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Review Article

NOVEL APPROACHES IN ETHOSOMAL DRUG DELIVERY: APPLICATION IN DERMATOLOGY AND BEYOND

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ABSTRACT

Skin is a complex and dynamic structure with multiple layers, and it is the body's largest organ. It is the protective barrier between the external and internal environment; it comprises three layers (epidermis, dermis, and hypodermis). The skin performs various vital functions in the body. A conventional drug delivery system (CDDS) is the method of administering drugs into the body through oral, parenteral, and topical administration. This delivery system has several drawbacks, including low bioavailability, uncontrolled release, and poor solubility. A novel carrier and TDDS (Transdermal Drug Delivery) systems were introduced to overcome these drawbacks. It is an advanced drug delivery system designed to overcome the drawbacks of conventional methods and improve therapeutic outcomes. Some examples of novel and transdermal carriers are liposomes, niosomes, ethosomes, and microspheres. Ethosomes are preferred over liposomes and niosomes due to their high ethanol content, which enhances skin penetration and allows deeper drug delivery. TDDS delivers drugs into the deeper layer of the skin and provides a therapeutic effect by avoiding first-pass metabolism. They are generally used to treat various diseases. Ethosomes are highly advanced lipid-based nano-carriers designed to improve transdermal and dermal drug delivery systems. The main aim of writing this review paper is to summarize the focus on the key aspects, such as types of ethosomes, the mechanism of action of ethosomes, the method of preparation, composition, application, characterization, the patent, marketed formulation, and factors of ethosomes.

Keywords: Ethosomes, Skin, Applications, Transdermal, Bioavailability

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INTRODUCTION

Skin is the body's largest organ, which regulates the body's temperature and protects against germs. Skin comprises minerals, fat, protein, water, and other essential nutrients [1]. The skin is composed of three layers: the Epidermis, the top layer of skin, which helps in forming new skin; it also serves as a protective barrier and provides skin color. The middle layer, the Dermis layer, helps in hair growth. It has collagen and elastin, helps in feelings and sensations, produces sweat, and supplies blood to the body. The bottom layer of skin is known as the Hypodermis layer. This layer helps regulate body temperature, helps to connect nerves and blood vessels, and has connective tissues [2]. The skin's main job is to act as a protective agent and prevent harmful substances from entering the body. Various barriers are present in the skin, which make it difficult for medication to reach the site of action. The stratum corneum is the most significant barrier. It is a foremost barrier that decreases drug permeability and decreases the therapeutic effect of bioactive components of the drug [3]. Medication in the form of creams and gels was used in the layer of skin to get therapeutic results, but now novel drugs are being used to achieve better results. One of these is ethosomes. The significant drawbacks of the conventional drug delivery system (CDDS) were an uncontrolled release of drugs, unregulated doses of drugs, and they had low bioavailability, lower efficacy, and sometimes toxicity was observed. Transdermal drug delivery system (TDDS), or a novel drug delivery system (NDDS), was introduced to overcome these drawbacks. As this drug delivery system is highly advanced, it avoids first-pass metabolism, reduces toxicity, directly reaches the systemic circulation, enhances permeation of the drug, they are highly stable, and has several benefits over conventional drug delivery systems [4].

TDDS is a procedure of directly delivering drugs into the bloodstream. TDDS encounters the barriers property of stratum corneum (Horny layer). It aims to achieve systemic medication by directly or topically applying medication to interact with the skin layer and avoiding first-pass metabolism. Liposomes, niosomes, and ethosomes are used in the vesicular or TDDS [5]. Firstly, if we talk about the liposomes, they are tiny, spherical-shaped vesicles made up of cholesterol and natural phospholipids. They are biodegradable and biocompatible and are used in making medical applications. However, they are less stable and exposed to oxidation, which is a more stable evaluation of the niosome. Niosomes are synthetic vesicles, and they are made up of non-ionic surfactant and cholesterol. They are very much identical to liposomes, but compared to liposomes, niosomes are more stable, less expensive, and pocket-friendly. Niosomes are further used to deliver drugs, especially in a TDDS [6]. Ethosomes are an advanced formulation of niosomes. Ethosomes are known as ethanolic vesicles as they contain more ethanol in the vesicular structure, as shown in fig. 1 and table 1 [7]. In ethosomes, ethanol breaks the gaps of the intensely packed lipid present in the outermost layer of skin that is known as stratum corneum; ethanol makes it simple for the ethosomes to deeply penetrate, as they are highly flexible and permit them to squeeze through the small gaps in the skin barrier, as shown in fig. 3. Once the drug reaches the skin's deepest layer, it ensures effective delivery. This unique combination of ethanol and flexible vesicles makes ethosomes very efficient for TDDS [8]. Ethosomes have a size range from 10 nm to a specific micron. The size of ethosomes is dependent on the concentration of ethanol and phospholipid [9]. Ethosomes are highly advanced TDDS systems that are produced to improve the absorption of medicines through the different layers of skin. These are very tiny and soft vesicles that consist of ethanol, phospholipid, water, and many more essential components and excipients [10, 11]. Ethosomes are very flexible, carrying hydrophilic and lipophilic drugs. Ethosomes are painless, meaning they do not require a needle, making them more comfortable for patients. They are commonly used to cure hormonal imbalance, skin disorders, pain, and nowadays they are widely used in the formulation of cosmetics [12]. Ethosomes are very stable, and we can store medicine for a longer duration of time. Generally, ethosomes are promising a new revolution, by making treatment more effective and safer. Ethosomes are very stable, and we can store medicine longer [13, 14].

To ensure a thorough review of ethosomes and their role in transdermal drug delivery systems (TDDS), a systematic literature search was conducted using major scientific databases, including PubMed, Scopus, Web of Science, and Google Scholar. The search

strategy incorporated Boolean operators (AND, OR) to refine results with relevant keywords such as *transdermal drug delivery*, *ethosomes*, *vesicular systems*, *skin permeability*, and *ethanol-enhanced penetration*. Articles published between 2010 and 2024 were prioritized to include the latest advancements in ethosomal formulations. Selection criteria focused on peer-reviewed studies detailing the formulation, mechanism, advantages, and clinical applications of ethosomes, while excluding papers that were solely based on animal models with limited translational relevance or those lacking experimental validation.

Types of ethosmes systems

Ethosomes are an advanced novel carrier of TDDS that can be classified based on their composition and application [15]. As shown in fig. 2, ethosomes are classified into three types: classical ethosomes, binary ethosomes, and trans ethosomes.

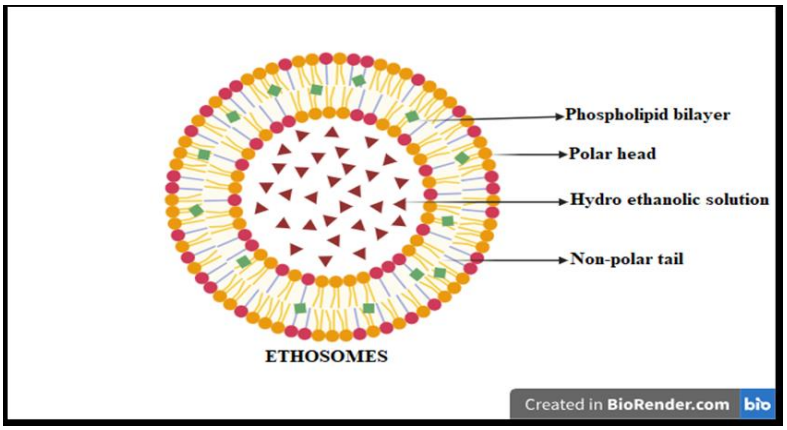

Fig. 1: Systemic structure of ethosome

Table 1: Ethosomes vs. liposomes vs. niosomes

Parameter	Ethosomes	Liposomes	Niosomes	References
Permeation efficiency	High—due to ethanol-enhanced skin penetration	Moderate—relies on phospholipid bilayer	Moderate—depends on non-ionic surfactants	[16]
Stability	Improved stability due to ethanol, but sensitive to high temperatures	Moderate—prone to oxidation and degradation	Higher stability than liposomes, but susceptible to surfactant phase transitions	[17]
Clinical efficacy	Enhanced drug absorption and bioavailability	Effective for localized delivery, but limited deep penetration	Suitable for controlled drug release, but may have lower permeability than ethosomes	[18]

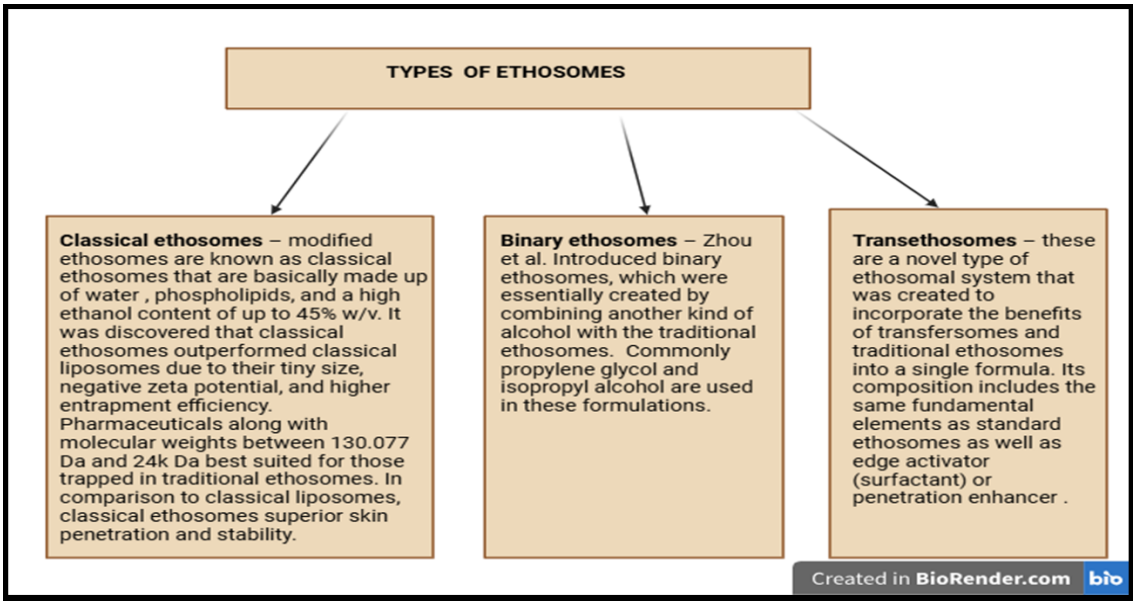

Fig. 2: Types of ethosomes

Mechanism of action

Ethosomes utilize a high ethanol concentration to enhance transdermal drug delivery. Ethanol disrupts the stratum corneum's lipid organization by reducing lipid packing density, weakening van der Waals forces, and breaking hydrogen bonds between ceramides, fatty acids, and cholesterol. This increase in membrane fluidity lowers the phase transition temperature and makes the lipid bilayer more permeable. The altered lipid structure allows ethosomes to penetrate deeper into the skin and efficiently deliver hydrophilic

and lipophilic drugs, significantly improving therapeutic efficacy as shown in fig. 3 [19, 20].

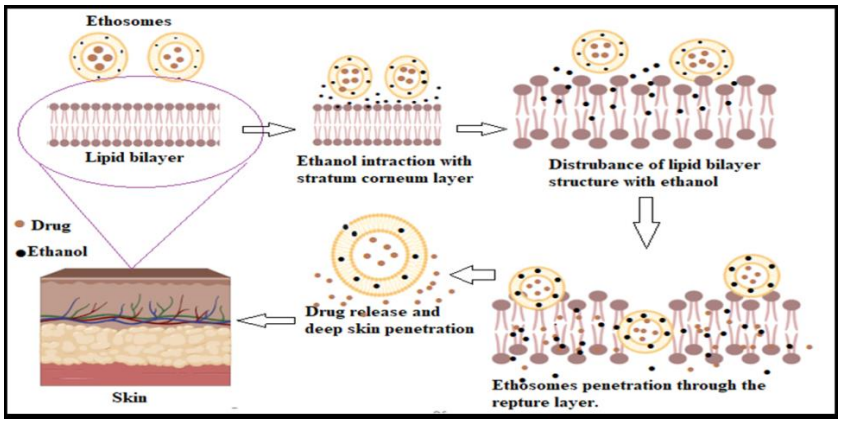

Fig. 3: Mechanism of penetration of the ethosomal drug delivery system

Table 2: Different excipients used in ethosomes

Excipients of ethosomes	Uses	References
Phospholipids	Essential components of the vesicle bilayer aid ethosome formation. *Examples:* Phosphatidylcholine, Dipalmitoylphosphatidylcholine (DPPC), Soy phosphatidylcholine (SPC).	[20]
Ethanol	Enhances skin penetration by fluidizing the lipid bilayer, facilitating better drug delivery—a standard concentration of 20% to 40%.	[21, 22]
Water	Solvent disperses lipids and other components, such as distilled and purified water.	[23]
Cholesterol	Modulates lipid bilayer fluidity and improves ethosome stability—typical *usage:* 10% to 20% w/w.	[24]
Glycerol	Functions as a humectant, stabilizing the formulation and improving texture.	[25, 26]
Sodium Chloride	Adjusts osmolarity and ensures isotonicity of formulations, such as sodium chloride (NaCl).	[22]
Carrier	Used to enhance drug encapsulation or modify the release profile. *Examples:* Poloxamers, Cyclodextrins (β-cyclodextrin).	[22]
pH Adjuster	Maintains the desired pH, influencing formulation stability and drug release, such as citric acid and sodium hydroxide.	[22]

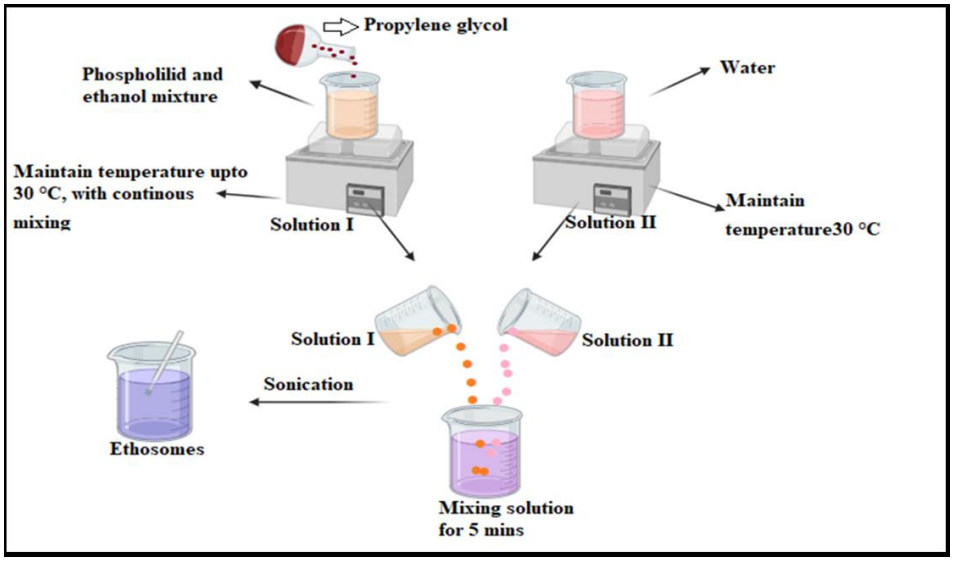

Fig. 4: Systematic representation of the cold method

Ethosome compositions

Ethosomes are very tiny, soft vesicles that consist of ethanol, phospholipid, water, and many other essential components and excipients. Table 2 highlights the excipients used in the formulation of ethosomes.

Method of preparation of ethosomes

Cold method

Phospholipids and lipid components are mixed with ethanol at a controlled temperature while continuously stirring. Polyol or propylene glycol is added to stabilize the mixture maintained in a water bath. Water is heated and gradually incorporated into the ethanol-lipid blend with continuous stirring until a uniform ethosomal dispersion is obtained. Vesicle size can be further reduced through sonication, as shown in fig. 4 [27]. This method is moderately scalable, requires controlled mixing conditions, and is particularly suitable for heat-sensitive drugs, ensuring drug stability throughout the process.

Hot method

This process involves heating the phospholipid at 40 °C in a water bath to form a colloidal solution. Meanwhile, ethanol and propylene glycol are heated to 40 °C in a separate vessel. Once both solutions reach the same temperature, they are combined to form ethosomes, ensuring efficient drug encapsulation depending on its hydrophilic or lipophilic nature. Vesicle size reduction can be achieved using sonication, as shown in fig. 5 [27]. This highly scalable method has low production costs and higher encapsulation efficiency, making it ideal for lipophilic drugs. However, due to thermal exposure, it may not be suitable for heat-sensitive compounds.

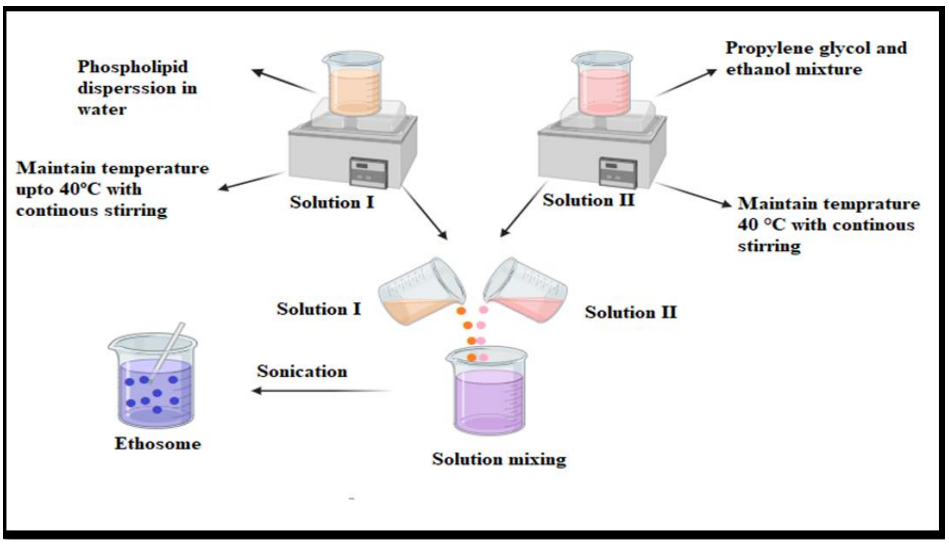

Fig. 5: Systematic representation of the hot method

Thin film hydration technique

Lipids and an organic solvent are dissolved in a round-bottom flask, followed by evaporation using a rotary evaporator above the lipid transition temperature. This process creates a thin lipid film along the flask's inner walls, then hydrated with an ethanolic mixture. The final ethosomal suspension is obtained through sonication, improving uniformity, as shown in fig. 6 [28]. This highly scalable method allows for precise control over vesicle size, making it suitable for hydrophilic and lipophilic drugs. However, it requires specialized equipment like rotary evaporators, which may increase production costs.

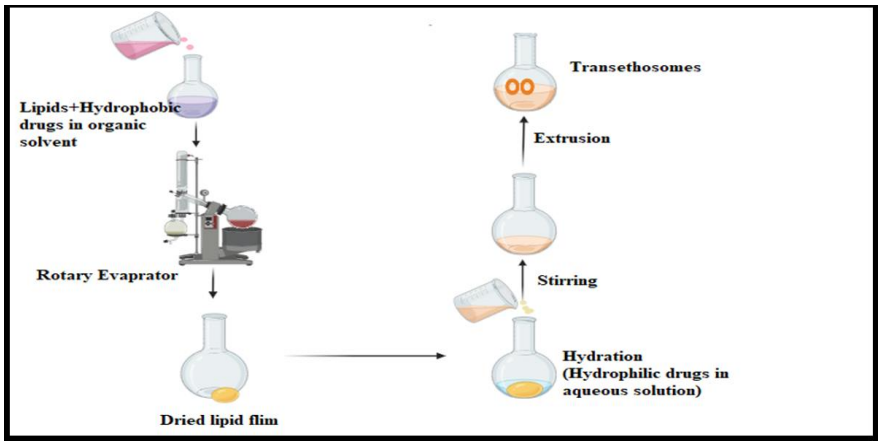

Fig. 6: Systematic representation of the thin film hydration method

Classic method

When the drugs and phospholipids are mixed with ethanol and then heated in a water bath heated to 30 °C. In a covered vessel, double-distilled water is provided to the solution that contains lipids in a stream while continuously stirring at 700 rpm. A hand extruder is utilized to homogenize the obtained solution of vesicles by passing it through a polycarbonate membrane 3 times [28].

Ethosomal-based formulation for TDDS

Ethosome-based formulations are a recent approach in transdermal drug delivery, and their unique combination of excipients improves skin penetration. These formulations are highly effective for hydrophilic and lipophilic drugs; they penetrate the skin and give therapeutic responses. Some drugs based on ethosome formulations are mentioned below in table 3.

Application of ethosomes

Ethosomes are primarily used in skin care products to enhance skin color, provide moisture, prevent ageing, and reduce acne marks and pigmentation. However, they are often used to improve effectiveness in antiviral and antifungal medicines such as clotrimazole and acyclovir. They are also exploring the potential of ethosomes in cancer treatment and how to deliver a vaccine without needing a needle. These specialties make ethosomes valuable in cosmetic and medicinal fields [40].

Antifungal

Clotrimazole and ketoconazole are active antifungal agents, and an ethosomal system has been used to encapsulate antifungal drugs. For example, Wang *et al.*, through their study, it was revealed that the use of ethosomes as an antifungal agent enhances skin permeation and improves antifungal activity against fungal infections like Candida albicans with the help of hexyl-amino levulinate [41].

Table 3: Ethosomes-based formulations

Drugs	Application	Method	Excipients	Key finding	Reference
Minoxidil	Alopecia treatment.	Hot method.	Phospholipid 90G, Ethanol.	When phospholipid and drug were mixed in a 1:4 ratio, 75% of the drug was successfully encapsulated, leading to better release than other mixtures.	[29]
Clotrimazole.	Antifungal.	Mechanical dispersion method.	Phosphatidylcholine, Soya lecithin, Carbopol 934.	The best formulation achieved 52.6% to 60% drug entrapment efficiency, with RE5* being the most effective.	[30]
Acyclovir	Antiviral	Hot method.	Palmitoyl chloride, Phosphatidyl choline, Cholesterol.	Encapsulation efficiency was 87.75%, compared to 39.13% for ACV ethosomes. After 24 h, ACV-C16 ethosomes achieved 5.3 times higher skin absorption than ACV-C16 hydroalcoholic solution and 3.43 times higher than ACV ethosomes.	[31]
Silver sulfadiazine	Antibacterials also reduce the bacterial burden and healing time in burn injuries.	Cold method	Soya lecithin, Propylene glycol, Ethanol, Cholesterol.	Optimized ethosomal suspension resulted in high SSD encapsulation efficiency (92.03±0.79%) and significantly reduced microbial colonies. It also enhanced wound healing, achieving 96.83% contraction compared to 59.41% in the untreated group.	[32]
Curcumin	Skin cancer	Ethanol injection method	Lecithin, Ethanol, Cholesterol, Glycerol, Water.	The optimized formulation achieved 92.24±0.20% entrapment efficiency with a vesicle size of 247±5.25 nm, making it highly effective.	[33]
Thymoquinone	Brest cancer	Conventional mechanical Dispersion method.	Soya lecithin, ethanol, cholesterol, and chloroform.	Researchers discovered an optimized formulation using specific polymers in controlled quantities, achieving 99% drug encapsulation. The formulation has an average vesicle size of 20±1 nm and a zeta potential of-63±2 mV.	[34]
Ketoconazole	Antifungal	Thin film hydration method.	Phosphatidylcholine, Tween80, Ethanol, Methanol, Fluorescein, Carbopol940,	Optimized vesicles were round, with an average size of 151.34±8.73 nm and a zeta potential value of+34.82±2.64 mV. Entrapment efficiency was approximately 95% of the drug.	[35]
Rosmarinic Acid	Anti-aging treatment	Ethanol injection method	Soya lecithin, propylene glycol, ethanol, cholesterol	The resulting vesicle size is (453.10-796.80 nm) and good efficiency of entrapment (46.73-65.99%), and the negative zeta potential is(-45.40±-86.90mv).	[36]
Anthralin	Psoriatic	The thin-film hydration method	Phosphatidylcholine, cholesterol, chloroform, ethanol, methanol, diethyl ether.	The efficiency of the drug to encapsulate ≥97.2% and ≥77% was obtained for ethosomes, and the size of the particle, 116-199 nm and 146-381 nm, was recorded.	[37]
Cryptotanshinone	Acne	Ethanol injection technique	Soybean phosphatidylcholine, Oleic acid, Carbomer 974, Polyethylene glycol 400 (PEG-400), and Tyrosinase.	This acne activity was observed in rabbits, and the resulting ethosomes have an average vesicle size of 69.1±1.9 nm. Drug encapsulation efficiency is 0.445±0.007 mg/ml 40.31±0.67%, and the optimized gels were 2.5 and 2.1 times that of conventional gels.	[38]
Carvedilol	Antihypertensive	The ethanol injection Method	Phospholipone 100 H, Cholesterol, Transcutol P.	The ethosomes' vesicular size ranges between 201.55 and 398.55 nm. The drug's efficiency of entrapment is 30.00-90.66%, and the capacity of loading is 7.64-43.04%, with a zeta potential of-30.30 to-44.90 mV.	[39]

Topical drug delivery

Topical formulation of ethosomes that are used for the treatment of eczema and dermatitis. Ethosomal preparation allows drugs (corticosteroids) to penetrate the deeper layer of skin for therapeutic responses. For example, Goindi *et al.* Their study or review includes the fact that ethosomes are successful and highly effective carriers in tropical drug delivery systems that increase skin penetration and improve drug stability. Their analysis reveals that ethosomes can be used for systemic and localized disease treatment, specifically those requiring long-term therapy [42].

Cosmetic application

Cosmetic ethosomal formulations are used in moisturizing and anti-aging creams because they contain APIs like vitamin C. They deliver the drug deep into the skin, which helps reduce pigmentation and wrinkles [43]. For example, Akhtar *et al.*, [44]. Their study concluded that the development of stable tocopherol succinate-loaded ethosomes is significant in cosmetic and TDDS. Their study highlights the capability of ethosomes to improve the permeation of cosmetic ingredients like antioxidants, retinol, and sunscreen agents, which is challenging to deliver effectively using traditional formulations. Their study also suggests that ethosomes have better efficacy, stability, and skin penetration of these ingredients, improving their performance in cosmetic treatments.

Anticancer

Ethosomal preparation has been used to deliver anticancer agents like doxorubicin to the tumour, and it also improves targeting and decreases systemic toxicity [51]. For example, Shinde *et al.* concluded that ethosomes are a good carrier for the therapy of skin cancer by offering innovative formulations like gel and patches. They provide an effective, stable, and safe alternative to conventional therapy [52].

Anti-inflammatory and antioxidant

Potent drugs like curcumin contain anti-inflammatory and antioxidant compounds, and they can be encapsulated in an ethosomal preparation to enhance transdermal absorption and also help in the cure of inflammatory skin conditions [45]. For example, Pathan *et al.*, [46]. In this research, he revealed that ethosomes are carriers for loxoprofen, a non-steroidal anti-inflammatory drug, to improve the delivery of transdermal preparation. As a result, the ethosome system significantly improved the drug permeation through skin and anti-inflammatory effects. He also mentioned that it has potential as an effective transdermal delivery system.

Vaccination

Ethosomes can deliver transdermal vaccines, providing a painless alternative to traditional injections [47]. For example, Panwar *et al.* [48]. Demonstrated that ethosomes enhance the transdermal delivery of bioactive substances, including vaccines, by improving skin permeability and bypassing first-pass metabolism. These features make ethosomes a promising, innovative solution for vaccine delivery, reducing patient discomfort while ensuring adequate immunization [48].

Recent advancements

Recent advancements in ethosomes have mainly focused on improving their stability and efficacy and expanding their application in drug delivery. Various formulations have been developed for commercial use, some of which are mentioned below in table 4, and several patents related to ethosomes, concentrating on their preparation, composition, and application, are discussed below in table 5. Ethosomal formulations have been evaluated in several clinical studies to assess their efficacy and safety. One notable example is ethosomal minoxidil for alopecia, which demonstrated enhanced transdermal penetration and improved hair regrowth compared to conventional formulations. Studies have also reported that ethosomes improve drug bioavailability while maintaining low systemic toxicity, making them viable candidates for skin-targeted drug delivery. However, ethanol content may cause mild irritation in some patients, emphasizing the need for optimized formulations with stabilizers to mitigate potential side effects [49]. Regulatory agencies such as the FDA (Food and Drug Administration) and EMA (European Medicines Agency) oversee transdermal ethosomal formulations under guidelines for topical and nanocarrier-based drug delivery systems [50]. These frameworks emphasize safety, efficacy, and quality control, requiring comprehensive data on drug permeation, stability, and skin compatibility before market approval. Ethosomes incorporated into transdermal patches must comply with Good Manufacturing Practices (GMP) and demonstrate sustained drug release while minimizing skin irritation risks [51].

Table 4: Marketed formulation of ethosomes

Formulation type	Product name	Active ingredient	Uses	Manufacturing country	Reference
Topical gel	Etoderm	Diclofenac sodium	Pain relief conditions like muscle pain, arthritis, and inflammation	India	[52]
Ointment or Topical cream	Dermovate (clobetasol propionate)	Clobetasol Propionate	Inflammatory skin condition	UK	[53]
Tropical cream	Eli Quin	Ketoconazole	Anti-fungal	India	[54]
Topical gel	Minoxidil ethosomal gel	Minoxidil	Hair growth	USA	[55]
Transdermal patch	Klonopin	Clonazepam	Anxiety, panic attacks, and seizures	USA	[56]
Topical gel	Curaheal	Curcumin	Antioxidant, anti-inflammatory	India	[57]

Table 5: Patents on ethosomes-based formulations [58]

Patent number	Title	Year
US 20220304903A1	The method of preparing bioactive substance is encapsulated ethosomes, ethosome composition, and cosmetic composition, including ethosome composition.	2022
WO2021201310A1	The composition of the ethosomes includes vitamins, Dexpanthenol encapsulated therein, and the preparation method.	2020
AU2019206649B2	Encapsulated cannabinoid formulations for transdermal delivery	2019
TR201818665A2	Rosmarinic acid-loaded liposomes and ethosomes are suitable for use in cosmetics.	2018
JP7181880B2	A core/shell structural platform for immunotherapy	2018
KR101810160B1	Generating method for ethosomes with bioactive compounds, ethosomes, and cosmetic composition including ethosomes.	2017
US11452679B2	Method of preparing bioactive substance-encapsulated ethosome, ethosome composition, and cosmetic composition including ethosome composition.	2017
US20220304903A1	Method of preparing bioactive substance-encapsulated ethosome, ethosome composition, and cosmetic composition including ethosome composition.	2017

Challenges and future prospects

Ethosomes are very small based on their lipid structure, which allows efficient drug delivery through the skin. They can potentially treat various diseases and skin conditions; however, several challenges must be addressed to enhance their future applications. One primary concern is stability, as ethosomes lose structural integrity over time, affecting drug delivery efficiency. Recent studies have explored stability enhancement strategies, including lyophilization, which removes water content to prevent degradation. Additionally, cryoprotectants such as trehalose and sucrose help stabilize ethosomes during freezing and drying, preventing vesicle rupture and improving formulation robustness. Polymer coatings, like chitosan or PEG, further enhance mechanical stability, drug retention, and prolonged release, reducing premature degradation.

Recent advancements in ethosomal drug delivery are exploring combinatorial approaches and hybrid systems to enhance therapeutic efficacy. Microneedle-assisted ethosomes improve penetration by creating microchannels, facilitating better drug

absorption, while iontophoresis, using electrical currents, increases drug flux across the skin barrier, optimizing transdermal delivery. Additionally, Transethosomes, a hybrid formulation incorporating penetration enhancers alongside ethanol, have shown superior skin permeation, drug retention, and bioavailability compared to traditional ethosomes. These emerging technologies highlight innovative directions in ethosomal research, offering enhanced stability, efficiency, and broader applications for future pharmaceutical formulations.

CONCLUSION

Through this review paper, we briefly describe ethosomes and the discovery of ethosomes, which introduced a new era for successfully delivering drugs through the skin. Ethosomes are lipid-based nanocarriers with a high ethanol concentration, as ethanol helps increase the drug's permeability through the skin by dissolving the skin barrier layer (stratum corneum). Ethosomes have many positive aspects, such as being safe to use, easily prepared, stable, and having no side effects. They also improve drug bioavailability and have better patient compliance. Twosomes indicate the capability to deliver a large-scale therapeutic agent for treating conditions like acne, anti-fungal, anti-diabetic, anti-cancer, etc. However, more research is required to determine the cost of the formulation, enhance stability, and increase capability; skin irritation remains an area for further study.

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AUTHORS CONTRIBUTIONS

Shalu Verma: Investigation, Conceptualization, drafting, Supervision. Alka Singh: Review, editing, and visualization. Simran Negi: Writing review and editing. Prayag Raj: writing and analysis.

CONFLICT OF INTERESTS

Declared none

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