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Ethosomes: An Advanced Vesicular Carrier for Transdermal Drug Delivery

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Abstract: *Drugs can enter the deep layers of the epidermis and the systemic circulation thanks to ethosomes, which are non-invasive delivery vehicles. Soft, pliable vesicles designed for improved active drug distribution are called ethosomes. Ethosomes' special structure allows them to encapsulate and distribute cationic medications like propranolol, trihexyphenidyl, cyclosporine, insulin, salbutamol, and others via the skin, as well as extremely lipophilic compounds like cannabinoids, testosterone, and minoxidil. An ethosomal carrier's improved ability to transport bioactive chemicals through the skin and cellular membranes presents both potential and problems for future study and the creation of new, better treatments. On the other hand, ethosomes made using the sonication method were smaller and more homogeneous, which is crucial for skin penetration.*

Keywords: Ethosomes, Non-invasive Delivery, Carrier, Sonication

I. INTRODUCTION

"Ethanolic liposomes" are ethosomes. These are lipid vesicles that have phospholipids and ethanol or isopropyl alcohol in comparatively high concentrations in water. A novel medicine delivery method called ethosomes was created by Touitou in 1997. Ethosome vesicles range in size from 30 nm to a few microns. They were said to enhance the way different medications were delivered via the skin. In areas like transdermal, they are effective delivery systems. Alcohol, cholesterol, phospholipids, polyglycol, dyes, and vehicles are examples of additives used in ethosomal composition[1]. Phospholipids and ethanol are found in large concentrations in ethosomes. They function similarly to a sac. Ethosomes administered the medication in a cream-gel form for patient comfort[2]. In recent years, ethosomes have emerged as a novel drug delivery mechanism with significant applications in pharmaceutical technology[3].

The largest and most accessible organ in the body is the skin. The skin serves as both a permeability barrier and a protective tissue. It stops foreign substances from the outside world from penetrating. The stratum corneum (SC), the skin's topmost layer, effectively forms the skin barrier. Liposomes and their derivatives, including transferosomes, niosomes, and ethosomes, are the most common lipid dosage forms for transdermal delivery. A system called ethosomes interacts with the skin barrier and breaks through the lipid barriers of the SC[4]. Ethosomes are a method utilized in the vesicular system to increase the skin penetration of medications and numerous compounds used in cosmetics. Ethosomes are made of ethanol, which is added to vesicular systems to create elastic nanovesicles since it is an effective permeability enhancer[5]. They were created to enhance the distribution of several medications through the skin. Drugs can enter the systemic circulation or the deep layers of the skin thanks to ethosomes. It contains 20% to 45% ethanol[6].

Ethosomes are appropriate for a variety of applications in the pharmaceutical, biotechnology, veterinary, cosmetic, and nutraceutical industries. They are non-invasive delivery systems that allow medications to enter the deep layers of the skin. Advanced vesicular delivery vehicles called ethosomes are used to transport a variety of chemical applications[7]. They are modified versions of traditional liposomes that contain more ethanol. Phospholipids are often employed at 0.5–10% in ethosomes, while cholesterol is used at 0.1–1%[8]. A less intrusive method of administering medication that offers regulated drug distribution is transdermal drug delivery. Ethosomes can be classified as binary, classical, or transethosomes based on their content and the ingredients that are derived from alcohol, ethanol, etc.[9]. This carrier is

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highly deformable and has intriguing properties relating to its capacity to pass through human skin unharmed. These vesicular phospholipids can form vesicles as part of the ethosomal system due to the physicochemical properties of ethosomes. Because of the high concentration of alcohol in the formulation, which gives the vesicles stability and soft, flexible properties while also disrupting the structure of the skin's lipid bilayers, membrane permeability rises[10]. To give ethosome vesicles more stability, cholesterol can be added in amounts ranging from 0.1 to 1%. Both ethanol and isopropyl alcohol, which are frequently used, are examples of approved alcohols[11]. As a system of vesicles, they display beneficial characteristics, functioning as elastic ethosomes[13].

ADVANTAGES

The formulation uses a harmless raw material[11].

- It raises the drug's transdermal permeability via the skin[2].
- The ethosomal system can be commercialized right away and is non-invasive and passive[1].
- The fields of pharmaceuticals, biotechnology, veterinary medicine, cosmetics, and nutraceuticals can all benefit from the use of ethosomal drug delivery systems[4].
- All drug molecules, whether hydrophilic, lipophilic, or amphiphilic, can be entrapped by it[16].
- Excellent patient adherence[17].
- A wide range of different drug groups can be delivered by ethosomes[6].
- Ethanol gives the ethosomes a negative charge, which reduces the size of the vesicles and raises the active components' bioavailability[12].
- Proteins and peptides can be readily provided with this delivery technique[9].

DISADVANTAGES

- Product loss when switching from organic to water media[1].
- It is restricted to strong medications that need a low daily dosage[1].
- If the patient has an allergy to ethanol or any of the ethosomal components, an allergic reaction can be detected[4].
- Not all skin types may respond favourably to adhesive[4].
- Dermatitis or skin irritation can be brought on by medication delivery system excipients and penetration enhancers[4].
- Only potent drugs may be administered; those that require elevated blood levels cannot[5].
- The drug's molecular size should be appropriate for percutaneous absorption[5].

AIMS AND OBJECTIVES

To give a thorough summary of the evaluation of its potential as an effective nanocarrier for the transport of active substances to the skin. The makeup of ethosomes, the process of skin penetration, and their possible uses in many diseases—especially skin diseases such as acne, psoriasis, atopic dermatitis, skin cancer, and infections—are given focus19.

Objectives:

- To improve the drug's transdermal permeability via the skin[2].
- To trap all drug molecules, whether they are amphiphilic, lipophilic, or hydrophilic[16].
- To readily supply proteins and peptides[9].
- To improve medicine penetration via the skin in dermal and transdermal delivery[15].

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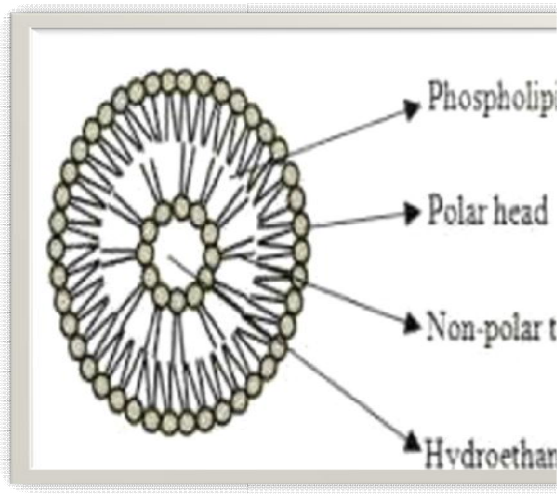


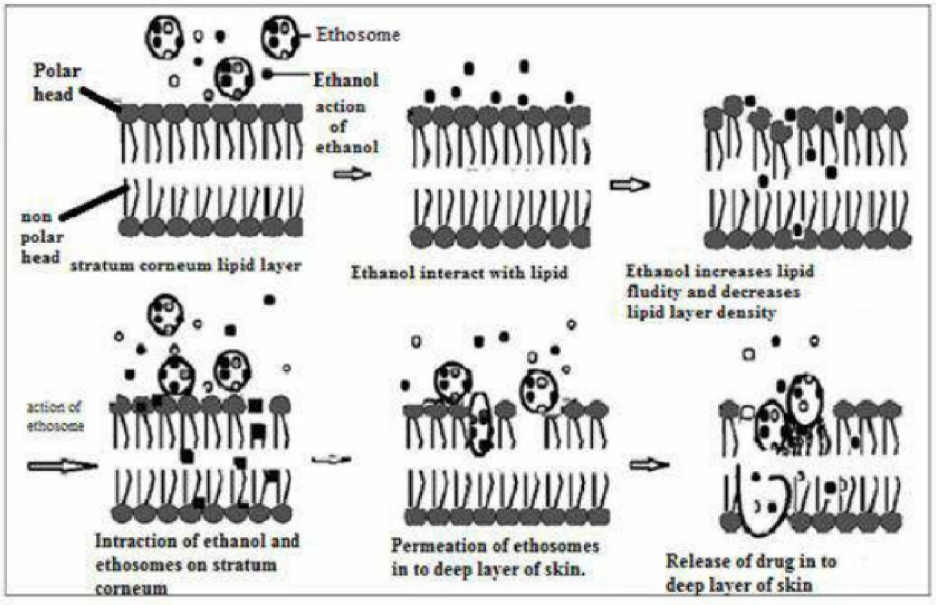
Figure 1: Structure of Ethosome]

MECHANISM OF ACTION

Ethosome's mechanism of action is based on medication absorption, which most likely happens in the following two ways:

Effect of ethanol: Ethanol acts as a skin penetration enhancer. It enters intercellular lipids, enhances the fluidity of the lipid in the cell membrane, and reduces the density of the lipid multilayer in the cell membrane.

Ethosome effect: Ethanol causes an increase in the fluidity of cell membranes, which raises skin permeability. Therefore, the ethosomes readily penetrate the deep layers of the skin, fuse with the lipids there, and release the medication.



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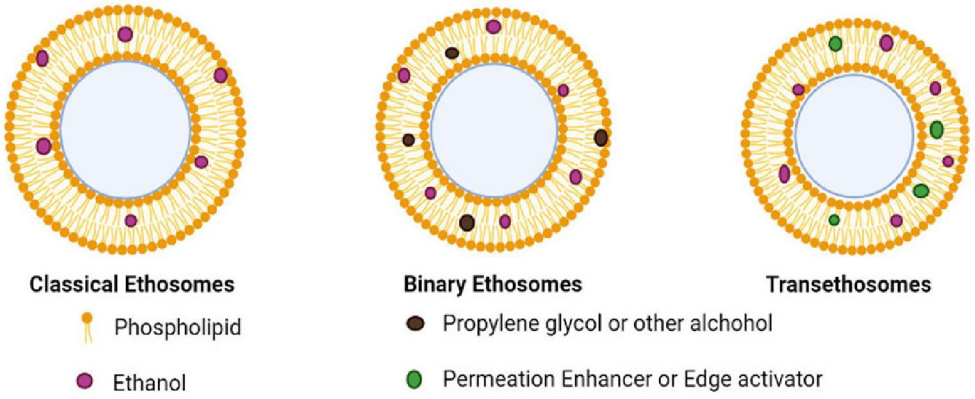
TYPES

CLASSICAL ETHOSOMES: A variation of traditional liposomes, conventional or classical ethosomes are composed of phospholipids, water, and ethanol in high concentrations (up to 45% w/w).

BINARY ETHOSOMES: Zhou et al. made the initial discovery of binary ethosomes in 2010. In addition to ethanol, binary ethosomes contain two other alcohols, often isopropyl alcohol and propylene glycol (PG).

TRANSETHOSOMES: Ultra-deformable lipid vesicles known as transethosomes can deliver medications into deeper tissues. Phospholipids, ethanol, surfactants, and edge activators or permeation enhancers comprise their composition.



APPLICATIONS

1. Transdermal Administration of Medicine

Enhanced Skin Penetration: Because the ethanol in the formulation aids in improving skin penetration, ethosomes are frequently utilized for transdermal medication delivery. Ethosomes can transport medications deeper into the layers of the skin because ethanol alters the lipid structure of the stratum corneum, the skin's outermost layer.

Topical Treatments: These include psoriasis, eczema, fungal infections, and other dermatological diseases. They used to deliver drugs locally. By releasing the medications at the site of action, systemic adverse effects are minimized.

2. Cosmetic Applications

Ethosomes are widely used to optimize the transport and deep targeting of cosmetic agents into skin layer depths.

3. Pain Management

Topical Analgesics: While reducing systemic adverse effects, ethosomes can carry opioids or NSAIDs (non-steroidal anti-inflammatory medicines) to the location of pain, such as in musculoskeletal problems or arthritis.

Local Anesthesia: To reduce the need for invasive injections, ethosomal formulations containing local anesthetics (such as lidocaine) are utilized to distribute these medications to specific skin regions.

4. Gene Delivery

Gene Therapy: It has been demonstrated that ethosomes may transport DNA, RNA, and other genetic material for use in gene therapy. They are a viable option for targeted gene delivery, such as in skin or mucosal tissues, due to their capacity to encapsulate and safeguard genetic material while promoting its passage across cell membranes.

5. Vaccines

Vaccine Delivery: Ethosomes can be used as vaccine carriers, particularly to transport antigenic compounds to immune cells located on the skin or mucosal surfaces. They are a strong contender for needle-free vaccination delivery due to their capacity to penetrate the skin, which would facilitate administration and possibly increase patient compliance.

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6. Systemic Drug Delivery

Enhanced Bioavailability: Ethosomes can be used topically, but they can also be absorbed through the skin to deliver drugs systemically. For medications that experience substantial first-pass metabolism when given orally, this may be beneficial. Ethosomes can decrease side effects and improve absorption by distributing the medication through the skin.

Hormone Replacement Therapy: Because they can avoid hepatic metabolism and ensure more effective systemic absorption, ethosomes are employed for the transdermal administration of hormones like estrogen or testosterone.

7. Treatment of Infectious Diseases

Antifungal and Antibacterial Therapy: Since ethosomes' improved skin penetration enables more effective drug delivery to the infection site, they can be utilized to deliver antibiotics or antifungal agents (like clotrimazole) to treat skin infections.

HIV Treatment: Additionally, they can act as carriers for antiretroviral medications used to treat HIV, either systemically or topically.

8. Cancer Therapy

Localized Cancer Treatment: Anticancer drugs can be delivered by ethosomes to tumor cells in the skin or other tissues, enabling targeted therapy and lowering systemic toxicity.

Photodynamic Therapy: Ethosomes can be loaded with photosensitizers used in photodynamic therapy, where the drug, upon activation by light, kills cancer cells. Ethosomal formulations can enhance the bioavailability and target delivery of these agents.

Neurological Applications

CNS Drug Delivery: Ethosomes can also help in the transdermal administration of medications meant for the central nervous system (CNS). This is crucial when treating neurological disorders like Parkinson's or Alzheimer's, as transdermal formulations may offer a more reliable drug release profile than oral administration.

10. Applications in Ophthalmology

Drops: Ethosomal formulations can be applied to ocular drug delivery systems to improve the way medications pass through the corneal barrier to treat glaucoma, dry eye, or infections of the eyes.

PLAN OF WORK

Botanical	Formulation	Biological activity	Active Ingredient	Application	Method of preparation
Sophora flavescens	Matrine ethosome	Cardioprotective, Anti-inflammatory	Matrine and oxymatrine alkaloid	Improve percutaneous permeation	Solvent dispersion method
Glycyrrhiza glabra	Ammonium Glycyrrhizinate ethosomes	Anti-inflammatory	Glycyrrhizin acid	Increases percutaneous permeation	Solvent dispersion method
Sophora alopecuroides	Sophora ethosome	Antiendotoxic, Anticancer	Sophocarpine, matrine	Enhance drug delivery and stability	Transmembrane pH gradient active loading method
Tripterygium wilfordii	Triptolide	Anti-inflammatory	Diterpene triepoxide	Higher entrapment efficiency and good permeation	Ultrasonic method
Sesbania grandiflora	Sesbania ethosome	Antimicrobial	Leucocyanidin and cyanidin	Enhance transdermal permeation	Solvent dispersion method
Podophyllum	Podophyllotoxin	Purgative, antiviral	Etoposide and	Higher	Solvent dispersion

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hexandrum		and antitumor	teniposide	entrapment efficiency and enhance its therapeutic effect	method

Literature Survey.
Selection of API and Excipient.
Procurement of API and Excipient.
Result.
Conclusion.
Reference.

FORMULATION OF HERBAL ETHOSOMES

METHOD OF PREPARATION:

COLD METHOD: One of the most popular techniques for preparing ethosomes is this one. There are two basic and straightforward setup options. This approach involves heating the phospholipid in a water bath at 40°C until a colloidal solution is achieved. This mixture, on the other hand, is then heated to 30°C. In a similar manner, hot water is added to the ethanolic mixture and occasionally swirled. In a covered vessel, combine both mixtures for five minutes while stirring. By applying the sonication or extrusion methods, the ethosomal formulation's vesicle size can be reduced to the required extent. Lastly, the mixture is refrigerated for storage.

HOT METHOD: This process involves dispersing the phospholipids in water and heating it to 40°C until a colloidal solution is obtained. Ethanol is similarly heated to the same temperature as the aqueous phase. Depending on its solubility, the medication should be dissolved in either water or ethanol. The ethosomes' vesicle size can be decreased by either the extrusion method or probe sonication. After formulation, the vesicles are either sonicated or extruded to reach the required size.

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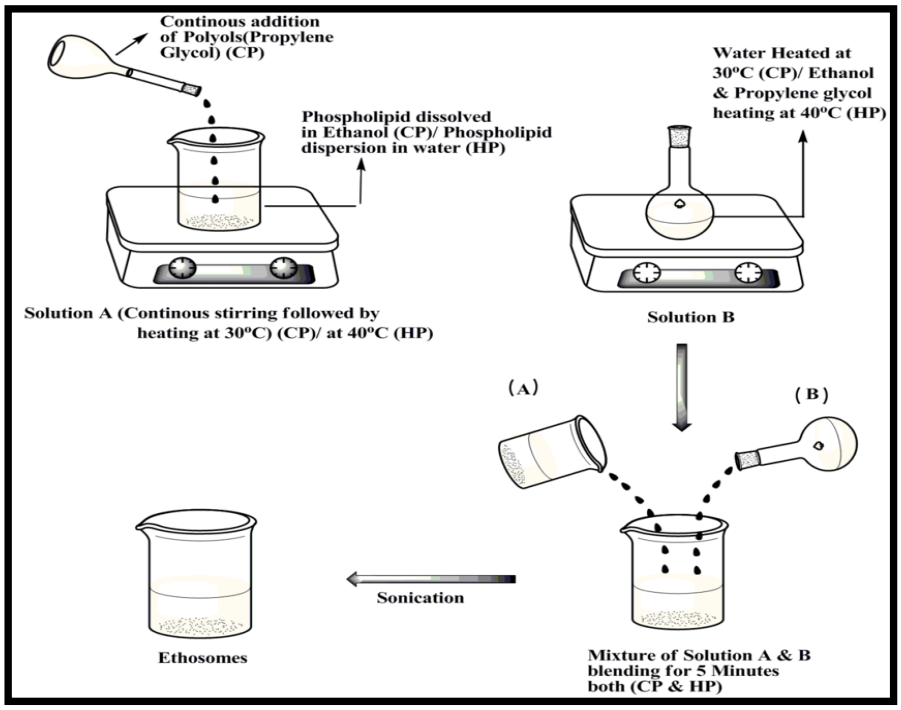

RESULT

Advanced drug delivery systems called ethosomes use soft, elastic vesicles made of water, ethanol, and phospholipids. By increasing the skin's permeability, ethanol enables ethosomes to deliver hydrophilic and lipophilic drugs deeper into the skin, increasing their bioavailability and therapeutic effectiveness[20,21,22,23].

II. CONCLUSION

For in-vitro release experiments, every ethosome formulation exhibited a zero-order release. There are differences between the sonicated and unsonicated products, even though the ethosomes penetrate the skin quickly. Stability tests conducted over an 8-week period revealed no alterations in the ethosomes' characteristics, and the drug loss was less than 3%. Sonicated formulations had better or more appropriate characterization (lower size, uniform size distribution, maximum entrapment efficiency, and higher transdermal flow) than unsonicated formulations when the effect of sonication on ethosomal formulation is compared. It is clear from the fact that sonication is a crucial technique for ethosome preparation[24].

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