WORLD JOURNAL OF PHARMACY AND PHARMACEUTICAL RESEARCH

Review Article

2025
Volume: 02
Issue: 04
Page: 85-101

ETHOSOMES: A REVIEW

Prakash S.*[1], Parthasarathi K. Kulkarni[2], Tanuja A. J.[3], Venkatesh[4], Hanumanthachar Joshi[5]

[1,2,3,4]Department of Pharmaceutics, Sarada Vilas College of Pharmacy, Mysuru, Karnataka, India.

[5]Department of Pharmacognosy, Sarada Vilas College of Pharmacy, Mysuru, Karnataka, India.

Received: 21 February 2025 **Revised: 11 March 2025** **Accepted: 01 April 2025**

Corresponding Author: Prakash S.

Address: Department of Pharmaceutics, Sarada Vilas College of Pharmacy, Mysuru, Karnataka, India.

ABSTRACT

Ethosomes are advanced lipid-based carriers designed for enhanced transdermal and dermal drug delivery. Composed primarily of phospholipids, ethanol, and water, ethosomes possess unique properties that enable deeper penetration of active pharmaceutical ingredients into the skin layers, as well as systemic absorption. Ethanol, a key component, acts as a penetration enhancer by increasing the fluidity of skin lipids and creating new pathways for drug transport. Ethosomes exhibit greater stability, higher drug entrapment efficiency, and smaller vesicle sizes compared to traditional liposomes, making them highly effective for both hydrophilic and lipophilic drugs. This review article aims to explore the composition, preparation methods, characterization techniques, alongside their mechanisms of action in drug delivery and potential therapeutic applications of ethosomes. Additionally, it highlights the advantages of ethosomes over other vesicular carriers, including their ability to deliver drugs under both occlusive and non-occlusive conditions. The article also discusses recent advancements in ethosomal technology and their role in improving transdermal drug delivery for various clinical applications.

KEYWORDS: Ethosomes, Ethanol, Vesicular carrier, Transdermal, Phospholipid.

INTRODUCTION

Since the skin is one of the body's largest and easiest organs to access, medication distribution through it is appealing. Transdermal distribution has a number of benefits over conventional drug delivery techniques, including less variation in plasma drug levels, prevention of gastrointestinal problems and first-pass metabolism, and increased patient compliance. The limited permeability of the skin, however, limits the range of medications that may be administered efficiently through transdermal distribution, which is one of the main disadvantages of this method. With the exception of lipophilic and low molecular weight medications, the stratum corneum acts as the main barrier to molecular transport through the skin, which is an excellent barrier. For topical and transdermal drug delivery methods to work, the medication needs to cross the epidermal barrier.[1]

Enhancers for chemical skin penetration, iontophoresis, sonophoresis, electroporation, and microneedles are just a few of the techniques that have been investigated to increase transdermal medication delivery's effectiveness. However, none of these strategies have been extensively used up to this point because to their low efficacy, risk of causing skin irritation, difficulty in application, and/or expensive cost.[2] Lipid-based suspensions like liposomes, niosomes, and microemulsions have also been proposed as low-risk drug carriers; but, because they tend to stay in the top layers of the skin rather than penetrate deeply, they don't really help with transdermal drug delivery.[3]

Innovative elastic lipid vesicular systems have been developed by researchers to facilitate deeper and easier skin penetration. Bile salts, phospholipids, ethanol, and other surfactants are used to form these systems. Despite their vesicular size being greater than the holes themselves, these elastic vesicles are able to pass through the stratum corneum pores due to the extraordinary flexibility of their vesicular membranes.[4] The first-generation elastic lipid vesicular carrier, known as Transferosomes, was presented by Cevc et al. in 1992. It was mostly composed of phospholipids and a non-ionic surfactant that acted as an edge activator. It has been claimed that these vesicles can efficiently permeate intact skin to carry medications both through and into it. [5]

STRUCTURE OF SKIN

As the outermost layer of the epidermis, the stratum corneum is made up of 10 to 25 layers of fully keratinized, elongated, dead corneocytes encased in a lipid bilayer matrix. The main defense against skin penetration is this layer. The active ingredient in a topical preparation

needs to penetrate the stratum corneum in order to reach the live tissue underneath the skin. This mechanism is mostly limited by the slow diffusion through the skin's hardened, non-living layer. The stratum corneum, which serves as a hydrophobic membrane, controls how quickly low- and high-molecular-weight organic nonelectrolytes permeate.[6]

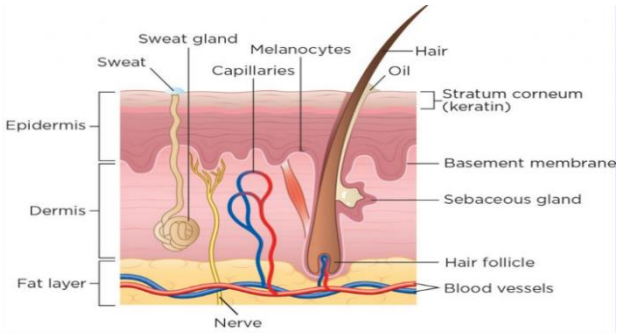

Fig. 1: Structure of skin.[7]

VESICULAR APPROACHES FOR TOPICAL DRUG DELIVERY

It is known that medications contained in phospholipid- and nonionic surfactant-based lipid vesicles can pass through and into the skin. The lipids found in the skin help to maintain its barrier qualities, which typically stop medications from being absorbed systemically. However, lipid vesicles may function as non-toxic drug penetration enhancers because of their amphiphilic nature. Furthermore, medications with low and high molecular weights, as well as hydrophilic and lipophilic pharmaceuticals, can be encapsulated in vesicles. Consequently, it is hypothesized that these lipid-rich vesicles enhance systemic absorption of medications by transporting a substantial amount of them through the skin.

Several uses for liposome-based drug delivery in transdermal formulations have been investigated. However, they are not as effective when used topically due to their instability and low skin permeability. Proliposomes are a notion that was put up to increase liposome stability. Afterwards, niosomes-which demonstrated greater stability than liposomes-were considered using this concept. Even with this advancement, liposomes and niosomes inadequate skin permeability limited their application to topical treatments and hindered their capacity to be successfully used for systemic drug administration.

Recently, Cevc and Touitou presented ethosomes, a new vesicular carrier system for non-invasive medication delivery into or across the skin, to solve the problem of poor skin permeability. Alcohols and polyols, which improve penetration, are included in ethosomes and have an impact on the stratum corneum's and the vesicles characteristics. The function of

vesicles in particle transport and cellular communication has long been understood. By tagging vesicles for cell selectivity, researchers have improved medication delivery within their cavities by utilizing the structural characteristics of vesicles. The creation of ethosomes, or vesicle derivatives, represented a substantial breakthrough in vesicle research.[8]

ETHOSOMES

Ethosomes, soft and flexible vesicles, serve as non-invasive drug delivery systems that effectively transport active agents into the deep skin layers or systemic circulation. Composed mainly of phospholipids (like phosphatidylcholine, phosphatidylserine, and phosphatidic acid), water, and a high concentration of ethanol as illustrated in fig 2, ethosomes are uniquely designed to enhance drug penetration. The high ethanol content disrupts the lipid bilayer structure of the skin and, when integrated into the vesicle membrane, facilitates the penetration of the stratum corneum.

The high ethanol concentration in ethosomes leads to a more loosely packed lipid membrane compared to traditional vesicles while maintaining similar stability. This flexible structure improves drug distribution within the stratum corneum lipids. While ethosomes share lipid bilayers with liposomes (fig 2), their composition differs due to the high ethanol content. Compared to conventional liposomes, ethosomes exhibit smaller vesicle sizes, greater drug entrapment efficiency, and enhanced stability.[8]

Ethosomes formulations provide sustained drug delivery, acting as a reservoir system for continuous release of drugs. Transmission electron microscopy has shown that ethosomes can be either unilamellar or multilamellar, extending to the core. The size of ethosomes vesicles can range from tens of nanometres to a few microns, depending on the method of preparation, composition, and techniques like sonication. Unlike Transferosomes®, ethosomes enhance drug delivery through the skin in both occlusive and non-occlusive conditions.[1]

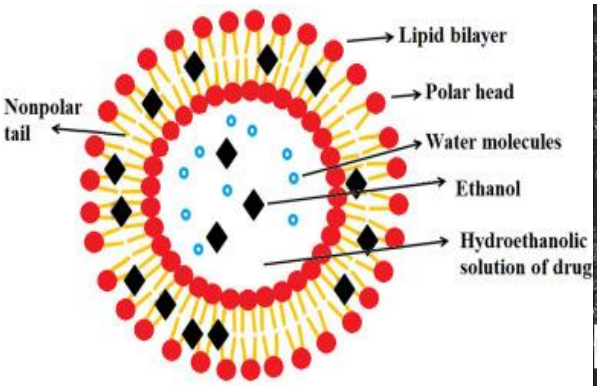

Fig. 2: Proposed diagram of ethosomes vesicle.[9]

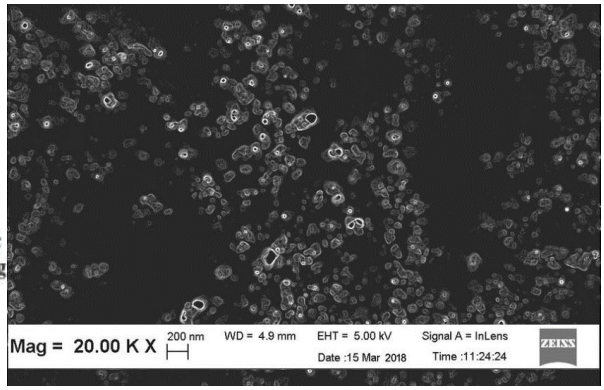

Fig. 3: SEM image of ethosomes.[10]

ETHOSOMES COMPOSITION

Ethosomes are composed of phospholipids (such as phosphatidylcholine, phosphatidylserine, and phosphatidic acid), a high concentration of ethanol, water, and the active drug or therapeutic agent. The phospholipids form the vesicular bilayer, ethanol enhances skin penetration and vesicle flexibility, and water provides structural support. Optional stabilizers or additives may also be included to improve performance and stability. [11,12]

Table 1: Different Additive Employed in Formulation of Ethosomes.

Class	Example	Uses
Phospholipid	Soya phosphatidyl choline Egg phosphatidyl choline Dipalmityl phosphatidyl choline Distearyl phosphatidyl choline	Vesicles forming component[13]
Polyglycol	Propylene glycol Transcutol RTM	As a skin penetration enhancer[14]
Alcohol	Ethanol Isopropyl alcohol	For providing the softness for vesicle membrane as a penetration enhancer[15]
Cholesterol	Cholesterol	For providing the stability to vesicle membrane[16]
Dye	Rhodamine-123 Rhodamine red Fluorescen Isothiocyanate (FITC) 6- Carboxy fluorescence	For characterization study[17]
Vehicle	Carbopol 934	As a gel former[18]

MECHANISM OF DRUG PENETRATION[19,20]

The initial phase of the mechanism involves the effect of ethanol, where its interaction with intracellular lipids increases lipid fluidity and reduces the density of the lipid multilayer. This

is followed by the action of ethosomes, which penetrate and permeate the lipids, creating new pathways as the ethosomes fuse with the skin lipids.

The drug absorption occurs in following two steps

a) Ethanol effect

b) Ethosomes effect

a) Ethanol effect

Ethanol functions as a penetration enhancer for the skin. The mechanism behind its enhancing effect is well understood: ethanol penetrates the intercellular lipids, increasing the fluidity of cell membrane lipids and reducing the density of the lipid multilayer within the cell membrane.

b) Ethosomes effect

The increased lipid fluidity in the cell membrane caused by the ethanol in ethosomes leads to enhanced skin permeability. As a result, ethosomes easily penetrate into the deep layers of the skin, where they fuse with skin lipids and release the drugs into these deeper layers.

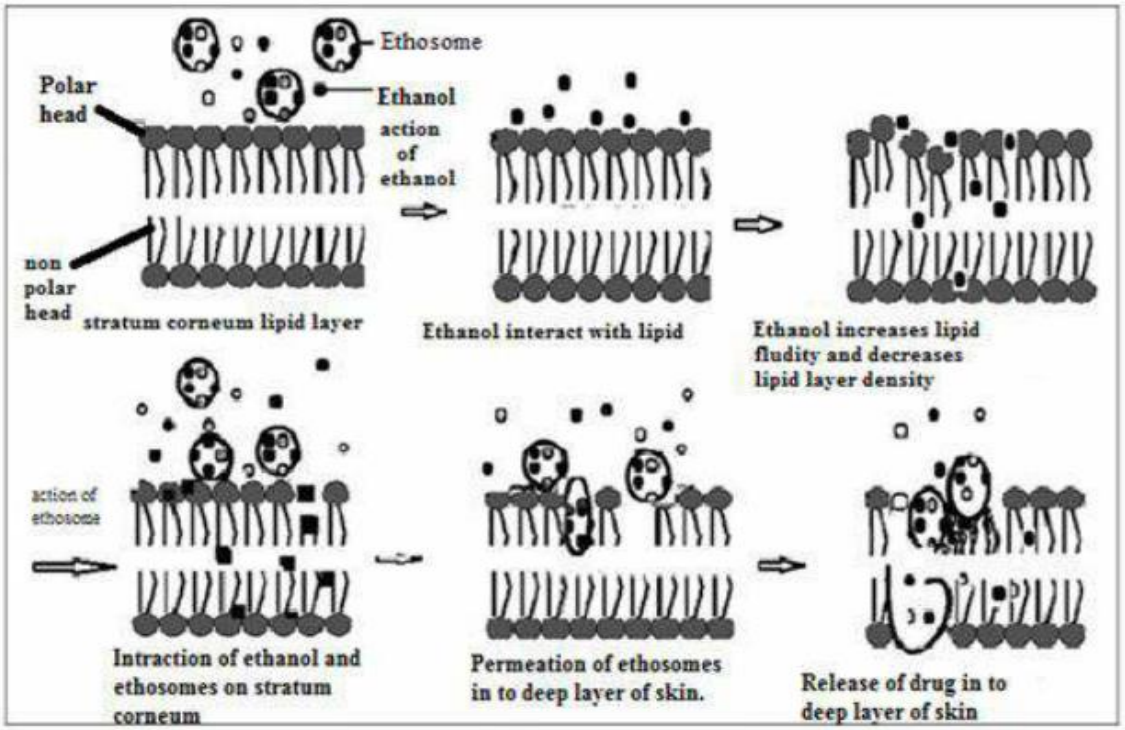

Fig. 4: Mechanism of action of Ethosomes.

Advantages Of Ethosomal Drug Delivery[21]

- Enhanced permeation of drug through skin for transdermal drug delivery.
- Delivery of large molecules (peptides, protein molecules) is possible.
- It contains non-toxic raw material in formulation
- Simple method for drug delivery in comparison to Iontophoresis and Phonophoresis and other complicated methods.
- Ethosomal drug delivery system can be applied widely in Pharmaceutical, Veterinary,
- Cosmetic fields.
- High patient compliance- The Ethosomal drug is administrated in semisolid form (gel or cream) hence producing high patient compliance.
- The Ethosomal system is passive, non-invasive and is available for immediate
- Commercialization.

DISADVANTAGES OF ETHOSOMAL DRUG DELIVERY[22,23]

- Product loss when switching from organic to water media.
- Limited yield of products.
- If shell locking fails, the ethosomes may agglomerate and disintegrate when transferred into the water.
- Poor yield.
- Skin irritation brought on by excipients and enhancers used in medication delivery system.
- The drug molecular size needs to be appropriate for percutaneous absorption.
- May shows poor adherence to all types of skin.
- Not all varieties of skin will adhere to adhesive as well.

METHODS OF PREPARATION ETHOSOMES[24]

Ethosomes can be prepared by two very simple and convenient methods that are hot method and cold method.

1. COLD METHOD

This is the most commonly used method for preparing Ethosomal formulations. In this process, phospholipids, drugs, and other lipid materials are dissolved in ethanol in a covered vessel at room temperature while being vigorously stirred using a mixer. Propylene glycol or another polyol is added during the stirring. The mixture is then heated to 30°C in a water

bath. Separately, water is also heated to 30°C and added to the mixture, which is stirred for an additional 5 minutes in a covered vessel. The vesicle size of the Ethosomal formulation can be reduced to the desired extent using sonication or extrusion methods. Finally, the formulation is stored in a refrigerator.

2. HOT METHOD

In this method, phospholipids are dispersed in water and heated in a water bath at 40°C until a colloidal solution is formed. Meanwhile, ethanol and propylene glycol are mixed and heated to 40°C in a separate vessel. Once both mixtures reach 40°C, the organic phase is added to the aqueous phase. The drug is dissolved either in water or ethanol, depending on its hydrophilic or hydrophobic properties. The vesicle size of the Ethosomal formulation can be reduced to the desired extent using probe sonication or extrusion methods.

CHARACTERIZATION OF ETHOSOMES [19,21]

1. **Vesicle shape:** Ethosomes can be readily visualized using transmission electron microscopy (TEM) or scanning electron microscopy (SEM).
2. **Transition temperature:** The transition temperature of vesicular lipid systems can be measured using differential scanning calorimetry (DSC).
3. **Particle size and zeta potential:** The particle size of ethosomes can be determined using dynamic light scattering (DLS) and photon correlation spectroscopy (PCS). The zeta potential of the formulation can be measured with a zeta meter.
4. **Drug content:** The drug content of ethosomes can be measured using a UV spectrophotometer. It can also be quantified using a modified high-performance liquid chromatography (HPLC) method.
5. **Drug entrapment:** The entrapment efficiency of ethosomes can be measured by the ultracentrifugation technique.
6. **Surface tension measurement:** The surface tension activity of drug in aqueous solution can be measured by the ring method with a Du Nouy ring tensiometer.
7. **Stability studies:** The stability of vesicles can be evaluated by monitoring the size and structure of the vesicles over time. Mean size is measured by DLS and structure changes are observed by TEM.
8. **Skin permeation studies:** The ability of the Ethosomal preparation to penetrate into the skin layers can be determined by using confocal laser scanning microscopy (CLSM).

EVALUATION TESTS[25,26,27]

1. Filter Membrane: Vesicle Interaction Study by Scanning Electron Microscopy

Take a 0.2 mL suspension of vesicles and a 50 nm-pore-sized filter membrane. The combination is used on the putting the filter membrane into the diffusion cells. The filter membrane's upper side was open to the atmosphere and the filter membrane's lower side comes into contact with the pH 6.5 phosphate buffer solution. The screen after an hour, membranes were removed, and they were ready for SEM investigations using fixation at 4°C in Carnovsky's fixative overnight, then gradually reduce fluid intake solutions of ethanol (30%, 50%, 70%, 90%, 95%, and 100% volumetric relative to volume in water). Ultimately, membrane filters were covered with gold and subjected to a SEM analysis.

2. Skin Permeation Studies

The test subjects (rats) hair was clipped using scissors to a short length (<2 mm), and a knife was used to detach the abdomen skin from the underlying connective tissue. The skin that had been removed was spread out on aluminum foil, and any residual fat or subcutaneous tissue was carefully removed from the dermal side. The diffusion cell's receptor cell volume was 10 mL, and its effective permeation area measured 1.0 cm^2. A constant temperature of 32°C ± 1°C was maintained. The receptor compartment held 10 milliliters of pH 6.5 PBS. After the skin was removed, it was placed between the donor and receptor compartments and the epidermal surface was covered with 1.0 mL of the ethosomal formulation. Samples (0.5 mL) were removed via the diffusion cell's sampling port.

3. Vesicle-Skin Interaction Study by Fluorescence Microscopy

Fluorescence microscopy was performed following the protocol used for TEM and SEM studies. Skin sections, 5 μm thick, were cut using a microtome and examined under a fluorescence microscope. For the cytotoxicity assay, MT-2 cells (T-lymphoid cell lines) were cultured in Dulbecco's modified Eagle medium supplemented with 10% fetal calf serum, 100 U/mL penicillin, 100 mg/mL streptomycin, and 2 mmol/L L-glutamine at 37°C in a 5% CO2 environment. Cytotoxicity was measured as the CD50 (cytotoxic dose 50), which represents the concentration that causes a 50% reduction in absorbance at 540 nm.

4. HPLC Assay

The amount of drug permeated into the receptor compartment during the *in vitro* skin permeation experiments, as well as in MT-2 cells, was quantified using an HPLC assay. The mobile phase consisted of a methanol: water: acetonitrile mixture (70:20:10 vol/vol),

delivered at a flow rate of 1 mL/min using an LC 10-AT vp pump (Shimadzu, Kyoto, Japan). A 20-microliter sample was injected and eluted through a C-18 column (4.6×150 mm, Luna, 54, Shimadzu) at room temperature. The eluent was detected at 271 nm using an SPDM10A vp diode array UV detector. The coefficient of variance (CV) for the standard curve ranged from 1.0% to 2.3%, with a squared correlation coefficient of 0.9968.

5. Drug Uptake Studies

The uptake of drug into MT-2 (T-lymphoid cell lines) were incubated with 100 µL of the drug solution in phosphate-buffered saline (pH 7.4), ethosomal formulation, or a marketed formulation. The drug uptake was then assessed by determining the drug content using an HPLC assay.

6. Vesicle-Skin Interaction Study by TEM and SEM

Obtain the animal and prepare ultrathin sections using an ultramicrotome (Ultra cut, Vienna, Austria). Collect the sections onto coated grids and analyze them using a transmission electron microscope (TEM). For SEM analysis, dehydrate the skin sections and mount them on stubs using adhesive tape. Coat the samples with gold-palladium using a fine coat ion sputter coater, then examine the sections under a scanning electron microscope (SEM).

7. Stability Study

The stability of the vesicles was assessed by storing them at 4°C ± 0.5°C. After 180 days, the vesicle size, zeta potential, and entrapment efficiency were measured using the previously described method.

APPLICATION OF ETHOSOMES

1. Transdermal delivery of hormones [21,28]

Hormones administered orally are linked to issues such as limited oral bioavailability, high first pass metabolism, and a number of dose-dependent adverse effects. Every missed medication is known to raise the chance of treatment failure. Touitou et al. contrasted the testosterone ethosomes' (Testosome) capacity to penetrate rabbit pinna skin with that of a commercially available transdermal testosterone patch (Testoderm patch, Alza). When compared to the commercial formulation, they found that the ethosomal formulation had almost 30 times the skin penetration of testosterone.

2. Delivery of Anti-Viral Drugs[21,29]

Zidovudine is a potent antiviral agent effective against the acquired immunodeficiency virus. However, its oral administration is associated with significant side effects, necessitating an optimal zero-order delivery system to sustain its anti-AIDS efficacy. Jain et al. demonstrated that ethosomes enhance transdermal flux, prolong drug release, and offer a promising approach for sustained zidovudine delivery. Similarly, acyclovir, widely used topically for treating Herpes labialis, faces challenges with conventional formulations due to poor penetration into the dermal layer, resulting in limited therapeutic effectiveness. As viral replication occurs in the basal dermis, Horwitz et al. developed an ethosomal formulation for acyclovir's dermal delivery. Their findings indicated shorter healing times and a higher percentage of abortive lesions when acyclovir was delivered via ethosomes.

3. Topical delivery of DNA[24,30]

The skin acts as a robust barrier against environmental pathogens, being both immunologically active and capable of gene expression. This makes it a promising target for ethosomes in the topical delivery of DNA to facilitate gene expression in skin cells. Touitou et al. encapsulated a GFP-CMV-driven transfecting construct within an ethosomal formulation and applied it to the dorsal skin of 5-week-old male CD-1 nude mice for 48 hours. CLSM analysis revealed effective delivery and gene expression of the construct in skin cells. The study proposed ethosomes as carriers for gene therapy applications requiring transient gene expression and highlighted their potential for transdermal immunization. Supporting this, Gupta et al. demonstrated the immunization potential of transfersomal formulations. Ethosomes' superior skin permeation capabilities present opportunities for delivering immunizing agents, expanding their role in advanced therapeutic applications like gene therapy and vaccination.

4. Delivery of anti-parkinsonism agent[21,31]

The distribution efficiency of an ethosomal formulation of the psychoactive medication trihexyphenidyl hydrochloride (THP) was compared to that of a traditional liposomal formulation by Dayan and Touitou. Parkinson's disease is frequently treated with THP, an M1 muscarinic receptor antagonist. The findings showed that the ethosomal-THP formulation had a higher capacity for skin penetration, indicating that it may be used to treat Parkinson's disease more successfully.

5. Delivery of Anti-Arthritis Drug[24,32]

The issue with traditional oral therapy is resolved by topical application of anti-arthritis medications, which is a better option for site-specific delivery. A newly created medication contender for the treatment of rheumatoid arthritis is cannabidol (CBD). Lodzki and associates prepared formulation of CBD ethosomal for transdermal administration. Tested using a rat paw edema model generated by carrageenan, the CBD-ethosomal formulation's biological anti-inflammatory efficacy was found to have greatly boosted. It was determined that encapsulating CBD in ethosomes greatly enhanced its biological activity by increasing its skin penetration and accumulation.

6. Delivery of Antibiotics[33]

Topical antibiotic delivery provides a superior alternative to traditional oral therapy, which often causes allergic reactions and side effects. Conventional external antibiotic preparations face challenges in penetrating deep skin layers and subdermal tissues. Ethosomes overcome these limitations by efficiently delivering antibiotics into the deeper skin layers, targeting infections at their source. Godin and Touitou developed ethosomal formulations with bacitracin and erythromycin for dermal and intracellular delivery. Their study demonstrated that ethosomal antibiotics penetrate the epidermis effectively, delivering significant drug amounts to deeper tissues. This approach offers a promising solution to the limitations of conventional antibiotic therapies.

7. Transcellular Delivery[34]

In their study, Touitou et al. demonstrated enhanced intracellular uptake of bacitracin, DNA, and erythromycin using CLSM and FACS techniques across various cell lines. The superior cellular uptake of the anti-HIV drugs zidovudine and lamivudine in the MT-2 cell line from ethosomal formulations, compared to the marketed alternatives, highlights the potential of ethosomes as a promising clinical option for anti-HIV therapy.

8. Delivery of Problematic drug molecules[27,35]

The oral delivery of large biogenic molecules, such as peptides and proteins, is hindered by their degradation in the gastrointestinal tract, making non-invasive protein delivery a promising alternative. Dkeidek and Touitou studied the in vivo effects of ethosomal insulin delivery on blood glucose levels (BGL) in normal and diabetic SDI rats. A Hill Top patch containing insulin-loaded ethosomes was applied to the abdominal area of overnight-fasted rats, resulting in a significant reduction (up to 60%) in BGL, while the control formulation

showed no effect. Similarly, Verma and Fahr demonstrated the potential of cyclosporin A ethosomal formulations for managing inflammatory skin conditions like psoriasis, atopic dermatitis, and hair follicle disorders such as alopecia areata. Paolino et al. investigated ethosomes for delivering ammonium glycyrrhizinate, a triterpene from Glycyrrhizinate Glabra, effective in treating inflammatory skin diseases. These studies highlight ethosomes' versatility in targeted and non-invasive drug delivery.

9. Pilosebaceous targeting[25,36]

Localized therapy has made use of pilosebaceous units, especially in the treatment of follicle-related conditions like alopecia or acne.

Minoxidil, a lipid-soluble medication used to treat baldness, has an ethosomal version that accumulates two to seven times more in the skin of naked mice. For improved therapeutic efficacy, it can be employed for pilosebaceous targeting.

Table 2: MARKETED ETHOSOMES FORMULATION.

Name of product	Uses	Manufacturer
Decorin cream	An anti-aging cream designed to treat, repair, and delay visible signs of aging in the skin, including wrinkles, sagging, age spots, loss of elasticity, and hyperpigmentation.	Genome Cosmetics, Pennsylvania, US [38]
Noicellex	Topical anti-cellulite cream	Novel Therapeutic Technologies, Israel [38]
Skin Genuity	Powerful cellulite buster reduces orange peel	Physonics Nottingham, UK [38]
Nanominox	First Monoxidil containing product, which uses Ethosomes. Contains 4% Monoxidil, well-known hair growth promoter that must be metabolized by sulfation to the active compound	Sinere, Germany [27]
Supravir cream	For the treatment of herpes virus infections	Trima, Israel [37]
Body Shape	The gel facilitates solidification, helping to tighten and stretch the skin	Maccabi CARE [37]
Cellutight EF	The topical cellulite cream contains a potent blend of ingredients designed to boost metabolism and aid in fat breakdown	Hampden Health, USA [27]
Physonics	Anti-cellulite gel	London [25]
Lipoduction TM	Used in treatment of cellulites	USA [25]

CONCLUSION

Ethosomes represent a groundbreaking advancement in transdermal and topical drug delivery systems, offering superior skin permeation and enhanced therapeutic efficacy for a wide range of applications. Their unique structure and composition allow for the efficient delivery of challenging therapeutic agents, including large molecules such as peptides, proteins, and DNA, as well as small lipophilic and hydrophilic drugs. Studies have demonstrated their potential in addressing limitations of conventional formulations, such as low permeability and systemic side effects, making them particularly valuable for gene therapy, immunization, and the treatment of various skin diseases. With proven success in delivering antibiotics, anti-HIV drugs, insulin, and anti-inflammatory agents, ethosomes open new horizons for non-invasive and targeted therapy. Future research and clinical studies may further establish ethosomes as a versatile and effective platform for innovative pharmaceutical and cosmetic applications.

REFERENCE

1. Rakesh R, Anoop KR. Ethosomes for transdermal and topical drug delivery. Int J Pharm Pharm Sci., 2012; 4(3): 17-24.
2. Essa EA, Bonner MC, Barry BW. Electroporation and ultradeformable liposomes; human skin barrier repair by phospholipid. Journal of controlled release, 2003 Sep 19; 92(1-2): 163-72.
3. Cevc G. Lipid vesicles and other colloids as drug carriers on the skin. Advanced drug delivery reviews, 2004 Mar 27; 56(5): 675-711.
4. Honeywell-Nguyen PL, Bouwstra JA. Vesicles as a tool for transdermal and dermal delivery. Drug discovery today: technologies, 2005 Mar 1; 2(1): 67-74.
5. Cevc G. Transfersomes, liposomes and other lipid suspensions on the skin: permeation enhancement, vesicle penetration, and transdermal drug delivery. Critical reviews™ in therapeutic drug carrier systems. 1996;13(3-4).
6. Roy SD, Flynn GL. Transdermal delivery of narcotic analgesics: comparative permeabilities of narcotic analgesics through human cadaver skin. Pharmaceutical research, 1989 Oct; 6: 825-32.
7. Lawton SJ. Skin 1: the structure and functions of the skin. Nurs. Times, 2019 Dec; 115: 30-3.
8. Vijayakumar KS, Parthiban S, Senthilkumar GP, Mani TT. Ethosomes-A new trends in vesicular approaches for topical drug delivery. Asian J. of Res Pharm Sci and Biotech, 2014; 2(1): 23-30.

9. Ahad A, Akhtar N, Gupta DK, Waheed A, Aqil M, Al-Jenoobi FI, Al-Mohizea AM. Ethosomes: a potential vesicular carrier for drug delivery. InSystems of Nanovesicular Drug Delivery, 2022 Jan 1; 221-237.
10. Sin KY, Kumar JR. DEVELOPMENT AND IN-VITRO EVALUATION OF CATECHIN LOADED ETHOSOMAL GEL FOR TOPICAL DELIVERY.
11. Parashar T, Sachan R, Singh V, Singh G, Tyagi S, Patel C, Gupta A. Ethosomes: A recent vesicle of transdermal drug delivery system. Int J Res Dev Pharm Life Sci., 2013 Feb; 2(2): 285-92.
12. Touitou E, inventor; Yissum Research Development Co of Hebrew University of Jerusalem, assignee. Compositions for applying active substances to or through the skin. United States patent US 5,540,934, 1996 Jul 30.
13. Aute PP, Kamble MS, Chaudhari PD, Bhosale AV. A comprehensive review on ethosomes. International journal of research and development in pharmacy & life sciences, 2012 Jan 15; 2(1): 218-24.
14. Thadanki M, Babu AK. Review on Ethosomes: A novel approach of Liposomes. International Journal of Pharmacy & Life Sciences, 2015 Jan 1; 6(1).
15. Patrekar PV, Inamdar SJ, Mali SS, Mujib MT, Ahir AA, Hosmani AH. Ethosomes as novel drug delivery system: A review. The pharma innovation, 2015 Nov 1; 4(9, A): 10.
16. Hariharanb S, Justinc A. Topical delivery of drugs using ethosomes: A review. Indian drugs, 2019 Sep; 56(08): 7.
17. Mohanty D, Mounika A, Bakshi V, Haque MA, Sahoo CK. Ethosomes: a novel approach for transdermal drug delivery. Int. J. ChemTech Res., 2018; 11(8): 219-26.
18. Gupta NB, Loona S, Khan MU. Ethosomes as elastic vesicles in transdermal drug delivery: An overview. International Journal of Pharmaceutical Sciences and Research, 2012 Mar 1; 3(3): 682.
19. Jain H, Patel J, Joshi K, Patel P, Upadhyay UM. Ethosomes: A novel drug carrier. International journal of clinical practice, 2011; 7(1): 1-4.
20. Satyam G, Shivani S, Garima G. Ethosomes: A novel tool for drug delivery through the skin. J Pharm Res, 2010 Apr; 3(4): 688-91.
21. Kesharwani R, Patel DK, Sachan A, Kumar V, Mazumdar B. Ethosomes: A novel approach for transdermal and topical drug delivery. Research Journal of Topical and Cosmetic Sciences, 2015; 6(1): 15-20.

22. Vijayakumar KS, Parthiban S, Senthilkumar GP, Mani TT. Ethosomes-A new trends in vesicular approaches for topical drug delivery. Asian J. of Res Pharm Sci and Biotech, 2014; 2(1): 23-30.
23. Shahwal V, Samnani A, Dubey B, Bhowmick M. Ethosomes: an overview. International Journal of Biomedical and Advance Research, 2011 Oct; 2(5): 159-66.
24. Parashar T, Sachan R, Singh V, Singh G, Tyagi S, Patel C, Gupta A. Ethosomes: a recent vesicle of transdermal drug delivery system. Int. J. Res. Dev. Pharm. Life Sci., 2013 Feb; 2(2): 285-92.
25. Nandure HP, Puranik P, Giram P, Lone V. Ethosome: A Novel Drug Carrier. International journal of pharmaceutical research & allied sciences, 2013 Jul 1; 2(3).
26. Ramakrishna GA, Manohar SD, Bhanudas SR. Ethosomes: carrier for enhanced transdermal drug delivery system. Journal of Advanced Pharmacy Education and Research, 2014; 4(4-2014): 380-7.
27. Jaiswal PK, Kesharwani S, Kesharwani R, Patel DK. Ethosome: A new technology used as topical & transdermal delivery system. Journal of Drug Delivery and Therapeutics, 2016 May 15; 6(3): 7-17.
28. Johnsen S, Bennett E, Jensen VG. Therapeutic effectiveness of oral testosterone. The Lancet, 1974 Dec 21; 304(7895): 1473-5.
29. Fiddan AP, Yeo JM, Strubbings R, Dean D. Vesicular Approach for Drug Delivery into or Across the Skin. Br. Med. J., 1983; 286: 1699.
30. Tüting T, Storkus WJ, Falo Jr LD. DNA immunization targeting the skin: molecular control of adaptive immunity. Journal of investigative dermatology, 1998 Aug 1; 111(2): 183-8.
31. Lopez-Pinto JM, Gonzalez-Rodriguez ML, Rabasco AM. Effect of cholesterol and ethanol on dermal delivery from DPPC liposomes. International journal of pharmaceutics, 2005 Jul 14; 298(1): 1-2.
32. Fang JY, Hong CT, Chiu WT, Wang YY. Effect of liposomes and niosomes on skin permeation of enoxacin. International journal of pharmaceutics, 2001 May 21; 219(1-2): 61-72.
33. Zuidam NJ, Crommelin DJ. Chemical hydrolysis of phospholipids. Journal of Pharmaceutical Sciences, 1995 Sep 1; 84(9): 1113-9.
34. Razavi H, Janfaza S. Ethosome: a nanocarrier for transdermal drug delivery. Archives of advances in biosciences, 2015 May 6; 6(2): 38-43.

35. Kumar KP, Radhika PR, Sivakumar T. Ethosomes-a priority in transdermal drug delivery. International Journal of Advances in Pharmaceutical Sciences, 2010 Apr 1; 1(2).
36. Biju S, Talegaonkar S, Mishra P, Khar R. Vesicular systems: an overview. Indian journal of pharmaceutical sciences, 2006 Mar 1; 68(2).
37. Jadhav PU, Gujare SG, Shende MA. Ethosomes: A novel tool for vesicular drug delivery. Asian Journal of Pharmaceutical Research, 2024; 14(1): 45-52.
38. Mazhar K, Khan AA, Maqbool A, Sultana H. A review on ethosomes as nanocarrier for skin delivery of drugs. Journal of Contemporary Pharmacy, 2024 Dec 31; 8(2): 122-31.