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Review Article

Ethosomes : As promising nanocarriers for novel drug delivery system

Shivam Singh*, Arpita Singh, Ritunja Singh, Anupama Maurya, Urmila Nishad, Priyanka Tyagi, Harshit Yadav

Department of Pharmaceutics, SethVishambhar Nath Institute of Pharmacy, Dewa Road Lucknow

ABSTRACT

Ethosomes, a kind of vesicle, are microscopic structures that aid in the efficient delivery of drugs over the epidermal barrier by focusing their action on certain cells. Due to their unique composition and structural properties, ethosomes, which are innovative phospholipid vesicular carriers containing elevated concentrations of ethanol, provide efficient absorption and enhanced permeability through the skin. Pharmacosomes, which are drug-lipid complexes with improved drug dispersion and administration, are new drug delivery technologies being developed. Improved drug permeability and targeting are provided by sophisticated systems including aquasomes, cubosomes, and ethosomes, which increase the efficacy of drug delivery. Different techniques, including as the hot method, cold method, and dispersion approach, can be used to manufacture ethosomes, and each has an impact on the end product's properties. Ethosomes are a kind of lipid vesicle that show promise for drug delivery applications because they are flexible and enhance medication penetration into the circulation and deep skin layers. A comprehensive overview of drug delivery ethosomes, including their types, compositions, preparation methods, characterizations, marketed formulations, applications, and ultimately, future prospects, is also included in this article.

Keywords:
Vesicles; Ethosome; Ethanol; Penetration; Topical route; Transdermal delivery

1. INTRODUCTION

Traditional drug delivery methods, often referred to as classical approaches, primarily aim for rapid drug release and quick absorption. However, these methods fall short in addressing critical challenges such as frequent dosing, inconsistent drug plasma levels, and systemic side effects. These limitations have driven the development of Novel Drug Delivery Systems (NDDSs), which enable targeted and controlled drug release thereby enhancing therapeutic efficacy and patient safety. NDDSs include a broad range of advanced formulations, technologies, and devices engineered to control the time and location of drug release in the body [1].

Since their inception several decades ago, numerous types of NDDSs such as nanocarriers, microcarriers, cell-based systems, and implantable devices have been developed. These systems are designed to overcome biological barriers and are suited for a wide range of therapeutic applications[2]. Emerging technologies such as self-powered devices and microelectromechanical systems are further transforming drug delivery strategies. Among these innovations, nanotechnology has shown particular promise in improving therapeutic delivery and disease management[3]. Nanocarriers key components of NDDSs offer tunable size, surface characteristics, and controlled release capabilities, which enable precise targeting of specific tissues. As a result, they improve drug bioavailability and therapeutic efficiency. Developing safe and effective NDDSs requires a clear understanding of drug release mechanisms and potential toxicological risks[4].

***Corresponding author:**
* Shivam Singh Email: shivamchotu08@gmail.com

2. VESICULAR SYSTEMS IN DRUG DELIVERY

Microscopic vesicles, composed of lipid bilayers that mimic cellular membranes, serve as efficient carriers for drugs with diverse physicochemical properties. The stratum corneum, the outermost layer of the skin, is the primary barrier to transdermal drug delivery. Vesicular systems such as liposomes and ethosomes are capable of penetrating this layer and delivering drugs transdermally[5, 6].

Research has shown that vesicle morphology plays a crucial role in drug delivery efficiency. Modifying vesicles for cellular targeting further enhances their therapeutic potential. For example, ethosomes, an advanced version of liposomes, have demonstrated improved performance in transdermal applications [7].

The skin consists of three main layers: the epidermis, dermis, and subcutaneous tissue. Drugs typically penetrate either through lipid bilayers or intercellular routes. Transdermal drug delivery systems (TDDS) offer several benefits[8, 9]:

- Bypass of first-pass metabolism
- Reduced dosing frequency
- Improved patient compliance
- Easy discontinuation of therapy
- Suitability for self-administration

The integumentary system, being the most accessible organ, allows for efficient and sustained delivery of therapeutic agents. It is estimated that approximately 40% of modern pharmaceuticals are administered via the transdermal route[10]. However, the stratum corneum presents a significant barrier to drug permeation due to its dense lipid and protein matrix composed of corneocytes and keratins [11].

This necessitates the use of specialized carriers capable of transporting hydrophilic and lipophilic drugs through the skin's layers and into systemic circulation. In essence, the skin acts as both a protective and regulatory barrier[12].

3. ETHOSOMES

Ethosomes were first introduced by Touitou et al. in 1997. These are flexible lipid vesicles with high ethanol content, enabling them to penetrate deeper skin layers and enter systemic circulation[13, 14]. In nanomedicine, ethosomes hold great potential for drug delivery and clinical applications. Their unique composition allows for non-invasive, deep skin penetration and efficient delivery of both hydrophilic and lipophilic drugs[15].

Structurally, ethosomes consist of an aqueous core surrounded by a phospholipid bilayer. Their size can range from nanometers to micrometers, depending on the formulation. Ethosomes can encapsulate highly lipophilic drugs and are tailored for enhanced transdermal delivery[16]. Their notable ability to entrap a variety of compounds stems from their composition primarily phospholipids, ethanol, and water which makes the skin more permeable[17].

The ethanol component is particularly important, as it disrupts the stratum corneum's lipid structure, increasing skin permeability. Moreover, ethanol imparts a negative charge to ethosomal vesicles, reducing their size and increasing stability. An optimal ethanol concentration of 30-40% is typically recommended to achieve stable and efficient ethosomes[18, 19].

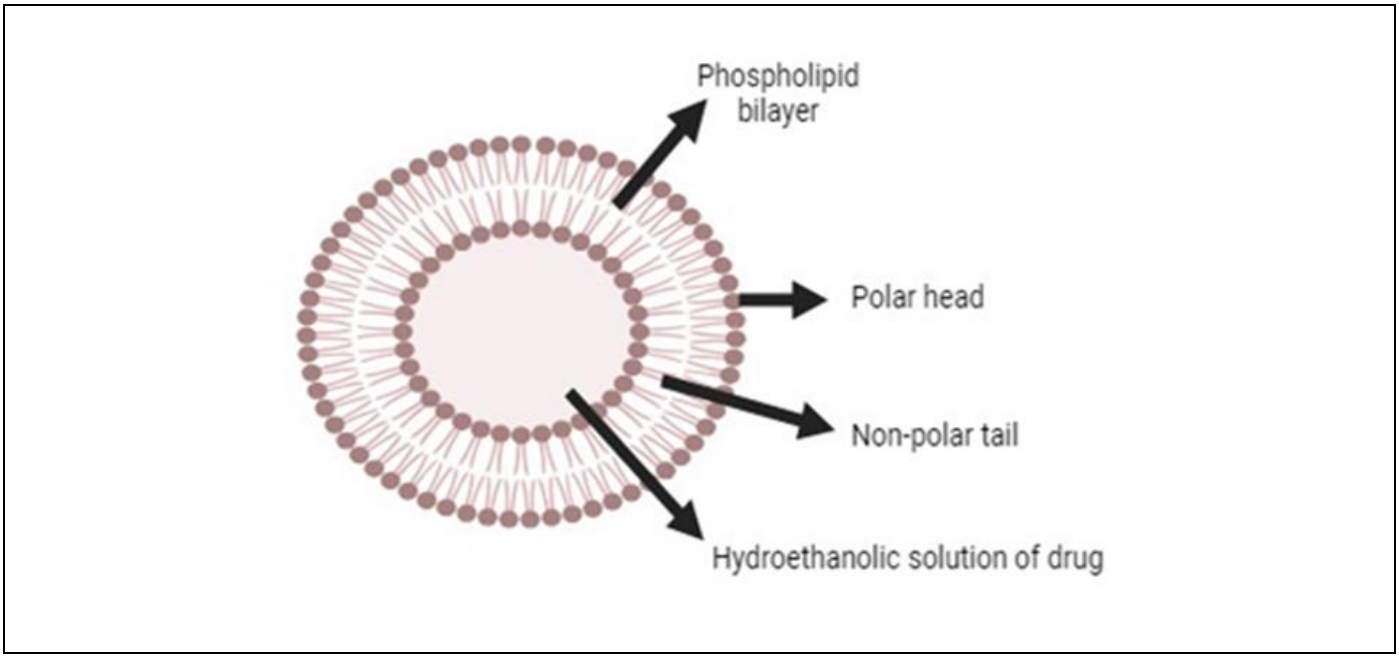

Figure.1. Ethosome Structure

Table 1. Classification of ethosomes based on composition[44-47].

Classical Ethosomes	Binary Ethosomes	Transethosomes
These formulations are essentially modified versions of traditional liposomes with a 45% w/w alcohol content. When compared to standard ethosomes, they display an elevated negative zeta potential and enhanced entrapment efficiency. The molecular weight spectrum ranges from 24 kDa to 130.07 Da. This results in improved stability and penetration characteristics.	Zhou et al. were the ones who originally presented them. Because another alcohol is added to the mixture to improve the desired qualities, they are binary in nature. Two typically used types of added alcohol are propylene glycol (PG) and isopropyl alcohol (IPA).	Song et al. created the most recent generation of vesicular systems in 2012.Despite having an extra ingredient as a penetration enhancer or edge activator (often a surfactant), they are comparable to standard formulations. Transethosomes are a unique delivery technology that combines the greatest qualities of traditional ethosomes with the transferosomes' flexibility and deformability.

4. CLASSIFICATION OF VESICULAR SYSTEMS[34, 35]

1. Liposomes
2. Niosomes
3. Transferosomes
4. Spingosomes
5. Pharmacosomes
6. Virosomes
7. Colloidosomes
8. Aquasomes
9. Cubosomes
10. Ethosomes

4.1. Liposomes

These microscopic vesicles, filled with aqueous content, mimic the phospholipid bilayer structure of the skin. They are composed of chains of phospholipids typically derived from soy, egg yolks, and occasionally cholesterol[36, 37].

4.2. Niosomes

Niosomes are structurally similar to conventional liposomes, but they are composed of non-ionic surfactants instead of phospholipids, which enhances their stability and reduces production costs. Their effectiveness depends on the physicochemical properties of the drug, the type of vesicle, and the lipids used[38, 39].

4.3. Transferosomes

Transferosomes, also known as ultra-deformable or elastic liposomes, exhibit enhanced flexibility and deformability. This flexibility is conferred by a combination of phospholipids and surfactants, making them effective for transdermal drug delivery[40, 41].

4.4. Spingosomes

Spingosomes are concentric bilayer vesicles with an aqueous core fully enclosed by a sphingolipid-based bilayer membrane, which may be natural or synthetic. Their size ranges from 0.05 to 0.45 microns. Due to their structure-comprising amide and ether bonds and fewer double bonds than lecithin-they demonstrate greater stability and longer circulation times compared to conventional vesicular systems[42].

4.5. Pharmacosomes

Pharmacosomes are considered promising alternatives to conventional vesicular systems. The term combines "pharma" (drug) and "some" (carrier), indicating a colloidal dispersion in which the drug is covalently bound to lipids. Depending on the nature of the drug-lipid interaction, they may form ultrafine vesicles, micelles, or hexagonal aggregates[43].

4.6. Virosomes

Virosomes are spherical, unilamellar phospholipid bilayer vesicles incorporating viral proteins, allowing them to fuse with target cells. Influenza-derived virosomes retain the nucleocapsid and genetic material from the parent virus within their envelope[44, 45].

4.7. Colloidosomes

Colloidosomes are hollow-shelled microcapsules formed by the coagulation of colloidal particles at the emulsion droplet interface. Their particle-based membrane enables adjustable permeability, allowing for targeted and controlled drug release. Despite their potential, they remain largely in the developmental stage with limited practical application[46].

4.8. Aquasomes

Aquasomes are three-layered self-assembling nanoparticles designed for targeted molecular delivery and protection. They consist of a ceramic core of nanocrystalline carbon covered by a glassy cellobiose layer, enabling structural integrity and stability[47, 48].

4.9. Cubosomes

Cubosomes are nanostructured particles used to enhance the delivery of herbal medicines, such as KIOM-MA 128, for atopic dermatitis. Compared to suspensions, cubosomes significantly improve the permeability of the active ingredient[49, 50].

4.10. Ethosomes

Ethosomes are composed of water, ethanol, and phospholipids. Their size can range from nanometers to micrometers depending on the preparation method, including the use of sonication and other processing techniques[51, 52].

5. ETHOSOME ADVANTAGES[53- 55]

- Applicable via semisolid forms like creams or gels
- Non-invasive and commercialization-ready
- Capable of delivering large molecules
- Broad applicability in pharmaceutical, cosmetic, and veterinary sectors
- Simple method compared to iontophoresis or electrophoresis

6. ETHOSOME PREPARATION METHODS

1. Hot Method: Combine aqueous and organic phases at 40°C with continuous stirring.
2. Cold Method: Mix ethanol-dissolved lipids with water under high shear.
3. Ethanol Injection-Sonication: Inject ethanol phase into water, then sonicate.
4. Reverse-Phase Evaporation: Use ether and ultrasound to create a water-in-oil emulsion.
5. Transmembrane pH Gradient: Use pH shifts to load drug into vesicles.
6. Ethanol Injection: Stirred and filtered ethanol-lipid mix with aqueous phase.
7. Injection-Ultrasound: Combine ethanol and buffer phases followed by ultrasonication.
8. Microfluidic Technique: Ethanol and water phases are mixed using devices like NanoAssemblr.

The **Hot Method** involves heating phospholipids in water at 40 °C to form a colloidal mixture. In a separate container, ethanol is heated to the same temperature and then slowly added to the colloidal mixture while stirring continuously to ensure proper blending. The drug is incorporated into the system based on its solubility-either in water or lipids[64]. In the **Cold Method**, phospholipids are first dissolved in ethanol to prepare the organic phase. Separately, water or a saline solution is prepared as the aqueous phase. The aqueous phase is then added slowly to the organic phase under high-speed stirring. The system is mixed for 5 to 30 minutes to form an ethosomal suspension, and the drug is introduced based on its solubility profile[65]. The **Ethanol Injection–Sonication Method** starts with dissolving

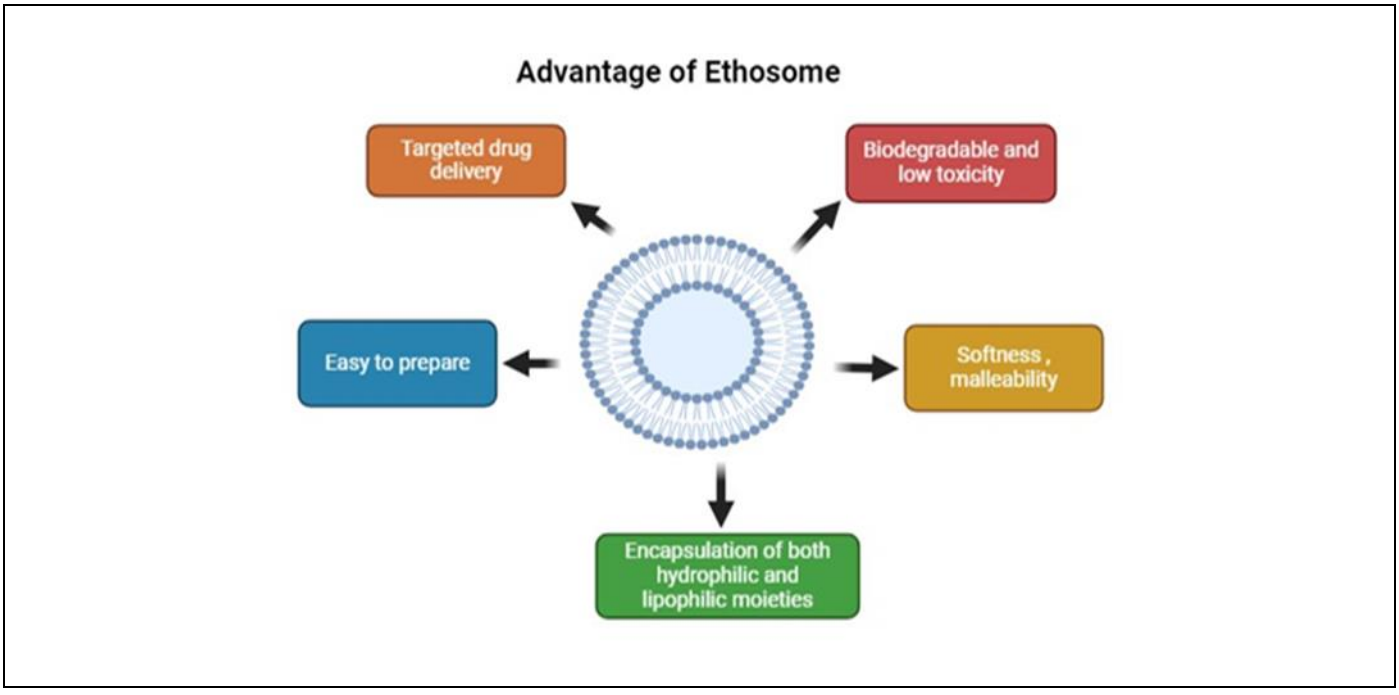

Figure 2. Advantage

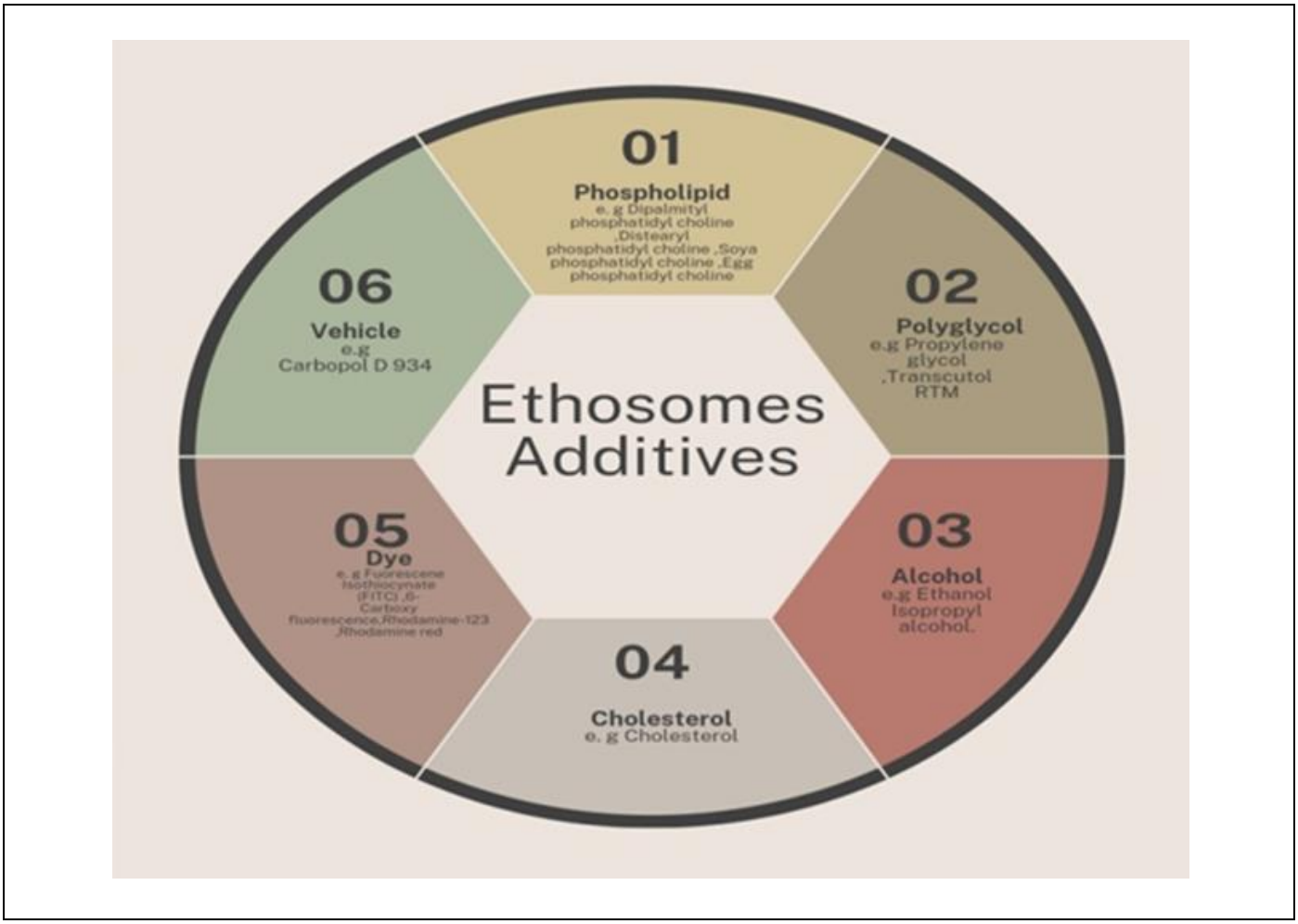

Figure 3. Ethosomes Additives[40-43]

phospholipids in ethanol to create the organic phase. This ethanol solution is injected into water at a controlled rate of 200 µL/min using a syringe. To ensure uniform mixing and vesicle formation, an ultrasonic probe is used to sonicate the solution for 5 minutes, resulting in well-dispersed ethosomal vesicles encapsulating the drug[66]. In the **Reverse-Phase Evaporation Method**, phospholipids are dissolved in diethyl ether and mixed with water in a 3:1 ratio. This mixture undergoes ultrasound treatment at 0 °C for 5 minutes to form a water-in-oil emulsion. The diethyl ether is then removed under vacuum to form a gel-like structure, which is stirred vigorously to yield a colloidal ethosomal dispersion[67]. The **Transmembrane pH-Gradient Method** begins with the preparation of blank ethosomes using an acidic buffer at pH 3. After drug addition, the external solution is made alkaline (pH 7.4) using sodium hydroxide. The system is incubated at a

Table 2. Preparation Method of Ethosomes[50-52]

Method of preparation	Component		Addition Order	Temperature	Duration and speed
	Organic	Aqueous			
Hot method	Phospholipid, Ethanol, PEG Drug, Water	Ethanol, Drug	Aqueous to organic	40 ºC	5 min at 700–1000 rpm
Cold method	Drug, ethanol Phospholipid and other lipidic materials	Water	Aqueous to organic	30 ºC	5 min at 700–1000 rpm
Dispersion method	Phospholipid, cholesterol, Drug	Drug, Hydro Ethanolic mixture	Aqueous to organic	Heating above the temperature of transition to produce films	Adequate speed, temperature, and timing

temperature between 30 and 60 °C to facilitate drug penetration into the vesicles. This method is especially suitable for water-soluble drugs containing amine groups and produces a pH-driven ethosomal formulation[68]

In the **Ethanol Injection Method**, phospholipids and cholesterol are dissolved in ethanol and maintained in a sealed container. Water is gradually added to the ethanol solution under stirring conditions, with the addition rate determined by the solubility of the drug (hydrophilic or lipophilic). The resulting mixture is thoroughly stirred and filtered through a microporous membrane to produce a clear ethosomal solution with effective drug encapsulation[69]. The **Injection-Ultrasound Combination Method** involves dissolving phospholipids and the drug in ethanol, followed by magnetic stirring. Phosphate buffer is then injected slowly into the mixture while stirring to initiate vesicle formation. The mixture is sonicated in an ice bath to reduce particle size and is subsequently filtered to obtain a uniform ethosomal suspension with small, well-defined vesicles[70]. Finally, the **Microfluidic Technique** employs advanced microfluidic devices such as the NanoAssemblr. In this method, phospholipids, cholesterol, and the drug are dissolved in ethanol and stirred to form the organic phase. This ethanol-based phase is then mixed with water in a precisely controlled ratio, and the mixture is processed through a microfluidic device. The result is ethosomes with highly uniform size, efficient drug loading, and a monolayer vesicular structure[71].

Table 3. Characterization Studies of Ethosomes

Parameter	Characterization techniques	References
Ethanol-phospholipid interaction	31-nm radioactive differential scanning calorimeter	53
Deformability level	Extrusion method	54
Analysis of Zeta potential	Zeta meter	55
Turbidity	Nephelometer	56
Stability study	Dynamic light scattering, Transmission electron microscopy	57
Study of drug deposition	Franz diffusion cell	58
Vesicle shape	Transmission electron microscopy (TEM), Scanning electron microscopy (SEM)	59
***In vitro* drug release study**	Franz diffusion cell or Biological membrane, Dialysis bag diffusion	60
Efficiency of entrapment	The Fluorescence Spectrophotometer and the Mini Column Centrifugation Method	61
Size distribution, Size of vesicles	Size distribution, Size of vesicles	62
Study on Vesicle-Skin Interaction	Transmission electron microscopy and fluorescence microscopy	63

Table 4. Marketed ethosomal formulations [64-67]

Marketed Formulation	Drug	Use	Company Name
Lipoduction	Pure Grape Seed Extract	Anti Cellulite Cream, Antioxidant	Osmotics, Israel
Decorin Cream	Decorin Proteoglycan	Anti-Aging Cream	Genome Cosmetics
Nanominox	Minoxidil At 4% Concentration	Growth Promoter for Hair	Sinere, Germany
Supravir cream	Acyclovir	In opposition to Retroviral Diseases Such as Herpes Virus.	Israel's Trima
Noicellux	Methylxanthine Caffeine	Applying Anti-Cellulite Cream Topically	Novel Therapeutic
Skin Genuity	Retinol/Caffeine	Anticellulite Gel	Physonics Nottingham, United Kingdom

7. APPLICATIONS OF ETHOSOMES

Ethosomes are advanced vesicular carriers that demonstrate significant potential in modern drug delivery systems, especially for transdermal applications. Their unique ethanol-rich composition enhances skin permeability, enabling improved transport of various therapeutic agents[88, 89].

7.1. Transdermal drug delivery

Ethosomes are particularly effective in delivering hydrophilic and poorly permeable drugs through the skin. Their high ethanol content disrupts the lipid structure of the stratum corneum, allowing deeper penetration and enhanced drug absorption[90].

7.2. Antiviral drug delivery system

Ethosomes have been used to enhance the transdermal delivery of antiviral drugs such as Zidovudine for HIV treatment. They improve skin penetration and support sustained release, offering therapeutic advantages in chronic viral infections[91].

7.3. Hormone delivery via skin

Ethosomal systems help overcome limitations of oral hormone therapy, such as first-pass metabolism and systemic side effects. An example is the Testoderm patch (Alza), which utilizes ethosomes for efficient testosterone delivery through the skin[92].

7.4. Transdermal delivery for arthritis treatment

Cannabidiol (CBD), used in treating rheumatoid arthritis, has been successfully incorporated into ethosomal formulations. Studies by Lodzki et al. demonstrated increased skin penetration and improved therapeutic outcomes using this approach[93].

7.5. Cosmetic uses of ethosomes

In cosmetics, ethosomes are employed to stabilize active ingredients, reduce irritation, and improve skin absorption. Their vesicle size and flexible structure contribute to their effectiveness in delivering skincare agents[94].

7.6. Enhanced skin penetration and infection control

Ethosomes can traverse the epidermis and release drugs deep into the skin or inside target cells. This has been demonstrated with antimicrobial agents like bacitracin and erythromycin, enhancing infection control[95].

7.7. Improved delivery of difficult-to-absorb drugs

Macromolecules such as peptides, proteins, and insulin, which are typically degraded in the gastrointestinal tract, benefit from ethosomal delivery. Ethosomes significantly improve their skin absorption and therapeutic efficacy, surpassing limitations of traditional transdermal systems[96].

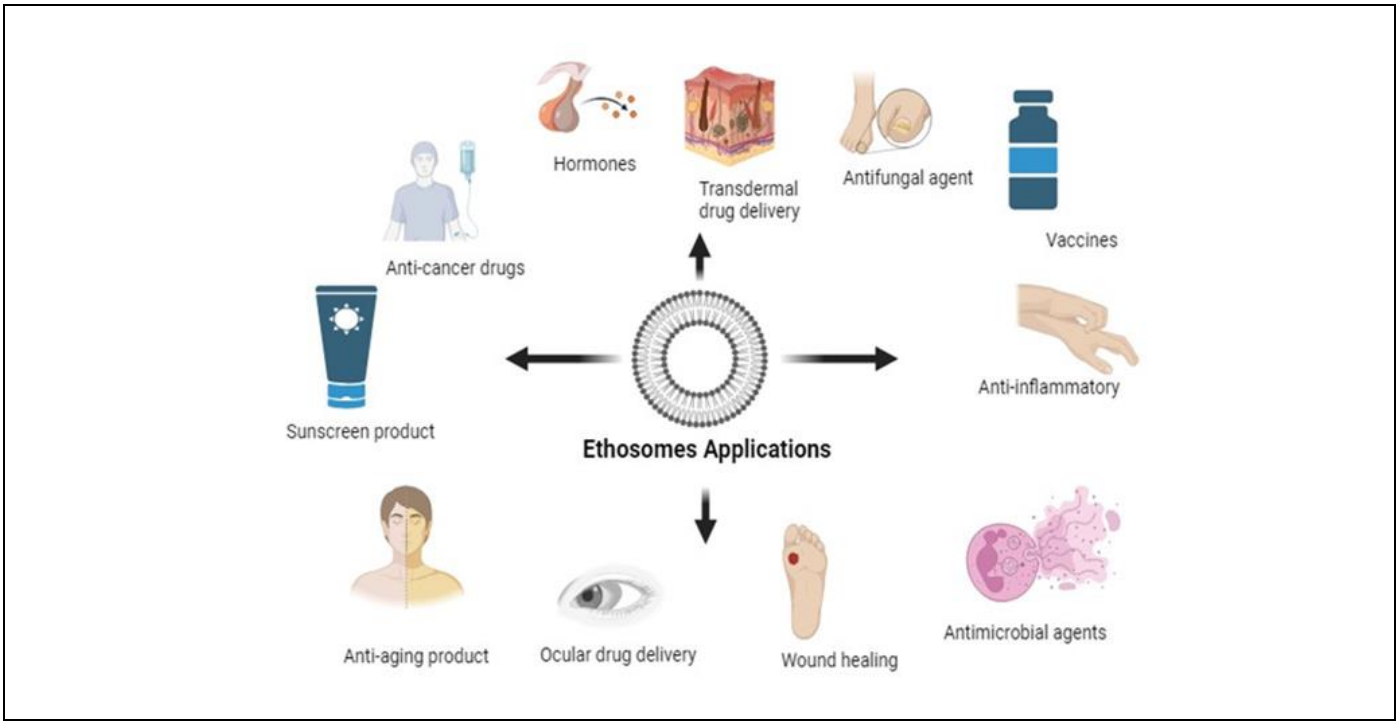

Figure 4. Applications of Ethosomes

8. FUTURE PROSPECTS OF ETHOSOMES

The transdermal route has been predominantly overlooked as an optimal modality for drug administration due to the inherent challenges associated with penetrating the stratum corneum layer, which ultimately results in diminished access to the underlying tissue layers. Consequently, achieving an effective concentration at the targeted site has proven to be exceedingly arduous. Innovative delivery systems, such as ethosomes, utilize vesicular architectures to significantly enhance the permeation of hydrophilic and macromolecular therapeutics. Moreover, they have proven to have excellent transport capabilities for peptides, proteins, and cationic agents all of which contain much bigger molecules and are notoriously challenging to distribute using conventional methods. These systems facilitate the controlled delivery of requisite drug dosages, thereby augmenting patient adherence and therapeutic efficacy. Notable pharmaceuticals, including insulin, testosterone, salbutamol, and minoxidil, have benefitted from enhanced topical and transdermal delivery achieved through this innovative approach. Ethosomal therapy has recently made strides in pilosebaceous delivery, topical DNA administration, antiviral agent delivery, arthritis treatments, hormone replacement therapy, cardiovascular therapies, anti-Parkinsonian medications, and topical hormone delivery. Some of the best qualities of ethosomes include their effectiveness, simplicity, and better medication resistance management. Using these cutting-edge delivery techniques, Biopharmaceutical business Novel Therapeutic Technology Inc. committed to creating treatments for erectile dysfunction, postoperative nausea, inflammatory conditions, hormonal deficiencies, alopecia, and deep-seated skin infections. Transethosomes, a unique vesicular technology that is considered a major breakthrough in the area, have emerged the future appears promising for broader applications that could render numerous therapies more economically viable and clinically effective, while concurrently mitigating various complications[97-116].

9. CONCLUSION

Ethosomal drug delivery systems, including ethosomes, provide a simple, non-invasive way to distribute medications via the skin, increasing patient compliance and drug penetration. Vesicular systems that can pass through the skin barrier and provide focused action, such as liposomes and ethosomes, have demonstrated promise in improving drug delivery. Antiquated vesicular systems may give way to novel drug delivery techniques like pharmacosomes, which offer unique drug-lipid interactions that improve drug dispersion. Advanced vesicular systems, such as ethosomes, cubosomes, and aquasomes, are useful in drug delivery applications because they provide particular benefits such improved drug permeability qualities, precision targeting, and molecular shielding. It is vital to stress that ethosomes demonstrate regulated and prolonged release of active chemicals, excellent biocompatibility alongside several advantages within the pharmaceutical sector. In particular, ethosomes are attractive as drug delivery methods due to their simple manufacturing and composition. In topical and transdermal applications, the presence of ethanol in these vesicles offers unique benefits over other lipid-based vesicles. Moreover, ethosomes can be seamlessly integrated into various dosage forms, including gels, lotions, and patches. It is just to assume that ethosomal formulations will be crucial in the therapeutic area given their higher permeability, which allows greater therapeutic efficacy.

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