

ETHOSOMAL GEL; AS NOVEL DRUG CARRIER FOR TRANSDERMAL DRUG DELIVERY SYSTEM¹*Swarupa Thavare, ²Tejeswini Deshmukh and ³Rutuja Rayjade

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ABSTRACT

Ethosomal systems are lipid vesicular carriers that have a high ethanol content. These nanocarriers have been designed to circumvent the limits of traditional oral treatment. Which transport drugs deep into the layers of the skin. The production of these nanocarriers involves a variety of approaches. For its structure and content, this system provides increased skin permeability and efficient bioavailability. Ethosomal dispersions are included in gels for patient compliance and stability. This publication gives a composition, detailed type of ethosomes, mechanism of drug penetration, formulation methods, advantages and disadvantages, evaluation, and examples for drugs used in ethosomal systems. Enhanced delivery of bioactive molecules through the skin and cellular membranes using an ethosomal carrier opens numerous challenges and opportunities for the research and future development of novel improved therapies.

KEYWORDS: Transdermal drug delivery, Nanocarrier; Ethosomes.**INTRODUCTION**

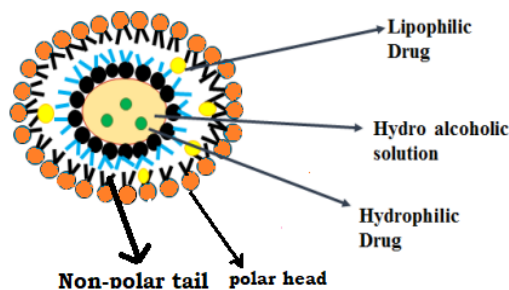
Optimization of drug delivery through human skin is important in modern therapy. In comparison to oral drug delivery systems, transdermal drug delivery systems (TDDS) have shown promising results since they avoid gastrointestinal interferences and the need for a first pass of the drug's metabolism.^[1] It is possible to avoid the problem of medication breakdown by digestive enzymes following oral delivery, as well as the pain associated with parenteral drug administration. It is the predominated method for systemic medication administration to juvenile, geriatric, and dysphasia patients. However, the fundamental disadvantage of TDDS is that it interacts with the Stratum Corneum's barrier characteristics, allowing only lipophilic medicines with molecular weights less than 500 Da to pass through can travel through it.^[2]

The skin is a multi-layered structure^[4] consisting of the stratum corneum (SC), the topmost layer, and the epidermis and dermis underneath it. Fibroblasts, hair follicles, and sweat glands that originate in the dermis blood supply are distributed throughout various layers of skin. Drug permeability across the skin barrier has also been improved by liposomes, niosomes, transferosomes, and ethosomes. Permeation enhancers increase the permeability of the skin, allowing medications to easily pass through. Unlike traditional liposomes, which are best recognized for delivering medications to the skin's outer layers, ethosomes can improve permeability through the stratum corneum barrier. In comparison to

conventional liposomes, ethosomes penetrate the skin layers faster and have a much higher transdermal flow.

ETHOSOMES^[2,5,6,7]

Elastic nanovesicles based on phospholipids, containing a high percentage of ethanol are known as ethosomes (20-45%). Ethosomes are noninvasive drug delivery vehicles that allow medications to penetrate deep into the epidermal layers to the systemic circulation.^[2] These are soft, deformable vesicles designed to distribute active substances more effectively. Vesicles are well-known for their role in cellular communication and particle transport.

**Fig.1 Structure of Ethosomes.**

Ethosomes are made up of a variety of phospholipid structures, water, and a high concentration of low molecular weight alcohol (ethanol or isopropyl alcohol) that gives the vesicle membrane malleability. The ethosomal lipids are more fluid than those in liposomes

with the same components but no ethanol. As a result, ethanol can act as a "mixing" agent for lipid vesicles,

giving them softness properties that allow them to spread more widely across different skin layers.

Table 1: Different Additives Employed In Formulation of Ethosomes.

Class	Example	Uses
Phospholipid	Soya phosphatidylcholine, Dipalmityl phosphatidylcholine, Egg phosphatidylcholine	Membrane forming agent
Dye	Rhodamine red, Rhodamine-123, 6- Carboxy fluorescence, Fluorescence Isothiocyanate (FITC)	For characterization
Cholesterol	Cholesterol	For providing the stability to the vesicle membrane
Vehicle	Carbopol D-934	As a gel former
Polyglycol	Propylene glycol, Transcutol RTM	As a skin penetration
Alcohol	Isopropyl alcohol, Ethanol	For providing the softness for the vesicle membrane As a penetration enhancer

TYPES OF ETHOSOMAL SYSTEMS^[2,9]

Ethosomal systems come in a variety of shapes and sizes. There are three types of ethosomal systems based on their structure.

1. Classical ethosomes^[5,9,17]

They are modified ethosomes that include phospholipids, water, and a high concentration of DNA. ethanol concentrations up to 45 percent w/v Because of its small size, negative zeta potential, and greater zeta potential, Classic ethosomes outperformed classical liposomes in terms of entrapment efficiency. Drugs are appropriate for the entrapment in traditional ethosomes, with molecular weights ranging from 130.077 Da to 24 k Da. In addition, traditional ethosomes have better skin penetration and stability profiles than traditional liposomes.^[9]

2. Binary ethosomes

Zhou et al. first proposed binary ethosomes. They were created by mixing another sort of alcohol with the traditional ethosomes. Propylene glycol (PG) and ethanol are the most often employed alcohols in binary ethosomes.

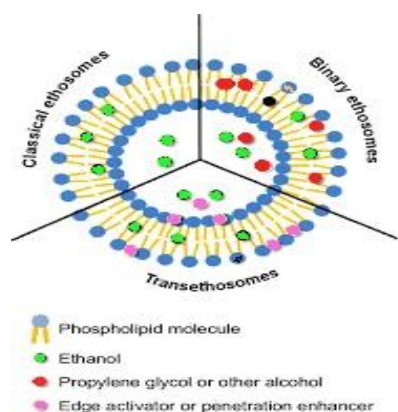


Fig.2: Schematic representation of different types of ethosomal systems.

3. Transethosomes^[2,12] Transethosomes are the new form of ethosomal systems. Their formula contains basic components from classical ethosomes and a penetration enhancer or an edge activator (surfactant). These novel vesicles were developed to combine the advantages of classical ethosomes and transfersomes in one formula to produce transethosomes.^[12]

MECHANISM^[2-8]

The primary advantage of ethosomes over liposomes is increased drug penetration. The method by which ethosomes penetrate into and through the skin is still unknown. However, it has been suggested that medication absorption happens in two stages.

1. Ethanol effect: In the first method, ethosomal formulations contain ethanol, which interacts with intercellular lipid molecules in the polar head group region, enhancing fluidity and decreasing the density of the lipid multilayer, resulting in increased membrane permeability.

2. Ethosomes effect: greater skin permeability is expected due to the high alcohol concentration. As a result, the ethosomes easily penetrate deep into the skin layers, where they mix with skin lipids and release.

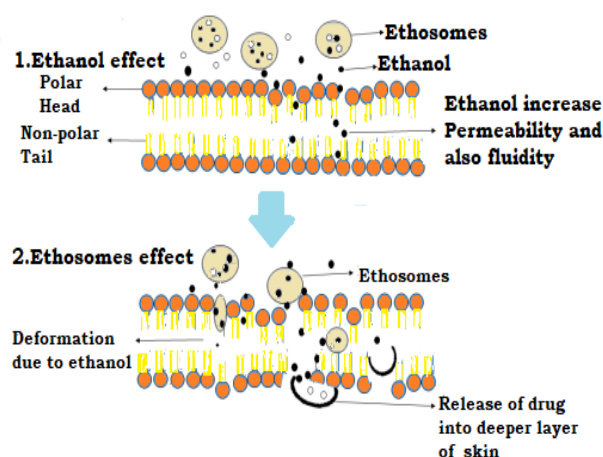


Fig. 3: Mechanism of ethosomal drug penetration through the skin.

PREPARATION METHOD OF ETHOSOMES**1] Cold Method^[27-35]**

For the preparation of ethosomal formulation, this is the most used procedure. Phospholipids, drugs, and other lipid compounds are dissolved in ethanol in a covered vessel at room temperature using a mixer and rapid agitation. During the stirring process, propylene glycol or another polyol is incorporated. In a water bath, this combination is heated to 30°C. In a separate vessel, heat the water to 30°C and add it to the mixture, which is then agitated for 5 minutes in a covered vessel.

Using the sonication or extrusion methods, the vesicle size of an ethosomal formulation can be reduced to the desired extent. The ethosomal suspension was kept overnight at 4 °C for maturation. Finally, the mixture must be kept refrigerated.

2] Hot Method^[26,36]

This involves dispersing phospholipid in water by heating it in a water bath at 40°C until it forms a colloidal solution. Properly combine ethanol and propylene glycol in a separate vessel and heat to 40°C. Combine the organic and aqueous phases. Depending on the drug's solubility, dissolve it in water or ethanol. Using probe sonication or extrusion, the vesicle size of an ethosomal formulation can be minimized to the desired size.

3] Classic Mechanical Dispersion Method^[29]

In a round bottom flask, soya phosphatidylcholine is dissolved in a 3:1 mixture of chloroform and methanol. The organic solvents are evaporated using a rotating vacuum evaporator at temperatures above the lipid transition temperature, resulting in the formation of a thin lipid coating on the flask's wall. Finally, by vacuuming the contents overnight, traces of the solvent mixture are removed from the deposited lipid coating. Hydration is accomplished by spinning the flask at a proper temperature while using various concentrations of a hydroethanolic mixture containing medication.^[14,15]

ADVANTAGES^[11]

1. Ethosomes improve medication penetration through the skin, allowing for transdermal and topical delivery.
2. Ethosomes are biologically tailored and biodegradable, with a higher surface area due to smaller vesicles. (When properly prepared) vesicular systems Procedures that do not include any size-reduction.
3. Ethosomes act as a basis for the delivery of a wide range of medicines (peptides, protein molecules)
4. The components of ethosomes have been approved for medicinal and cosmetic usage.
5. Minimal risk profile- Because the toxicological profiles of the ethosomal components are extensively described in the scientific literature, the technique poses little danger to large-scale medication development.
6. Patient compliance is high-the Ethosomal medication is administered in a colloidal suspension form (gel or cream), resulting in great patient compliance. On the

other hand, Iontophoresis and Phonophoresis are more difficult to employ, which may impair patient compliance.

7. Products with patented technology have a high market appeal. Ethosomes are quite easy to produce and do not require any complicated technical investments.

8. The Ethosomal system is a passive, non-invasive device that may be commercialized right away.

9. Numerous applications in the sectors of pharmaceuticals, animal health, and cosmetics.

DISADVANTAGES^[10]

1] Poorly shelled ethosomes may cluster together, resulting in precipitation.

2] To enter the dermal microcirculation and obtain access to the systemic circulation, the medication must be soluble in both lipophilic and aqueous conditions.

3] Excipients and enhancers in medication delivery systems cause skin irritation or dermatitis.

4] Ethosomal administration is often meant to provide steady, sustained medication delivery rather than a quick bolus kind of drug intake.

5] Medicines that demand high blood levels cannot be given - only powerful drugs are allowed.

6] The loss of product occurs when ethosomes are transferred from the organic to the aqueous layer.

7] The drug's molecular size should be reasonable so that it may be absorbed percutaneously.

8] The adhesive may not apply to all skin types.

9] Practical yield is poor. It might not be cost-effective.^[13]

CHARACTERIZATION OF ETHOSOMES^[28-37]

1) Vesicle shape: Ethosomes can be easily visualized by using transmission electron microscopy (TEM) and by Scanning electron microscopy. (SEM) To visualize the vesicular structure, lamellarity of ethosomes.

2) Vesicle size and zeta potential: The particle size of the ethosomes can be determined by dynamic light scattering (DLS) and photo correlate on spectroscopy (PCS). The Zeta potential of the formulation can be measured by the Zeta meter.

3)PH Measurement: The pH measurement of the formulation was carried out using a pH meter by dipping the glass electrode completely into the colloidal suspension formulation to cover the electrode.^[25]

3) Transition temperature: The transition temperature of the vesicular lipid systems can be determined by using differential scanning calorimetry (DSC).

4) Drug entrapment: The entrapment efficiency of ethosomes can be measured by the ultracentrifugation technique. ultra-centrifugation was used to test the vesicles' potential to entrap drugs. To determine the entrapment efficiency, ultra-centrifugation was employed to separate ethosomal vesicles carrying drugs from un-entrapped or free drug.

5) Drug content: The drug content of the ethosomes can be determined using a UV spectrophotometer. This can also be quantified by a modified high-performance liquid chromatographic method.

6) 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.

7) Stability studies: The stability of vesicles can be determined by assessing the size and structure of the vesicles over time. completely. The stability of ethosomes can also be determined quantitatively by monitoring the size and morphology of the vesicles using DLS and TEM.

8) Skin permeation studies: The ability of the ethosomal preparation to penetrate the skin layers can be determined by using confocal laser scanning microscopy (CLSM)

Method of preparation of ethosomal gel^[28,33]

The preparation of the ethosomal gel involves the preparation of the gel base. Carbopol 934 is a widely used gel forming that forms a transparent gel with good consistency at low concentrations. It will be made by dispersing carbopol 934 in hot distilled water that has already had glycerol added to it. A precise amount of methyl paraben and propyl paraben was applied to this. Triethanolamine will next be used to neutralize the mixture. The ethosomal formulation was then gently stirred into the carbopol 934 gelling agent. Then, the ethosomal gel is obtained.

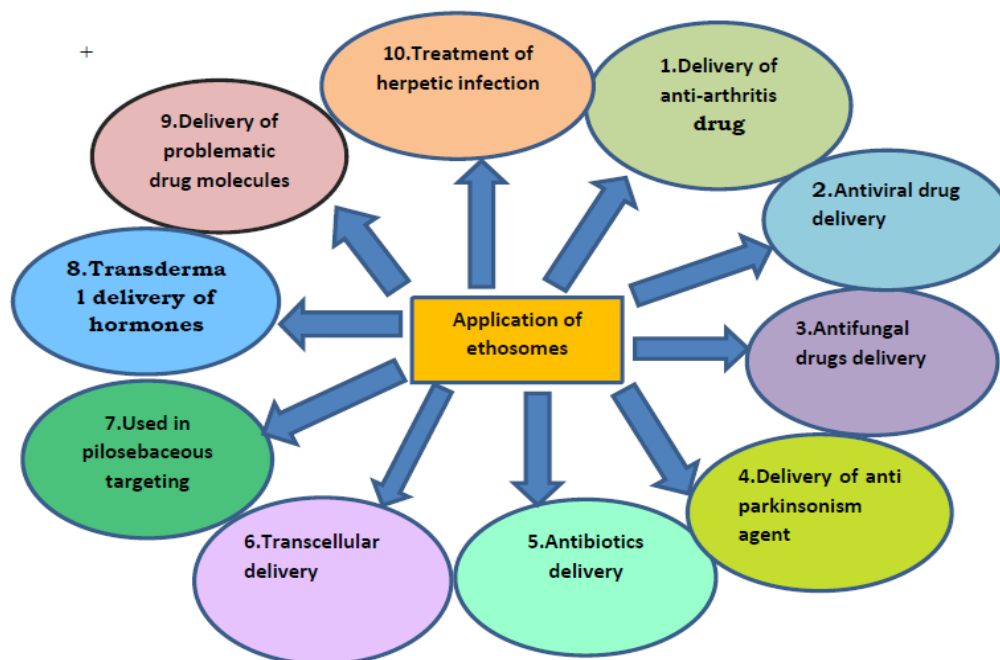
EVALUATION OF ETHOSOMAL GEL^[19]

The prepared ethosomal gels were evaluated for the following parameters.

1. pH: The pH measurement of formulations was carried out using a pH meter by dipping a glass electrode completely into gel to cover the electrode
2. Rheological studies: The rheological analysis of prepared gels was measured using Brookfield Viscometer.
3. Drug content: Gel formulations were dissolved in phosphate buffer and filtered and the volume was made to 100 ml with phosphate buffer. The resultant solution was suitably diluted with phosphate buffer and absorbance was measured of drugs.
4. In-vitro drug permeation studies: In-vitro drug release study of ethosomal gel formulation was studied using a Franz glass diffusion cell.

APPLICATIONS^[23,24]

Several research using ethosomal formulations have found that medicines had better skin penetration. The application of ethosomes as a carrier system for transdermal/topical medication administration is reviewed.



1. In the treatment of herpetic infection: As compared to 5 % acyclovir cream, the ethosomal preparation of 5% acyclovir exhibits a considerable improvement in the treatment of herpetic infections, as well as an enhanced pharmacodynamic profile and increased skin permeability.

2. Delivery of anti-arthritis drug: Topical anti-arthritis drug administration is a superior choice for selective

drug delivery to the appropriate position for a longer period. The results reveal that its skin penetration, and hence its action, has significantly enhanced.^[31,33,36]

3. Antiviral drug delivery: Acyclovir and zidovudine are two powerful antiviral drugs. The first targets the human immunodeficiency virus, while the second is commonly used topically to treat Herpes labialis.

Ethosomes have been shown to boost the transport of both of these antiviral medicines.^[19]

4. Delivery of antifungal drugs^[18] As a vesicular carrier system, ethosomes were proven to have incredible potential to improve Ketoconazole transdermal penetration. Ethosomes have the benefits of quick onset and maximum medication release while reducing negative effects. Furthermore, because ethosomes do not destroy the skin's architecture, drugs are delivered into the systemic circulation via the undamaged skin. In the treatment of candidiasis patients, ethosomal fluconazole gel formulation provides improved disease remission and decreases therapy duration.

5. Delivery of anti-parkinsonism agent^[17]

Dayan and Touitou created an ethosomal preparation of the psychoactive substance trihexyphenidyl hydrochloride (THP) and compared it to traditional liposomal formulations. THP is an antagonist of M1 muscarinic receptors that are used to treat Parkinson's disease. The results demonstrated that the ethosomal-THP formulation had a higher skin penetration potential and can be used to help control Parkinson's disease.^[17]

6. Antibiotics delivery^[23]

Antibiotics may be used topically, which is a convenient technique to increase their therapeutic efficacy. Antibiotics are widely given orally and are linked to several immune reactions, side effects, and limited therapeutic efficacy. Conventional topical antibiotic preparations have poor penetration to deep layers of skin and subdermal tissues, making them useless. Ethosomes can help by delivering an appropriate quantity of antibiotics to the skin's deeper layers. Ethosomes easily penetrate the epidermis, releasing a high number of drugs to the skin's deeper layers and controlling infection at the source. Godin and Touitou were able to produce an ethosomal genetically improved bacitracin and erythromycin for cutaneous and intracellular delivery as a consequence. They demonstrated how to make an antibiotic formulation with an ethosomal structure.^[23]

7. Transcellular delivery

In comparison to the commercial formulation, ethosomes appear to be a viable anti-HIV treatment option. As a result, medication action is prolonged, drug toxicity is reduced, and transdermal flux is improved. Touitou et al. revealed that CLSM and FACS methods can improve intracellular uptake of bacitracin, DNA, and erythromycin in various cell lines. Ethosomes may offer a more appealing clinical option for anti-HIV therapy than the currently available formulation.^[21]

8. Ethosomes are used in pilosebaceous targeting

The concentration of ethanol in the ethosomal vesicle is considerable, allowing it to penetrate deep into the skin. This vesicle appears to be a viable option for transdermal medication delivery of hydrophilic and impermeable drugs via the skin, as it improves dermal deposition, intercellular transport, and bioavailability. Minoxidil, a lipid-soluble drug used to treat baldness, accumulates two to seven times more in the skin of nude mice and can thus be utilized for pilosebaceous targeting for better clinical efficacy.^[22]

9. Transdermal delivery of hormones

Oral hormone administration is hampered by difficulties such as first-pass metabolism, limited oral bioavailability, and a variety of dose-dependent adverse effects. Transdermal delivery is employed to avoid this. Each missing dose increases the chances of treatment failure.^[20]

10. Delivery of problematic drug molecules

As larger biogenic compounds like peptides or proteins, as well as insulin, are destroyed in the gastrointestinal tract, transdermal distribution is a superior option. However, traditional transdermal formulations of biogenic agents like peptides or protein, as well as insulin, have low penetration. Making these compounds into ethosomes increases penetration and therapeutic efficacy considerably.^[23]

Table 1: List of various drug molecules used for Ethosomal gel formulation.

Sr.No	Drug	Use	Preparation method	Conclusion	Reference
1	Aceclofenac	Treatment of rheumatoid arthritis	Hot method	Enhanced delivery of aceclofenac through the skin	[26]
2	Acyclovir	Treatment of Herpes Zoster	Cold method	Ethosomal gel at the targeted site	[27]
3	Atorvastatin	For anti-hypertensive	Cold method	Enhance bioavailability was formulated into ethosomal gel	[28]
4	Carvedilol	Enhancement of antihypertensive effect	Thin-film hydration method	Enhance skin permeation with extended antihypertensive action of carvedilol	[29]
5	Ciclopirox	Topical use antiacne effect	Cold method	The better penetration rate for antiacne effect	[30]
6	celecoxib	Treatment of rheumatoid arthritis and osteoarthritis	Cold method	Transdermal delivery with targeted and prolonged release of a drug	[31]
7	Dapsone	For Treatment of antileprotic	cold method	Ethosomal drug delivery, enhance the recovery rate of the skin barrier	[32]
8	Etoricoxib	Anti-inflammatory	Cold method	Ethosomal gels where to increase the efficacy	[33]

				and reduce its side effects.	
9	Fluconazole	Topical fungal infection	Cold method	As efficient carriers for fluconazole topical delivery	[34]
10	Methotrexate	Psoriasis	Cold method	Good penetration of skin delivering the drug to the deeper skin layers without any systemic side effect	[35]
11	Lornoxicam	Treatment of Arthritis	Hot method	Superior drug carrier for topical delivery in the treatment of inflammation.	[36]
12	Tazarotene	Topical use antiacne effect	Cold method	Ethosomal gel form can increase penetration for its better antiacne effect.	[37]
13	Tetrandrine	Treatment of Arthritis	Cold method	Ethosomes were shown to generate enhancement of therapeutic efficacy of tetrandrine	[38]

FUTURE PERSPECTIVES

The introduction of ethosomes has initiated a new area in vesicular research for transdermal drug delivery. Different reports show a promising future of ethosomes in making transdermal delivery of various agents more effective. Further research in this area will allow better control over drug release in vivo, allowing the physician to make the therapy more effective. Ethosomes offer a good opportunity for the non-invasive delivery of small-, medium-, and large-sized drug molecules. The results of the first clinical study of the acyclovir-ethosomal formulation support this conclusion. Studies will continue to further improve the skin delivery of drugs using lipid vesicles. Special emphasis seems to be given to the skin delivery of proteins and other macromolecules and transcutaneous immunization. The near future also holds the emergence of new commercial ethosome-based topical products. NTT, Novel Therapeutic Technology is a biopharmaceutical company with a portfolio of pharmaceutical formulations based on ethosomal technology including formulations for the treatment of alopecia, deep skin infection, herpes, hormone deficiencies, inflammation, postoperative nausea, atopic dermatitis, and erectile dysfunction.

CONCLUSION

As previously stated, multiple investigations have demonstrated that ethosomes can significantly increase medication penetration through the stratum corneum and hence effectiveness. They are improving patient compliance and comfort, and decreasing the total cost of therapy are all significant advantages. Many hydrophilic substances, cationic medicines, proteins, and peptides can be conveniently administered through a transdermal route thanks to ethosomal encapsulation. As a result, the primary advantage is improved treatment. The incorporation of ethosomal systems in suitable vehicles such as gels represents an important step to get better skin-permeation and therapeutic results.

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