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A REVIEW ON ETHOSOMES AS ALTERNATIVE CARRIERS CURRENTLY FOCUSING ON TRANSDERMAL DRUG DELIVERY SYSTEMS

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ABSTRACT

The skin is a crucial barrier to delivering mucous/topical /transdermal medicines. Different techniques have been made to improve drug skin penetration, and vesicle carrier systems, such as Ethosomes, liposomes and niosomes, are utilized for many cosmetic chemicals. One of the latest promising methods with different pharmaceutical applications is the ethosomal drug delivery method. These are elastic Nano vesicles based on phospholipids that contain a high ethanol content (20-45%). Ethosomal carriers are soft vesicles of hydro-alcoholic or hydro-glycolic phospholipids with a relatively high alcohol concentration. Theoretically, ethosomal systems are sophisticated, characterized by ease in planning, effectiveness and protection. Ethosomes can encapsulate and distribute extremely lipophilic molecules such as testosterone, cannabinoids, and minoxidil through the skin due to their unique structure and cationic drugs such as cationic drugs trihexyphenidyl and propranolol. The primary goal of the transdermal drug delivery system is Crossing the stratum corneum. This review concentrates on various aspects of ethosomes, including their penetration mechanism, preparation, structure, characterization, and implementation.

KEYWORDS: Ethosomes, Nano vesicles, Phospholipids, Hydro-alcoholic, Hydro glycolic, Stratum corneum.

INTRODUCTION

The skin is one of the most extensive and readily accessible organs of the human body. Human skin has a multifunctional role, including its significant role as a barrier against both

the outlet of endogenous substances (water) and the entrance of xenobiotic material (chemicals and drugs). It is regarded as the first line of protection in the human body. The stratum corneum consisting of corneocytes mainly accounts for the skin's barrier properties. For some time, several aspects have come out which has given immense esteem and rapid progress to transdermal delivery formulations over conventional formulations because circumvention of variations which appear at gastrointestinal absorption, improvement in bioavailability of drugs by delivering the active principles directly into the systemic circulation, bypassing the hepatic metabolism by giving a constant, controlled drug enter decreasing the variations in drug plasma levels augmentation in patient compliance by providing a simplified way of administration, the lowest risk of trauma or any other injury of tissue.[1]

One of the most significant disadvantages to transdermal drug delivery is the skin's low permeability that limits the number of drugs delivered in this manner. Ethosomes as novel vesicles in transdermal drug delivery show significant drug penetration through the biological membrane. Nowadays, we better know vesicles have importance in cellular communication. Ethosomes are conceptually sophisticated; they are simple in preparation and safe for use. The transdermal route is a promising alternative to drug delivery for systemic effect. An attempt was made to formulate a highly efficient ethosomal drug delivery system. Ethosomes have a higher penetration rate through the skin than liposomes; hence these can be used widely in place of liposomes. Ethosomes enhanced skin permeation, improved drug delivery.[2]

Ethosomes are non-invasive delivery carriers that enable drugs to reach the deep skin layers and the systemic circulation. It is a soft lipid vesicle containing phospholipids (phosphatidylcholine, phosphatidylserine, phosphatidic acid) and relatively high alcohol concentrations (Ethanol and isopropyl alcohol) water. The high concentration of Ethanol makes the Ethosomes unique and valuable for transcellular delivery; Ethanol is known for its disturbance of skin lipid bilayer. Because of their high ethanol concentration, it can penetrate the stratum corneum. The Ethosomes size range varies from 10nm to microns.[3,4]

Need for transdermal drug delivery

Despite the challenges, Transdermal delivery (TDD) offers several unique advantages, including a relatively large and readily accessible surface area for absorption, ease of application and termination of therapy. Further, the evolution of better technologies for

delivering drug molecules, safe penetration enhancers and the use of vesicular carriers have rejuvenated the interest in designing TDD systems for drugs that were thought to be unfit for transdermal delivery.

Ethosomes

Ethosomes are a modified form liposome, which has proved to be suitable carriers in the transdermal area. Ethosomes are mainly lipid vesicles made of phospholipids, ethanol, and water. Ethosomes have an aqueous core that contains the ethanolic solution of the drug, and the outer layer comprises the lipid bilayer (Fig. 1). The effect of ethanol fluidizing the bilayers of phospholipids.[5]

Structure of ethosomes

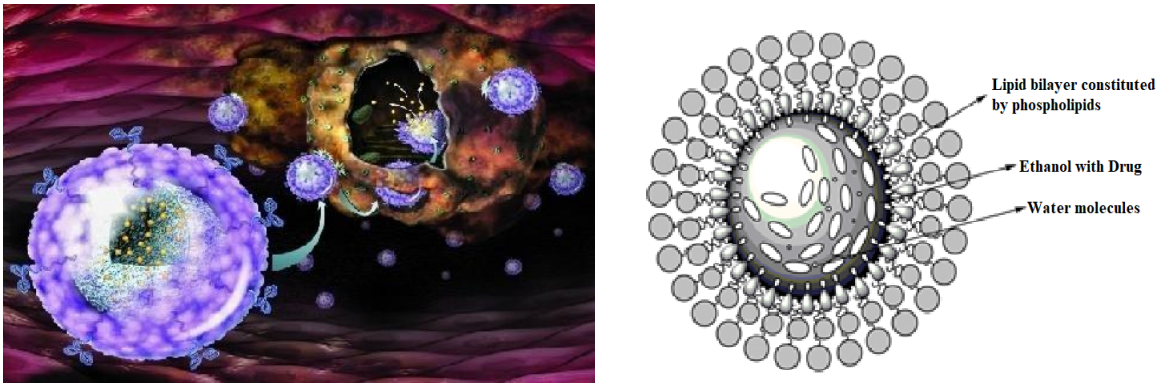


Fig. 1: Microscopic view of ethosome vesicle structure of ethosomes.

It contributes to the creation of blisters with a malleable structure which enables to attain molecules (drugs, pharmaceuticals, or active agents) to deeper layers of the skin. The medicine delivery from liposomes has limited results in the transdermal formulations due to its unstable nature and low permeability. Due to the concern owing to the stability of liposomes, a new vesicular carrier, niosomes, was developed to fight the problems of low stability. Despite that, liposomes and niosomes couldn't resist the problems of poor skin permeability. Hence, ethanolic vesicles have been developed to enhance the saturation of medicines across the skin. The size range of ethosomes ranges from tens of nanometres to microns, and the transdermal flux of ethosomes is more and its skin permeability.[6]

Classification of ethosomes[7]

1. **Classical ethosomes:** In transdermal drug delivery, ethosomes were superior to classical liposomes because they were lower and had negative ζ- potentiality and high entrapment effectiveness. Also, classical ethosomes f showed better skin permeation and stability

pathographies compared to classical liposomes. The molecular weights of drugs entrapped in classical ethosomes have ranged from130.077 Da to 24 kDa.

2. **Binary ethosomes:** Binary ethosomes were introduced by Zhou et al. Principally, they were developed by adding another type of alcohol to the classical ethosomes. The most generally used alcohols in binary ethosomes are propylene glycol (PG) and isopropyl alcohol (IPA).
3. **Classic ethosomes:** The phospholipid and drug are dissolved in ethanol and warmed to 30 °C ± 1 °C in a water bath. Double distilled water is added in a fine stream to the lipid mixture in an unrestricted vessel, with constant stirring at 700 rpm. The performing vesicle suspension is homogenized through a polycarbonate membrane using a hand extruder for three cycles.

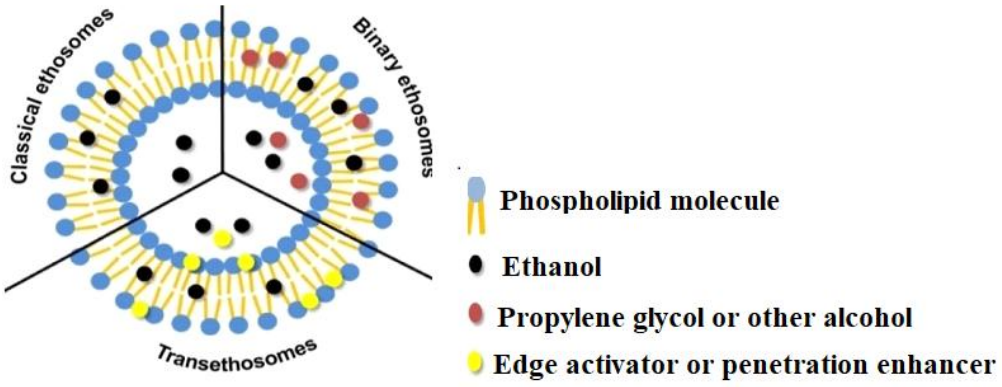


Fig. 2: Ethosomal systems are classified into three types based on the composition.

Ethosomes composition

They are composed mainly of phospholipids, high concentrations of ethanol and water. The high concentration of ethanol makes the ethosomes unique. Ethosomes are vesicular carriers composed of hydroalcoholic or hydro/ alcoholic/ glycolic phospholipid in which the attention of alcohols or their combination is reasonably close. They consist of phospholipids with different chemical structures,[8] like phosphatidylcholine (PC), hydrogenated PC, phosphatidic acid (PA), phosphatidylserine (PS), phosphatidylethanolamine (PE), phosphatidylglycerol (PPG), phosphatidylinositol (PI), hydrogenated PC, alcohol (ethanol or isopropyl alcohol), water and propylene glycol (or other glycols). Such a composition enables the delivery of a high concentration of active ingredients through the skin. ethosomes can modulate drug delivery by altering alcohol: water or alcohol-polyol: water ratio. Some preferred phospholipids are soya phospholipids such as Phospholipon 90 (PL90). It is usually employed in a range of 0.5-10% w/w. The preparation can also add cholesterol at

concentrations ranging between 0.1-1%. Examples of alcohols, which can be used, include ethanol and isopropyl alcohol. Among glycols, propylene glycol and Transcutol are generally used. In addition, these preparations can combine non-ionic surfactants (PEG-alkyl ethers) with phospholipids. Cationic lipids like cocamide, POE alkyl amines, dodecyl amine, cetrimide etc., can be added to the concentration of the nonaqueous phase (alcohol and glycol combination) may range between 22 to 70%.[9] Alcohol water polyol, then water rate may modulate the delivery of ethosomal drugs. The different kinds of complements used in the Ethosomal preparations are shown in Table.[9]

Table 1: Composition of ethosomes for transdermal delivery.

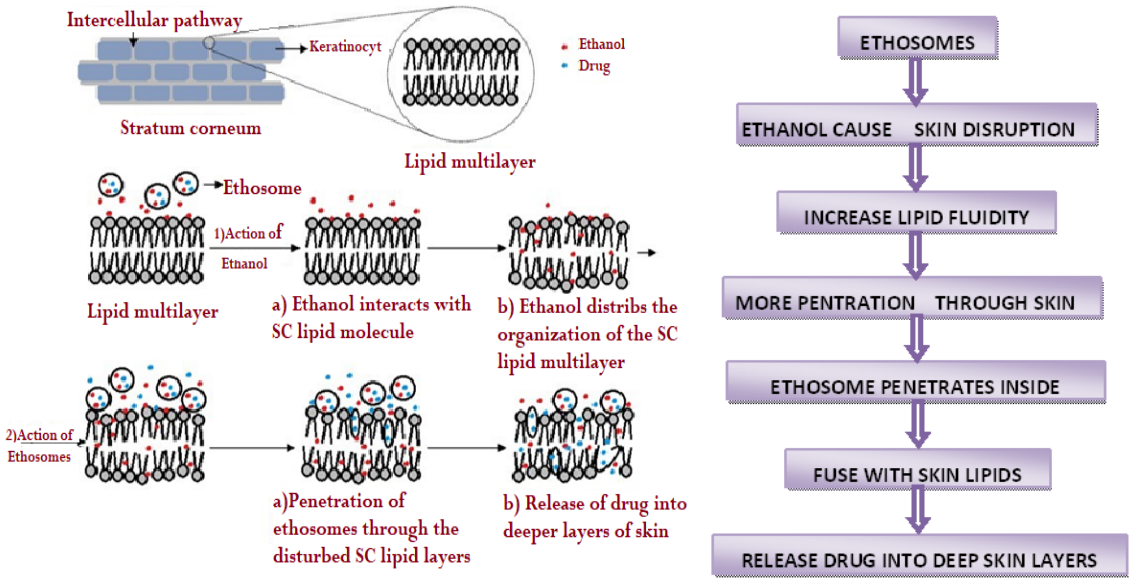
Additives used in Ethosomal Preparation	Examples	Application
Phospholipid	Soya phosphatidyl choline, Egg phosphatidyl choline, Dipalmityl phosphatidyl choline, Distearyl phosphatidyl choline	Vesicles forming component
Polyglycol	Propylene glycol, Transcutol RTM	As a skin penetration enhancer
Alcohol	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 Fluorescene Isothiocynate (FITC), 6-Carboxy fluorescence	For characterization study
Vehicle	Carbopol 934	As a gel former

Mechanism of drug penetration

The mechanism of the drug absorption from ethosomes is not precise. The drug absorption probably occurs in the following two phases.[10]

1. **Ethanol effect:** Ethanol acts as a penetration enhancer through the skin. The mechanism of its penetration enhancing impact is well known. Ethanol penetrates intercellular lipids, increases cell membrane lipids' fluidity, and decreases the density of lipid multilayer of the cell membrane.[11]
2. **Ethosomes effect:** Increased cell membrane lipid fluidity caused by the ethanol of ethosomes results in increased skin permeability. So, the ethosomes permeate very easily

inside the deep skin layers, where they got fused with skin lipids and released the drugs into the deep layer of skin.[12]



(a) Proposed mechanism of penetration of Ethosomal drug delivery system. **(b) Mechanism of action of Ethosomes.**

Fig. 3

Method of preparation[12-14]

Ethosomes can use two methods for the formulation and preparation. Both of these are very simple and convenient and do not involve any sophisticated instrument or complicated process.

Methods are

1. Hot method.
2. Cold method

Hot method: In this method, phospholipids are dispersed in water by heating in a water bath at 40^0C until a colloidal solution is obtained. In a separate vessel, ethanol and propylene glycol are mixed and heated to 40 ^{0}C. Once both the mixtures reach 40 ^{0}C, the organic phase is added to the aqueous one. The drug is dissolved in water or ethanol depending on its hydrophilic/ hydrophobic properties.

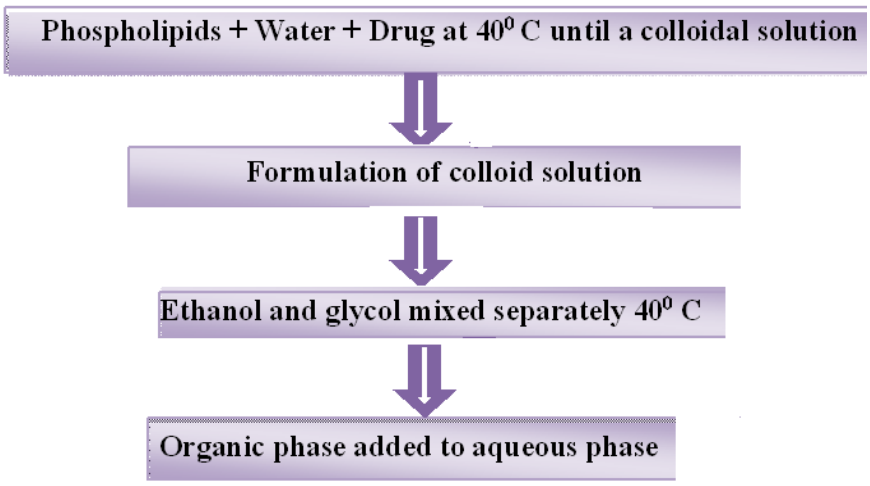


Fig. 4

Cold method: This is the most common method to prepare an Ethosomal formulation. In this method, phospholipid, drug and other lipid materials are mixed. Propylene glycol or other polyol is added during stirring. This mixture is heated to 30°C in a water bath. The water heated to 30°C in a separate vessel is added to the mixture, then stirred for 5 min in a covered container. The vesicles can be decreased to the desired extent using the sonication or extrusion method. Finally, the formulation is stored under refrigeration.

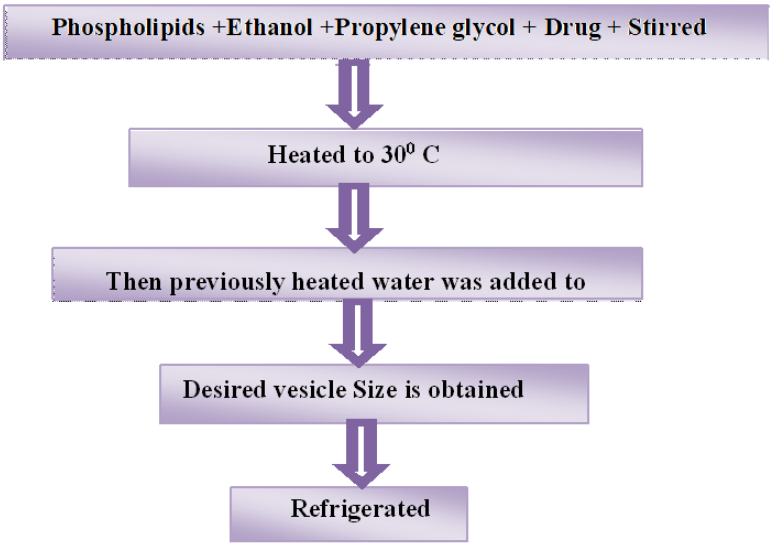


Fig 5:

Advantages of ethosomal drug delivery[15]

1. Enhanced drug permeation through skin.
2. Delivery of large and different group of drugs (peptides, Protein molecules
3. Safe composition and the components are approved for Pharmaceutical and cosmetic use.

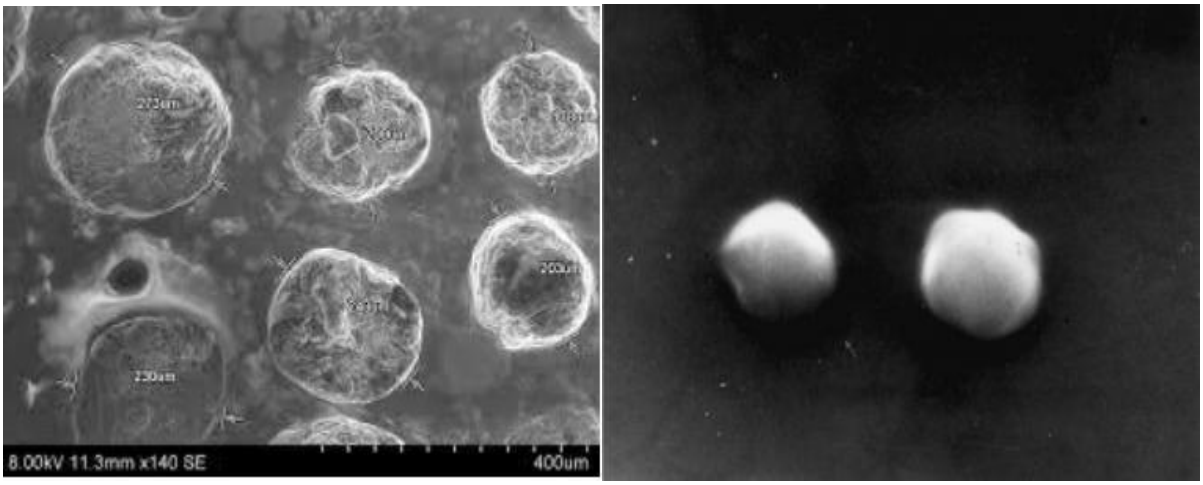
4. Low risk profile.
5. High patient compliance.
6. Application in Pharmaceutical, Veterinary, Cosmetic Field.

Disadvantages of ethosomal drug delivery[16]

1. Drugs that require high blood levels cannot be administered.
2. Ethosomal administration is not a means to achieve rapid bolus type drug input.
3. The molecular size of the drug should be reasonable that it should be absorbed percutaneously.
4. The adhesive may not adhere well to all types of skin. Uncomfortable to wear.
5. It may not be economical-poor yield.
6. Skin irritation due to excipients and enhancers of drug delivery systems.
7. In case if shell locking is ineffective, then the ethosomes

Characterization of ethosomal formulation[17-22]

1. **Optical microscope observation:** The ethosomal dispersion is spread on the glass slide with the help of a glass rod. Prepare the multilamellar vesicles were detected by examining the ethosomal suspension using an optical microscope with the magnification power of 100 X.
2. **Visualization:** Visualizing ethosomes can be done using instrument transmission electron microscopy (TEM) and scanning electron microscopy (SEM). Visualizing an ethosomal formulation by electron microscopy reveals exhibited vesicular structure 300-400 nm in diameter.
3. **Transition temperature:** scanning calorimetric can measure the transition temperature of the vesicular lipid systems.
4. **Drug content:** UV spectrophotometer can determine drug substance or content of the ethosomes. It can also be quantified by a modified high-performance liquid chromatographic method.
5. **Vesicle Size and Zeta potential particle size:** The ethosomes can be detected by dynamic light scattering (DLS) and photon correlation spectroscopy (PCS). The Zeta potential of the ethosome suspension can be measured by the Zeta meter.



(a) **(b)**

Fig. 3: Visualization of ethosomal vesicles, (a) Sem Image of Ethosome, (b) Tem image of ethosomes.

6. **Scanning electron microscopy (SEM):** The different type of lipid affects the surface morphology or shape of the particles. Solid lipid microparticles are deposits on the metallic surface, then placed in liquid nitrogen and dried under vacuum. The microparticles are coated uniformly with gold by freeze-drying. A scanning electron microscope can measure the morphology and surface properties of ethosome formulation.
7. **Stability studies:** The stability of vesicles can be determined by assessing the size and structure of the vesicles over time. It means DLS measures size, and a structural change is observed by TEM.
8. **Entrapment efficiency:** The ultracentrifugation Technique can measure the entrapment efficiency of a drug by ethosomes. The vesicles were separated at 20,000 rpm for 90 minutes at a temperature held at 4 ° C in a high-speed cooling centrifuge. The sediment and supernatant liquids in the sediment are divided by the amount of drug that can be measured using methanol by lysing the vesicles. From this, the efficacy of entrapment can be calculated by the following equation,

Entrapment Efficiency = DE/DT x 100

Where,

DE - Amount of drug in the ethosomal sediment

DT - Theoretical amount of drug used to prepare the formulation (equal to the amount of drug in supernatant liquid and the sediment)

9. **Surface tension measurement:** The surface tension activity of the drug in an aqueous solution can be measured by the ring method in a Du Nouy ring tensiometer.
10. **Skin permeation studies:** The ability of the ethosomal preparation to penetrate the skin layers can be measured by confocal laser scanning microscopy (CLSM).

Table 2: Methods for the characterization of ethosomal formulation.

Parameters	Methods
Vesicle shape (morphology)	Transmission electron microscopy Scanning electron microscopy
Entrapment efficiency	Mini column centrifugation method Fluorescence spectrophotometry
Vesicle size and size distribution	Dynamic light scattering method
Vesicle Skin interaction study	Confocal laser scanning microscopy Fluorescence microscopy Transmission electron microscopy Eosin-Haematoxylin staining
Phospholipid ethanol interaction	^{31}P NMR Differential scanning calorimeter
Degree of deformability	Extrusion method
Zeta potential	Zeta meter
Turbidity	Nephelometer
In vitro drug release study	Franz diffusion cell with artificial or biological membrane, Dialysis bag diffusion
Drug deposition study	Franz diffusion cell
Stability study	Dynamic light scattering method Transmission electron microscopy

Evaluation of ethosomes

1. **Filter membrane:** Vesicle Interaction Study by Scanning Electron Microscopy: It involves the application of vesicle suspension (0.2 mL) to filter membrane having a pore size of 50 nm and placing it in diffusion cells. The upper side of the filter was exposed to the air, whereas the lower side was in contact with phosphate buffer saline solution (having pH 6.5). The filters were removed after 1 hour and were prepared for SEM studies by fixation at 4°C in Karnovsky's fixative overnight followed by dehydration with graded ethanol solutions (30%, 50%, 70%, 90%, 95%, and 100% v/v in water). Finally, filters were coated with gold and examined in SEM.[23]

2. **Skin permeation studies:** Carefully trimmed the hair of test animals (rats) short (<2 mm) with a pair of scissors and separated the abdominal skin from the underlying connective tissue with a scalpel. The excised skin was placed on aluminium foil and gently teased off

the dermal side of the skin for any adhering fat and subcutaneous tissue. The effective permeation area of the diffusion cell and receptor cell volume was 1.0 cm2 and 10 mL, respectively and maintained the temperature at 32°C ± 1°C. The receptor compartment contained phosphate buffer saline solution (10 mL of pH 6.5). Excised skin was mounted between the donor and the receptor compartment. Ethosomal formulation (1.0 mL) was applied to the skin's epidermal surface. Samples (0.5 mL) were withdrawn through the sampling port of the diffusion cell at 1, 2, 4, 8,12,16,20 & 24-hour time intervals and analyzed by high-performance liquid chromatography assay.[24]

3. **Stability study:** The vesicles determined the stability by storing the vesicles at 4°C ± 0.5°C. The measured vesicle size, zeta potential, and entrapment efficiency of the vesicles after 180 days using the method described earlier.[25]

4. **Vesicle-Skin Interaction Study by TEM and SEM:** From animals, cut ultra-thin sections (Ultra cut, Vienna, Austria), collected on form coated grids and examined under the transmission electron microscope. For SEM analysis, the skin sections after dehydration were mounted on stubs using adhesive tape and were covered with gold-palladium alloy using a fine coat ion sputter coater. The sections were examined under the scanning electron microscope.[26]

5. **Vesicle-Skin Interaction Study by Fluorescence Microscopy:** Fluorescence microscopy was carried according to the TEM and SEM study protocol. Paraffin blocks are used, were made, 5-µm thick sections were cut using a microtome (Erma optical works, Tokyo, Japan) and examined under a fluorescence micro–Cytotoxicity Assay MT-2 cells (T-lymphoid cell lines) were propagated in Dulbecco's modified Eagle medium (HIMEDIA, Mumbai, India) containing 10% fetal calf serum, 100 U/mL penicillin, 100 mg/mL streptomycin, and 2 mmol/L L glutamine at 37°C under a 5% CO2 atmosphere. Cytotoxicity was expressed as the cytotoxic dose 50 (CD50) that induced a 50% reduction of absorbance at 540 nm.[27]

6. **Drug uptake studies:** The uptake of the drug into MT-2 cells (1×106 cells/mL) was performed in 24-well plates (Corning Inc), in which 100 µL RPMI medium was added. Cells were incubated with 100 µL of the drug solution in phosphate buffer saline solution (pH 7.4), Ethosomal formulation, or marketed formulation. Then drug uptake was determined by analyzing the drug content by HPLC assay.

7. **HPLC Assay:** The amount of drug permeated in the receptor compartment during in vitro skin permeation experiments and in MT-2 cell was determined by HPLC assay using methanol: distilled-water: acetonitrile (70:20:10 vol/vol) mixture as mobile phase delivered at 1 mL/min by LC 10-AT VP pump (Shimadzu, Kyoto, Japan). At room temperature, A twenty-micro litre injection was eluted in the C-18 column (4.6×150 mm, Luna, 54, Shimadzu). The column Eluent was monitored at 271 nm using the SPDM10A VP diode array UV detector. The coefficient of variance (CV) for the standard curve ranged from 1.0% to 2.3%, and the squared correlation coefficient was 0.9968.[28]

8. **Statistical analysis:** Statistical significance of all the data generated was tested by employing ANOVA followed by a studentized range test. A confidence limit of $P < .05$ was fixed to interpret the results using the software PRISM.

Table 3: Therapeutic applications of ethosomes.[29]

S. no.	Application	Drug	Purpose of Ethosomal delivery
1	Treatment of acne	Azelaic acid	Improves the sustained release
2	NSAIDS	Diclofenac	Selective targeting the cells
3	Steroidal hormone	Testosterone	low oral bioavailability dose dependent side effects
4	Treatment of Parkinson's disease	Trihexyphenidyl hydrochloride	4.5-times higher than that from liposome
5	Anti-HIV	Zidovudine and lamivudine	Better cellular uptake
6	Antibacterial	Bacitracin	Better cellular uptake
7	Antimicrobial	Erythromycin	Better cellular uptake
8	Treatment of genetic disorders	DNA	Expression into skin cells
9	Treatment of rheumatoid	Cannabidol	low bioavailability
10	Treatment of Herpes labialis	Acyclovir	Poor skin permeation
11	Treatment of diabetes	Insulin	GIT degradation
12	Treatment of Inflammatory skin disease	Cyclosporin	GIT degradation Poor oral
13	Treatment of inflammatory based skin diseases	Ammonium glycyrrhizinate	Poor skin permeation Poor oral bioavailability
14	Treatment of candidiasis	Fluconazole	Poor skin permeation
15	Treatment of psoriasis	Methotrexate	Poor skin permeation
16	Anti-asthmatic	Salbutamol	Enhanced drug delivery through skin with ethosomes
17	Treatment of baldness	Minoxidil	Pilocebaceous targeting Accumulation in skin increased

18	overcoming the problems associated with oral delivery	Proteins and Peptides	Large molecules
19	Treatment of Hypertension	Enalapril maleate	Low oral bioavailability Major side effects in oral delivery

Patented and Marketed formulation of ethosome

Ethosomes were invented and patented by Prof. Elka Touitou and her students of the Department of Pharmaceutics at the Hebrew University School of Pharmacy. Novel Therapeutic Technologies Inc (NTT) of Hebrew University has successfully brought several products to the market based on the Ethosomal delivery system. Noicellex TM, an anti-cellulite formulation of Ethosome, is currently marketed in Japan. Liposuction TM, another formulation, is presently used to treat cellulite containing pure grape seed extracts (antioxidant) is marketed in the USA. Similarly, Physonics is marketing anti-cellulite gel Skin Genuity in London. Nanominoxc contained minoxidil as a hair tonic to promote hair growth.[30]

Table 4: Marketed products based on ethosomal drug delivery system.

Name of product	Uses	Uses Manufacturer
Celltight EF	Topical cellulite cream contains a powerful combination of ingredients to increase metabolism and break down fat.	Hampden Health, USA
Decorin cream	Anti-ageing cream, treating, repairing, and delaying the visible ageing signs of the skin, including wrinkle lines, sagging, age spots, loss of elasticity, and hyperpigmentation	Genome Cosmetics, Pennsylvania, US
Nanominox	First minoxidil containing product, which uses Ethosomes. It contains 4% Minoxidil, well-known hair growth promoter that must be metabolized by sulfation to the active compound.	Sinere, Germany
Noicellex	Topical anti-cellulite cream	Novel Therapeutic Technologies, Israel
Skin genuity	Powerful cellulite buster, reduces orange peel	Powerful cellulite buster, reduces orange peel

CONCLUSION

Ethosomes as alternative carriers currently focus on transdermal drug delivery systems. Ethosomes have initiated a new area in vesicular research for transdermal drug delivery, providing better skin permeation than liposomes. The main limiting factor of the transdermal

drug delivery system, i.e., the Epidermal barrier, can be overcome by ethosomes significantly. Ethosomes can therefore infer that in the future, ethosomes can become a promising drug carrier not just for topical treatment but also for the local and systemic diseases, cosmetic and cosmeceutical fields to create new, improved therapies. Application of ethosomes provides the advantages such as improved permeation through the skin and targeting deeper skin layers for various skin diseases. Ethosomes have been tested to encapsulate cationic, hydrophilic, proteins, and peptides. Further, research in this area will allow better control over drug release in vivo and long-term safety data, allowing the therapy more effective. Thus, ethosomal formulations possess a promising future in effective dermal/transdermal delivery of bioactive agents.

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