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Formulation and Evaluation Ethosome Based Gel for Atropic Dermatitis

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Abstract: Atopic dermatitis (AD) affects about 20% of people worldwide, including children, and its incidence is rising dramatically. The pathophysiology of AD is thought to be largely influenced by complex interactions between abnormalities in the function of the epidermal barrier, the environment, infectious agents, and immunological deficiencies. Ethosomes are soft, elastic lipid vesicles composed of phospholipids, alcohol, poly glycol, and water. The presence of alcohol plays a crucial role by acting as a penetration enhancer, thereby increasing skin permeability. A key characteristic of ethosomes is their high deformability, which allows them to pass through the skin in an intact form and deliver drug molecules more effectively in terms of both depth of penetration and amount transported. These vesicular systems are capable of facilitating efficient intracellular delivery of hydrophilic, lipophilic, and amphiphilic drugs. Ethosomes typically range in size from a few tens of nanometers to several microns. Ethosomes have garnered a lot of scientific interest because of their special qualities, which include improved drug delivery effectiveness, increased drug entrapment capacity, and improved skin penetration.The advantages, disadvantages, composition, preparation techniques, characterisation, penetration mechanism, and therapeutic applications of ethosomal drug delivery systems are all covered in this review. Ethosomal systems have been the focus of ongoing research, which indicates that these carriers could be effective drug delivery vehicles in the form of gels, patches, and creams when combined with penetration enhancers. To improve the stability of the ethosomal system, however, more extensive research is needed. The synthesis and characterization of ethosomal gel drug delivery is the aim of this review.

Keywords: *Atopic Dermatitis, Ethosomes, Transdermal Drug Delivery, Skin Penetration, Phospholipids.*

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I. INTRODUCTION

- *Drug Delivery:*

The optimization Regarding medication administration by means of human skin is important in modern therapy. Clearly, the topical route of drug delivery for treating skin diseases offers an attractive alternative to the conventional drug delivery methods of oral administration/injection and it is becoming a most innovative research area in drug delivery[1]. A skin disease like acne, is very common and normally happens to everyone once in their lifetime. The delivery of drugs is the process or system that carries a medication to its intended location in the body in order to safely and successfully provide a therapeutic effect. Many medicinal substances, such as hormones, antibiotics, antifungal, anti-inflammatory, and anti-acne medications, can be encapsulated in ethosomal systems.

- *Different Medication Administration Based on Carries Core Material:*

Drug delivery systems can be categorised according to the drug's carrier core material. Phospholipids or lipids are used to encapsulate medications in lipid-based carriers such liposomes, ethosomes, and solid lipid nanoparticles. Nanoparticles, microspheres, and dendrimers composed of synthetic or natural polymers are examples of polymeric carriers. For targeted delivery, inorganic carriers such as magnetic, silica, and gold nanoparticles are employed. Cell-based carriers and viral vectors are examples of biological carriers. To enhance stability, targeting, and controlled medication release, hybrid carriers incorporate two or more materials.[2]

The type of carrier core material used to carry the therapeutic substance can be utilised to classify drug delivery systems. Drug loading, stability, release behaviour, targeting

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ability, and overall therapeutic efficacy are all greatly impacted by the choice of core material. Lipid-based, polymer-based, vesicular, inorganic, biological, and carbon-based[3] carriers are the general categories into which drug delivery methods are divided.

➢ *Ethosomal Delivery of Drugs*

Ethosomes are lipid-based vesicular carriers composed mainly of phospholipids and a high proportion of alcohol. Ethanol is most commonly employed as the alcoholic component, which is why these systems are known as ethosomes. The materials used in ethosomal formulations are generally regarded as safe for pharmaceutical applications.[4]

An method of ethosomal drug delivery consists of phospholipids, a substantial amount of ethanol, and water, making it an advanced approach for administering drugs transdermally. Ethanol improves medication penetration through the stratum corneum by disturbing the lipid skin's structure and by increasing the flexibility of the vesicles. As a result, ethosomes are capable of effectively transporting both water-soluble and fat-soluble drugs.[5]

Ethosomes are often described as ethanolic liposomes. They comprise soft, malleable vesicles formed from hydroalcoholic or hydroglycolic phospholipids, containing relatively high levels of alcohol, either alone or in combination such as ethanol with isopropyl alcohol.[6] The elevated ethanol content, typically ranging from 20% to 45%, distinguishes ethosomes from other vesicular systems. Their particle size can vary widely, extending from the nanometer scale to micrometer dimensions.

The concept of ethosomes was first introduced by Touitou in 1997 and her research team.

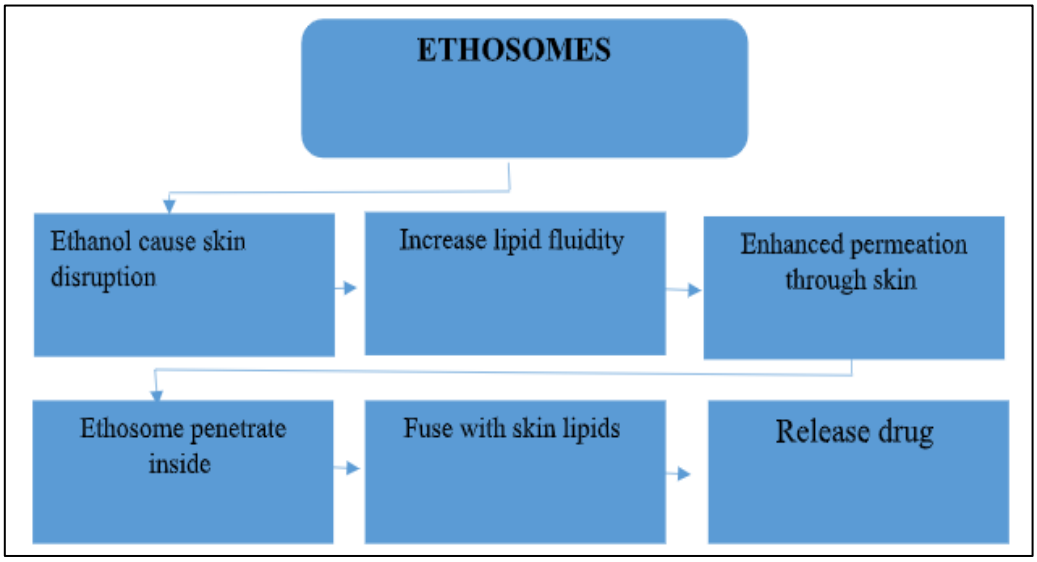

Fig 1 Schematic Representation of Drug Release of Ethosomal System

II. TYPES OF ETHOSOMAL SYSTEMS

Systems for ethosomal drug delivery are broadly classified into three main categories.

➢ *Classical Ethosomes*

Classical ethosomes are made of water, phospholipids, and high ethanol concentrations (up to 45% w/w). Due of their modest size and possessed a negative ζ-potential for increased efficiency without clogging, classical ethosomes were said to be preferable to Traditional liposomes for transdermal medication administration. Additionally, classical ethosomes showed improved penetration of the skin and stability profiles than classical liposomes[7]. Drugs found in conventional ethosomes had molecular weights ranging from 130.077 Da to 24 kda.

➢ *Binary Ethosomes*

Zhou et al. introduced binary ethosomes. In essence, we were produced by combining a distinct kind of alcoholic beverage with the conventional ethosomes[8]. The most popular Ethosomes in alcohols that are binary are isopropyl alcohol (IPA) and propylene glycol (PG).

➢ *Transethosomes*

Song et al. initially described transethosomes, the most recent creation of ethosomal systems, in 2012. The essential components of conventional ethosomes are included in this ethosomal system, together with an extra substance like a surfactant, or edge activator or penetration enhancer. These unique vesicles were created in an effort to combine the benefits of traditional ethosomes with Transfersomes, or deformable liposomes, in a single formula to produce transethosomes. Superior transethosomal characteristics over conventional ethosomes have been documented by a number of researchers. To create more distinctive ethosomal systems, Numerous kinds of penetration enhancers and edge activators were investigated.

It has been observed that transethosomes with molecular weights ranging from 130.077 Da and 200–325 kda can capture medications[9].

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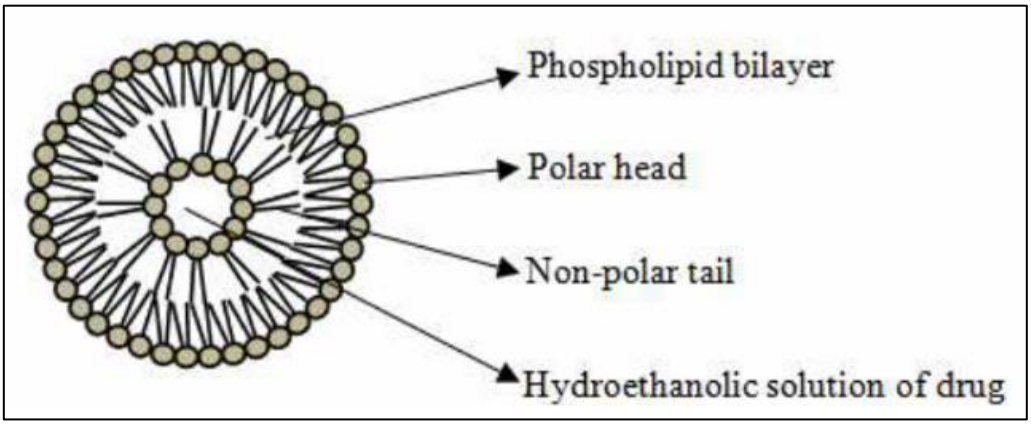

Fig 2 Structure of Ethosome

➢ *Ethosomal Drug Delivery System Benefits*

Although the exact mechanism is not completely understood, it varies in comparison with other Transdermal and dermal drug administration systems.[10-19]

- Improved penetration of the drug across the skin for efficient medication administration through the skin.
- The system enables the delivery of large biomolecules, such as peptides and proteins.The formulation is composed of non-toxic ingredients.
- High patient compliance is a result of the ethosomal medication being given in in a semisolid state (cream or gel).
- The ethosomal system can be commercialised and is non-invasive and passive.
- The pharmaceutical, veterinary, and cosmetic industries can all make extensive application of ethosomal drug delivery methods.
- High patient compliance: The ethosomal medication is given in a semisolid form (gel or cream), which results in high patient adherence. However, in contrast, patient compliance will be impacted by the relative complexity of iontophoresis and phonophoresis.
- Ethosomes enhance the skin's ability to absorb medications for dermal and transdermal administration. An extensive variety of medications, including peptides and protein compounds, can be delivered by ethosomes.
- Iontophoresis, phonophoresis, and other complex Systems for delivering drugs are more complex than this straightforward approach.
- Low risk profile: Since the ethosomal components' toxicological profiles are well-documented Within the scientific literature, technology poses no significant danger to the creation of new drugs.
- Products with exclusive technologies are highly appealing to consumers. Ethosomes are quite easy to manufacture and don't require complex technical investments.
- Pharmaceutical and cosmetic use of ethosome components are authorised.
- Ethosomes were designed to improve medicine distribution into the deep skin layers. distribution can be intended for systemic use or local distribution, based on how it is formulated.

➢ *Ethosomal Drug Delivery System Drawbacks*

- If the patient is allergic to ethanol or any of the ethosomal components, an allergic reaction can be detected.[20-25]
- Ethosomal carriers are primarily designed for transdermal delivery, whereas other carriers like lipid nanoparticles that are solid and polymeric nanoparticles can be applied through multiple administration routes.
- Ethosomal delivery is not intended to produce a rapid, bolus-type drug release; instead, it is generally designed to ensure controlled and continuous drug delivery over time.
- Planning, application, transportation, and storage should all be done with adequate caution because ethanol is combustible.
- Very low yield, therefore it could not be cost-effective.
- Product loss occurring during transfer from the organic phase to the aqueous medium.
- Sufficient drug solubility in both lipid and aqueous environments is necessary to enable movement through the dermal microcirculation and facilitate entry into systemic circulation.
- For the medication to be absorbed percutaneously, its molecular size must be suitable.
- Not all skin types will respond favorably to adhesive.
- Dermatitis or skin irritation brought on by drug delivery system excipients and penetration enhancers.
- If the shell is not properly stabilized, ethosomes may merge and disintegrate upon transfer into an aqueous medium.

III. INGREDIENT USED IN ETHOSOMAL MEDICATION SYSTEM

➢ *Phospholipids*

The vesicular bilayer structure is formed by phospholipids, which are the basic components of ethosomes. When distributed in an aqueous media, their hydrophilic and lipophilic characteristics enable them to self-assemble into vesicles.[7] Phospholipids including lecithin, egg phosphatidylcholine, and soy phosphatidylcholine are frequently utilised. These substances are safe for use in pharmaceuticals and are biocompatible and biodegradable. Ethosomes are a flexible drug carrier because phospholipids

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help encapsulate lipophilic medications inside the lipid bilayer and hydrophilic medications in water core.[26]

➢ *Ethanol*

The most significant and distinctive element of ethosomal systems is ethanol. It is found in comparatively high amounts, usually between 20% and 45%.[9] By upsetting the stratum corneum's lipid structure, ethanol increases the skin's permeability and permits deeper medication penetration. Additionally, it makes the phospholipid vesicles more flexible and fluid, allowing them to bend and fit through tiny skin pores. Ethanol also increases the stability of the formulation of ethosomal and enhances medication solubility.[27]

➢ *Water*

The ethosomal system's aqueous phase is made up of distilled or purified water. It offers the medium through which ethanol and phospholipids combine to form vesicles. Water also makes it possible for hydrophilic medications to become trapped inside ethosomes. Water quality and purity are crucial since contaminants can impact medication release behaviour, vesicle formation, and stability.[28]

➢ *Drug's Active Pharmaceutical Ingredient*

The medication used in an ethosomal system is a medicinal substance that is meant to function topically or transdermally. Many medications, such as corticosteroids, antibiotics, antifungals, anti-inflammatory medications, and anti-acne medications, can be administered via ethosomes.[29] Drugs that are lipophilic or hydrophilic can be effectively loaded into ethosomes. The medication should not significantly irritate the skin when applied topically and should be stable when ethanol is present.

➢ *Additional Alcohols and Co-Solvents*

Certain topical ethosomal formulations contain co-solvents or extra alcohols such isopropyl alcohol or propylene glycol. These elements contribute to increased epidermal penetration, vesicle stability, and drug solubility. When such elements are included, binary ethosomes are created, which may perform better than classical ethosomes.[30]

➢ *Enhancers of Penetration (Optional)*

Sometimes, especially in transethosomal systems, substances such as Tween 80, Span 60, or bile salts are used to improve medication penetration of the epidermis.[31]

➢ *Gelling Agents (for Application Topically)*

Ethosomal suspensions are made into gels for simple skin application using carbopol, HPMC, or xanthan gum.[32]

➢ *Preservatives, Antioxidants, and Stabilisers*

Stabilisers and preservatives may be added to topical ethosomal preparations to guarantee their stability and safety while being stored. Preservatives like parabens stop microbiological growth, while antioxidants like tocopherol and butylated hydroxytoluene (BHT) aid in preventing phospholipid oxidation. To prevent skin sensitivity, these substances are used in very little amounts.[33]

Table1 Additives Used in Formulation of Ethosomes

S.no	Ingredients	Examples	Application
1.	Phospholipid	Soya phosphatidyl choline Egg phosphatidyl choline Dipalmityl phosphatidyl choline Distearyl phosphatidyl choline	Vesicle forming agent
2.	Vehicle (alcohol)	Isopropyl alcohol Ethanol	skin penetration enhancer and provide softness to vesicle membrane
3.	Poly glycol	Propylene glycol	skin penetration enhancer
4.	Cholestrol	Cholestrol	provide the stability to vesicle membrane, as a stabilizer
5.	Polymer	Carbopol 934	Used as a gel former

IV. ETHOSOMAL DRUG DELIVERY SYSTEM FORMULATION METHOD

➢ Cold Method.
➢ Hot Method
➢ Classic Mechanical Dispersion Method
➢ Injecting ethanol and other Methods

• *Cold Method*

This technique is the most commonly employed and widely accepted approach for the preparation of ethosomes. Phospholipids, the drug, and other lipid components are ethanol-dissolved in a closed container at room temperature with continuous vigorous stirring. Propylene glycol or other polyglycols are then added while stirring is maintained. The resulting mixture is heated to 30°C using a water bath[34]. Additionally, water is heated in a different container to 30°C and subsequently incorporated into the mixture, followed by stirring for 5 minutes in a covered vessel. The vesicle size of the formulation of the ethosomal reduced to the required range by applying sonication or extrusion techniques[35].

• *Hot Method*

This technique disperses phospholipid in water by heating it to 40°C in a water bath until a colloidal solution is produced. Propylene glycol and ethanol should be carefully combined in a different container and heated to 40°C. Incorporate the organic phase into the aqueous phase. Depending on the drug's solubility, dissolve it in either ethanol or water. Probe sonication or the extrusion technique can be applied to reduce the ethosomal formulation's vesicle size to the desired degree[36].

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- *Classic Mechanical Dispersion Method*

Phospholipids are combined in a 3:1 ratio with organic solvents such as methanol and chloroform in a round-bottom flask. The solvent is eliminated by rotary evaporation until just a thin layer of lipid remains.[19] The film is hydrated using a drug-containing hydroethanolic solution. The mixture is gently stirred and rotated to create vesicles.[37]

- *Injecting Ethanol and Other Methods*

The organic phase's lipids are introduced into the aqueous phase while vigorously mixing. The final vesicle's size is determined by sonication and/or extrusion[38].

V. ETHOSOMAL DRUG DELIVERY SYSTEM EVALUATION

- Vesicles size and shape
- UV Spectroscopy study
- Measurement of drug loading capacity
- Entrapment efficiency measurement
- PH
- Spreadability
- Zeta potential
- In vitro drug release study

- *Vesicles Size*

The Horiba SZ-100 nano-particle analyser was used to measure the size distribution and size of the vesicle of ethosomes using the laser light scattering technique.[22] Particle size analysis was performed on the diluted samples at a temperature of 25°C and an angle of 90°.[39]

- *Vesicles Shape*

The Compound Microscope was used to investigate the ethosomes' shapes. The formulation was applied to the spotless glass slide, which was then covered with cover slip so that not a single bubble remained. After that, the slide was placed under a 100 X eye piece, and the compound microscope was used to analyse the sample. The pictures were gathered.[40]

- *UV Spectroscopy Study*

The solvent for the UV Spectroscopy investigation was cyclohexane. A 100 ppm stock solution was created by dissolving the extract in cyclohexane. The stock solution was diluted to provide the dilutions of 2 ppm, 4 ppm, 6 ppm, 8 ppm, and 10 ppm. The spectrum analysis was used to calculate the λmax.[41]

- *Measurement of Drug Loading Capacity*

The ethosomes were centrifuged for 30 minutes at maximum rpm in order to determine the drug loading capacity. The sediment and supernant were kept apart. Cyclohexane was used to dilute the sediment and supernant, and the diluted solutions were filtered.[42]Sediment and diluted supernant were both tested using UV spectroscopy.

$$D = \frac{U}{W}100$$

Where:

D stands for drug loading capacity.
W is the overall amount of medication consumed,
U is the amount in ethosomes.

- *Entrapment Efficiency Measurement*

Entrapment efficiency was measured using the same method as drug loading capacity. The following formula was used to determine the entrapment efficiency.[43]

$$EE = \frac{W-L}{W}100$$

Where:

W is the entire quantity of medication taken
L is the unentrapped drug

- *pH*

An essential component of a successful topical formulation was skin compatibility. A digital pH meter (Sigma-27 DP) was all that was needed to conduct the pH investigation.Prior to taking data in triplets, the pH meter was calibrated using buffer solutions with pH levels of 9.2 and 7.[44]

- *Spreadability*

Spreadability refers to the ability of a formulation to spread easily over the surface of application. It is an important parameter, as good spreadability ensures uniform application and improved therapeutic effectiveness. To evaluate spreadability, a specially designed apparatus is used in which two glass slides of standard size (6 × 2 cm) are taken. A measured quantity of the formulation is placed on one slide, and the second slide is placed on top so that the formulation is uniformly sandwiched between them over a length of 6 cm.[45]

- *Zeta Potential*

The net charge on the ethosomal surface can be measured using zeta potential. It was measured at 25.1°C using a zeta potential analyser (Horiba SZ 100 nanoparticle analyser). Zeta potential values were acquired straight from the measurement, which provides electrophoretic mobility.[46]

- *Drug Release Study in Vitro*

Cellophane membranes were used in the formulation's diffusion research. Phosphate buffer was utilised as the diffusion medium (6.8).Phosphate buffer (6.8) was added to the receptor chamber. The water jacket's temperature was kept at 37°C ± 0.5 by circulating hot water. The magnetic stirrer was used to constantly stir the dilution medium at the maximum r/min. The drug chamber was kept above the cellophane membrane, which was carefully placed on top of the receptor chamber.[47] The clamp was put in place to prevent the membrane from moving and the formulation from leaking. Using a syringe, the sample was extracted through the sample port during a 60-minute period.

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VI. ETHOSOMAL DRUG DELIVERY SYSTEM APPLICATIONS

There are several uses for ethosomes in medication delivery. They are mostly utilized to replace liposomes; transdermal medication administration is the preferred method. Ethosomes can be used to deliver hydrophilic and impermeable medications through the skin.

Ethosomes are also employed as antineoplastic, steroidal, antiasthmatic, and cerebrovascular medicines, as well as for the transcellular transfer of DNA and antiviral medications.A number of additional uses for ethosomes are detailed in

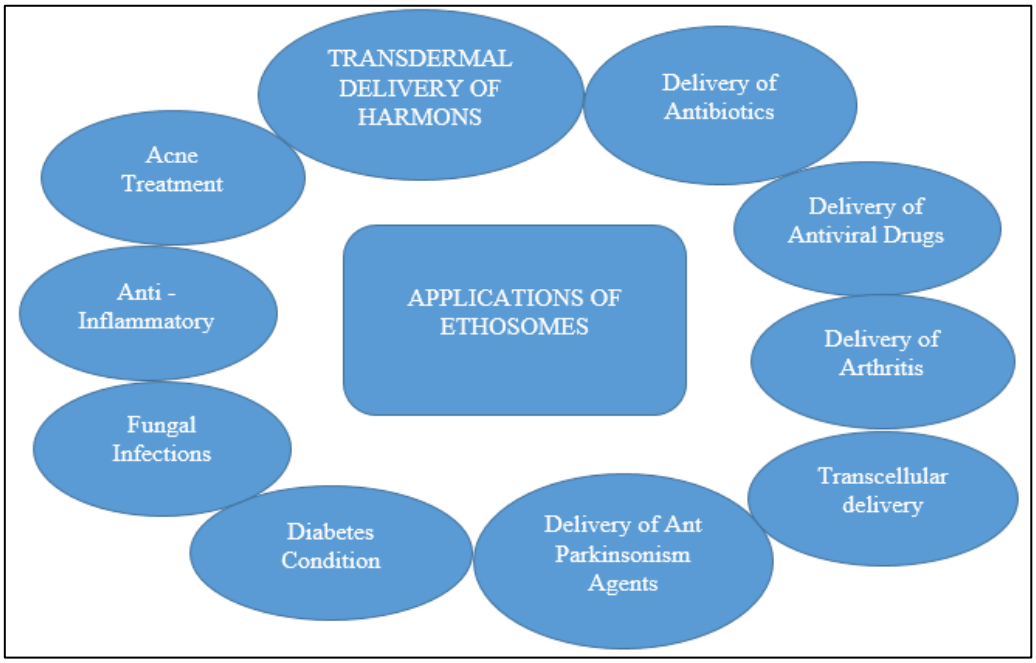

Fig 3 Ethosomal Drug Delivery System Applications

VII. ETHOSOMAL DRUG DELIVERY SYSTEM LIMITATIONS

- Higher levels are required. It is only allowed to use strong substances with a daily dosage of 10 mg or less.
- It is frequently designed as a means to accomplish rapid bolus type drug intake rather than providing moderate, continuous medication delivery.
- In both lipophilic and watery circumstances, the medication must be sufficiently soluble to pass through cutaneous microcirculation and go into the bloodstream.
- For percutaneous absorption, the drug's molecular size must be suitable.
- Not every type of skin will stick to an adhesive.
- It might not be economical.
- A poor yield.
- Excipients and enhancers used in methods for delivering drugs might cause dermatitis or skin irritation.

VIII. MARKETED REMEDES BASED ETHOSOMAL MEDICATION SYSTEM

Professor Elka Touitou of Hebrew University created and made the etherosome. Novel Therapeutic Technologies (NTT) at Hebrew University has demonstrated results in bringing a range of medicines based on ethosome delivery systems to market. The list of ethosome-marketed items is seen in

Table 2 Marketed Remedes Based Ethosomal Medication System

S.No	Products	ingredients	Narrative	Drug Action
1.	Cellutight EF (Hampden Health, USA)	Phospholipids caffeine, ethanol, and propylene glycol	A potent combination of ingredients in topical cellulite cream boosts metabolism and breaks down lipids	Increased skin penetration depth
2.	Body Shape (Maccabi CARE)	Ethosomal caffeine, phospholipids (soy phosphatidylcholine) Glycerin, ethanol, menthol,and methyl lactate	Based on a technology known as Ethosome, Gel Executive solidification reduces cellulite and stretches the skin.	deeper skin penetration

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3.	Nanominox (Sinere, Germany)	Water (hydro-alcoholic solution), phospholipids, ethanol, minoxidil (4%), and propylene glycol (optional)	The active components are delivered via ethosomes in Nanominox, which is made up of 4% minoxidil, adenosine, extract from Sophora flavescens, creatine ethyl ester, cepharanthine, B12, ethanol, and distilled water. While other Minoxidil solutions, such as those containing nanosomes and/or liposomes, recommend 2-4 hours for sufficient absorption, Nanominox absorbs for 10 minutes before washing your hair.	High penetration into the skin's deep layers and pilosebaceous targeting
4.	Osmotics Lipoduction Cellulite Cream (Osmotics, Israel)	Sodium Hyaluronate, Bupleurum Chinensis Extract, and Zingiber Zerumbet (Ginger) Extract	When used topically, the ethosomal cream is designed to reduce cellulite and improve fat metabolism.	Enhanced medication distribution through deeper skin layers
5.	Supravir cream (Trima, Israel)	Purified water, phospholipids (soy phosphatidylcholine), ethanol, and acyclovir (5%)	Acyclovir's formulation for treating herpes virus has a long shelf life and no stability issues; it remains stable at 25ºC for at least three years. Skin penetration tests revealed that even after three years, creams maintained their original ability to increase penetration.	Disruption of the membrane's lipid arrangement
6.	SkinGenuity (Physonics, Nottingham,UK)	Titanium Dioxide (4%), Octocrylene (10%), and Ethylhexyl Methoxycinnamate (7%).	Skin Genuity significantly eliminates those dimples by using a special combination of active anti-cellulite ingredients and the clever Ethosomes™ Delivery System to ensure good penetration. Additionally, it gives you the peachy thighs and dimple-free derrièr by firming and softening your skin with natural antioxidants and moisturizing substances.	High penetration into the skin's deep layers.
7.	Noicellex (NTT, Israel)	Phospholipids, ethanol, water, cholesterol, propylene glycol,and grape seed extract	Anti-cellulite topical creams	deeper skin penetration

IX. ETHOSOMES OVER THE PAST YEARS

- Over the past fifteen years, ethosomes have been employed as antiviral, antineoplastic, anti-diabetic, and steroidal agents in herbal medications. The best option for increasing The effectiveness of the treatment of antibiotics is topical administration.
- In addition to a number of adverse effects, conventional oral treatment causes several allergic reactions. Deep skin layers and subdermal tissues are less permeable to conventional external preparations. By releasing a sufficient amount of antibiotic into the skin's deeper layers, ethosomes can circumvent this issue.
- Ethosomes quickly pierce the epidermis, carry a significant amount of medication into the skin's deeper layers, and prevent infection at its source. Godin and Touitou created an ethosomal formulation filled with erythromycin and bacitracin for cutaneous and intercellular distribution with this goal in mind.
- The findings showed that ethosomal antibiotic formulation could be very successful and overcome the issues associated with traditional treatment.

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X. FUTURE PROSPECTS

- A new field of vesicular research for administering drugs transdermally has been sparked by the development of ethosomes. According to many reports, ethosomes have a bright future in enhancing the effectiveness of several medications' transdermal delivery
- Ethosomes have a bright future in terms of improving the effectiveness of transdermal distribution of different medicines. Research in this field will help doctors achieve more effective therapy by improving control over drug release in vivo. The non-invasive delivery of small, medium, and large-sized therapeutic molecules is made possible via ethosomes.
- Therefore, it shouldn't be long before the relevant medication formulation makes its way into clinics to be examined for general use.
- The corneum's stratum is the primary barrier layer for medication penetration in the administration of drugs transdermally. Numerous techniques have been discovered to improve the skin penetration of medications; the lipid vehicle-based augmentation strategy has garnered a lot of attention lately. Further research will be done to enhance medication delivery through lipid vesicles.
- A new field of vesicular research for transdermal medication administration has emerged with the introduction of ethosomes. Several papers claim that ethosomes have a bright future in enhancing the effectiveness of transdermal drug delivery.
- This conclusion is explained by the first clinical investigation of acyclovir ethosomal formulation. It is fairly simple to formulate ethosomal preparation in multiliter amounts. Thus, it is reasonable to conclude that ethosomal preparations have a bright future in the efficient transdermal administration of bioactive substances.

XI. CONCLUSION

Ethosomes represent a significant advancement In systems for vesicular drug delivery, particularly for transdermal and topical applications. Their unique composition, mainly phospholipids combined with a high concentration of ethanol, enables enhanced penetration of drugs throughout the corneum stratum, which is the major barrier to medication delivery through the skin. This distinctive property allows ethosomes to deliver a broad variety of therapeutic agents, including small molecules, peptides, proteins, and antiviral or antibacterial drugs, into deeper skin layers with improved efficacy.

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