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# Ethosomes – A Modernistic Approach for Drug Delivery

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**ABSTRACT**
Delivery over skin is impressive because it is so simple and convenient. Drug delivery across skin, however, continues to be a challenge in biomedical sciences. Various effective inventions of devices and procedures have been developed over the past few decades to maximise medicine delivery over skin, whose barricading behavior restricts penetration of the majority of medicinal substances. Drugs can enter the deep layers of the skin and/or the systemic circulation by way of ethosomes, a non-invasive delivery route. Systems based on ethosomal principles are easy to construct, secure, and efficient. Gelatinous, adaptable vesicles known as ethosomes were developed to enhance the delivery of drugs. This review article discusses how ethosomal systems research is prepared, applied, and characterised. Ethosomes can enter and disseminate through the skin in cationic drugs like trihexyphenidil and propranolol as well as in highly lipophilic substances like testosterone, cannabis, and minoxidil. Through the use of an ethosomal system, bioactive compounds can be delivered more effectively through epidermal and cellular membranes, opening up a variety of challenges and opportunities for future study and the creation of novel, superior treatments.Ethosomal drug delivery also used for antihypertensive drugs like Metoprolol, Amlodipine ,Telmisartan and antihyperlipidimic drugs like Atorvastatin.Ethosomes are usefull to deliver large biomolecules such as peptide and proteins. It shows improved drug administration and better patient compliance.Drug permeation shows ethosome effect and ethanol effect.Different methods used to produce ethosomes such as cold method , hot method , classical method and mechanical dispersion method.

**KEYWORDS-** Ethosomes, Skin Permeation, Penetration,Vesicles

## I.INTRODUCTION

The literature has extensively commented on the forthcoming advantages of transdermal medication administration. Compact side effects, first-pass hepatic clearance, and intestinal degradation prevention are a few of these benefits. However, due to the skin's natural barrier function, which functionally prevents the entry of exogenous materials, percutaneous distribution of the majority of molecules is frequently disallowed[1].Various methods for enhancing skin permeation have been used to overcome this challenge, as detailed in numerous scientific papers and patents[2]. Human skin serves as a barrier to prevent the admission of xenobiotic material as well as the expulsion of endogenous substances, primarily water, chemicals, and medications. It serves as the first line of defence for the body [3,4]. The corneocyte-containing stratum corneum is principally responsible for the skin's barrier properties. Transdermal administration formulations have substantially advanced and accelerated above conventional formulations in recent years due to a variety of characteristics, including their ability to prevent changes that occur at the gastro-intestinal junction[5]. It reduces the possibility of tissue damage or trauma, improves patient compliance through straightforward administration, and increases the bioavailability of medications by delivering the active ingredients directly into the systemic circulation, skipping hepatic metabolism [6] and avoiding metabolic variations.[7].

It has been proposed that penetration enhancers, iontophoresis, supersaturated systems, electroporation, phonophoresis, microneedles, jet injectors, etc. are required to increase the skin's permeability for transdermal drug administration.. Phospholipids, alcohol in significant amounts (20–45%), and water make up the majority of the soft, flexible lipid vesicles known as ethosomes (Fig. 1). Touitou and her associates created ethosomes for the first time in 1997[8-10]. Due to its great degree

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of deformability, ethosomes exhibits intriguing characteristics that are connected with its capacity to completely penetrate human skin. The ethosomal system's vesicle-forming element is made up of phospholipids. Between 0.5 to 10% of phospholipids with a variety of chemical configurations, including phosphatidyl choline and phosphatidyl ethanolamine, are used.

**STRUCTURE OF SKIN**

The epidermis' highest layer, the stratum corneum, is made up of 10 to 25 layers of fixed, fully keratinized, dead corneocytes that are broaden and arranged in a matrix of lipid bilayers. The stratum corneum has been identified as the primary impediment to skin penetration. After being applied to the skin, the active ingredient in a topical medication needs to pass through the stratum corneum to reach live tissue. (Fig.1). These actions are constrained by the sluggish diffusion that occurs through the dead skin layer. Water is repelled by the stratum corneum, which acts as a hydrophobic membrane. Low and high molecular weight organic non electrocytes' rate of skin penetration is significantly influenced by the stratum corneum. [13,14].

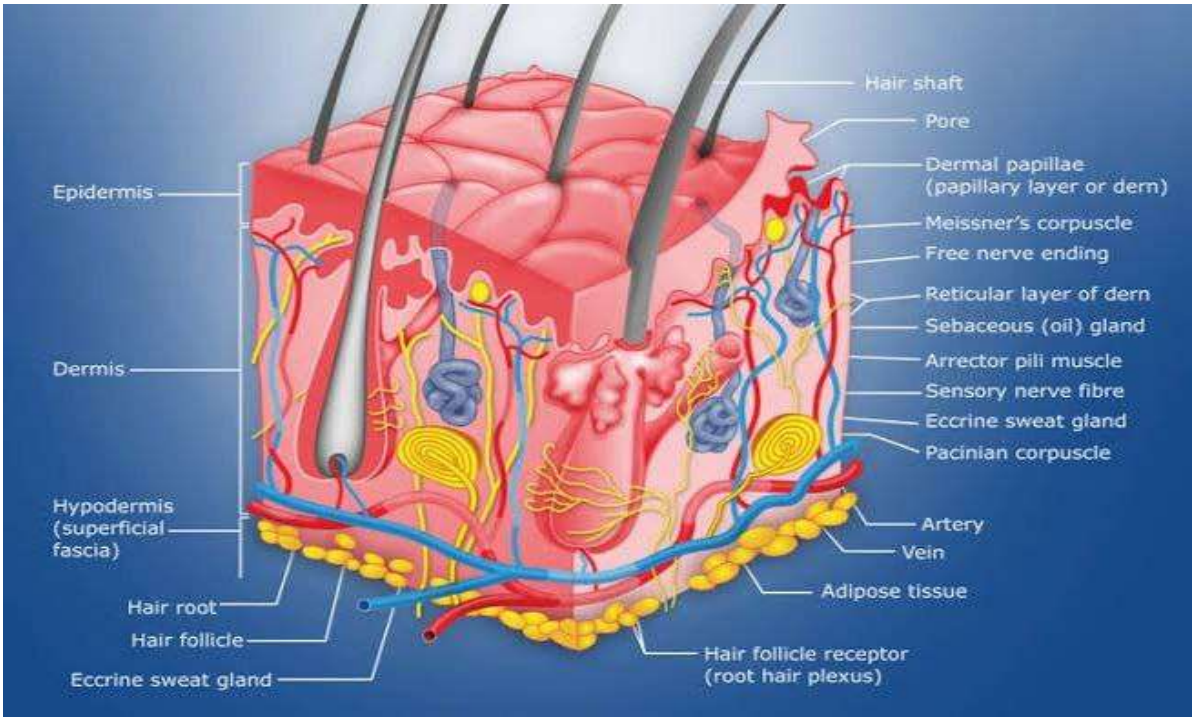


**Figure 1 STRUCTURE OF SKIN [15]**

**CONSTIUENTS OF ETHOSOMES**

Ethosomes are differ in composition when compared to liposomes, they exhibit a lipid bilayer resembling that of liposomes ( but have greater content of ethanol). The ethosomes' constitutes a hydroalcoholic or hydro/glycolic phospholipids have a higher alcohol content. Phospholipids, such as water, propylene glycol, soya lecithin , phosphatidic acid, phosphatidylethanolamine, and phosphatidyl glycerol, may be present in ethanolosomes (or other glycols). Among the preferred phospholipids are 90 Phospholipon (PL-90). It frequently ranges from 0.5 to 10% weight per weight. The ethosomal preparation may contain cholesterol in concentrations ranging from 0.1% to 1%. Propylene glycol and transcutol are two of the glycols that are widely used, accounting for 20–50% of the final product. The formulations use alcohols like ethanol and isopropyl alcohol. When phospholipids are mixed with cationic lipids (cocoamide) and non-ionic surfactants, the alcohol and glycol mixture's non-aqueous phase composition can range from 22 to 70%. (PEG-alkyl ethers) [16].

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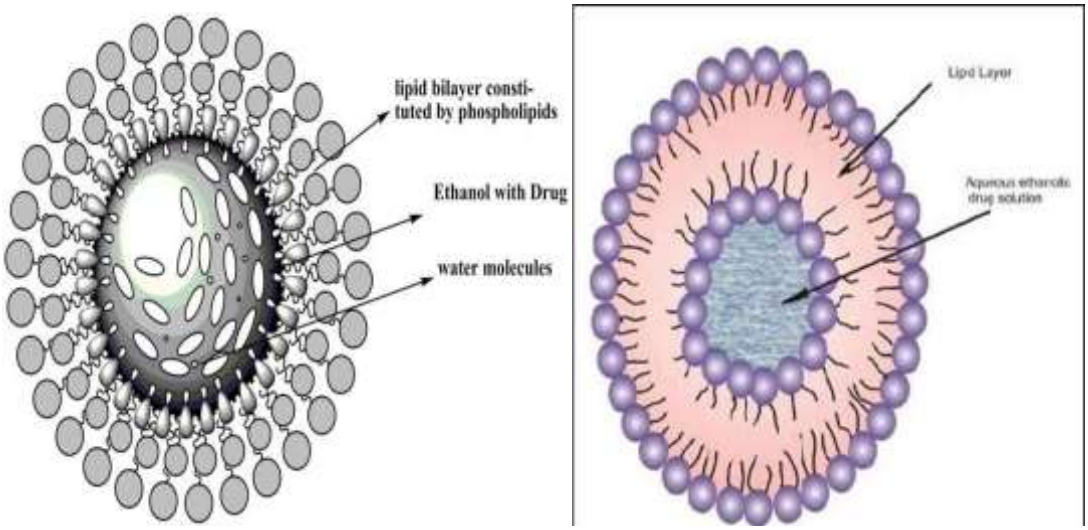


**Figure 2 A) Structure of Ethosomes [11]** **B) Structure of Ethosomes [12]**

**Table 1- In the creation of Ethosomes, many additives are used.** [17-21]

| **Class** | **Example** | **Uses** |
|---|---|---|
| Alcohol | Ethanol<br>Isopropyl Alcohol | Bring forth softness to vesicle membrane<br>Act as Penetration Enhancer |
| Phospholipids | Soya Lecithin<br>Egg Lecithin<br>Dipalmityl phosphatidyl choline | The vesicles' size, entrapment efficiency, zeta potential, and penetration characteristics are impacted. |
| Polyglycol | Propylene glycol , Transcutol | Act as a skin Penetration Enhancer |
| Cholesterol | Cholesterol | Ensures the stability of the vesicle membrane. |
| Dye | Rhodamine-123 Isothiocyanate | Used for characterization study |
| Edge activators | N-DMSO , Tween ,Span | Boosts skin permeability |
| Vehicle | Carbopol , HPMC | Used as a gel forming agent |

**Merits of Ethosomal Drug Delivery System**

Ethosomal drug delivery systems have various advantages over other transdermal & dermal administration technologies as listed below:

1. It is used as a innocuous raw materials in its formulation.
2. It is heplful to deliver larger size molecules such as peptides, protein molecules.
3. Improved drug administration through the skin for transdermal medication.
4. Greater patient adherence because the ethosomal medication is administered as a semisolid (gel or cream) preparation .
5. A straightforward drug delivery technology as opposed to complex ones like phonophoresis and iontophoresis.
6. The pharmaceutical, veterinary, and cosmetic industries can all benefit from the use of ethosomal drug delivery systems.
7. A fluorescent probe (quantum dots) used to

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measure the volume and depth of tissue is supplied to the skin through the ethosomal system.
8. Ethosomes have the largest transdermal flux, which improves the drug's penetration of deeper skin layers.
9. Because the toxicological profiles of the ethosome components have been thoroughly investigated and published in the scientific literature, there is no apparent danger associated with using the ethosome technology to produce formulations.
10. It is non-invasive (painless), passive, and commercially available right away.
11. When compared to other nano-carriers, drugs encapsulated in ethosomes exhibit a high degree of penetration despite having differing physicochemical properties.
12. Under both occlusive and non-occlusive circumstances, ethosomes enhances skin delivery.
13. Ethosomes manufacturing is rather simple and doesn't require significant financial inputs in technology [22].

**Demerits of Ethosomal Drug Delivery System**

1. Ethosomes with weak outer shells may congregate, causing scrambling.
2. Medication cannot pass through aqueous and lipophilic barriers to the cutaneous microcirculation and systemic circulation due to insufficient solubility..
3. Skin irritation or dermatitis may be brought on by the drug delivery method, excipients, andenhancers.
4. Ethosomal administration frequently aims to give medication in a continuous, sustained manner rather than in a fast bolus.
5. Drugs requiring greater blood levels cannot be delivered, only powerful drugs can be (dailydose -10mg or less) administered.
6. Inadequate practical yield.
7. Product loss results from ethosome transfer from the organic to the aqueous layer.
8. The molecular size of medication should be appropriate for percutaneous absorption.
9. Different types of skin responds differently to adhesives.
10. Possibly not budget friendly.
11. The ethosomes may agglomerate and disintegrate upon transfer into water if shell locking isineffective [23-27].

**Mechanism of Drug Permeation**

The stratum corneum lipid bilayer is affected by the ethanol effect and the ethosome effect simultaneously as part of the mechanism of ethosome penetration. Ethanol is used to produce the ethosomes, which increases the vesicles' deformability. The stratum corneum lipids should be partially extracted by the high alcohol concentration (Fig 3). Ethosomes' increased intercellular and intracellular permeability is caused by these processes. The stratum corneum is disorganised, and the extremely deformable vesicles can follow it and eventually release the medicine into the deeper layers of the skin[28].

**Ethosomes Effect**

The ethanol in ethosomes makes lipids in cell membranes more fluid, which makes the skin morepermeable. Because of this, the ethosomes can effortlessly penetrate the skin's deep layers, where they mix with lipids to release the drugs.

**Ethanol Effect**

Ethanol improves penetration through the skin. It has a well-known mechanism for increasing penetration. The density of the cell membrane's lipid multilayer is decreased by ethanol, while the fluidity of the lipids within the membrane is increased. [29].

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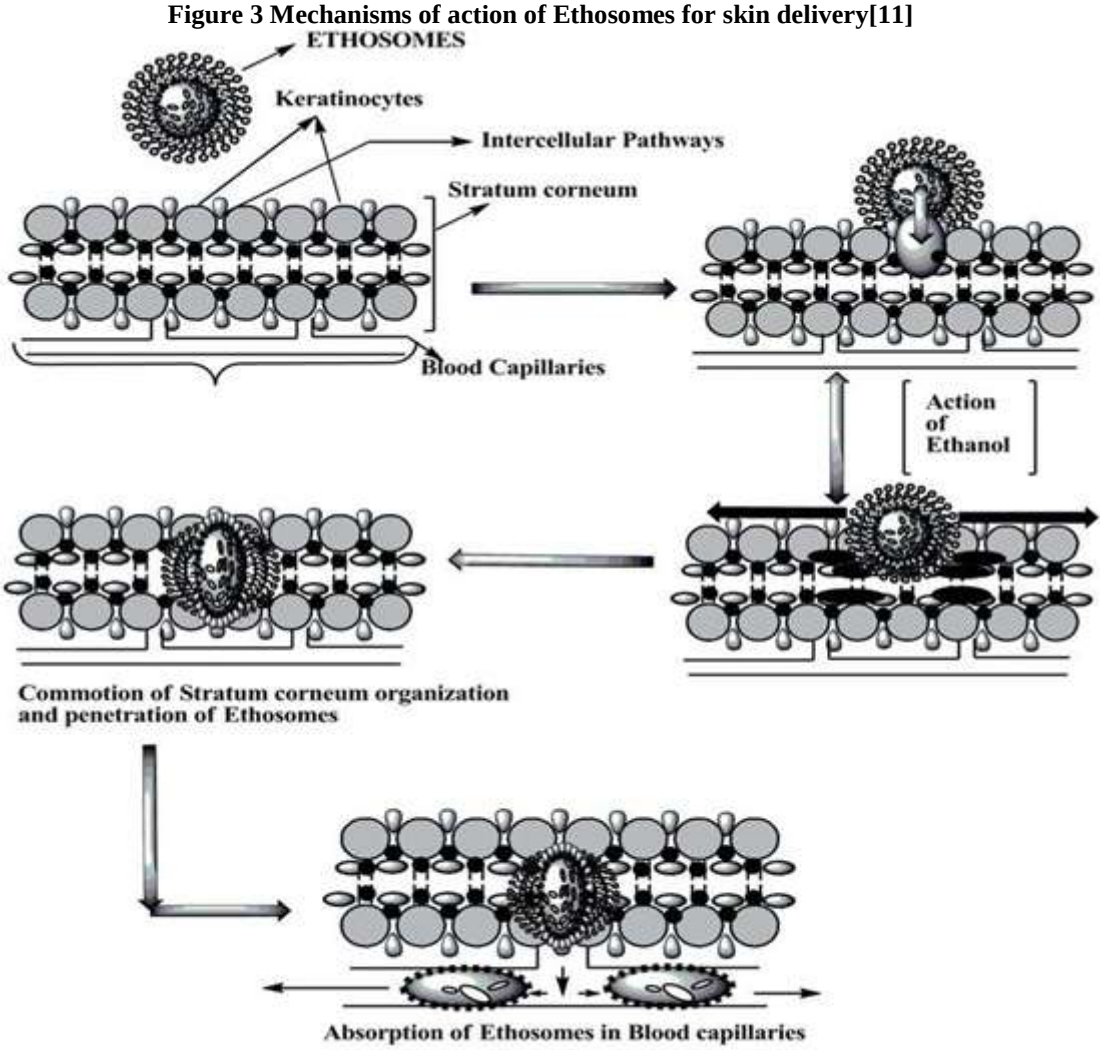
**Figure 3 Mechanisms of action of Ethosomes for skin delivery[11]**




**Ethosome Preparation Methods**

There are four ways to formulate ethosomes. Because there is no need for complicated procedures or specialised technology, all methods are sound straightforward and practical.

**Cold Method**

This method is the most often used for producing ethosomal mixtures. Phospholipids, drugs, and other lipid components are dispersed in ethanol at room temperature by aggressively spinning with a mixer. Propylene glycol or polyol is added while stirring. This mixture is warmed to 30°C in a water bath. The mixture is then stirred for a further five minutes while being covered with water that has been cooked in a different pot to 30°C. The vesicle size of the formulation can be decreased to the required level by the use of the sonication[30] or extrusion[31] procedures.. The mixture is then placed in a refrigerator for storage[32].

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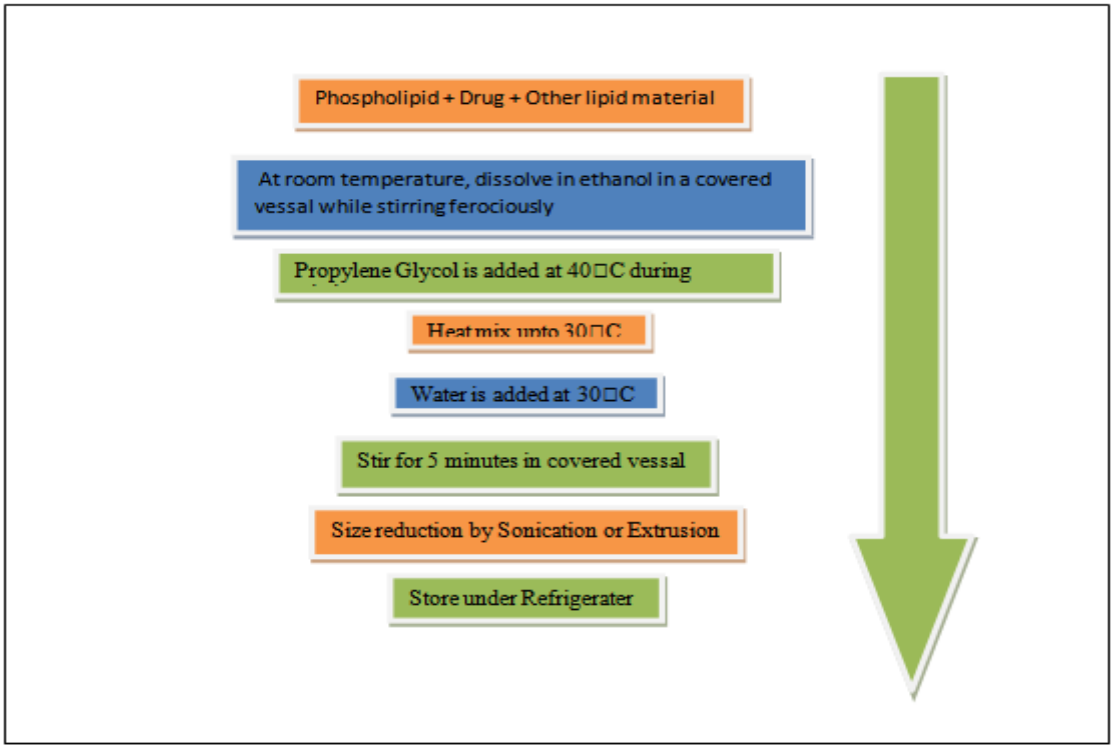
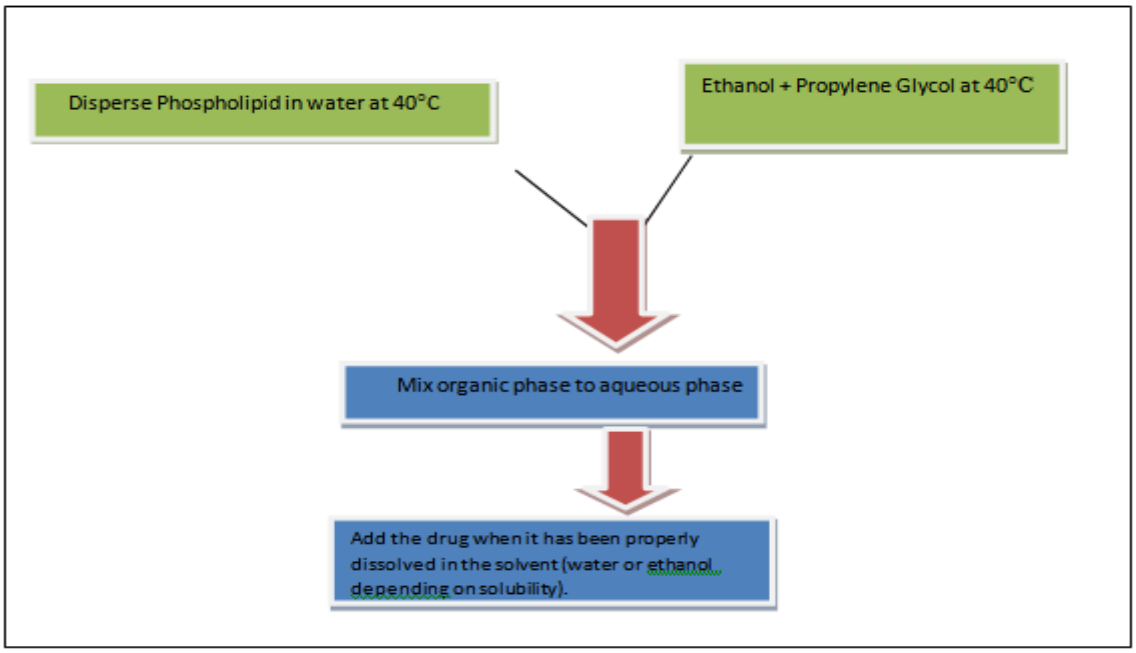



**Hot Method**

The phospholipid is heated in a water bath to 40 °C until a colloidal solution forms, at which point it is dissolved in water. Propylene glycol and ethanol are combined in a separate tank and heated to 40°C. The organic phase is incorporated into the aqueous phase once both solutions have reached 40 °C. The hydrophilic or hydrophobic nature of a medicine determines whether it will dissolve in ethanol or water. To make the ethosomal formulation's vesicle size as small as necessary, employ the probe sonication or extrusion procedure.[33].



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**Classical Method**

The drug and phospholipid are then heated in a water bath to 30°C + 1°C after being dissolved in ethanol. In a closed jar, the lipid mixture is vigorously stirred at 700 revolutions per minute and fed a stream of double-distilled water.The resultant vesicle solution is homogenised by three cycles of hand extrusion through a polycarbonate membrane [34].

**Mechanical Dispersion Method**

A flask with a flat bottom is used to dissolve soy phosphotidylcholine in a chloroform and methanol solution (RBF). By extracting the organic solvents with a spinning vacuum evaporator above the lipid transition temperature, a thin coating of lipid is applied to the RBF wall. Following that, the container's contents are vacuumed all night long to eliminate the remaining solvent combination. The concentration of the drug-containing hydroethanolic mixture varies in the hydrates by spinning the RBF at the proper temperature.[34]

## II.CHARACTERIZATION OF ETHOSOMES [35]

**Vesicle size and Zeta Potential**

Using a computerised inspection system, photon correlation spectroscopy (PCS), and dynamic light scattering (DLS), the particle size and zeta potential were determined.

**Vesicle Shape**

Transmission electron microscopy (TEM) and scanning electron microscopy(SEM) can both be used to visualise ethosomes. An electron microscope image shows a ethosomal formulation with a 300–400 nm-diameter vesicular structure. The imperfectly rounded shape of the vesicles makesthem appear to be alleable.

**Entrapment Efficiency(EE)**

The ultracentrifugation method can be used to determine how well a medication is captured in ethosomes. The EE of the drug in the ethosomes is significantly influenced by the chemical composition of the lipid because a lipid that creates a bilayer structure effectively holds the drug. Yet, the imperfections in the lipid structure may allow the medication to fit. The separation of the vesicles takes place in a high-speed cooling centrifuge that spins for 90 minutes at 20,000 rpm while maintaining a 4°C temperature.

Calculating the drug concentration in the sediment after lysing the vesicles in methanol and separating the liquid supernatant from the sediment by using formula below

% Entrapment= Actual Content /Theoritical Content x 100

**Surface Tension**

The ring method can be used to assess a drug's aqueous surface tension activity using a Du Nouy ring tensiometer.

**Surface Morphology**

The surface morphology or form of particles is affected by various lipid types. Metallic stubs were coated with lipid microparticle suspensions, which were subsequently submerged in liquid.nitrous oxide and vacuum-dried. The gold coating on the freeze-dried microparticles was consistent. Using a scanning electron microscope, its shape and surface characteristics are examined.

**Drug Content**

UV spectrophotometer is used to calculate the amount of drug present. By using a modified HPLC technique, amount of drug can also be determined.

**Transition Temperature**

While delivering a constant stream of nitrogen and heating the pan at a rate of 10°C per minute, DSC measures the transition temperature (T) of vesicular lipids in the 20–30°C temperature range.

**Stability Studies**

When ethosomal preparations are stored for variable lengths of time at different temperatures, such as 25 °C (room temperature, RT), 37 °C, and 45 °C (1, 20, 40, 60, 80, and 120 days), their capacity to retain the drug (i.e., exhibit drug-retentive behaviour) can be assessed. The ethosomal preparations were placed in sealed vials (10 mL in volume) after being nitrogen flushed. DLS and TEM were used to assess the size and appearance of the vesicles in order to determine the stability of the ethosomes.

**Degree of Deformability and Turbidity**

Extrusion can be used to measure the ethosomal preparation's degree of deformability, and a nephelometer can be used to measure the preparation's turbidity.

**Studies on Skin Permeation**

To measure the depth of ethosome penetration, confocal laser scanning microscopy

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(CLSM) is used. A means for dermal and transdermal distribution may have been provided by the ethosomes' significantly increased skin deposition as a result of the interaction between ethanol and phospholipid.

**Drug deposition and in vitro drug release studies**

Franz diffusion cells or dialysis bag diffusion with artificial or biological membranes can be used for drug deposition of ethosomal preparation and in vitro drug release studies.

**Ethanol and Phospholipid Interaction**

Differential scanning calorimetry and proton decoupled 31P-NMR were used to investigate the interaction between phospholipids and ethanol

## III.EVALUATION OF ETHOSOMES [36]

**TEM and SEM studies of vesicle-skin interactions**

Animals were chopped into ultra-thin slices, which were then collected on grids coated with formvar and analysed using a transmission electron microscope (Ultracut, Vienna, Austria). For SEM examination, the dehydrated skin fragments were adhered to stubs with adhesive tape. After that, they were coated with a fine coat of gold palladium alloy using a fine coat ion sputter coater. The portions underwent a scan electron microscopic examination.

**SEM investigation of the interaction between filters and their membrane-containing vesicles**

In diffusion cells, 0.2 mL of vesicle solution was applied to a filter membrane with a 50 nm pore size. The filter was coated with phosphate buffered saline solution (PBS) on the bottom and air on the top (pH 6.5). The filters were removed, fixed in Karnovsky's fixative for an hour at 4°C, and dehydrated in ethanol solutions at various concentrations (30%, 50%, 70%, 90%, 95%, and 100% vol/vol in water) before being ready for SEM studies. Before SEM inspection, filters received their final gold coating.

**Fluorescence microscopy examination of the vesicle-skin interaction**

The TEM and SEM examinations used the same methodology as fluorescence microscopy. The microtome (Erma Optical Works, Tokyo, Japan) was used to investigate sections of paraffin blocks that were cut into 5-mm-thick pieces. T lymphoid cell lines were grown in Dulbecco's modified Eagle medium (HIMEDIA, Bombay) together with 10% foetal calf serum, 100 U/mL penicillin, 100 mg/mL streptomycin, and 2 mmol/L L-glutamine for the micro-Cytotoxicity Assay MT-2. The medium was maintained at 37°C in a 5% $CO_2$ atmosphere. As an illustration of cytotoxicity, the cytotoxic dosage 50 (CD50), which results in a 50% decrease in absorbance at 540 nm, was employed.

**Studies on Skin Permeation**

The abdomen skin was removed from the underlying connective tissue, and the hair was precisely clipped to a length of 2 mm on the test animals. The skin was carefully peeled off, and the dermal side was examined for any subcutaneous tissue or fat adhering to it. After that, the skin was placed on aluminium foil. The diffusion cell's receptor cell's effective permeation area and volume were 10 mL and 1.0 cm2, respectively. Plus or minus 1°C, a steady 32°C was kept. A phosphate-buffering saline solution was found in the receptor compartment (10 mL of pH 6.5). The area between the donor and receptor compartments was lined with detachable skin.

An ethosomal formulation was applied to the skin's epidermal surface (1.0 mL). The hair of the test subjects (rats) was meticulously cropped short. At intervals of 1, 2, 4, 8, 12, 16, 20 & 24 hours, samples (0.5 mL) were collected using the diffusion cell's sampling port, and they were afterwards assessed using a high performance liquid chromatography assay.

**HPLC Analysis**

During in vitro skin penetration tests and in the MT-2 cell, the amount of drugs that made it to the receptor compartment was measured using an HPLC assay.

**Drug Intake Research**

The evaluation of the drug absorption into MT-2 cells (1.006 cells/mL) was done on 24-well Corning Inc. plates with 100 L RPMI medium. After incubation, drug content was measured using an HPLC method to assess how much of the drug was absorbed by the cells. 100 litres of a commercial formulation, an ethosomal formulation, or a drug solution in phosphate buffered saline solution (pH 7.4) were applied to the cells in order to treat them.

**Statistic Evaluation**

After utilising ANOVA to determine the

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statistical significance of all the collected data, a studentized range test was conducted. The PRISM software produced a P.05 confidence level for the results' interpretation. California, San Diego, version 2.01 of GraphPad

**Applications of Ethosomes**[37-43]
**Antiviral drug delivery**-Antiviral agent targeting the acquired immunodeficiency virus is delivered. Zidovudine's release, for example, could be prolonged by ethosomes, increasing the transdermal flux[37]

**Applications of Ethosomes in Cosmeceuticals:**One advantage of employing ethosomes in cosmetic goods is that they improve the stability of the irritating cosmetic components and minimise the skin irritation they cause, in addition to providing percutaneous sweetening, especially in stretchy forms. Nonetheless, it is important to take into account the vesicles' compositions and sizes in order to reap these benefits of elastic vesicles for cosmetic applications.[40]

**Hormone Transdermal Delivery**- Oral hormone administration results in a number of dose-dependent side effects, a high first pass metabolism, and a limited oral bioavailability. Ethosomes alleviate these problems by promoting medication absorption through the skin. the hormone testosterone (Testoderm patch, Alza). [37,38]
**In Parkinson's disease treatment**-Trihexyphenidyl hydrochloride (THP), a psychoactive drug, was made into an ethosomal formulation by Dayan and Touitou, and their study compared the drug's distribution to that of a conventional liposomal formulation. Parkinson's disease is treated with THP, an M1 muscarinic receptor antagonist. The outcomes suggested that the ethosomal-THP formulation had a greater skin penetration potential and might be used to manage Parkinson's disease more effectively.[42]

**Transcellular Transport**
**Drug delivery for arthritis**-A recently created pharmacological candidate for the treatment of rheumatoid arthritis, cannabidol (CBD), is administered as an anti-arthritis drug. A CBD ethosomal formulation for transdermal delivery was made by Lodzki et al. Results show that it has greatly increased in activity and skin penetration.[39].
**Providing antibiotics**-Ethosomes quickly penetrate the epidermis, bringing significant amounts of medication into the deeper layer of skin and squelching infections at their source. Studies showed that ethosomes penetrated cellular membranes and released medication molecules that had been captured there. These formulations of bacitracin and erythromycin were designed for cutaneous and intracellular delivery.[41]

**Delivery of troublesome therapeutic molecules**: Oral distribution of big biogenic molecules, such as peptides, proteins, and insulin, is difficult since the GIT tract completely destroys these compounds. Delivery through the skin is preferable. However, typical transdermal formulations of biogenic molecules, like peptides, proteins, and insulin, have limited skin permeability. The formulation of the aforementioned chemicals into ethosomes significantly improves the penetration and therapeutic efficacy. [43]

**Marketed Preparations of Ethosomes [44,45]**
The ethosomes technology began to be commercialised around 2000. Many businesses have created ethosomes-related items. Some of the commercialised ethosome preparations are included below.

**TABLE 2 Some marketed preparations of ethosomes:**

| Name of Product | Manufactured by | Uses |
|---|---|---|
| Noicellex | Novel Therapeutic Technologies, Israel | Used as topical anti-cellulite cream |
| Cellutight EF | Hampden Health , USA | A potent combination of chemicals in topical cellulite lotion boosts metabolism and breaks down fat |

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| | | |
|---|---|---|
| Skin Genuity | Physonics Nottingham, UK | Powerful cellulite buster reduces orange peel |
| Supravir Cream | Trima, Israel | In treatment of herpes virus |
| Decorin Cream | Genome Cosmetics ,Pennsylvania,US | As anti aging cream |
| Body Shape | Maccabi CARE | Flexible skin stretching, ethosomes-based technology, and gel executive solidification cellulite education |

## IV.FUTURE PERSPECTIVE

To prevent medicine penetration during transdermal drug administration, the stratum corneum acts as the main barrier. There are several ways to increase drug absorption through the skin, but a recent augmentation technique based on lipid vehicles has garnered a lot of attention. Further research will be done to enhance lipid vesicle-based medication delivery to the skin. The discovery of ethosomes has opened up a brand-new field of study for transdermal medication administration. Ethosomes have a promising future in enhancing the effectiveness of transdermal dispersion of numerous medications, according to multiple studies. The enhanced physician control of drug release in vivo as a result of this research will also increase the therapeutic efficacy. Therapeutic chemicals in small, medium, and large sizes can be delivered without intervention via ethosomes. This opinion is supported by the preliminary clinical study data for the acyclovir-ethosomal formulation. It is very easy to create huge quantities of ethosomal formulation. As a result, the time it takes for the appropriate drug formulation to enter clinics for testing before it is widely utilised should be short. Therefore, ethosomal formulations have a bright future in the efficient topical and transdermal delivery of bioactive substances.

## V.CONCLUSION

This unique, non-invasive carrier, known as ethosomes, has been the subject of numerous investigations. Because of the way they are built, ethosomes are soft vesicles that can transport the active component past SC lipids and into the skin's deeper layers. It has been proven that these vesicular systems in both people and animals are effective at delivering a variety of energy components both dermally and transdermally. Only a few of the several conditions where ethosomal transdermal administration may be beneficial include rheumatic diseases, Parkinson's disease, hormone replacement therapy, and cardiovascular drugs. By delivering antibiotics and antivirals to the deepest layers of the epidermis and alopecia-treating medications to the hair follicles, an ethosomal carrier may significantly improve the efficacy of drug therapy and the comfort of patients.This technique is a strong contender for the administration of chemical and biological molecules because to its extremely competent delivery, absence of toxicity, and ease of preparation. These new breakthroughs might broaden the range of transdermal applications even more.

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