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Ethosomes as Versatile Nanovesicular Systems for Transdermal Drug Delivery: Mechanistic Insights, Formulation Strategies, and Emerging Applications

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Abstract: Transdermal drug delivery has gained significant attention as a non-invasive alternative to conventional oral and parenteral routes; however, the formidable barrier function of the stratum corneum limits effective drug permeation. Ethosomes, ethanol-rich lipid vesicular systems composed primarily of phospholipids, ethanol, and water, have emerged as an advanced nanocarrier capable of overcoming this limitation. The high ethanol content imparts exceptional deformability to ethosomal membranes while simultaneously disrupting the lipid organization of the stratum corneum, thereby enhancing skin penetration and drug deposition. This review comprehensively discusses the composition, structural characteristics, types of ethosomes (classical, binary, transethosomes, nanoethosomes, composite and ligand-targeted systems), mechanisms of skin permeation, characterization parameters, and various preparation techniques. Furthermore, current applications of ethosomes in dermatological, transdermal, oncological, phytopharmaceutical, and cosmeceutical drug delivery are highlighted, along with their comparative advantages over conventional vesicular carriers. The review also addresses recent advances and future perspectives, emphasizing the potential of ethosomes as versatile and efficient nanovesicular systems for topical and transdermal therapeutic delivery.

Keywords: *Ethosomes, Skin Permeation Enhancement, Stratum Corneum, Transdermal Drug Delivery, Nanovesicular System, Future Perspectives.*

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I. INTRODUCTION

Transdermal drug delivery (TDD) has come up as a useful alternative to the traditional use of oral administration since it has a number of benefits, such as avoiding first-pass metabolism, enhanced therapeutic compliance, regulated drug release, and decreased gastrointestinal side effects(1). Though these advantages exist, high-performance transdermal delivery of most therapeutic molecules is constrained by the highly arranged and dense lipid structure of the stratum corneum which is the primary protective layer of the skin(2). Traditional carriers of vesicles like liposomes have minimal penetration capabilities through the deep epidermal strata as it has rigorous structures, and lacks sufficient contact with intercellular lipids(3).

To overcome these weaknesses ethosomes were presented as a superior vesicular system that can increase drug penetration through the skin(1). Ethosomes are pliable, compressible lipid vesicles that consist mainly of phospholipids, ethanol, water and active pharmaceutical agents. They are characterized by the inclusion of large percentages of ethanol, usually between 20 and 45 percent, which highly changes the structure and fluidity of the vesicle membrane(1,2).

Not only does such high ethanol content increase the solubility of a wide range of drug classes, but also destabilizes the tightly packed lipids of the stratum corneum causing the drug to permeate deeper and with a higher degree of effectiveness, as compared to the conventional liposomes(1,4). Dermatological, cosmetic and systemic transdermal Ethosomes offer high versatility in transporting small hydrophilic molecules to large hydrophobic and macromolecular agents, which makes them an effective carrier of various molecules(3).

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Over time, various modifications to the basic ethosomal composition have led to the development of binary ethosomes, transethosomes, composite phospholipid ethosomes, and ligand-targeted vesicular systems(3,4).

➢ *Composition and Structural Features of Ethosomes*

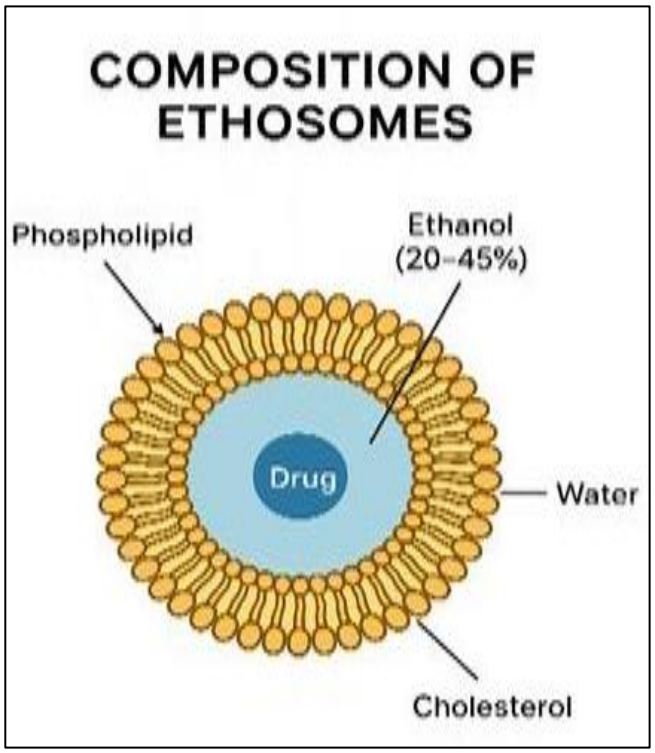

Fig 1 Composition and Structural Features of Ethosomes

Ethosomes have a composition and structural features similar to those of phosphatidylinositides. Ethosomes are lipid vesicles that are specifically created to deliver therapeutic agents into the skin using a highly flexible ethanol-containing vesicle(5). They have a basic structure of liposomes, except that with high levels of ethanol added on them, the physicochemical properties of the bilayer are modified, giving them incredible deformability, high penetration ability, and efficient entrapment of hydrophilic and lipophilic molecules(5,6). Phospholipids, ethanol, and water are the basic structural elements of ethosomes, whereas such optional ingredients as cholesterol, surfactants, stabilizers, and charge-inducing agents can be included depending on the formulation needs(5,7).

The ethosomal bilayer is made of the phospholipids that are the major components of this structure and it provides a semi-permeable membrane which can entrap various drugs(5). Phospholipids used commonly are phosphatidylcholine, which is a phospholipid obtained either by hydrolyzing soy or egg lecithin, and synthetic phospholipid derivatives which are selected due to their improved purity and stability(6). Increased fluidity of phospholipid bilayer in ethosomes because of ethanols disrupting hydrophobic interactions resulting in increased vesicle flexibility and skin penetration(8).

Ethanol, which is usually found in the range of 20-45 percent, is essential in dual functions in ethosomal systems(5). It serves as an excellent penetration enhancer by disrupting tight lipid domains of the stratum corium leading to high skin permeability(5,8). Furthermore, ethanol increases the solubility of drugs and increases the creation of smaller and highly deformable vesicles(5). Ethanol and phospholipid have a synergist interaction that separates ethosomes and traditional liposomes as well as other vesicular carriers(8).

Water is the aqueous component of ethosoms and it is involved in forming vesicles by hydrating the phospholipid head groups(7). It also permits the entrapment of hydrophilic drugs under the aqueous core or within the hydrophilic parts of the bilayer(8).

Other formulation factors can be added in order to maximize performance. Cholesterol may also be used to enhance the stability of vesicles, but ethosomes tend to be stable to lower cholesterol than liposomes because ethanol stabilizes the vesicles(5,8). To control the charge of the vesicles, aggregation, and stability during storage, stabilizers, buffers or charge-inducing agents may be added(5,7).

Ethosomes are structurally diverse, as in some formulations and preparations, ethosomes can have unilamellar or multilamellar vesicular architecture(7). Having a relatively small vesicle size, they have a deeper penetration into dermal layers(6,8). Ethosomes usually have a negative zeta potential that is affected by the presence of ethanol and phospholipid mixture that provides the stability of the colloid due to a reduction of vesicles aggregation(5). In sum, the combination of phospholipids, ethanol, and water is unusual which leads to very deformable system of vesicles that can bypass the skin barrier(5). This is the structural advantage enabling ethosomes to entrap a broad variety of therapeutic agents and achieve superior permeability, controlled drug release, and therapeutic efficacy in transdermal and dermatological practices(5,8).

➢ *Types of Ethosomes*

Ethosomes are vesicular vehicles that enhance transdermal drug delivery to overcome the stratum corneum of the skin. Their lipid bilayer is flexible with high ethanol concentration, which enables the vesicles to be easily penetrated into the epidermis and dermis. A number of ethosomes have been produced in order to maximize drug loading, stability, deformability, and penetration efficiency.

➢ *Classical Ethosomes*

Classical ethosomes The classical ethanol-based vesicular carriers are developed to surmount the barrier properties of stratum corneum and increase transdermal drug delivery. They consist of mainly phospholipids, water and high contents of ethanol (20-45 w/w). The addition of ethanol plays several essential roles: it flattens the phospholipid layer of the vesicle, enhances vesicle deformability, and disrupts tightly packed lipid architecture of the stratum corneum thus helping in the movement of active molecules in the skin. Classical ethosomes have the capacity of entraping lipophilic

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and hydrophilic drugs with the phospholipid bilayer providing a protective surrounding environment that maintains labile compounds and enhances their bioavailability. The size distribution of the vesicles is influenced by small to nanoscale (usually 50200 nm), negative zeta potential and rounded or slightly elliptical morphology, which is the property that can lead to its penetration through intercellular lipid channels and prevent structural damage of the skin. The technique of preparation, including cold method, hot method, or thin-film hydration, determine the size of the vesicles, entrapment efficiency, and stability, and optimization of formulations during the clinical performance is the key factor. All modified ethosomal systems such as binary ethosomes, transethosomes, composite phospholipid ethosomes and actively targeted ethosomes are based on classical ethosomes, and offer an adaptable platform that combines high permeation, structural flexibility and biocompatibility(9,10).

- *Binary Ethosomes*

Binary ethosomes are an adapted type of classical ethosomes that enhances the vesicle flexibility, stability, and entrapment of drugs with the addition of a second alcohol or cosolvent (e.g., propylene glycol, isopropyl alcohol) and ethanol. The secondary component reacts with the ethanol phospholipid phosphate ester head group to augment the membrane fluidity, minimize vesicle aggregation, and preserve the structural integrity during the storage. The system permits greater deformability of the vesicle which facilitates the passage of the vesicle across the fine intercellular spaces of the stratum corneum. Binary ethosomes preserve ethanol-induced permeation enhancement of classical ethosomes and the cosolvent additionally stabilizes vesicles and can alter vesicle size, zeta potential, and encapsulation. These vesicles are generally nanoscale in diameter (50-250 nm), morphologically homogeneous and have negative surface charge which increases their structural stability and biophysical compatibility with skin. Binary ethosomes have been viewed as a compromise between classical ethosomes and more sophisticated modified systems like transethosomes or actively targeted ethosomes, offering all three properties of deformability, stability, and solubilization capacity(9,10).

- *Transethosomes*

Transethosomes represents a progressive variant of ethanol based vesicular carriers which is an expansion of the classical ethosomes by adding edge activators or surfactants to the ethanol-phospholipid bilayer, the effect of which is a highly deformable and penetrative vesicular system. Transethosomes are structurally made of phospholipids, water, high concentration of ethanol and an edge activator like a non ionic surfactant (e.g., Tween 20/80, Span), which intercalates in the membrane resulting in enhanced bilayer fluidity and elasticity. It is this dual improvement of ethanol and surfactants that enables the transethosomes to adapt to the lipid content of the stratum corneum and entrap intercellular lipids, and traverse narrow skin channels more easily compared to classical ethosomes. The existence of edge activators not only enhances vesicle deformability, but also affects physicochemical characteristics of vesicle size, zeta potential, and entrapment efficiency that can frequently allow smaller sizes and greater drug encapsulation than non activated ethosomal systems. Since transethosomes combine penetration enhancing properties of ethanol with surfactant mediated flexibility, they have enhanced membrane interactions of skin and transdermal permeation potential, which is a big advancement in ethosomal carrier development(11,12).

- *Composite Phospholipid Ethosomes.*

A hybrid vesicular system, composite phospholipids ethosomes, is a system that combines classical ethanol-rich ethosomes with extra lipid or polymeric components to improve the stability, encapsulation capacity and skin compatibility of vesicles. Such vesicles are usually comprised of phospholipids, water, ethanol and secondary lipids or polymers including cholesterol, ceramides or chitosan that strengthen the vesicle bilayer and limit the leakage of drugs carried. The incorporation of the additional components adjusts the bilayer rigidity, the surface charge, the size of the vesicles and the general physicochemical stability, preserving the ethanol-based boost of skin permeation.

Composite phospholipid ethosomes possess adequate flexibility and deformability to pass through the narrow intercellular spaces of the stratum corneum and the reinforcing elements enhance mechanical stability during storage. Optimization of the ratio of phospholipids to the secondary lipids or polymers enables the size, zeta potential, and entrapment efficiency of vesicles to be adjusted to meet desired size, zeta potential and entrapment efficiency requirements in the effective encapsulation of both hydrophilic and lipophilic compounds. The design approach is a significant improvement on classical ethosomes, with a tradeoff between skin permeability and structural integrity(6,13).

- *Ligand-Targeted Ethosomes(Active Targeted Ethosomes)*

Actively targeted ethosomes are artificial vesicular systems that are engineered to transport therapeutic agents to the skin, directly, and to the cells or tissue of interest. In contrast to the traditional ethosomes, which use active diffusion and ethanol-mediated permeation as the main means of action, targeted ethosomes are actively functionalized on their surface with ligands. These ligands work with special receptors or labels on target cells and promote receptor-mediated endocytosis and enhances intracellular drug delivery. The membrane fluidization caused by ethanol and the ligand-mediated targeting leads to improved penetration, site-specific accumulation and less exposure to the system(14).

Strategies of functionalization of actively targeted ethosomes comprise peptides, antibodies, folate, hyaluronic acid (HA), or carbohydrates, and each of them is designed to meet a specific therapeutic purpose. Inflamed or hyperproliferative skin diseases can be targeted using conjugated peptides to overexpressed receptors or antibodies to select cells expressing the antigens. HA and carbohydrate-modified ethosomes are able to bind to CD44 receptors or

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lectins which induces uptake of the cell and enhances local bioavailability of encapsulated compounds(8).

Also, actively targeted ethosomes are highly stable, exhibit a high degree of entrapment and sustained delivery, thus suitable in the delivery of both small molecule and macromolecular drugs. These systems use the combination of ligand-mediated targeting with the natural deformability of ethanol-rich vesicles to produce targeted and efficient delivery of drugs into the skin with minimal off-target effects. They may serve to deliver anti-inflammatory molecules, antioxidants, and other therapeutic biomolecules which need skin permeation and site-specific deposition(15).

➢ *Nanoethosomes*

The nanoethosomes are a fine, high-fine alteration of the classical ethosomes and are generally between 30 and 150 nm in diameter, which are created to enhance skin permeability, vesicle integrity, and encapsulation efficiency. They are structurally made of similar components as classical ethosomes: phospholipids, water and high levels of ethanol (20-45%), but their smaller size enhances surface area and allows easy passage through small intercellular spaces in the stratum corneum. In addition to putting into motion the phospholipid bilayer of nanoethosomes, making it deform, the ethanol molecules in the nanoethosomes disrupt the tightly packed lipids of the skin barrier making it more permeable.

Nanoethosomes are usually characterized by homogeneous spherical morphology, negative zeta potential and a high entrapment efficiency, which would lead to physicochemical stability as well as sustained release characteristics. These vesicles can be a versatile system of delivering hydrophilic and lipophilic molecules and their nanoscale size enables a deeper penetration of epidermal layers in comparison to traditional ethosomes, binary ethosomes, or the transethosomes. Through optimisation of the composition and preparation parameters researchers can tune vesicle size, surface charge, and bilayer rigidity in order to have a balance between stability and increased skin permeation(6,13).

➢ *Mechanism of Skin Penetration by Ethosome:*

- *Stratum Corneum as the Primary Barrier*

The primary barrier to transdermal drug delivery is the stratum corneum because it has a very well-organized structure that is comprised of corneocytes that are held together by a dense intercellular lipid matrix. This organization has a serious inhibitory effect on the dispersion of drugs through the skin(16,17). Traditional liposomes cannot penetrate through the deepest layers of the stratum corneum in large quantities hence is primarily used as drug reservoirs on the skin surface . Conversely, the peculiarities of ethosomes, which are created to address this obstacle with the help of their specific composition and physicochemical characteristics, allow overcoming it(1,18).

- *Ethanol-Induced Lipid Fluidization of the Stratum Corneum*

The feature of the ethosomes is a high content of ethanol. Ethanol is a famous penetration enhancer that reacts with lipids of stratum corneum resulting in decreasing the lipid transition temperature, augmenting lipid fluidity, and disturbing tightly packed lipid lamellae among cells(19). Nonetheless, comparative research done on ethosomal formulations and their respective hydroethanolic drug solutions showed that ethosomes exhibit a much higher degree of enhancement of skin penetration with respect to ethanol alone and, therefore, ethanol is synergistic with phospholipid vesicles as opposed to acting independently(1,8,18).

- *Vesicle Elasticity and Deformability.*

Ethanol also gives the phospholipid bilayers of ethosomes soft and flexible properties that are highly deformable. This is elasticity that enables the ethosomal vesicles to conform and squeeze through small intercellular channels of the stratum corneum that are in the plane of rigid liposomes. The characteristic of size and shape variability of ethosomes allows them to adjust to the dissimilarity microstructure of the skin that allows penetration of deeper layers without the vesicle- rupture(1,8).

- *Interaction with Stratum Corneum Lipid Matrix*

The ethosomal phospholipids are highly attracted to lipids on the skin as they are composed of similar elements. Ethosomes are activated upon penetration and partially incorporated into the intercellular lipid domains of the stratum corneum, causing short-lived structural rearrangements and deteriorated barrier functioning . These lipid-lipid interactions lead to a higher level of permeability and a high degree of drug partitioning into deeper layers of skin(17,20).

- *Vesicle-Mediated Drug Transport and Release*

Trap -Ethosomes are carrier system through which entrapped drug molecules are delivered to the stratum corneum. It is the release of drugs in the skin, and transdermal flux is reliant on the connection between the drug affinity to the vesicles and the drug solubility in stratum corneum lipids. The experimental results proved that ethosomes with entrapped drug had a considerable positive effect on skin deposition and permeation, but the use of ethosomes with non-entrapped drug did not positively affect skin delivery, which is important to note that vesicle-associated transport is important(8).

- *Characterization of Ethosomes*

Ethosomes are defined as small bubbles of water, formulated by the mixture of ethanol and water. Ethosomes Characterization Ethosomes are small bubbles of water that is formed by the blend of water and ethanol. Ethosomes are soft vesicular carriers that consist majorly of phospholipids, ethanol and water which are formed to facilitate transdermal delivery of therapeutic and cosmeticeutical agents. Ethosomes have to be properly characterized to comprehend

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their physicochemical characteristics, stability, and functionality in skin delivery systems(21,22).

The vesicle size and size distribution are important in regulating the skin penetration as well as the drug release pattern. Ethosomal preparations tend to be nanoscale vesicles with a narrow polydispersity, facilitating simplicity of permeation into the stratum corneum. Dynamic light scattering measurements are usually employed to measure the vesicle size and polydispersivity index, and the zeta potential measurements allow understanding the surface charge and colloidal stability(21,23).

Transmission electron microscopy or scanning electron microscopy morphological characterization shows that ethosomes are usually spherical vesicles with unilamellar or multilamellar structure. When ethanol is present, it enhances the fluidity of lipid-bilayers to form soft and deformable vesicles that can penetrate the deeper layers of the skin(21,23).

Formulation efficiency is determined by the entrapment efficiency and drug loading capacity. Both lipophilic and hydrophilic drugs are highly entraped in ethosomes because of high solubilization of drugs in the ethanol layer and effective incorporation of drugs into the phospholipid bilayer. The most common way of determining the efficiency of enrapture is by centrifugation or dialysis followed by the quantitative analysis of the drugs(22,23).

Drug encapsulation and stability of formulation is confirmed using Thermal and compatibility studies. DSC shows the variation of drug thermal behavior, including the shifting or disappearance of peaks, at which crystallinity decreases. Fourier transform infrared spectroscopy is used to ensure that the drug and formulation constituents do not interact with one another significantly(21,23).

Another characteristic feature of ethosomes is vesicle elasticity which helps a lot in the increased transdermal effectiveness. The adaptability of the lipid bilayer caused by ethanol allows the ethosomes to enter the pore that is smaller than its own diameter which leads to increased skin permeation of the ethosomes as compared to the conventional liposomes.

Franz diffusion cell in vitro studies of drug release have generally shown sustained and controlled drug release of ethosomal formulations. Further evivo experiments of skin permeation and deposition also testify to the high drug flux and high drug concentration in deep skin layers(22,24).

According to stability studies, the ethosomes are physically stable during prolonged storage periods, and there are minimal alterations on the size of the vesicles, surface charge, and drug content. Ethanol is also important in avoiding the aggregation and leakage of the vesicles and drugs during storage(21,22).

II. METHODS OF ETHOSOME PREPARATION

Ethosome Preparation Various methods exist in the preparation of ethosomes. During the years, numerous preparation methods have been designed and streamlined to fit certain therapeutical requirements. Such techniques are simple and low-energy techniques including cold, hot, conventional and ethanol injection techniques versus high-energy techniques including sonication, extrusion, microfluidization and high-pressure homogenization. Also, more specific methods like reverse phase evaporation, freeze-thaw cycling, supercritical fluid based methods and processes that use ultrasound have been investigated to improve drug loading, uniformity of vesicles and stability of formulations.

The two methods have their own strengths and weaknesses in terms of processing conditions, encapsulation efficiency, vesicle deformability, and industrial feasibility. The rational design and optimization of ethosomal formulations to promote effective and controlled delivery of drugs through transdermal is impossible without a proper comprehension of these preparation methods. The next section is a systematic description of the different methods used in preparing ethosomes, its principles, the process, benefits and shortcomings. According to the ethosome preparation method, the solution comprised the following: 1, 2-dihydroxy-1, 2-benzo-benzene, 1, 2-dihydroxy-2, 2-benzo-benzene, and 1, 2-dihydroxy-3, 3, 4-benzo-benzene.

- *Cold Method of Ethosome Preparation*

In ethosome preparation method, the following solution was used: 1, The most common and more popular technique used in the preparation of ethosomes is the cold method as it is simple, reproducible and can be used in thermolabile drugs. This technique does not involve the use of high temperatures and as such, preserves the stability of the active pharmaceutical ingredient as well as the phospholipid constituents. Cold method has been effectively employed in the preparation of ethosomal formulations to be used as an in-topical and transdermal drug delivery method as evidenced by a number of in-vitro, ex-vivo, and in-vivo studies(25,26).

The phospholipids e.g. phosphatidylcholine are initially dissolved in ethanol and stirred in a continuous stirring at room temperature in the cold procedure(25,27). Ethanol has a dual feature in this system, it is a solvent to lipids, and it is a penetration enhancer, which fluidizes the stratum corneum lipids(26). Both the ethanol concentration and its degree of concentration is a formulation factor that is important, with the normal range being 20-45% v/v, because it determines the size of the vesicle, entrapment capacity and the skin permeation properties(28). Depending on the dissolution profile of the drug molecules, they are dissolved either in ethanolic phase or in aqueous phase(25).

Individually, the aqueous phase (usually pure water, buffer solution or polyol-containing water) is kept at the same temperature as the ethanolic phase to avoid abrupt separation of the phases. The water solution is then slowly dripped into the ethanolic lipid phase as it is stirred under constant

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motion(27). This is a controlled addition and results in the spontaneous creation of soft and malleable vesicles called ethosomes(26). The slow drying of phospholipids under ethanol leads to high deformability nanosized vesicles.

In order to achieve a smaller size and a homogeneous size distribution, the dispersion is then subjected to size reduction methods including probe sonication, bath sonication or extrusion through polycarbonate membranes. The duration and strength of sonication is important in determining the ultimate size of vesicles and their stability(25,27). The ensuing ethosomal suspension can then be added into an appropriate gel base to be applied topically or transdermally.

The cold technique has proven to have very good results in regard to high drug entrapment efficiency, increase in skin permeation and prolonged drug release. The research with febuxostat, anti-acne drugs, and bioactive factors like curcumin and betanin has provided evidence that the cold method of ethosome preparation is much more efficient in transdermal delivery in comparison with the conventional formulations used(25). Moreover, animal and ex-vivo skin models have more often reported that ethosomal gels made by the method have better anti-inflammatory efficacy, enhanced skin penetration, and increased therapeutic effect(29).

- *Hot Methods:*

Hot method Ethosomal vesicles preparation is a commonly used and reproducible method and is particularly effective with lipophilic drugs and those that are moderately thermally stable. This technique relies on the regulated heating of lipid and aqueous phases, which assist in the creation of vesicles when a large concentration of ethanol is present, causing the increase of the vesicle flexibility and the enhancement of the skin permeation.

In this technique the phospholipids like phosphatidylcholine are first dispersed in distilled water and then heated to a temperature normally between 40 degC and 60 degC. To ensure an appropriate degree of lipid fluidization and hydration, it is recommended to keep the temperature at a level that is greater than the phase transition temperature of the phospholipid. The individual dissolution is made in ethanol, and the ethanolic solution is heated to the same temperature as the aqueous lipid phase. The solution containing the ethanol drug is then added gradually to the heated aqueous lipid dispersion, and they are stirred.

Heat-ethanol interaction influences the reorganization of phospholipid bilayers in the hydroethanolic medium enabling the spontaneous formation of ethosomal vesicles(30,31). They continue with constant stirring up until a predetermined time to confirm the uniformity of vesicles formation and uniform distribution of drugs within the system. To obtain the desired vesicle size and enhance homogeneity, the resultant dispersion can be passed through size reduction procedures, including probe sonication or extrusion.

This may result in the large or small unilamellar vesicles depending on the processing conditions(30). Once the size has been reduced, the ethosomal dispersion is left to cool slowly to room temperature which stabilizes the vesicular structure and reduces aggregation.

The hot technique has been demonstrated to obtain nano-sized ethosomes with a small size distribution and a large drug entrapment efficiency(31). Ethanol is very critical as it enhances the fluidity and the deformability of the lipid bi-layer. Ethanol also increases solubility of drugs and promotes better penetration in the skin through destabilization of the structure of lipids in the stratum corneum(26,32). The synergistic effect of heat and ethanol helps to make the vesicles form efficiently and enhance drug loading.

Although the two approaches are useful in the preparation of ethosomes, the hot technique has a benefit of reduced processing time and higher lipid hydration. It is however not appropriate in drugs that are thermolabile since exposure to high temperatures can lead to the degradation of the drug. Thus, the choice of the preparation method depends on the physicochemical characteristics of the drug and the purpose it is to be used(33).

In general, hot method is a straightforward yet sturdy and scalable ethosomes preparation method. It is also appropriate in the pharmaceutical, transdermal, or cosmetic formulations as it is reproducible and capable of formulating stable nano-vesicular systems(26,32).

- *Conventional Method:*

The most popular method of preparing ethosomes is conventional or classical because it is simple, repeatable and produces stable vesicular systems in the delivery of drugs across the dermis. The principle of this technique is the regulated contact between phospholipids, relatively large concentration of ethanol, and aqueous medium, which results in the spontaneous creation of soft and supple vesicles that are able to penetrate deep skin layers(4,26,32,34).

Phospholipids, including phosphatidylcholine are dissolved in ethanol in the first step in this technique, which is continuously stirred. This is normally done at room temperature or with a slight heating effect so that all the lipid elements dissolve fully. Ethanol is essential in the design of ethosomal since it does not only dissolve the phospholipids, but also gives the vesicular bilayer elasticity and deformability. This ethanolic phase typically contains lipophilic drugs and the aqueous phase solubility of hydrophilic drugs can be soluble separately in the aqueous phase or not, depending on the physicochemical properties of the drugs(4,26).

With a slow addition of distilled water or another suitable buffer, the ethanolic solution, which has been completely dissolved, is stirred with the lipid components, to the amount of water. The slow addition of the water phase triggers the spontaneous formation of the vesicles because ethanol causes the rearrangement of the phospholipid

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molecules. Adding water makes the system turbid, which means that ethosomal vesicles were formed. Constant stirring is also kept at a certain period of time to achieve good vesicle formation and proper drug entrapment(26,32).

In order to achieve nanosized ethosomes with a fine size distribution, the resultant dispersion is usually treated to size reduction methods like sonication or extrusion. Sonication is used to reduce the size of larger vesicles into smaller ones (more uniform) to increase stability and penetration efficacy of the formula through the skin. The ethosomal suspension that is ready is normally kept at refrigerated temperatures so as to keep the vesicles intact and reduce the loss of ethanol(34,35).

The traditional approach has a few benefits, such as it is easy to prepare, has a high drug entrapment efficiency, and can be combined with a variety of therapeutic agents. Transdermal permeation Ethanosomes formed in this manner are found to be more than twice that of traditional liposomes, with the discovery of ethanol-induced lipid fluidization and the flexibility of the phospholipid bi-layer(4,32). Topical and transdermal application of drugs with low skin penetrability is especially appropriate to use the classical method because of enhanced penetration(34).

The traditional approach has some drawbacks regardless of its benefits. state that high ethanol content can make the skin irritable to individuals, and the stability of the vesicles is subject to failure by improper optimization of the formulation parameters like ethanol concentration, lipid content, and stirring conditions. As such, optimization of the formulation is crucial in order to obtain safe, stable and efficient ethosomal systems(26,35). However, the traditional technique still remains as a base and one of the widely used techniques of making ethosomes particularly in the study of dermatological and transdermal drug delivery.

- *Reverse Phase Evaporation Technique (RPE)*

One of the well-established vesicle fabrication methods that are modified to prepare ethosomes is the reverse phase evaporation method (RPE) which is important in the preparation of ethosomes to attain high drug entrapment, especially of hydrophilic and amphiphilic molecules. The phospholipids, in this technique, are first dissolved in an organic solvent system like chloroform, ether or in a mixture of chloroform and methanol. It is dissolved in an aqueous phase separately with ethanol at a specific concentration which is normally 20-45% which is very important in giving the drug ethosomal properties. It is then mixed with the organic phase by probe or bath sonication where a water-in-oil emulsion is created(5,36).

Further evaporation of the organic solvent at low pressure in a rotary evaporator results in the development of a viscous gel. In case of further hydration, this gel collapses to give vesicular structures. The aqueous phase contains ethanol which is incorporated into the phospholipid bi-layer making the membranes fluid and deformable. This is what makes ethosomes different as compared to traditional liposomes prepared in the same method(36,37). The presence of the liquid containing ethanol disrupts the packing of lipids, and this results in the appearance of elastic nanovesicles that can penetrate deeper layers of the skin.

RPE method has a variety of benefits and they include a high encapsulation efficiency, enhanced drug loading, and the size of the vesicles is controlled. Solvents and lipid additions like cholesterol have a very strong effect on the properties of vesicles, they decrease the size of the vesicles and enhance the rigidity of the membrane(36). Nevertheless, the high cholesterol content might decrease the membrane flexibility so the optimization of the formulation is needed.

Although these benefits exist, the RPE approach has shortcomings like use of organic solvents, possible toxicity of remnant solvents, complicated processing procedures and scaling issues. Its industrial use is further restricted by the need to have as much solvent removal as possible. However, RPE is still useful as laboratory-scale method of making ethosomes in case of need to load drugs and make uniform vesicles(5,36,37).

- *Ethanol Injection Method*

An ethanol injection procedure is an easy and repeatable method of making ethosomes, especially lipophilic and moderately hydrophilic drugs. The phospholipids are then dissolved in ethanol in this technique, which doubles up as a penetration enhancer. The aqueous phase containing the drug is placed under constant stirring and controlled temperature so that ethanolic lipid solution is slowly injected to it(37,38).

Since ethanol spreads quickly into the aqueous solution, spontaneous self-assembly of phospholipids takes place and results in the creation of nanosized vesicles. The high concentration of ethanol which is usually 30-45 percent penetrates into the lipid bilayer, shrinking the size of the vesicles and raising the membrane elasticity. These properties are very critical in improved transdermal penetration(4,37). This is a relatively safer process as opposed to reverse phase evaporation because it does not involve use of any other organic solvents besides.

Ethanol injected ethosomes tend to be smaller in particle size and have a smaller size distribution than traditional liposomes. Ethanol improves the solubility of drugs and increases the entrapment efficiency of drugs which are insoluble in water. Also, ethanol disturbs the lipidal structure of the stratum corneum and also encourages drug permeation through the skin(38).

The weaknesses of this approach are however, vesicle instability in very high ethanol concentrations and low encapsulation of highly hydrophilic drugs. Drug leakage could also be caused by high rates of ethanol diffusion during vesicle formation when the formulation parameters are not optimized(5). Nevertheless, ethanol injection has been considered to be one of the most popular procedures used to prepare ethosomes because of its simplicity, low energy usage, reproducibility as well as scalability.

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➢ *Mechanical Dispersion Method*

The conventional ethosome method of preparation used is mechanical dispersion, especially in topical and gel based preparations. Here, the drug is dissolved in ethanol in which the phospholipids are dissolved and the water is gradually added during constant mechanical stirring. This is normally performed at room temperature or on the controlled conditions to reduce the process of evaporating ethanol.

The stirring that provides the mechanical energy facilitates lipid hydration and vesicle formation. Ethanol is inserted between the phospholipid bilayers which gives the vesicles flexibility and deformability. The technique is particularly appropriate when it comes to making ethosomal gels, in which the vesicular suspension may be directly added to an adequate gelling base(32).

Significant benefits of mechanical dispersion are that the dispersion is easy to operate, the cost of production is low and that it allows the dispersion of thermo-sensitive drugs since no heating is to be done. The process itself does not need any special equipment and therefore can be used in the laboratory and also in small scale production.

Nevertheless, larger vesicle sizes and wider size distributions are common to ethosomes formed as a result of mechanical dispersion. Thus, nanosized vesicles and enhancing uniformity are often obtained by post-processing methods like sonication or extrusion. Reproducibility could also vary due to variations in stirring speed, hydration rate, and ethanol concentration(5). Nevertheless, mechanical dispersion is still an attractive method of ethosomal gel preparation because of its convenience and applicability in dermatology(32).

➢ *Sonication Method*

Sonication technique is mainly employed as a vesicle size-reduction process but also has the potential of being applied as a single technique in the preparation of ethosomes. Here, the suspensions of ethosomal which are either prepared by dispersion or cold methods, are exposed to probe sonication or bath sonication. The ultrasonic waves with high frequency are used to decrease the size of the vesicles and enhance the homogeneity(39).

Sonication causes cavitation forces which rupture multilamellar vesicles and transform them into small unilamellar vesicles. This mechanism has a major impact on the size of vesicles, lamellarity, and distribution of drugs in the vesicles. Smaller vesicles formed by sonication have better penetration of the skin as the surface contacts are more and there is higher deformability(39).

Probe sonication is superior to bath sonication and has the disadvantage of localized heating, which can cause the destabilization of thermo-sensitive drugs. Sonication is usually done periodically and cooled down to avoid degradation. Even though sonication is effective, some of its limitations include the possibility of contamination of metals by the probe tips, scalability and potential degradation of drugs in case of excessive input of energy.

However, sonication is a necessary method to generate nanosized ethosomes that have a high penetration rate and uniformity of formulation(5,39).

➢ *Extrusion Method*

The extrusion technique which is used consists of passing ethosomal suspensions through polycarbonate membranes of a specified pore size to create vesicles of a homogenous size distribution. The technique is usually used following preliminary formation of the ethosomes by dispersion or injection technique(5).

The cyclic extrusion reduces the size of the vesicles and transforms the multilamellar vesicles into the unilamellar ones. Extruded ethosomes have been shown to be more size uniform, stable, and reproducible, resulting in predictable penetration behavior of the skin(4).

Extrusion, though beneficial, is not cost effective, time consuming and does not suit mass production. It is also limited in its industrial usage by membrane clogging, loss of the product and high cost of operation. Nevertheless, extrusion is useful in case of experimental formulations, where vesicle size has to be strictly controlled(4,5).

➢ *Freeze–Thaw Cycling Method*

The freeze-thaw cycling is a method of drug delivery that includes freezing and thawing of the ethosomal suspension repeatedly to enhance efficiency in drug encapsulation and the uniformity of the vesicles. Freezing interferes with lipid bilayers and thawing permits the rearrangement of lipids into more stable vesicles(5).

This is especially useful in increasing the encapsulation of hydrophilic drugs. Nevertheless, prolonged freeze-thaw steps can lead to the aggregation, leakage or instability of vesicles. Hence, this method is most commonly used as a supplement technique and not a major preparation method(5,40).

➢ *Microfluidization Method*

Microfluidization is a high energy method where lipid and aqueous phases are forced through microchannels with high velocity resulting in controlled collisions converting to ethosomes of uniform diameter. The technique has a good reproducibility and scalability.

Ethosomes generated via microfluidization have narrow size distribution, high stability, and increased transdermal penetration. The expensive nature of equipment and the danger of degradation of sensitive drugs due to shear is however a major problem.

➢ *High-Pressure Homogenization Method*

High-pressure homogenization is a method used to decrease the size of vesicles through subjecting ethosomal suspensions to high pressure through narrow valves. The process results in stable nanosized vesicles that have greater penetration properties(5).

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The process is appropriate in large scale production in industries because it can be duplicated and scaled. Nevertheless, the homogenization process may increase heat production, which can then impact on thermo sensitive medications and thus require efficient cooling devices(40).

- *Supercritical Fluid-Based Method*

A solvent-free method of preparation of ethosomes is provided by supercritical fluid-based procedures, especially in the case of carbon dioxide. At the supercritical conditions, the solubility of lipids is enhanced and they are quickly expanded to vesicles.

This greener way makes homogeneous vesicles that have a low amount of solvent left. Nevertheless, its use is restricted by the necessity to have special equipment and technical skills(5).

- *Ultrasound-Assisted Method*

Ethosome preparation UAE is the fusion of dispersion with regulated ultrasonic energy that promotes the formation of vesicles, drug loading, and uniformity. The procedure enhances efficiency of penetration by development of tiny and deformable vesicles.

Although effective, its drawbacks are the scalability issues and the possibility of degradation of the drug in high-energy settings. As a result, ultrasound-based techniques are primarily utilized during the optimization of the formulation at the laboratory level(39).

Table 1 Methods of Preparation of Ethosomes

Method	Principle	Temperature	Organic solvent used	Vesicle size control	Entrapment efficiency	Advantages	Limitations
Cold Method	Phospholipids and drug are dissolved in ethanol under continuous stirring, followed by slow addition of aqueous phase at room temperature, leading to spontaneous formation of flexible ethosomal vesicles	Maintained at room temperature throughout the process	Ethanol used as main solvent	Moderate control; often requires post-processing	High due to ethanol-induced bilayer flexibility	Simple, reproducible, suitable for thermolabile and sensitive drugs	Broad particle size distribution; may need sonication or extrusion
Hot Method	Lipids are dispersed in aqueous phase and heated above transition temperature, while ethanolic drug solution is added at the same temperature to form vesicles	Elevated temperature (40–60 °C)	Ethanol	Moderate	High	Faster lipid hydration and vesicle formation	Not suitable for heat-sensitive drugs or biomolecules
Conventional (Classical) Method	Ethanolic lipid solution is mixed with aqueous phase under continuous stirring, allowing spontaneous	Room temperature	Ethanol	Low to moderate	Moderate to high	Easy to perform; widely used in laboratory research	Limited control over vesicle uniformity

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	self-assembly of ethosomes						
Reverse Phase Evaporation Method	Water-in-organic solvent emulsion is formed, followed by solvent evaporation under reduced pressure to yield vesicles with large internal aqueous compartments	Controlled temperature under vacuum	Organic solvents plus ethanol	Good	Very high	Excellent entrapment of hydrophilic drugs	Uses toxic solvents; complex and time-consuming
Method	Principle	Temperature	Organic solvent used	Vesicle size control	Entrapment efficiency	Advantages	Limitations
Ethanol Injection Method	Ethanolic lipid solution is rapidly injected into aqueous phase, causing immediate vesicle formation due to solvent diffusion	Room temperature	Ethanol	Good	Moderate	Rapid, simple, easily scalable	Low lipid concentration; ethanol removal required
Mechanical Dispersion Method	Hydrated lipid film is mechanically agitated or stirred to produce multilamellar vesicles	Room or mild heating	Optional ethanol	Poor	Moderate	Low cost, minimal equipment	Produces large, heterogeneous vesicles
Sonication Method	High-energy ultrasonic waves are applied to reduce vesicle size and polydispersity	Room temperature	Ethanol	Very good	Moderate	Produces small, uniform ethosomes	Risk of drug degradation and metal contamination
Extrusion Method	Ethosomal suspension is repeatedly forced through polycarbonate membranes of defined pore size	Room temperature	Ethanol	Excellent	Moderate	Highly uniform vesicle size	Membrane clogging; time-consuming
Freeze–Thaw Cycling Method	Repeated freezing and thawing disrupts and reforms bilayers,	Alternating low and room temperatures	Ethanol	Moderate	High	Improves encapsulation efficiency	Labor-intensive; possible vesicle instability

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	enhancing drug entrapment						
Microfluidization Method	Lipid and aqueous streams collide at high velocity in microchannels, producing uniform nanosized vesicles	Controlled temperature	Ethanol	Excellent	High	Highly reproducible; scalable for industry	Expensive instrumentation
Method	Principle	Temperature	Organic solvent used	Vesicle size control	Entrapment efficiency	Advantages	Limitations
High-Pressure Homogenization Method	High-pressure shear forces break down vesicles into nanoscale ethosomes	Controlled (may generate heat)	Ethanol	Excellent	High	Suitable for large-scale production	High energy input; thermal stress
Supercritical Fluid-Based Method	Lipids precipitate using supercritical CO_2, forming ethosomes with minimal solvent residue	Precisely controlled	Minimal organic solvent	Excellent	High	Environment-friendly and solvent-free	Technically complex; high operational cost
Ultrasound-Assisted Method	Acoustic cavitation enhances lipid dispersion and vesicle formation	Room temperature	Ethanol	Very good	Moderate to high	Faster processing; reduced vesicle size	Over-sonication may destabilize vesicles

➢ *Applications of Ethosomes in Transdermal and Topical Drug Delivery*

The ethosomes are advanced lipid-based nanovesicular systems that are constituted by phospholipids, high concentration of ethanol and water. The existence of ethanol has been found to provide flexibility to the vesicular membrane and interrupt the lipid organization of the stratum corneum, which facilitates an increase in skin permeation. These distinct properties have led to a lot of interest in ethosomes as an effective delivery system of topical and transdermal drug delivery. Their capability to penetrate deeper layers of the skin and even into the blood has increased their curative uses in the dermatological, metabolic, chronic, oncological, cosmetic and herbal fields(6,13,14,41,42).

➢ *Dermatological Applications*

Ethosomes have undergone massive research in the treatment of different skin ailments because of their high penetration through the skin. Traditional topical preparations are usually incapable of delivering drugs that are deeper than the surface layers of the skin but ethosomes can effectively deliver active pharmaceutical molecules to deep epidermal and dermal layers. This renders them very effective in the management of inflammatory skin disorders like psoriasis, eczema, acne, dermatitis, fungal infections etc. The increased site of action drug deposition leads to better therapeutic effect and reduced systemic exposure and undesirable side effects. Also, ethosomal preparations have the advantage of extended retention of the drug in the skin, which can result in long-lasting therapeutic action and lower the frequency of the drug intake(40,43).

➢ *Transdermal Drug Delivery for Systemic Action*

Among the greatest uses of ethosomes is in transdermal drug delivery in the systemic treatment. The barrier properties of the stratum corneum can be overcome by ethosomal systems that are able to deliver drugs to systemic circulation in a controlled way. This is the non-invasive route of administration which is an efficient alternative to oral and injectable routes of dosage especially of drugs that experience a great deal of first-pass metabolism or cause gastrointestinal irritation. Transdermal delivery through ethosomes has also demonstrated potential in the area of increasing

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bioavailability, constant plasma drug levels, and patient compliance(13,22).

➢ *Applications in Metabolic and Chronic Diseases*

Ethosomes have shown significant promises in control of metabolic and chronic illnesses that involve long-term prescription of drugs. Ethosomal formulations have been used in transdermal delivery that offers prolonged and regulated drug delivery to reduce the variation in plasma drugs. It is especially beneficial when it comes to such conditions as diabetes, cardiovascular disorders, and neurological diseases: in these cases, regular exposure to drugs is a key to successful disease management. Ethosomes will help improve patient compliance and therapeutic response to chronic therapy by preventing the use of oral drug dosing frequently and invasive injections used in chronic therapies(14,43).

➢ *Oncological Applications*

Ethosomes have become of growing interest in oncology, especially in localized and skin-related cancer. Ethosomes increase the depth of penetration of anticancer drugs and are thus applicable in the treatment of melanoma, basal cell carcinoma, as well as other skin cancer cases. In addition, ethosomal carriers enhance the solubility and stability of anticancer drugs with poor water solubility, which is why they have a better therapeutic effect. Self targeting with ethosomes lowers systemic toxicity and decreases the side effects that are often correlated with traditional chemotherapy(14,43,44).

➢ *Phytopharmaceutical and Herbal Applications*

Delivery of herbal drugs via ethosomes has also become one of the possible methods to improve the performance of phytoconstituents. A lot of herbal compounds have low solubility and low skin penetration which limits their clinical use. Ethosomal encapsulation enhances penetration, stability and bioavailability of herbal actives. These systems have been effectively used in the treatment of inflammatory disorders, wound healing and skin infections, and they have also been used in cosmetic preparations. The use of ethosomal technology combined with herbal medicine is a safer and more effective treatment approach(32,45).

➢ *Cosmetic Applications and Cosmeceutical Applications*

Ethosomes have become widespread in cosmetic and cosmetical products because they are biocompatible, non-toxic, and have better skin penetration characteristics. They are used to provide active cosmetic agents like antioxidants, vitamins, anti-aging agents, moisturizers, and skin-lightening agents. The use of ethosomal formulations allows cosmetic actives to penetrate deep into the skin as opposed to standard systems and leads to better efficacy and extended effects. Also, due to the ability of ethosomes to preserve skin hydration and enhance the barrier activity, they are useful ingredients in high-tech skincare products(42,45).

➢ *Comparative Advantages Over Conventional Vesicular Systems*

The ethosomes have better permeation-enhancing properties than the traditional liposomes and other vesicles carriers. The elevated level of ethanol enhances the fluidity of the membrane and the greater the penetration into the skin barrier. Ethanol is released in a controlled manner by ethosomes as opposed to the alcohol-based topical solutions which are known to cause irritation to the skin thus avoiding irritation of the skin whilst ensuring a high permeation rate. Ethosomes can be used to deliver both lipophilic and hydrophilic drugs due to its capacity of flexibility in formulation design and use therapeutically(22,42,46).

➢ *Advanced and Emerging Applications*

The new ethosomal systems, such as ethosomal gels, patches, sprays, and hybrid nanocarriers, have been developed due to recent advances in nanotechnology. These higher order formulations are to enhance further stability of the drug, controlled release and convenience to the patient. Ethosomes have been demonstrated to have potentials of combination approaches with other nanoparticles to improve efficiency of delivery via transdermal methods. Such inventions increase the number of applications that ethosomal has in contemporary drug delivery research(43,47).

III. ADVANTAGES

- Ethosomes improve medicine penetration through dermal and transdermal skin administration.
- Ethosomes serve as delivery systems for a wide range of medications, including peptides and protein molecules.
- In terms of both quantity and depth, ethosomal systems are far more effective at delivering a fluorescent probe (quantum dots) to the skin.
- High patient compliance: The ethosome medications are administered as a semisolid (gel or cream), which results in high patient compliance.
- On the other hand, patient compliance will be impacted by the relative complexity of iontophoresis and phonophoresis.
- Products with exclusive technology are highly appealing to consumers.
- The creation of ethosomes requires no complex technical investments and is comparatively easy to create.
- The ethosomes system may be immediately commercialized and is both passive and non-passive(21).
- They are a safe and efficient medication delivery method since they are non-toxic, biocompatible, and biodegradable.
- They are an adaptable drug delivery system because they may transport a variety of medications, including hydrophilic and hydrophobic substances.
- They may transport a lot of medicine per vesicle due to their high drug-loading capacity, which increases the treatment's overall efficacy and lowers the number of applications required.
- Additionally, ethosomes' ethanol content might maintain the vesicles and shield them from deterioration.
- This prolongs the medication's shelf life and lessens the need for frequent reapplication. thosomes can be modified to target particular cells or tissues, increasing the treatment's overall specificity
- Adequate for administering medications with high molecular weight, such as peptide and protein

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compounds.
ethosome compositions are non-toxic, they can be used in pharmaceutical and cosmetic applications. Because it is simple to give as a gel or transdermal patch, patient compliance is improved.

- Compared to other complex techniques like phonophoresis, ethosomal formulation preparation is a straightforward process(48).
- Ethosomal systems is their ability to preserve and enhance the biological activity of natural extracts.
- Encapsulation of plant-derived compounds within ethosomes has been shown to significantly improve their antioxidant, anti-inflammatory, antimicrobial, and enzyme-inhibitory activities. For example, ethosome-loaded extracts demonstrated superior inhibition of oxidative stress markers and collagenase activity compared with non-encapsulated extracts, indicating enhanced therapeutic efficacy and protection of labile phytochemicals.
- Ethosomes enable selective therapeutic outcomes depending on extract source and composition, suggesting that vesicle-mediated delivery can modulate biological responses at the cellular and tissue levels(10).

IV. FUTURE PROSPECTS OF ETHOSOMES IN TOPICAL DRUG DELIVERY

Ethosomes have become one of the most promising nanovesicular systems in topical drug delivery because they have an outstanding capacity to circumvent the stratum corneum barrier as well as being compatible with the skin. It is anticipated that further research in ethosomal will be utilized in future therapy of dermatology, cosmeceuticals and localized therapy of chronic skin disorders.

The main prospect of ethosomes in topical application in the future is that they will transform into functionalized non-myocellular nanocarriers and hybrid non-myocellular nanocarriers. More recent studies have focused on the creation of modified ethosomes to include activators of edges, polymers, or surface ligands to improve skin targeting, retention, and controlled release. It is expected that such functionalized ethosomes would allow delivering the functionalized liposomes to particular skin layers, hair follicles, or inflamed tissues, which would enhance their therapeutic efficacy and reduce off-target effects to a minimum(19,49).

The second significant trend is greater adoption of ethosomes to deliver topical preparations using phytoconstituents. Ethosomes have demonstrated exceptional potentials in enhancing the stability, penetration and bioavailability of herbal actives and antioxidants which otherwise are affected by the poor penetration rate of skin. Ethosomes in the future topical products will continue to be exploited in delivery of flavonoids, polyphenols, essential oils, and anti-inflammatory plant extracts to chronic skin conditions like psoriasis, eczema, acne, and skin inflammation obtained in association with rheumatoid arthritis(50,51).

Ethosomes will also take a groundbreaking position in dermatocosmetic as well as anti-aging products. Relative analogy of liposomes and ethosomes in skin permeation and deposition in ethosomal system has shown better results and thus this is the carrier of choice of vitamins, antioxidants, skin brighteners and anti wrinkle formulations. Ethosomes are likely to be widely used in future cosmetic industry in the high-performance topical products that can have quantifiable functional advantages (as opposed to purely aesthetic effect) to provide(42).

Another potential future practice is the combination of ethosomes with novel nanotechnologies, including cubosomes and lipid-polymer hybrid systems. Such combination systems are designed to combine the deep skin penetration capability of ethosomes with the structural stability and sustained-release characteristics of other nanocarriers to develop superior topical delivery systems with the potential to achieve long-term skin retention and increased therapeutic effect(43).

Formulation and regulatory Regulatory The use of Quality by Design (QbD) and risk-based optimization strategies is likely to speed the process of making ethosomal topical formulations into commercial products. Structured manipulation of formulation parameters including ethanol content, phospholipid mix, vesicle diameter, and gel matrix properties will enhance reproducibility, scalability, and regulatory approval(44).

Moreover, the positive safety and tolerability profile of ethosomal topical systems, coupled with the tolerability of the systems, is a great boost that will lead to successful usage of ethosomal topical systems in the clinical and commercial settings. Ethosomes, being made of pharmaceutically acceptable excipients, and administered orally (as non-greasy gels or creams), provide an alternative to invasive or device-based delivery mechanisms that are not user-friendly(19,52).

To conclude, ethosomes can be viewed as the next generation of penetration-enhancing vesicles since they have the potential of evolving to multifunctional, skin-targeted nanoplatforms. Further development of formulation science, functionalization approach, and clinicalization will continue to establish ethosomes as the basis of technology in topical therapeutics and cosmeceuticals of the next generations(6,40).

➢ *Future Prospects of Ethosomal Drug Delivery Systems*

The ethosomal drug delivery system is a fast emerging platform that holds a high potential in future in dermatology, oncology, inflammatory diseases and cosmeceutical delivery. Recent developments show that current ethosomers are no longer of interest to traditional topical drug delivery but rather are being considered to treat disease specific, targeted, and biologically active treatments.

Their use in the treatment of skin cancer is one of the most promising directions of future research of ethosomal. Formulations based on ethosomes have shown the capability to interfere with cell growth in cancer cells by enhancing

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intradermal delivery of anticancer and antioxidant agents.Research on ethosomes in both melanoma and non-melanoma skin cancers has demonstrated improved cytotoxicity on tumor cells, high skin retention, and lower systemic toxicity, which suggests they can be used as non-invasive therapies, or as an add-on to existing chemotherapy(34,53). An additional factor in favor of the localized anticancer therapy with antioxidant and anti-inflammatory effects of ethosomes is the successful encapsulation of flavonoid compounds like gossypin and curcumin(53,54).

The provision of natural bioactive compounds and phytopharmaceuticals is another significant prospective approach in the future. Many studies have shown that ethosomes considerably improve stability of plant-derived molecules and skin penetration, and biological efficacy of curcumin, capsaicin, Chromolaena odorata extract, and black cohosh extract(31,54). Since the need to find natural and safer therapeutic agents is increasing, ethosomal systems should play an essential role in the conversion of phytochemicals into topical preparations with clinical usefulness.

Another area that is promising of ethosomes use is in chronic inflammatory and pain-related diseases. Indomethacin, flurbiprofen, and salicylic acid are non-steroidal anti-inflammatory drugs (NSAIDs) ethosomal preparations, which have been shown to achieve greater flux, longer therapeutic duration and lower dosing rate. Future studies should be aimed at the optimization of sustained-release ethosomal gels and patches as a long-lasting treatment of arthritis, musculoskeletal and inflammatory conditions of the skin(55,56).

Another significant direction in the future is the incorporation of Quality by Design (QbD) and highly sophisticated optimization methods. Recent reports that utilized the factorial design and risk-based optimization methods have shown a better control over the size of the vesicles, entrapment efficiency, stability, and reproducibility(56). It is anticipated that such systematic development of formulation will make it easier to obtain regulatory approval and mass production of ethosomal products.

Translational Ethosomes have high potential as they have a good safety profile and compliance rates by patients. Since the ethosomal constituents, which include phospholipids, ethanol, and water, are usually considered safe, risk posed by toxicity and regulatory challenges is also low. The fact they are ingested as semisolid dosage forms like gels and creams further bolsters their acceptability by the patient and marketability(32,57).

In general, the ethosomal drug delivery of the future is in their development into multifunctional, disease-targeted nanocarriers that can deliver synthetic drugs and phytoconstituents, as well as anticancer agents, with high precision and minimal invasiveness. Further interdisciplinary investigation, clinical verification and industrial scale optimization will lead to a solid position of ethosomes as a foundation of technology of next generation dermal and transdermal therapeutics(4,57).

V. CONCLUSION

Ethosomes represent a highly promising and versatile nanovesicular drug delivery system capable of effectively overcoming the stratum corneum barrier through synergistic ethanol-induced lipid fluidization and vesicle deformability. Compared with conventional liposomes and other vesicular carriers, ethosomes demonstrate superior skin penetration, higher drug entrapment efficiency, improved stability, and enhanced therapeutic efficacy for both hydrophilic and lipophilic drugs. The availability of multiple ethosomal variants and preparation techniques allows formulation flexibility tailored to diverse therapeutic needs. Their successful application in dermatological disorders, systemic transdermal delivery, oncology, phytopharmaceuticals, and cosmeceuticals underscores their broad clinical potential. With ongoing advancements in formulation optimization, surface functionalization, hybrid nanocarrier design, and Quality by Design approaches, ethosomes are poised to evolve into next-generation targeted and multifunctional delivery platforms. Continued translational research and clinical validation are expected to further establish ethosomes as a cornerstone technology in modern topical and transdermal drug delivery systems.

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