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Ethosome: A Novel Carrier Used in Transdermal and Topical Drug Delivery

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ABSTRACT –
Novel lipid vesicular carriers with a comparatively high ethanol content are called ethosomal systems. These nanocarriers are specifically made to carry therapeutic substances across the skin and into deep skin layers with varying physicochemical features. Since their invention in 1996, ethosomes have been the subject of much research; new compounds were added to their original formula, resulting in the creation of various types of ethosomal systems. These new carriers are prepared using a variety of preparation methods. Ethosomal dispersions are added to gels, patches, and creams for stability and convenience of use. In addition to clinical trials, very varied in vivo models are employed to assess their effectiveness in dermal/transdermal distribution. This review system shows a thorough analysis of ethosomal systems, classifying them into three categories: classical ethosomes, binary ethosomes, and transethosomes, based on the components of each system. The formulation, size, ζ-potential (zeta potential), entrapment efficiency, skin-permeation properties, stability, and other distinctions between these systems are examined. The effects of ethosomal system components, preparation techniques, and their important roles in defining the final properties of these nanocarriers are reviewed in detail in this work. Additionally, ethosomal gels, patches, and creams—new pharmaceutical dosage forms—are highlighted. The paper also offers comprehensive details on the in vivo investigations and clinical trials carried out to assess these vesicular systems.

Keyword – Ethosome, Lipid vesicle, nanocarrier, transdermal

I. INTRODUCTION –

Assessing transdermal medication delivery to other traditional drug delivery methods, such as oral and parenteral drug delivery, reveals numerous benefits. One of the better ways to maintain steady plasma levels for extended periods of time is by transdermal injection, which may also be beneficial due to fewer frequent dosage schedules [1]. The benefits are stated as follows: better physiological and pharmacological response; avoidance of first pass metabolism; predictable and prolonged duration of action; reduced side effects and usefulness of short half-lives medications; and avoided fluctuations in drug levels. The primary issue with medication administration via the skin is the barrier function controlled by the stratum corneum [2]. The lipid layers that envelop the corneocytes that make up the stratum corneum are crucial to the stratum corneum's barrier qualities [3,4]. To enhance the quantity of medications applied topically, innovative drug delivery methods must be developed. These systems employ a variety of physical and chemical techniques to increase drug permeability through the stratum corneum, including iontophoresis, sonophoresis, microneedles, and penetration enhancers (surfactants and organic solvents) and biochemical techniques like liposomes, niosomes, transfersomes, and ethosomes [5].

For many years, the significance of vesicles in particle transportation and cellular communication has been widely acknowledged. The structure of vesicles has been better known by researchers in order to tag the vesicle for cell specificity and improve drug delivery within its chambers. The discovery of a vesicle derivative known as an ethosomes was one of the most significant developments in vesicle research [6].

Ethosomes –

"Ethanolic liposomes are ethosomes." Ethosomes are noninvasive delivery vehicles that allow medications to enter the systemic circulation and/or deeply penetrate the skin's layers.

These are pliable, squishy vesicles designed to improve the distribution of active ingredients. For a long time, the vesicles' significance in particle transportation and cellular communication has been well established. Vesicles would also make it possible to regulate the

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medication's release rate over an extended length of time. This would protect the medicine from immune responses and other removal mechanisms, enabling it to release the precise amount of the drug and maintain a consistent concentration for longer. The discovery of an ethosome, a vesicle derivative, was one of the most significant developments in vesicle research [7].

The well-known liposome drug carrier has been slightly modified to create ethosomes. Phospholipids, water, and relatively high concentrations of alcohol (ethanol and isopropyl alcohol) are found in lipid vesicles called ethosomes. Soft vesicles called ethosomes are composed of phospholipids, water, and ethanol (in larger amounts). Ethosomes range in size from tens of nanometers (nm) to microns (μ). They have a substantially higher transdermal flux and penetrate the skin layers more quickly [8]. Structure of ethosome mentioned below in fig1

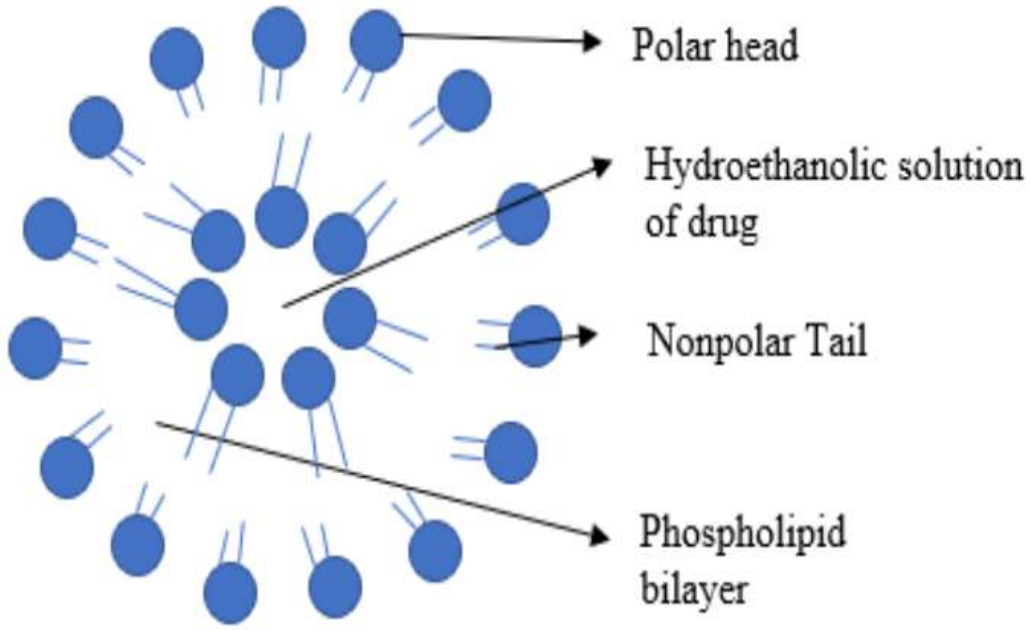

Fig 1 - Structure of Ethosome

Advantages of Ethosomes–

1. Drugs can be delivered intracellularly, transdermally, and via the skin more effectively when ethosomes are present.
2. Deliver a range of molecules, including proteins, peptides, and other macromolecules, as well as hydrophilic and lipophilic compounds with distinct physicochemical characteristics.
3. The ethosomes' constituent parts are widely acknowledged to be safe (GRAS), non-toxic, and permitted for usage in cosmetic and pharmaceutical applications.
4. Low risk profile: Since the toxicological profiles of ethosome features are well-established in the scientific literature, there is no danger associated with the large-scale medication development of ethosome structures.
5. The ethosomal system may be immediately marketed because it is non-invasive and passive.
6. A wide range of industries, including biotechnology, veterinary medicine, cosmetics, and nutraceuticals, can benefit from the use of ethosomal drug delivery systems.

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7. High patient compliance: Patients responded well to the ethosomal medication when it was given in a semi-solid form (gel or cream).
8. A simple drug delivery approach as opposed to sonophoresis, iontophoresis, and other complicated techniques.
9. Ease of industrial scale-up: The synthesis of ethosomes requires relatively little complex technical expenditure and is quite easy to make. It is convenient to prepare quantities in mili liters for ethosomal formulation.
10. Drugs can more effectively penetrate the skin due to ethosomes, which makes it possible for the medication to go to the intended location in the skin or blood.
11. It is discovered that medicines have higher entrapment efficiency than liposomes.
12. There is excellent stability over extended times.
13. Since alcohol functions as a natural preservative in ethosomes, no additional preservative needs to be added.
14. Manufacturing cost of ethosome is cheap [9,10]

Disadvantages of Ethosomes –

1. If a patient has an allergy to ethanol or any other ethosomal component, an allergic reaction can be diagnosed.
2. Ethosomal carriers are significant solely for transdermal application, in contrast to other carriers (solid lipid nanoparticles, polymeric nanoparticles, etc.) which can be employed for numerous routes.
3. Because ethanol burns easily, enough caution needs to be used when preparing, applying, transporting, and storing it.
4. Very low yield, therefore it might not be cost-effective.
5. Product loss that occurs while switching from organic to water media.
6. It is restricted to strong compounds that need a daily dosage of one or fewer [9,10].

ETHOSOMAL SYSTEM TYPES

1. Classical ethosomes –

A variant of classical liposomes, classical ethosomes are made of phospholipids, water, and high ethanol concentrations of up to 45% w/w. The superiority of classical ethosomes over classical liposomes for transdermal drug delivery was attributed to their smaller size and negative ζ-potential, which allowed for increased efficiency without clogging. Furthermore, classical ethosomes showed better skin penetration and stability profiles than classical liposomes. Drugs found in conventional ethosomes had molecular weights ranging from 130.077 Da to 24 k da.

2. Binary ethosomes -

It was basically made by mixing a different type of alcohol with the traditional ethosomes. The two ethosomes in binary alcohols that are most frequently utilised are propylene glycol (PG) and isopropyl alcohol (IPA).

3. Transethosomes –

Transethosomes, the most recent type of ethosomal systems, were identified for the first time in 2012. The fundamental elements of traditional ethosomes are included in this system, along with an extra ingredient like an edge activator (surfactant) or penetration enhancer. These unique vesicles were created in an effort to combine the benefits of traditional ethosomes with deformable liposomes (transfersomes) in a single formula to create transethosomes.

Transethosomes qualities have been reported by several researchers to be superior to those of regular ethosomes.

Various types of edge activators and penetration enhancers were studied to improve the ethosomal systems' characteristics. Drugs have been reported to be entrapped by transethosomes with molecular weights ranging from 130.077 Da to 200–325 kDa.[11]

Method of Preparation –

There are four ways to prepare and formulate ethosomes. All of the solutions are simple and cost-effective as they don't require complicated procedures or expensive equipment.

Cold Method –

This is the approach that is most frequently used to prepare ethosomal formulation. This approach involves using a mixer to vigorously agitate ethanol in a covered vessel at room temperature while dissolving phospholipid, medication, and other lipid components. While stirring, propylene glycol or another polyol is added. In a water bath, this combination is heated to 300C. After adding the water that has been heated to 300C in a different vessel, the mixture is covered and agitated for five minutes [12]. The methods of sonication and extrusion can be used to reduce the ethosomal formulation's vesicle size to the desired extent. Lastly, the mixture is refrigerated for storage [13,14]. Cold method explained in below fig 2.

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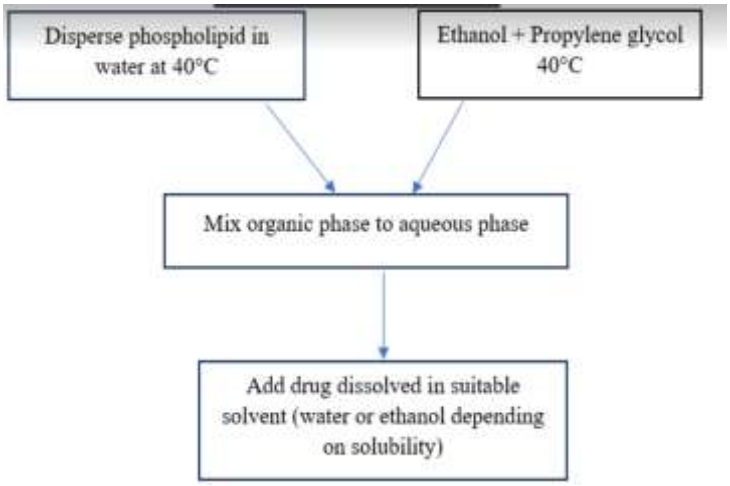
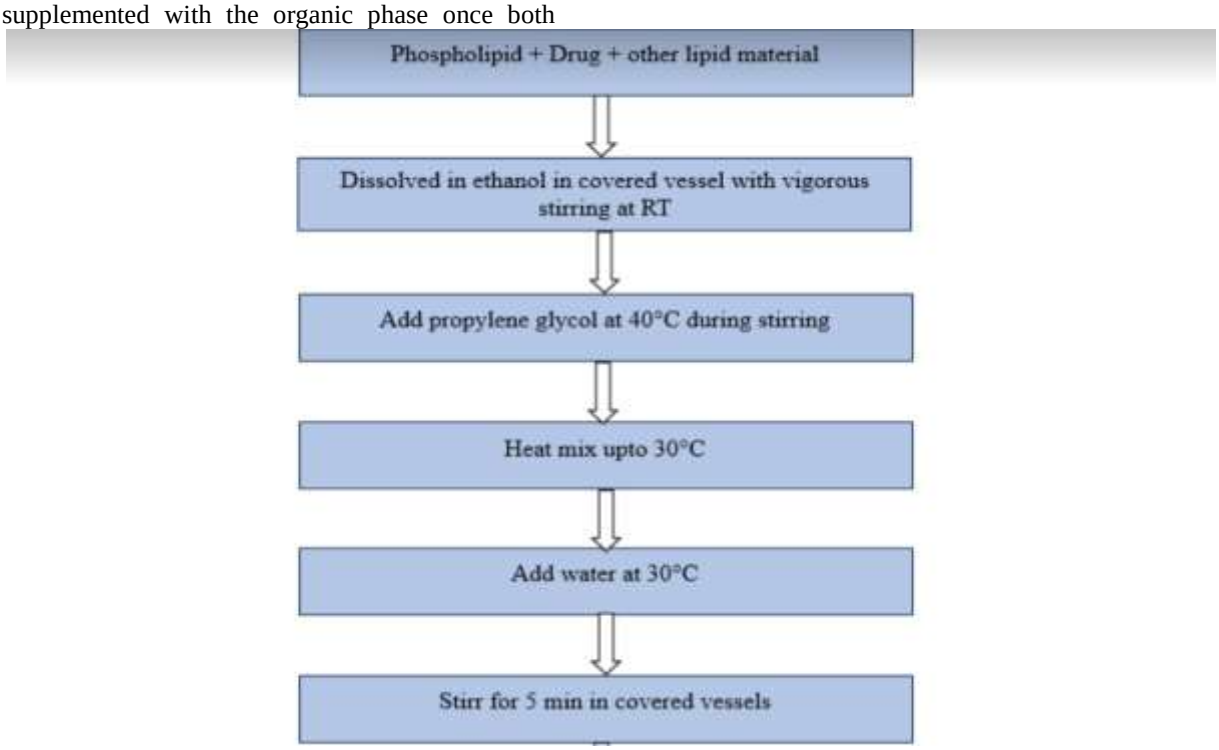


Fig 2 – Cold Method

Hot Method –

This process involves heating phospholipid in a water bath at 400C until a colloidal solution is produced, which disperses the phospholipid in the water. Ethanol and propylene glycol are combined and heated to 400 degrees Celsius in a different tank. The aqueous phase is supplemented with the organic phase once both mixes have reached 400C. Depending on whether the medication is hydrophilic or hydrophobic, it dissolves in either water or ethanol. Probe sonication or extrusion methods can be used to reduce the ethosomal formulation's vesicle size to the desired degree [15]. Hot method explained in below fig 3.



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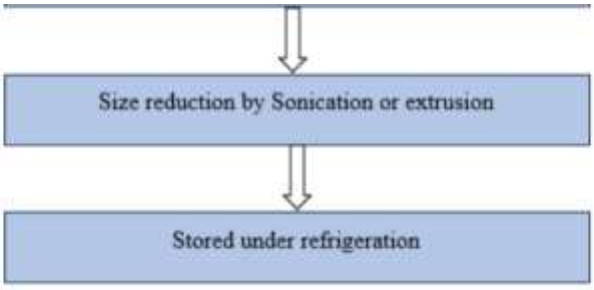

Fig 3 – Hot Method

Classic Method –

Drug and phospholipid dissolved in ethanol; the mixture is heated in a water bath to 30°C±1°C. The lipid mixture is added to double-distilled water in a fine stream in a closed vessel while being constantly stirred at 700 rpm. A hand extruder is used to push the resultant vesicle solution through a polycarbonate membrane three times in order to homogenize it [16].

Mechanical dispersion method –

In a round-bottom flask (RBF), soya phosphatidyl choline is dissolved in a combination of methanol and chloroform. To create a thin lipid coating on the RBF wall, the organic solvents are extracted using a rotary vacuum evaporator above the lipid transition temperature. Ultimately, the deposited lipid layer is cleared of any remaining solvent mixture by placing the contents under vacuum for a whole night. By rotating the RBF at an appropriate temperature, hydration is accomplished with varying concentrations of hydroethanolic mixture containing medication [17].

CHARACTERIZATION OF ETHOSOMES –

Vesicle size and Zeta potential

Using a computerized inspection system and photon correlation spectroscopy (PCS), dynamic light scattering (DLS) can be used to detect particle size and zeta potential.

Vesicle shape

Scanning electron microscopy (SEM) and transmission electron microscopy (TEM) can be used to visualize ethosomes. An ethosomal formulation with a diameter of 300–400 nm exhibited vesicular structure upon electron microscope visualization. The imprecise circular shape of the vesicles indicates that they appear to be alliable [18].

Entrapment efficiency

The ultracentrifugation method can be used to determine the drug's entrapment efficiency in ethosomes. The EE of the medication in the ethosomes is largely dependent on the chemical makeup of the lipid since the lipid creates a bilayer structure that precisely retains the drug. However, the medicine may be able to find room due to the lipid structure's defect. The vesicles are separated in a 4°C-maintained high-speed cooling centrifuge at 20,000 rpm for 90 minutes. By lysing the vesicles in methanol, separate the sediment and supernatant liquids to find the amount of drug in the sediment.

Surface tension measurement

Using a Du Nouy ring tensiometer, the ring method can be used to determine the surface tension activity of a medication in an aqueous solution.

Surface morphology study

Particle shape or surface morphology is influenced by various lipid types. On metallic stubs, lipid microparticle suspensions were applied. They were subsequently submerged in liquid nitrogen and vacuum-dried. The gold coating on the freeze-dried microparticles was consistent. Using a scanning electron microscope, its shape and surface characteristics are described.

Drug Content –

A UV spectrophotometer can be used to determine the drug content of the ethosomes. A modified high performance liquid chromatographic method can also be used to quantify this.

Transition temperature –

The DSC method is used to measure the Transition temperature (T) of vesicular lipids in duplicate in an aluminium pan at a rate of 10°C per

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minute, under a continuous nitrogen stream, and at a temperature range of 20º–300ºC.

Stability studies –

By preserving the ethosomal preparations at varying temperatures, such as room temperature (RT) of 25 ± 2°C, 37 ± 2°C, and 45 ± 2°C, over varying durations of time (1, 20, 40, 60, 80, and 120 days), one can assess the preparations' drug-retentive behaviour. Following a nitrogen flush, the ethosomal preparations were stored in sealed vials with a capacity of 10 mililiters. The size and shape of the vesicles were observed using DLS and TEM, which allowed for a quantitative assessment of the stability of ethosomes [19].

Skin permeation studies –

The technique known as Confocal Laser Scanning Microscopy (CLSM) is employed to ascertain the extent of Ethosome penetration. The ethosomes exhibit noticeably increased skin deposition, which may be the result of phospholipid and ethanol working together to provide a mechanism for transdermal and dermal distribution [20].

In vitro drug release study and Drug deposition study –

Franz diffusion cell with artificial or biological membrane, dialysis bag diffusion, can be used for in vitro drug release studies and drug deposition of ethosomal preparation [21].

EVALUATION OF ETHOSOME –

Vesicle Interaction Study by Scanning Electron Microscopy

It involves application of 0.2 mL of vesicle suspension on a membrane filter with a 50 nm pore size and inserting it into diffusion cells. While the lower side of the filter was in touch with the phosphate buffer saline solution (pH 6.5), the upper side of the filter was exposed to the air. After an hour, the filters were taken out and prepped for SEM research by fixing them for the entire night at 4°C in Karnovsky's fixative and then dehydrating them with ethanol solutions varying in volume (30%, 50%, 70%, 90%, 95%, and 100% v/v in water). Lastly, filters were subjected to a SEM examination (Leica, Bensheim, Germany) after being coated with gold.

Vesicle-Skin Interaction Study by TEM and SEM

From animals ultra-thin sections were cut (Ultracut, Vienna, Austria), collected on formvar coated grids and examined under transmission electron microscope. For SEM analysis, the sections of skin were mounted on stubs after dehydration using an adhesive tape and were coated with gold palladium alloy using a fine coat ion sputter coater. The sections were examined under scanning electron microscope [22].

Skin Permeation Studies –

Using a pair of scissors, the test animals' (rats') hair was carefully cut short (<2 mm), and a knife was used to separate the abdomen skin from the underlying connective tissue. After the skin was removed, it was placed on aluminium foil and the dermal side was carefully peeled off to remove any remaining fat or subcutaneous tissue. The diffusion cell's effective permeation area measured 1.0 cm2, while the receptor cell's volume measured 10 mL. A constant temperature of 32°C ± 1°C was maintained. There was phosphate buffer saline solution (10 mL, pH 6.5) in the receptor compartment. Between the donor and the receptor compartment, removed skin was positioned. The epidermal surface of the skin was treated with 1.0 mL of ethosomal formulation. At 1, 2, 4, 8, 12, 16, 20 and 24 hour intervals, samples (0.5 mL) were taken out of the diffusion cell through the sampling port and subjected to a high-performance liquid chromatography test for analysis [23].

Drug Uptake Studies –

100 µL of RPMI media was added to 24-well plates (Corning Inc.) to facilitate drug uptake into MT-2 cells (1×106 cells/mL). Following an incubation period of 100 µL of the drug solution in phosphate buffer saline solution (pH 7.4), ethosomal formulation, or commercial formulation, the drug content was analysed using an HPLC assay to evaluate the extent of drug uptake.

Statistical Analysis –

ANOVA was used to assess the statistical significance of all the data produced, and then a studentized range test was performed. The results were interpreted with a confidence level of P <.05, utilising PRISM software (GraphPad, Version 2.01, San Diego, CA) [24].

APPLICATION OF ETHOSOMES –

Ethosomes, which are vesicles with a high ethanol content, may penetrate the skin's deeper layers, they are frequently chosen for transdermal

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drug administration of hydrophilic and impermeable medications.

Table 1 – Application of Ethosome [36,37]

Principle ingredients	Formulation	Rationale of ethosomal delivery	Application
Matrine	Matrine Ethosome	Improves the percutaneous permeation	Anti-inflammatory
Erythromycin	Erythromycin ethosomes	Ethosomal erythromycin was highly efficient in eradicating S. aureus- induced intradermal infections	Anti - Bacterial
Methotrexate	Methotrexate ethosomes	Ethosomes showed favorable skin permeation characteristic	AntiCancer
5-aminolevulinic acid(ALA)	5-aminolevulinic Acid ethosomes	Significantly improved the delivery of ALA in the inflammatory skin.	Anti- psoriasis

Table 2 – Marketed product of ethosome [38,39]

Name of product	Uses	Manufacturer
Decorin cream	Anti-aging cream treating, repairing the visible aging signs of the skin including wrinkle lines, sagging, age spots, loss of elasticity, and hyper pigmentation	Genome Cosmetics, Pennsylvania, US
Noicellex	Topical anti-cellulite cream	Novel Therapeutic Technologies, Israel

Table 3 - Patents claimed for ethosomal formulations [40]

Title	Inventor	Patent no	Year	Results
Tretinoin ethosomes gel and preparation method	Hu Chunmei, Liu Yan2282', Wang Jing, Li Rong	CN104983675 A	2015	the prepared tretinoin ethosomes gel is an externally-used transdermal delivery preparation
Chinese medicinal ethosomal gel patch	Bu Ping; Hu Rong; Chen	CN103536700 (A)	2014	Easy in medication and convenient to

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Hormone delivery –

Numerous problems, including high first-pass metabolism, low oral bioavailability, and a host of dose-dependent adverse effects, are associated with oral hormone delivery. Furthermore, there are adverse effects associated with oral hormonal preparations that rely significantly on patient compliance. Every missed dose is known to increase the chance of treatment failure. By conducting a comparative analysis of transdermal delivery of testosterone-loaded ethosomes (Testosome) as compared to transdermal testosterone patch (Testoderm patch, Alza) through rabbit pinna skin, Touitou et al. demonstrated the ability of ethosomes in hormonal delivery. The results showed approximately 30-times higher skin permeation of testosterone from ethosomal formulation.

The amount of medication deposited in the ethosomal formulation was significantly (p50.05) higher, measuring 130.76 ± 18.14 and 18.32 ± 4.05 mg for Testosome and Testoderm, respectively, after 7 hours. When Testosome was used instead of Testoderm, the area under the curve (AUC) and Cmax of testosterone showed a considerable improvement. Thus, enhanced skin penetration and testosterone bioavailability from ethosomal formulation have been demonstrated in both in vitro and in vivo experiments [25,26].

Transcellular delivery –

In ongoing clinical trials, ethosomes have demonstrated their efficacy as a carrier and penetration enhancer for the transcellular administration of a variety of medicinal medicines. On the other hand, when incorporated in a hydroethanolic solution or traditional liposomes, hardly any fluorescence was seen. Following a 3-minute incubation period, it was clear that each of the three examined probes was intracellular [27].

Delivery of antibiotics –

A safer way to increase the therapeutic efficacy of those medications is through topical administration of antibiotics. Numerous allergic reactions are brought on by side effects and conventional oral medication. The permeability of conventional exterior formulations to subdermal tissues and deep skin layers is weak.

This problem can be avoided by using ethosomes to deliver enough antibiotics into the skin's deeper layers. Ethosomes may readily pass through the epidermis, transport large doses of medication into the skin's deeper layers, and eradicate infections from their source. The results of this investigation demonstrated that antimicrobial ethosomal formulation may be quite successful in resolving issues related to conventional therapy [28,29].

Cosmeceutical application of Ethosome –

Using ethosomes in cosmetics has the advantage of improving transdermal penetration, especially in elastic varieties, as well as improving the stability of irritating cosmetic compounds and reducing skin irritation. Moreover, the sizes and compositions of the gels are the primary factors that must be taken into account to realise these advantages of elastic gels for cosmetics [30,31,32].

Topical delivery of DNA –

Several environmental infections attempt to enter the body through the skin, which has evolved into an excellent barrier that is both immunologically active and gene-expressing. Based on the aforementioned information, one crucial application of ethosomes is the topical delivery of DNA molecules to activate genes in skin cells. Ethosomes have been suggested as potential carriers for gene therapy applications requiring temporary gene expression. The results also revealed that ethosomes may be used to successfully administer transdermal vaccinations. Therefore, the use of these dosage forms to provide immunisation agents becomes possible due to enhanced ethosomal skin penetration capacity [33,34,35].

Applications of ethosome are mentioned below in table 1.

Marketed product of ethosomes –

Ethosome Technology began to commercialise in 2000.

List of marketed products mentioned in below table 2.

Future perspective –

The stratum corneum serves as the primary barrier layer preventing drug penetration in transdermal administration. While many techniques have been found to improve medication penetration through the skin, the lipid vehicle-based augmentation strategy has garnered a lot of attention recently.

Research on using lipid vesicles to enhance medicine administration via the skin will not stop. The discovery of ethosomes has opened up new avenues for vesicular drug delivery research. According to several reports, ethosomes have great promise for improving the efficacy of

transdermal distribution of different medicines. More study in this field will enable physicians to better regulate drug release in vivo and increase the efficacy of the therapy. The non-invasive administration of tiny, medium, and large sized therapeutic molecules is made possible via ethosomes. This view is supported by the findings of the first clinical trial using the acyclovir-ethosomal formulation. It is quite simple to prepare ethosomal formulation in multiliter amounts. Therefore, it should not have taken long for the equivalent medication formulation to enter clinics where it would be studied before being used widely. Therefore, it stands to reason that ethosomal formulations have a bright future in terms of efficient dermal/transdermal administration of bioactive substances.
List of Patented products are mentioned below in table 3.

II. CONCLUSION –

Ethosomes were first developed about 20 years ago, these nanocarriers have demonstrated the unique ability to carry therapeutic substances with various physicochemical qualities via the skin for both local and systemic use. They are the non-invasive drug delivery vehicles that make it possible for medications to eventually enter the systemic circulation by penetrating the deep skin layers. Large molecules like peptides and protein molecules are delivered by it. Ethosomes can be designed to improve the penetration of active medications via the skin and are known for their ease of manufacture, safety, and effectiveness. Ethosomes can significantly overcome the principal obstacle to transdermal medication delivery, which is the epidermal barrier.

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The review paper was combined efforts and contribution of all authors.

Conflict of Interest –
The authors declared no conflict of interest.

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