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ETHOSOMES: A REVIEW

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Abstract:

Several transdermal therapeutic methods have been developed for topical application onto the intact skin surface to manage drug distribution and its subsequent penetration through the skin tissue in order to offer continuous medication infusion via an intact skin. A viable alternative to systemic medication delivery is transdermal method. The ethanolic phospholipid vesicles known as "ethosomes" are employed mostly for transdermal medication administration. Since ethosomes penetrate the skin more quickly than liposomes do, they can often be utilised in place of liposomes. Due to their enhanced skin penetration, improved drug delivery, greater drug entrapment efficiency, etc., ethosomes have attracted researchers' attention.

Key words: Ethosomes, Phospholipids, Transdermal, Skin permeation

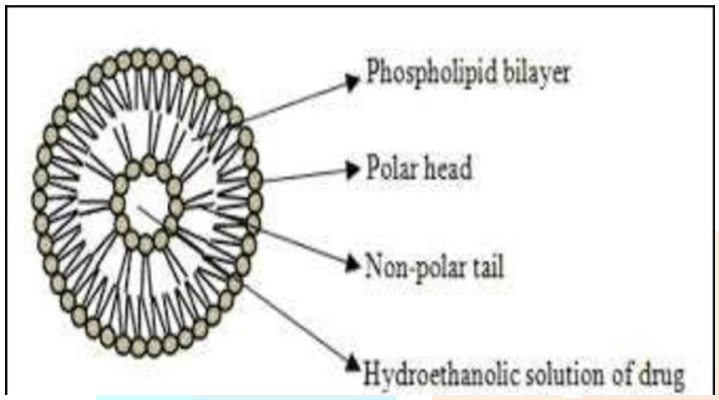
Introduction:

When compared to more traditional medication administration methods like oral and parenteral, transdermal drug delivery has a number of advantages. One of the better options for maintaining stable plasma levels for extended periods of time is the transdermal route, which may also be favourable due to fewer frequent dosing schedules [1]. Only lipophilic medicines with a molecular weight of less than 500 Da can pass through the stratum corneum when using a transdermal drug delivery device because of its barrier properties[2]. Other therapeutic advantages of TDD include bypassing the first pass metabolism effect for drugs with poor oral bioavailability, providing a steady state plasma profile and reducing systemic side effects, which may improve patient compliance[3]. Today, vesicular and non-invasive drug delivery systems including liposomes, niosomes, transferosomes, and ethosomes are employed to improve the penetration of drugs through the stratum corneum[4].

Ethosomes:

A modified version of liposomes, which have shown to be effective transporters in the transdermal area, are thosomes. Phospholipids, ethanol, and water are the major components of ethosomes, which are lipid vesicles. The ethanolic medication solution is contained in an aqueous core of ethosomes, and a lipid bilayer makes up the outer layer (Fig. 1). In order to deliver molecules (drugs, medicines, or active agents) to the deeper layers of the skin, the effect of ethanol fluidizing the phospholipid bilayers helps to the production of vesicles with a pliable shape [5,6].

Ethosomes are stretchy phospholipid-based vesicles that contain between 20 and 45 percent ethanol and water [7].



Ethanolic liposomes are called ethosomes. Ethosomes are non-invasive, flexible, pliable vesicular delivery systems that improve the distribution of active ingredients by allowing medications to reach deep skin layers and/or the systemic circulation. They are made up of phospholipids (phosphatidylcholine, phosphatidylserine, and phosphatidic acid), water, and a significant amount of ethanol. The high quantity of ethanol in ethosomes makes them special since ethanol is recognised for disrupting the organisation of skin lipid bilayers. As a result, when ethanol is incorporated into a vesicle membrane, the vesicle gains the potential to pierce the stratum corneum.

Additionally, the lipid membrane is packed less firmly than in usual vesicles because of the high alcohol content. Although it is equally stable, it allows for a more pliable structure and enhances the ability of drugs to distribute via stratum lipids.[8,9,10]

Types of ethosomal systems:

There are three types of ethosomal systems based on their composition.

Classical ethosomes:

The modified ethosomes known as "classical ethosomes" contain phospholipids, water, and a significant amount of ethanol (up to 45%w/v). Classical ethosomes were discovered to be superior to classic liposomes because of their tiny size, negative zeta potential, and increased entrapment efficiency. The best medications for those

caught in classical ethosomes have a molecular weight between 130.077 Da and 24 k Da. In comparison to traditional liposomes, traditional ethosomes exhibit improved skin penetration and stability profiles[11].

Binary ethosomes:

Zhou et al. first described binary ethosomes, which were essentially created by mixing a different kind of alcohol with the traditional ethosomes. Propylene glycol (PG) and isopropyl alcohol (IPA) are the two alcohols that are most frequently employed in binary ethosomes[12].

Transethosomes:

The advantages of traditional ethosomes and transfersomes were combined in one new ethosomal system known as a transethosome. Its composition includes the same fundamental elements as traditional ethosomes as well as a penetration enhancer or edge activator (surfactant)[13].

Advantages of ethosomal drug delivery:

- ✓ Large molecules (peptides, protein molecules) can be delivered.
- ✓ Its formulation uses non-toxic raw materials.
- ✓ Improved transdermal drug administration by the skin penetration of the drug.
- ✓ Ethosomal drug delivery systems are widely used in the medical, veterinary, and cosmetic industries.
- ✓ High patient compliance is achieved since the ethosomal medication is administered in semisolid form (gel or cream).
- ✓ A straightforward drug delivery technology as opposed to more complex ones like phonophoresis and iontophoresis.
- ✓ The Ethosomal system is passive, non-invasive, and presently available for sale[14,15].

Disadvantages of ethosomal drug delivery:

- ✓ Ethosomes with weak shells may aggregate, which causes precipitation.
- ✓ Sufficient solubility of the medicine to penetrate cutaneous microcirculation and enter the systemic circulation in both lipophilic and watery conditions.
- ✓ Dermatitis or skin irritation brought on by excipients and enhancers used in medication delivery systems.
- ✓ Ethosomal administration is often intended to provide steady, sustained medication delivery, not quick bolus type drug input.
- ✓ Drugs requiring high blood levels cannot be delivered; only powerful drugs (daily dose: 10 mg or less) are allowed.
- ✓ Lacklustre practical yield.
- ✓ Product loss results from ethosome transfer from the organic to the aqueous layer.
- ✓ The drug's molecular size needs to be appropriate for percutaneous absorption.

- ✓ Some types of skin may not respond well to adhesive.
- ✓ not cost-effective[16].

Table: 1 Different Additive Employed In Formulation of Ethosomes[17]

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

Ethosomes composition:

Drug distribution through ethosomes can be modified by adjusting the alcohol:water or alcohol:polyol:water ratios. Ethosomes are vesicular carriers that contain hydroalcoholic or hydro/alcoholic/glycolic phospholipid and have a relatively high concentration of alcohols or their combination[18,19].

Mechanism of drug penetration:

There is no known mechanism for how drugs are absorbed from ethosomes. The following two phases are probably when the medication is absorbed.

Ethanol effect:

Through the skin, ethanol enhances permeation. Its penetration-enhancing effect has a well-known mechanism. Ethanol permeates intercellular lipids, increasing their fluidity and decreasing the density of the cell membrane's multilayer of lipids[20].

Ethosomes effect:

The ethanol of ethosomes increases the fluidity of cell membrane lipids, which increases skin permeability. As a result, the ethosomes easily penetrate the deep skin layers, where they fuse with skin lipids and release the drugs[21].

Methods Of Preparation Ethosomes [22]

A. Cold Method:

The most popular technique for creating ethosomal formulations is this one. This approach involves vigorously swirling with the use of a mixer to dissolve phospholipid, drug, and other lipid components in ethanol in a covered vessel at room temperature. While stirring, propylene glycol or another polyol is added. In a water bath, this mixture is heated to 300 C. The mixture is then agitated for 5 minutes in a closed vessel while the water heated to 300 °C in a another pot is added. Using the sonication or extrusion process, the ethosomal formulation's vesicle size can be reduced to the desired extent. The formulation is then placed in a refrigerator for storage.

B. Hot method:

This technique involves heating phospholipid in a water bath at 4000C till a colloidal solution is produced. Propylene glycol and ethanol are combined and heated to 400°C in a separate vessel. The organic phase is introduced to the aqueous phase once both combinations have reached 400 °C. Depending on whether the medication is hydrophilic or hydrophobic, it dissolves in either water or ethanol. Using the probe sonication or extrusion approach, the vesicle size of the ethosomal formulation can be reduced to the desired extent.

Classic method:

The medication and phospholipid are dissolved in ethanol and heated in a water bath to 30°C + 1°C. In a closed vessel, the lipid mixture is added to with double-distilled water in a thin stream while being constantly stirred at a speed of 700 rpm. Three repetitions of running the resulting vesicle suspension over a polycarbonate membrane using a hand extruder homogenises it[13].

Mechanical dispersion method:

In a round bottom flask (RBF), soy phosphotidylcholine is dissolved in a solution of chloroform and methanol. A thin lipid coating is formed on the RBF wall by removing the organic solvents using a rotating vacuum evaporator above the lipid transition temperature. The deposited lipid layer is then cleaned of any remaining solvent combination by placing the container's contents under hoover for the night. Rotating the RBF at a sufficient temperature is used to hydrate with various concentrations of hydroethanolic mixture containing medication [24].

Characterizations of Ethosomes

1. Visualization

Transmission electron microscopy (TEM) and scanning electron microscopy (SEM) can be used to visualise ethosomes [25].

2. Vesicle size and Zeta potential

Using a computerised inspection system and photon correlation spectroscopy (PCS), dynamic light scattering (DLS) can be used to measure particle size and zeta potential[26].

3. Differential scanning calorimertry (DSC)

The Mettler DSC 60 computerised with Mettler Toledo star software system (Mettler, Switzerland) was used to calculate the transition temperature (Tm) of the vesicular lipid systems.The transition temperature was determined using aluminium crucibles heated at a rate of 10 degrees per minute, between 20 and 300 degrees Celsius [27,28].

4. Surface Tension Activity Measurement

By using a Du Nouy ring tensiometer, the ring method can be used to assess the surface tension activity of a medication in aqueous solution [27,28].

5. Entrapment Efficiency

The ultra centrifugation technique can be used to determine how well ethosomes entrap drugs[28].

6. Penetration and Permeation Studies

Depth of penetration from ethosomes can be visualized by confocal laser scanning[25]

7. Vesicle Stability

Analysing the evolution of vesicle size and structure provides insight into the stability of vesicles. DLS measures mean size, while TEM detects structural changes[25,27,28].

8. In vitro drug release study and Drug Deposition study

Franz diffusion cell with an artificial or biological membrane, dialysis bag diffusion, and drug deposition of ethosomal preparation can be used for in vitro drug release studies and drug deposition.

Applications of Ethosomes:

1. Delivery of Anti-Viral Drugs
2. Topical Delivery of DNA
3. Transdermal Delivery of Hormones
4. Delivery of anti-parkinsonism agent
5. Transcellular Delivery
6. Delivery of Anti-Arthritis Drug
7. Delivery of Antibiotics

Conclusion:

Ethosomes can significantly reduce the epidermal barrier, which is the principal obstacle to transdermal medication delivery. When compared to transdermal and dermal administration, ethosomes offer additional benefits. Drugs can be delivered to the systemic circulation and the deep layers of skin thanks to ethosomes, a non-invasive drug delivery mechanism. It transports big molecules like protein and peptide molecules. Comparing ethosomal drug delivery to Iontophoresis, Phonophoresis, and other complex procedures, it is a

simple method. High patient compliance because it is administered in semisolid form (gel or cream) and has several applications in the veterinary, pharmaceutical, and cosmetic fields.

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