Novel Carrier for Enhanced Drug Delivery: A Review on Ethosomes

Abstract:

A new vesicular carrier called ethosomes has shown promise as a means of improving medication administration. The goal of this review is to present a thorough analysis of ethosomes, covering its makeup, methods of manufacture, and characterisation strategies. There is discussion of the special qualities of ethosomes, including their capacity to improve skin penetration and offer prolonged drug release. Additionally highlighted are the uses of ethosomes in a variety of medicinal fields, such as gene therapy, dermatology, and oncology. Additionally, the difficulties and prospects for ethosomes as a medication delivery mechanism are examined. For scientists and researchers interested in creating innovative medication delivery methods, this review is a useful resource.

Keywords: Ethosome, Ethanol, Transdermal, Novel carrier, Phospholipid

1. Introduction:

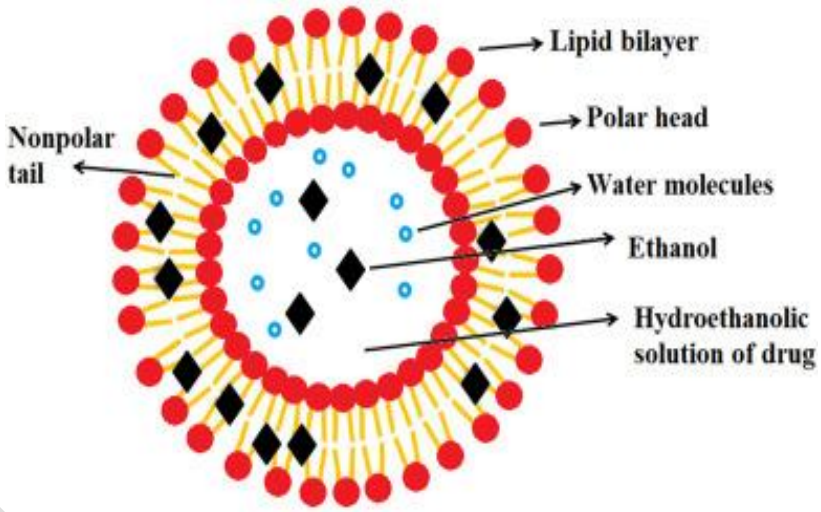
The skin, being a readily accessible and extensive organ, offers a promising route for drug delivery, providing advantages such as reduced plasma drug level fluctuations, minimized gastrointestinal adverse effects, avoiding first-pass metabolism, and better patient adherence in contrast to conventional medication administration methods.

In order to achieve systemic therapy, transdermal drug delivery devices have recently been developed with the intention of delivering topical medication to the intact skin surface. When applied to intact skin, transdermal treatment systems—self-contained, discrete dose forms—release medications into the systemic circulation at a regulated rate through the skin. There are numerous benefits to transdermal distribution, such as increased safety, better patient compliance, and increased efficacy. This method of drug delivery increases patient compliance while avoiding the risks and pain of parenteral therapy. In this regard, the transdermal route is an intriguing choice due to its convenience and security. Only lipophilic medications with molecular weights less than 500 Da can penetrate the stratum corneum due to the barrier properties of the stratum corneum, which the transdermal drug delivery method faces. The ability to avoid the first pass metabolism impact for medications with low oral bioavailability and continuous drug delivery, which results in a steady state plasma profile and less systemic side effects, are additional therapeutic benefits of TDD that may enhance patient compliance. Nowadays, to increase drug penetration into the stratum corneum, vesicular and non-invasive drug delivery techniques such liposomes, niosomes, transferosomes, and ethosomes are used [1].

Ethosomes:-

Drugs can enter the deeper layers of the epidermis and/or the organised flow thanks to ethersomes, which are noninvasive delivery vehicles. These are pliable, squishy vesicles

designed to improve active drug distribution. As seen in figure 1, they are mostly made up of phospholipids (phosphatidylcholine, phosphatidylserine, and phosphatitidic acid), as well as a significant amount of ethanol and water. Ethanol's high concentration in ethosomes makes them unique because it is known to alter the structure of the lipid bilayer in the skin. It permits the vesicle to penetrate the stratum corneum when it is integrated into its membrane. The lipid membrane is also less densely packed than that of conventional vesicles because of its high ethanol concentration, yet it is nonetheless as stable, giving stratum corneum lipids a more flexible form and improved drug dispersion. Like liposomes, ethosomes essentially display lipid bilayers (Fig. 1), but their composition (high ethanol concentration) sets them apart. Ethamomes exhibit reduced vesicle size, increased entrapment efficiency, and enhanced stability as compared to traditional liposomes. Drugs are delivered continuously by ethosome formulations, in which ethosomes serve as a reservoir system. Transmission electron microscopy visualization revealed that ethosomes might be either multilamellar or unilamellar all the way to the core. The size of ethosome vesicles can vary from tens of nanometers to a few microns, depending on the preparation, composition, and application techniques like sonication. Unlike Transfersomes, Ethosomes improve drug delivery through the skin in both occlusive and non-occlusive conditions.[2]



Fg 1:Ethosomes proposed diagram

2. Benefits of Ethosomes

1. Improved medication molecule penetration through the skin and into the bloodstream.
2. Unlike malformed liposomes, ethamomes improve medication distribution through the skin in both occlusive and non-occlusive conditions.
3. Ethamomes have a variety of uses in the veterinary, cosmetic, and pharmaceutical industries

because of their safe nature and constituent parts.

4. Improved adherence by patients.

5. Many medications have better solubility and stability than traditional vesicles.

6. Rather smaller in size than traditional vesicles.

3. The constraints of ethosomes

1. Low profit in ethosome production is a significant challenge.

2. When transferred to water, ethosomes may agglomerate and dissolve due to insufficient shell locking.

3. When switching from organic to aqueous media, there is a chance of product loss.

4. Cost and Production [3]

4. Classification of Ethosomes System

As seen in Figure 2, an ethosome classification scheme distinguishes three primary types: transethosomes, binary ethosomes, and standard ethosomes.

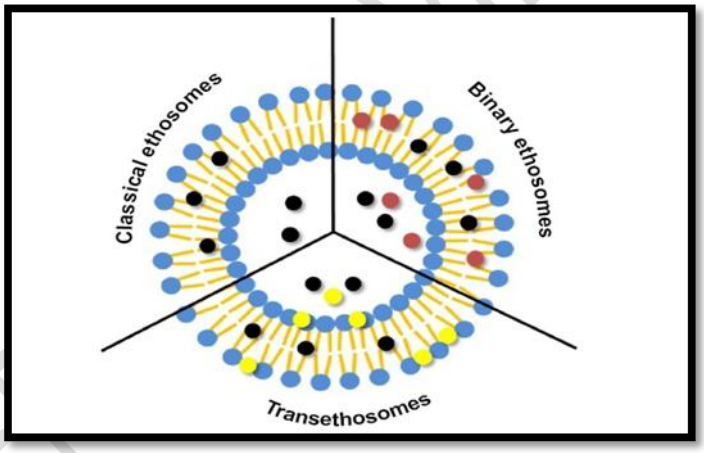


Fig 2: Ethosome systems of many types and their makeup

4.1.Traditional ethosomes & Classical ethosomes

Traditional or classical ethosomes are the original ethosomal system that changed the liposomal composition by adding water, phospholipids, and a comparatively high amount of ethanol (up to 45%). When compared to typical liposomes, traditional ethosomes had a strong potential for transdermal drug delivery, primarily because of their lesser size, adverse surface charge, and advanced entrapment efficacy (4,7). In addition, the ethosomal system demonstrated increased stability as compared to traditional liposomes.

4.2. Ethosomes Binary

"Zhou et al. (8) were the primary to describe this kind of ethosomal system, which involved altering the conventional ethosomes by adding various types of alcohol. The binary ethosomeshave been studied in different research that widely used propylene glycol/ethanol mixture (1, 9-13) or isopropanol /ethanol mixture .

4.3.Transethosomes

Song et al. initially described the transethosomal system, the most recent generation of ethosomes. With the addition of an edge activator or penetration enhancer to the vesicular structure, the components of this system are the same as those of traditional ethosomes. These vesicles were created as an experiment to combine the advantages of transfersomes (elastic liposomes) and traditional ethosomes into a single vesicular carrier. Several investigations have demonstrated the vesicles' notable superiority over standard ethosomes.[4]

5. Mechanism of Ethosomes Drug Penetration

The elements of this system are identical to those of conventional ethosomes, with the addition of an edge activator or penetration enhancer to the vesicular structure.

The two phases listed below are most likely when the medication is absorbed.

1. Ethosomes effect

2. Ethanol effect

5.1. Effect of Ethanol:

Ethanol is a key ingredient that enhances skin penetration. Its mode of action to enhance penetration is well known. Ethanol interacts with lipid molecules in the polar hard group region, reducing the stiffness of the stratum corneum lipids and making them more fluid. Ethanol may intercalate into the polar head group environment, increasing the membrane's permeability. In addition to the way ethanol alters the stratum corneum's structure, the ethosome itself may also interact with the barrier.[5]

5.2. Effect of Ethosomes:

Effects of Elevated Lipid Fluidity in Cell Membranes Ethanol increased the skin's permeability because of ethanolosomes. As a result, the ethersomes readily enter the skin's deep layers, where they combine with skin lipids to release the medications.[6]

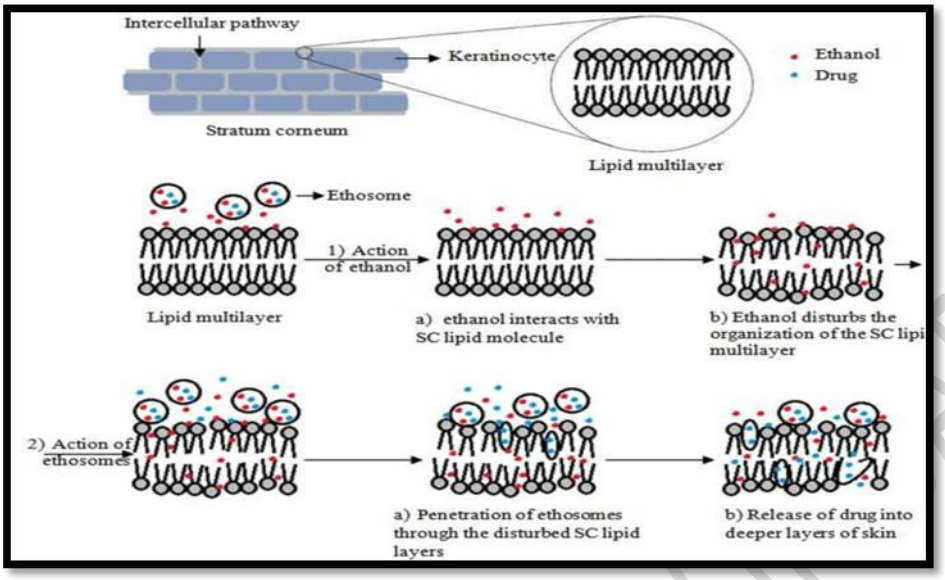


Fig3: The way that ethosomes work

6. Composition of Ethosomes [7]

Table No 1: Composition of Ethosomal

Class	Example	Use
Phospholipid	Soya phosphatidyl choline Egg phosphatidyl choline Dipalmityl phosphatidyl choline Distearyl phosphatidyl choline	Vesicles forming component
Alcohol	Ethanol Isopropyl alocohol	For providing the softness for vesicle membrance As a skin penetration enhancer
Polyglycol	Propylene glycol Transcutol RTM	As a skin penetration enhancer
Cholesterol	Cholesterol	For providing the stability to vesicle membrane
Dye	Rhodamine-123 Rhodamine red Fluorescene Isothiocynate (FITC) 6-Carboxy fluorescence	For characterization study
Vehicle	Carbopol D934	As a gel former

6. Method of preparation of ethosomes [8,9]

Two general techniques for ethosome preparation have been demonstrated by recent investigations and are described below:

6.1 The hot technique

By heating the phospholipid to 400 °C in a water bath until a colloidal structure is reached, the phospholipid is dispersed in the water. In a another jar, thoroughly mix the ethanol and propylene glycol and heat it to 400 °C. The organic phase should then be added to the watery phase. Now, dissolve the active ingredient in either ethanol or water, depending on how soluble the medication is. The ethosome vesicle's size can be reduced to the required level using the extrusion technique or probe sonication. The medication is mixed with either water or ethanol, depending on whether it is hydrophilic or hydrophobic. To achieve the desired size, the vesicles are either extruded or sonicated after formulation.

6.2 Cold Technique

The cold procedure is the most popular and straightforward approach for formulating the ethosomes. In a covered vessel, dissolve the phospholipid, medication, and any leftover lipid components in ethanol at room temperature while vigorously stirring. Next, add another polyol, such as propylene glycol, while stirring. The mixture is heated to 300 C in a water bath. The mixture is then combined with water that has been heated to 300 degrees Celsius in a separate vessel and stirred for five minutes while the vessel is covered. The ethosomal formulation's vesicle size might be reduced to the required level using extrusion or sonication procedures. Finally, the mixture must be stored in a refrigerator.

6.3 Hydration of thin films or mechanical dispersion:

Phospholipids (soy phosphatidylcholine) and organic solvents (methanol and chloroform) are combined in a 3:1 ratio in a round-bottom flask. The organic solvents are further removed from the contents using a rotary evaporator that is above the transition temperature of the lipid molecules present. This results in the formation of a thin coating of lipids on the walls.It is also kept under vacuum all night to eliminate any remaining solvent traces.With or without a sonicator, the film can be hydrated using a hydro-ethanolic solution of medication at room temperature.The suspension is refrigerated while the product is allowed to cool to room temperature. During the hydration process, the lipid is heated and rotated; the settings are chosen based on the characteristics of phospholipids. Process for 30 minutes, 1 hour, or 6 hours, 26.

6.4 Classic Technique:

The phospholipids, medicine, and ethanol were mixed in a water bath until the drug dissolved at 30 OC.The mixture was continually agitated at 700 rpm in a closed vessel as a fine stream of double-distilled water was added. Using a hand extruder and a polycarbonate membrane, the resulting solution was homogenized over three cycles.

7. Evaluation Parameters of Ethosomes[10,11,12,13,14,15]

Many different substances can be used in the creation of ethosomes. Whether or not cholesterol is present, phospholipids are usually the main component. The composition of the vesicle, which affects the bilayer's flexibility, size, charges, and thermodynamic state, among other things, is a significant aspect that directly affects the ethosome's physical and chemical characteristics. Below is an assessment of some of these characteristics.

7.1. **Shape and size of vesicle**

The shape of the vesicle can be seen using transmission and scanning electron microscopy. The dynamic light scattering technique and photon correlation spectroscopy22 are employed to measure the size of vesicles. Ethersomes' vesicular structures are usually between tens of nanometers and micrometers in size.

7.2.**Transition temperature**

The ethanol-skin phospholipid interaction, a characteristic linked to the fluidizing effect of ethanol on the phospholipid bilayers, is measured by differential scanning calorimetry (DSC), which is one technique for measuring the glass transition of the vesicular lipid structures.

7.3. Entrapment of drugs

The ultra centrifugation technique can be used to test the ethosomes' entrapment effectiveness.

7.4. Drug details

It is possible to ascertain the drug amount of the ethosomes using a UV spectrophotometer. It is also possible to quantify this using a modified high performance liquid chromatographic approach.

7.5.Measurement of surface pressure

The drug's surface tension activity in aqueous solution can be evaluated using the ring method using a Du Nouy ring tensiometer.

7.6. Observaions of Stability

One can determine the stability of the vesicles by tracking their size and form over time. TEM identifies structural changes, while DLS calculates mean size.

7.7.Research on Skin Permeation

Researchers can see and measure how deeply ethosomal preparations pierce epidermal layers using confocal laser scanning microscopy (CLSM).

8Application of Ethosomes[16,17,18]

8.1. Targeting with pilebaceous

Localized therapy has made use of plosebaceous units, particularly for follicle-related disorders like acne or alopecia. Since minoxidil's ethosomal nature allows it to accumulate two to seven times greater in the skin of nude mice, it can be utilized for pilosebaceous targeting for improved clinical efficacy. Minoxidil is a lipid-soluble drug used to treat baldness.

8.2 Transdermal delivery:

Since ethamomes increase the drug's permeability across the stratum corneum barrier, they can be utilized to deliver drugs with poor skin penetration, low oral bioavailability, first-pass metabolism, and dose-dependent adverse effects. According to Touitou et al., the ethosomal formulation of testosterone penetrates the skin over thirty times more deeply than the commercially available transdermal patch (Testosterone Patch, Alza). Additionally, they found that the area of application needed for the ethosomal testosterone formulation to generate the effective plasma concentration was ten times smaller than what was needed for the commercially available gel formulation.

8.3 Topical delivery of DNA

DNA transport to the skin The skin is the entry point for many environmental illnesses. Skin has therefore developed into a highly permeable and highly effective protective barrier. ability to express genes and have a functioning immune system. Another interesting use Given the aforementioned findings, the objective of ethosomes is to use them to transfer DNA molecules to skin cells so that genes can be expressed. Touitou et al. encapsulated the GFP-CMV-driven transfecting construct in ethosomal DNA for their study. This mixture was applied to the dorsal skin of 5-week-old male CD-1 nude mice for 48 hours. After the treated skin was removed 48 hours later, CLSM was used to observe the penetration of the green fluorescent protein (GFP) formulation. Gupta and collaborators It was recently reported that a transfersomal formulation possesses immunogenic potential. Therefore, the possibility of using these dosage forms to give immunization medicines is made possible by ethosomes' enhanced skin penetration capabilities.

8.4 Anti-Arthritis Drug Delivery

Topical application of anti-arthritic drugs solves the problem with standard oral therapy and is a superior option for site-specific delivery. CBD, or cannabidol, is a novel pharmacological option for the treatment of rheumatoid arthritis. For transdermal administration, Lodzki et al. created a CBD-ethosomal formulation. Tested using a rat paw edema model generated by carrageenan, the CBD-ethosomal formulation's biological anti-inflammatory efficacy was found to be greatly enhanced. It was determined that encasing CBD in ethosomes greatly enhanced its biological activity by increasing its skin penetration and accumulation.

8.5 Provision of Troublesome Medicinal Substances

Large biogenic molecules, such proteins or peptides, are difficult to administer orally since the GI system totally breaks them down. The issues with oral delivery can be resolved more effectively using non-invasive protein delivery.Dkeidek and Touitou examined how ethosomal insulin administration affected normal and diabetic SDI rats' in vivo blood glucose levels (BGL). In this investigation, an overnight-fated rat's abdomen was covered with a Hill Top patch that contained insulin ethosomes. The outcome shown that both normal and diabetic rats' BGL significantly decreased (by up to 60%) when insulin was administered via this patch.However, the BGL could not be decreased by administering insulin from a control formulation. Verma and

Fahr described the cyclosporin Aethosomal formulation for the treatment of inflammatory skin illnesses like psoriasis and atopic dermatitis, as well as diseases of the hair follicles like alopecia areata.The possible use of ethosomes for the topical administration of ammonium glycyrrhizinate was examined by Paolino et al. Glycyrrhiza Glabra is a natural source of ammonium glycyrrhizinate, a triterpene that is helpful in treating a variety of inflammatory skin conditions.

8.6 Antibiotics delivery

Topical application is the most effective way to increase the therapeutic efficacy of antibiotics. There are several side effects and allergic reactions associated with traditional oral medicine. Traditional external preparations have poor penetration to subcutaneous tissues and deep skin layers.By injecting a substantial amount of antibiotic into the deeper layers of the epidermis, ethersomes can get around this issue. Ethosomes quickly pierce the epidermis, deliver a sizable quantity of medications to the deeper skin layer, and stop infections at their source. With this objective in mind, Godin and Touitou developed an ethosomal formulation containing bacitracin and erythromycin for intracellular and cutaneous delivery.

8.7 Cosmeceutical Application of Ethosomal

Ethersomes are lipid-based vesicular transporters that are mostly composed of phospholipids, ethanol (in quite large amounts), and water. They are specifically made to improve the penetration of active medicinal and cosmetic compounds into the skin's deeper layers.

9. Conclusion

One innovative vesicular carrier that has shown promise for improved medication delivery is ethersomes. Their distinct qualities, like prolonged release and improved skin penetration, make them a desirable choice for a range of medicinal uses, such as gene therapy, dermatology, and oncology. The safety and effectiveness of ethosomes require more investigation, but this carrier system has a lot of potential for better drug delivery. Future studies should focus on optimizing ethosomal formulations and exploring their potential in clinical settings..

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