is stored under refrigerated conditions (at 4 °c) until needed. [47].

3.Ethanol Injection–Sonication Method:

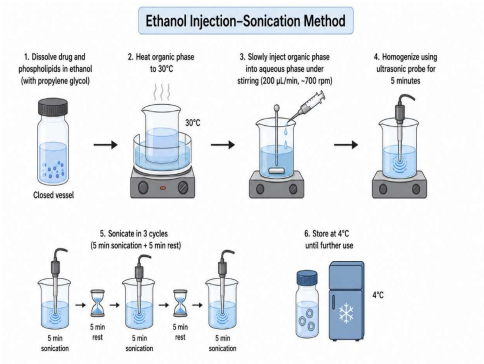

Fig.9 Ethanol injection- sonication method

1. In the ethanol injection-Sonication method, initially the drug and phospholipids are dissolved together in ethanol (with propylene glycol) within a sealed vessel.
2. Warming this organic phase to 30°c in a water bath ensures that the drug will dissolve completely.
3. It is then slowly injected into the aqueous phase while it is being stirred constantly at about 700 rpm via a syringe pump at a flow rate of approximately 200 µl/min.
4. An ultrasonic probe is used to homogenize this resulting dispersion for 5 minutes.
5. To reduce vesicle size further, after completing this initial cycle of sonication, the preparation undergoes three additional 5 minute cycles of sonication, followed by 5 min periods of rest between each of these additional sonication cycles.
6. Once ready for use, the finished preparation is stored at 4°c until needed [48].

4.Thin-Film Hydration Method

1. The Lipid dissolution step of the thin film hydration process begins with dissolving the phospholipids in a clean, dry round bottom flask using either chloroform alone or a chloroform-methanol combination (e.g. 3:1 or 2:1 v/v).
2. The solvent evaporation step involves removing the organic solvent from the flask containing the phospholipid film using a rotary vacuum evaporator operating above the lipid phase transition temperature. This causes a thin lipid film to form on the interior surface of the flask.
3. Any residual traces of solvent present on the lipid film are removed by allowing the film to remain under vacuum overnight.
4. The dried film obtained from steps a and b is then hydrated using either a water-ethanol solution or pbs-ethanol solution.
5. After hydrating the film with solution c, the flask is agitated and gently heated at a temperature suitable for the particular phospholipid being utilized.
6. The duration of hydration depends upon lipid composition and vesicle type. Hydration typically takes place over 30 minutes to six hours and leads to the development of the final ethosomal vesicles. [49]

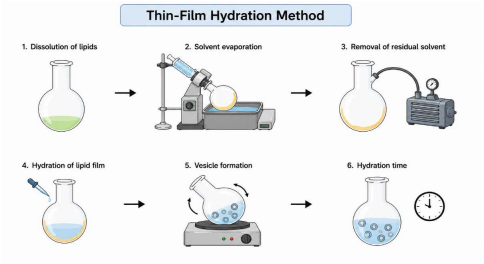

Fig.10 Thin film hydration method

5.Reverse-Phase Evaporation Method

1. Preparation of Organic Phase: Phospholipids are dissolved in a suitable organic solvent such as diethyl ether.
2. Emulsification: The organic phase is then combined with the aqueous phase in a 3:1 volume ratio and subjected to sonication using an ultrasonic bath at approximately 0°C for five minutes to produce a water-in-oil (W/O) emulsion.
3. Solvent Removal: Under vacuum the organic solvent is removed from the W/O emulsion and replaced by air. This results in the formation of a viscous gel.
4. Vesicle Formation: When this gel is vigorously agitated, it collapses to form a colloidal dispersion consisting primarily of large unilamellar vesicles. [50]

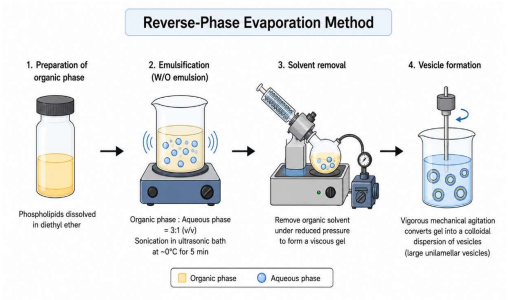

Fig.11 Reverse phase evaporation method

Characterization of ethosomes

Table 2: Characterization of ethosomes

Sr. No.	Parameter	Method / Instrument	Purpose / Significance	Reference
1	Vesicle size	Dynamic Light Scattering (DLS), Photon Correlation Spectroscopy	Establishes the particle size that governs skin penetration and drug release	51
2	Polydispersity Index (PDI)	DLS	Reflects how uniform the vesicle population is, a PDI below 0.3 signals a fairly monodisperse system	51
3	Zeta potential	Electrophoretic Light Scattering	Predicts physical stability, larger absolute values reduce vesicle aggregation	51
4	Vesicle morphology and shape	TEM, SEM, Cryo-TEM	Confirms spherical shape, lamellarity and structural integrity	51
5	Entrapment efficiency (EE%)	Ultracentrifugation, dialysis, gel filtration	Quantifies how much drug is held inside the vesicles	52
6	Drug content	UV-Visible spectrophotometry, HPLC	Confirms uniform drug distribution and formulation accuracy	52
7	Vesicle deformability / elasticity	Extrusion through polycarbonate membrane	Assesses how readily vesicles flex to pass through skin pores	52
8	Surface tension	Tensiometer	Reflects the penetration-enhancing contribution of the ethanol content	52
9	In-vitro drug release	Franz diffusion cell with dialysis membrane	Evaluates release kinetics and how well release is controlled	53

10	Ex-vivo skin permeation	Franz diffusion cell using animal/human skin	Determines flux, permeability coefficient, and penetration enhancement	53
11	Skin deposition	Tape stripping method	Measures how much drug is retained within different skin layers	53
12	Stability studies	Storage at 4°C and 25°C	Tracks changes in vesicle size, zeta potential, drug leakage and appearance over time	53

Applications of Ethosomes

1.Transdermal drug delivery.

Ethosomes increase skin fluidity and reduce interfacial resistance between the skin and the vesicle, which increases permeation through the stratum corneum. Therefore, they are used for drugs that do not penetrate well into the skin or suffer from extensive first pass metabolism
E.g. testosterone, propranolol and insulin [54].

2.Targeting pilosebaceous structures.

Another possible use of ethosomes is for targeted delivery to hair follicles and sebaceous glands. For example, for localized treatment of disorders affecting hair follicles, such as clindamycin and erythromycin for acne or minoxidil for alopecia [55].

3.Cosmeceuticals.

Ethosomes have been shown to improve the efficiency of cosmetic products by enhancing the stability, penetration and efficacy of cosmetic ingredients while reducing side effects such as skin irritation. In addition, the composition and size of the vesicles will determine how much deformation there is during application to achieve the desired level of elasticity. Vitamin E, vitamin C, coenzyme Q10 and minoxidil are all examples of cosmetic ingredients that have
been studied [53].

4.Drug delivery of proteins/peptide

Ethosomes improve the permeation of proteins and peptides that would normally not be able to cross the skin barrier as a result of their molecular structure, therefore allowing them to reach their site of action and deliver their therapeutic effect. Insulin, cyclosporine peptides,
growth hormone fragments are some examples [56].

5.Drug delivery of antipsoriasis drugs

Antipsoriatic agents such as methotrexate, tacrolimus and calcipotriol can also be delivered via ethosomes, which can increase their concentration in the skin and reduce systemic toxicity, thus making them easier to administer and resulting in better patient compliance and
better treatment outcome [57].

6. Transdermal drug delivery of central nervous system drugs

Central nervous system drugs can be formulated in ethosomal form to improve their transdermal absorption. This can allow for sustained drug levels and help control symptoms associated with Parkinson's disease. Trihexyphenidyl hydrochloride is one example [58].

7. Transdermal drug delivery of hyperlipidemia drugs

Ethosomal formulations can avoid first pass metabolism experienced with orally administered statins like simvastatin. As a result, transdermal administration can lead to higher plasma
concentrations and greater lipid reduction [59].

8.Antimicrobial/Antiviral Therapy

Because ethosomes can take antimicrobial/antiviral agents deeper into the skin than conventional formulations, they offer greater efficacy against microbial infections occurring on the skin surface. Clotrimazole, erythromycin, acyclovir are the examples [60].

9. Anti-inflammatory applications

Ethosomes can retain anti-inflammatory agents longer in the skin and make them available for a longer period of time than traditional formulations, making them useful in the treatment of inflammatory diseases affecting the skin. Diclofenac, ammonium glycyrrhizinate are the examples [61].

10. Hormone replacement therapy

In hormone replacement therapy ethosome patches can provide reliable and non-invasive transdermal drug delivery with long-lasting effects and good patient compliance. Testosterone, estradiol are the examples [60].

11. Gene/DNA delivery

A new area where ethosomes could potentially find application is gene/DNA delivery. Using ethosomes as a vehicle for delivering genetic material topically allows researchers to activate gene expression directly in the target tissue (skin). This has opened up exciting opportunities for gene therapy and basic dermatological research; plasmid DNA, antisense oligonucleotides are their examples [62].

12.Skin vaccine/cancer therapy

Ethosomes can be applied to enhance transcutaneous delivery of vaccines/anticancer agents while minimizing systemic toxicity and maximizing both local immune responses and drug efficacy. Protein antigens, 5-fluorouracil, paclitaxel are examples of such applications [63].

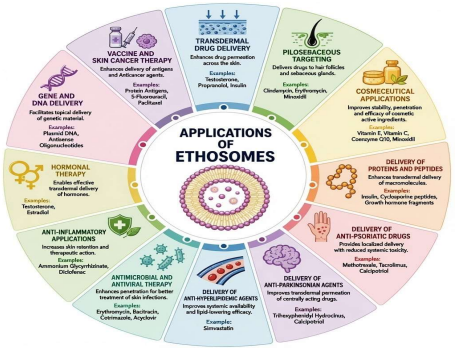

Fig.12 Applications of Ethosomes

Future Perspectives

The use of vesicles has been identified as an area of development for improving the clinical and commercial viability of ethosome based drug delivery systems. The development of newer forms of ethosomes including nano-ethosomes, trans-ethosomes and binary ethosomes is expected to improve the problems associated with ethosome based drug delivery systems i.e. improved stability, reduced drug leakage and increased scalability. Enhancements to the formulation can be achieved by incorporating additional components into the system, e.g. surface active agents, polymers or other biocompatible surfactants that can increase the deformation characteristics of the vesicles and thus the ability of the vesicles to penetrate the stratum corneum [64].

Research and product developments over the next decade will focus on developing stimulus responsive and targeted ethosome systems which release the drug payload in response to a specified trigger. E.g. pH shift, temperature change, enzyme activity. Incorporating ethosomes into hydrogel matrices, nanofiber scaffolds, microneedle arrays and 3-D printed transdermal devices presents opportunities to significantly improve both patient compliance and therapeutic outcomes. Ethosomes represent one of many approaches being investigated to develop carrier systems capable of delivering biologic drugs, peptides, vaccines and nucleic acid-based therapies through intact skin.

There are however several significant barriers that must still be overcome before ethosome based drug delivery systems become viable candidates for clinical translation. These include obtaining sufficient data regarding long term safety and feasibility of scaling up the manufacture of ethosomes. In addition, there is currently no standardization of regulations governing the use of ethosome based drug delivery systems. Therefore, future studies investigating this new class of drug delivery systems should utilize in vivo-in vitro correlations (IVIVCs), conduct clinical trials and employ quality by design methodologies to facilitate the transition of ethosome based drug delivery systems from bench top to commercialization. If research continues at its current rate, it seems probable that ethosomes will be part of the next generation of drug delivery technologies used for topical and transdermal applications.[65]

Conclusion

Ethosomes are versatile drug delivery systems characterized by high efficiency in various applications involving topical or transdermal administration of drugs. Due to their high content of ethanol, ethosomes present significantly better properties concerning drug penetration, encapsulation efficiency and drug bioavailability in comparison with other types of vesicles including liposomes.

The numerous benefits offered by ethosomes are supported by comprehensive characterization studies performed in vitro and preclinical trials evaluating their ability to deliver diverse groups of

therapeutics including hydrophilic/lipophilic compounds mainly for managing dermatological disorders.

However, despite the advantages presented by ethosomes several obstacles remain to be solved before their full application becomes feasible. Long term storage issues, scaling-up processes and regulatory approval are among the principal challenges facing the widespread introduction of ethosomes into practice. Recent advances in formulation strategies, incorporation of novel excipients and integration with modern delivery technologies will likely address many of these constraints.

Therefore, ethosomes appear to be promising candidates as "next generation" drug delivery systems whose therapeutic application should become increasingly viable if additional research is conducted aimed at establishing their clinical relevance and commercial viability.

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