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REVIEW ON ETHOSOMES: A NOVEL DRUG DELIVERY SYSTEM

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ABSTRACT

Transdermal drug delivery, self-contained, discrete dosage forms which, when applied to the intact skin, deliver the drug, through the skin at controlled rate to the systemic circulation. Ethosomes, noninvasive delivery carriers that enable drugs to reach deep into the skin layers or the systemic circulation made up of phospholipids, high concentration of ethanol and water. The main disadvantage of transdermal drug delivery system is the poor penetration of the most compound in to the skin. The upper most layer of the skin stratum corneum is the is the main barrier. Ethosomes and liposomes are the main approaches for enhancing the skin penetration of drugs and lot of cosmetic chemicals through vascular system. Ethosomes are the phospholipid based elastic nanovesicles and it has high content of ethanol about (20 – 50%). Ethanol is also known as an effective permeation enhancer and had been added in the vascular system to prepare elastic nanovesicles. It interacts with polar head group region of the lipid molecule causing the reduction of the melting point of stratum corneum (SC) lipid and enhances lipid fluidity and also enhances cell membrane permeability. If we compare with other conventional liposomes and hydroalcoholic solution, the ethosome system are more efficient in delivering substance through the skin in term of quality and depth. This review article summarizes structure, advantages, disadvantages, composition and mechanism of drug penetration method and of preparation, evaluation and applications of ethosomes.

KEYWORDS: Novel drug delivery system, Ethosomes, Stratum corneum, Percutaneous absorption, Penetration enhancer.

1. INTRODUCTION

Transdermal medication and vaccine delivery is a viable alternative to the oral and parenteral methods of administration. It is possible to avoid "first-pass" inactivation by the liver, reduce the likelihood of gastrointestinal irritation, provide consistent absorption of medication over long periods of time, reduce the frequency of dosing, which improves adherence, and lower the frequency of adverse effects by avoiding high serum drug peaks through transdermal drug delivery (Touitou *et al*., 2022) Following a thorough assessment of various transdermal formulations now on the market, as well as new data from a number of current clinical studies data from a number of current clinical studies for devastating human illnesses, it is abundantly obvious that this method of administration is very cost-effective. Aside from safety and effectiveness, improved patient acceptance of transdermal medications has resulted in unprecedented interest in innovative drug delivery methods to guarantee that maximal pharmaceuticals are receptive to administration by this route. (Verma and Pathak; 2022) (Zhang et al., 2012) Understanding the anatomy of skin is critical for designing a better transdermal delivery method. The skin is the largest organ in the body. The average adult body's skin is around 20 square feet in area and receives about one-third of total accessible blood. The human skin protects the body's interior structure and organs. It has a total surface area of around 1.8 m2 and an average thickness of 0.00394 in (0.1 mm), contributing for 15–18% of total body weight. The epidermis, dermis, and fat layer are the three layers of skin (also called the subcutaneous layer). The epidermis is the skin's outermost layer, which act as a waterproof barrier and determines our skin tone. The dermis, which lies under the epidermis, are made up of tough connective tissue, hair follicles, and sweat glands, whereas the deeper subcutaneous tissue (hypodermis) are made up of fat and connective tissue. (Sachan and Bajpai; 2012) It defends the organism from external influences and controls heat and water loss from the body. Figure 1. (Cevc; 2004).

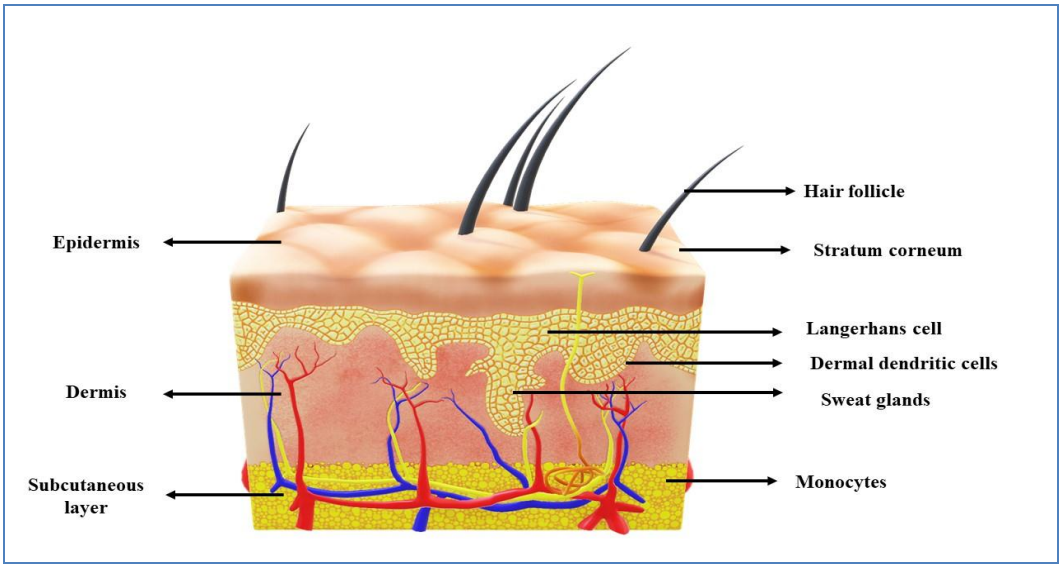

Figure 1: Structure of the skin.

The epidermis is the skin's outermost layer and is divided into four strata: the stratum germinativum (or basal layer), the stratum granulosum (the Malpighian layer), the stratum lucidum (the granular layer), and the stratum corneum (the horny layer). Stratum corneum (SC) are the epidermis's diverse outermost layer, measuring 10–20 µm thick. There are three kinds of cells in the epidermis: keratinocytes, melanocytes, and dendritic cells (DCs). DCs are also found in the dermis layer, where they aid in the identification of invading pathogens. The surface lipid coating and the SC form the contact with the environment, allowing drugs to be applied topically (Dayan and Touitou ;2000) (Elsayed *et al*.,2006) Depending on the location of the body, the dermis is 10–40 times thicker than the epidermis. They are a loose connective tissue matrix consisting of polysaccharides and protein (collagen and elastin) that are less metabolically active than the epidermis. This matrix is made up of nerves, blood vessels, hair follicles, sebaceous glands, and sweat glands (Elsayed *et al*.,2022) (Fang *et al*., 2009). The dermis also contains mast cells, macrophages, leukocytes, and endothelial cells from blood vessels. The dermis's role is to feed the epidermis and bind it to the subcutaneous tissue. Subcutaneous tissue acts as a container for fat synthesis and storage. It acts as a heat regulator in addition a shock absorber (Verma and Pathak; 2022) Skin serves as a barrier against mechanical, thermal, and physical harm, in addition nontoxic chemicals. Prevents moisture loss, UV radiation are reduced in its damaging effects. It acts as a sensory organ. Aids in temperature regulation. It participates in immune surveillance and synthesizes vitamin D3 (cholecalciferol) (Dhurve *et al*., 2015). Transdermal drug delivery system (TDDS) showed promising results when compared to oral drug delivery system because it eliminates gastrointestinal interferences and first pass metabolism of the drug. However, the main disadvantage of TDDS is that it encounters the barrier properties of the Stratum Corneum, which means that only lipophilic drugs with a molecular weight of 500 Da can pass through it (Kumaran et al., 2015) (Heeremans *et al*.,1995). Various strategies have been examined to promote medication penetration through the skin, including the use of chemical or physical enhancers such as iontophoresis, sonophoresis, and so on. Liposomes, niosomes, transferosomes, and ethosomes have also been shown to improve medication permeability over the stratum corneum barrier. Permeation enhancers improve the permeability of the skin, allowing medications to readily pass through it. Unlike traditional liposomes (Asbill et al., 2000), which are recognised primarily for delivering medications to the skin's outer layers, ethosomes can improve permeability through the stratum corneum barrier (Touitou et l., 2001) (Verma and Pathak ;2010). Ethosomes penetrate the skin layers faster and have much greater transdermal flow than regular liposomes (Jain et al.,2003) (Touitou et al., 2000).

1.1 Ethosomes

Ethosomes are soft, pliable ethanolic phospholipid vesicles designed for better active drug distribution. Because high ethanol concentrations disrupt skin lipid bilayer architecture, when integrated into a vesicular membrane, it enhances the vesicle's capacity to pass through the SC (Dubey et al., 2010). One of the most significant advancements in vesicle research was the discovery of a vesicle derivative known as an Ethosome (Manosroi et al., 2011). Although the lipid membrane is less densely packed than traditional vesicles, it has comparable durability and increases medication dispersion in SC lipids (Honeywell-Nguyen and Bouwstra;2005). This prolonged non-invasive delivery of medication molecules of varying sizes can also be used to transport cultured cells and microorganisms. Enhanced distribution of these bioactive compounds across the epidermal and cellular membranes through an ethosomal carrier presents various problems and opportunities for future study and development of

innovative better therapeutics (Dubey et al., 2007) (Dubey et al.,2007) (Pathan;2015).

Ethanolic liposomes, also known as ethosomes, are non-invasive lipid-based delivery vehicles that allow physiologically active substances to penetrate deeper epidermal layers and/or systemic circulation. These systems are mostly made up of phospholipids, a high concentration of ethanol (20–50%), and water Figure 2 (Panda et al.,2010). Previously, it was widely assumed that high alcohol concentrations destroyed lipid vesicular structure due to the interdigitation impact of alcohol on lipids. Following that, Touitou et al. (1997) revealed that phospholipid vesicles may coexist with a high concentration of ethanol, resulting in the development of soft, malleable, extremely fluid vesicles (Ainbinder and Touitou; 2005). Ethosomes size may be adjusted from tens of nanometers to microns (Sugino et al.,2010) (Zhou et al.,2010).

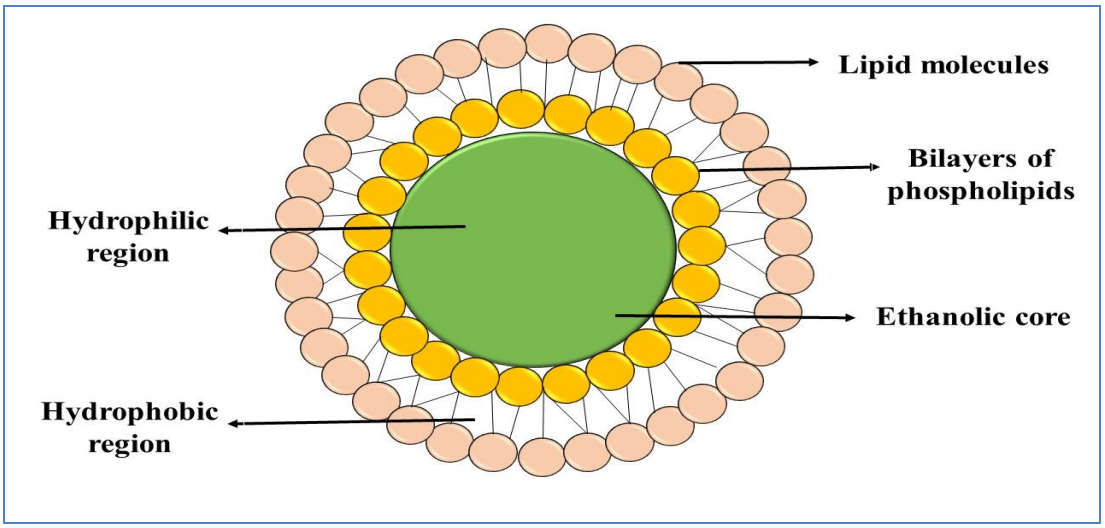

Figure 2: Structure of Ethosomes.

1.2 Composition of Ethosomes

Ethosomes are vesicular carriers made up of hydroalcoholic phospholipids with a high concentration of alcohols or their combination (Mishra et al.,2007). Table -1(Prasanthi and Lakshmi; 2012) (Godin and Touitou; 2003) (Zhang et al., 2012) (Zhaowu et al.,2009) (Zhou et al., 2010) (Akhtar and Pathak ;2012) (Bendas and Tadros;2007), show the various types of additives used in ethosomes preparations. Ethosomes are mostly comprised of phospholipids (phosphotidylcholine, phosph-atidylserine, and phosphatitidic acid), ethanol, and water. Non-aqueous phase concentrations vary from 22% to 70%. It is possible that the alcohol is ethanol or isopropyl alcohol. The high concentration of ethanol makes the ethosomes unique, as ethanol is known for its disturbance of skin lipid bilayer organization; therefore, when integrated into a vesicle membrane, it gives the vesicle the capacity to penetrate the stratum corneum. Furthermore, due to the high ethanol content, the lipid membrane is packed less tightly than typical vesicles but has equal stability, allowing for a more malleable shape and improving drug distribution ability in stratum corneum lipids (Touitou;2002) (Schreier and Bouwstra; 1994) The ability of ethosomes to adjust their size as a function of ethanol level is a distinguishing feature. For example, when the ethanol content increases from 20% to 50%, the size of 200 nm diameter vesicles consisting of 2% PC can be decreased by half. On the contrary, the size of the ethosomes is very slightly affected by PC concentration. An increase in PC concentration from 0.5 to 4% resulted in a two-fold increase in ethosome size (120 to 250 nm) (Dave et al., 2010) (Dubey et al., 2007) (Gevariya et al., 2009). Furthermore, the high ethanol concentration is to blame for the negative zeta potential. Because of the strong negative zeta potential, colloidal stability is greater than that of liposomal equivalents. As previously stated, the phospholipids in ethosomes are less densely packed than in ordinary liposomal bilayers, and the membrane is more permeable to hydrophilic/ionic solutes. As a result, ethosomes may be insufficiently adapted to entrap some hydrophilic solutes (Harish et al., 2009) (Patel et al., 2012). Despite the high ethanol content, the average size and size distribution of ethosomes normally remain stable at room temperature for at least two years. Ethosomes, unlike transferosomes, may be effectively delivered under occlusive circumstances using patches (Maxwell and Priya;2019) (Bahia et al., 2010).

Table 1: Different Additives Employed in Formulation of Ethosomes (Jain et al., 2005) (Verma and Fahr ;2004) (Jayaraman;1997) (Nan;2012).

S.No.	Class	Uses	Example
1.	Phospholipids	Vesicles forming component	Soya phosphatidyl choline, Egg phosphatidyl choline, Dipalmityl phosphatidyl choline, Distearyl phosphatidyl choline
2.	Alcohol	For providing the softness for Vesicle membrane as a penetration enhancer	Ethanol, Isopropyl alcohol
3	Glycerol	As a skin penetration enhancer	Propylene glycol, Transcutol RTM
4.	Cholesterol	For providing the stability to vesicle Membrane	Cholesterol
5.	Vehicle	As a gel former	Carbopol D934
6.	Dye	For characterization study	Rhodamine-123, Rhodamine red, Fluorescene Isothiocynate, (FITC)6-Carboxyfluorescence

1.3 Mechanism of Drug Penetration

The major benefits of ethosomes over liposomes are improved drug penetration. The mechanism of medication absorption from ethosomes remains unknown. Drug absorption divided into two stages:

1. Ethanol effect
2. Ethosomes effect

1. Ethanol effect

Ethanol improves permeation through the skin. The mechanisms underlying its penetration-enhancing action are well understood. Ethanol penetrates intercellular lipids, increasing the fluidity of cell membrane lipids. Decreasing the density of the cell membrane's lipid multilayer.

2. Ethosomes effect

The enhanced lipid fluidity of cell membranes produced by ethanol of ethosomes results in increased skin permeability. So, the ethosomes penetrate extremely readily into the deep skin layers, where they fuse with skin lipids and release the medicines (Heeremans et al., 1996).

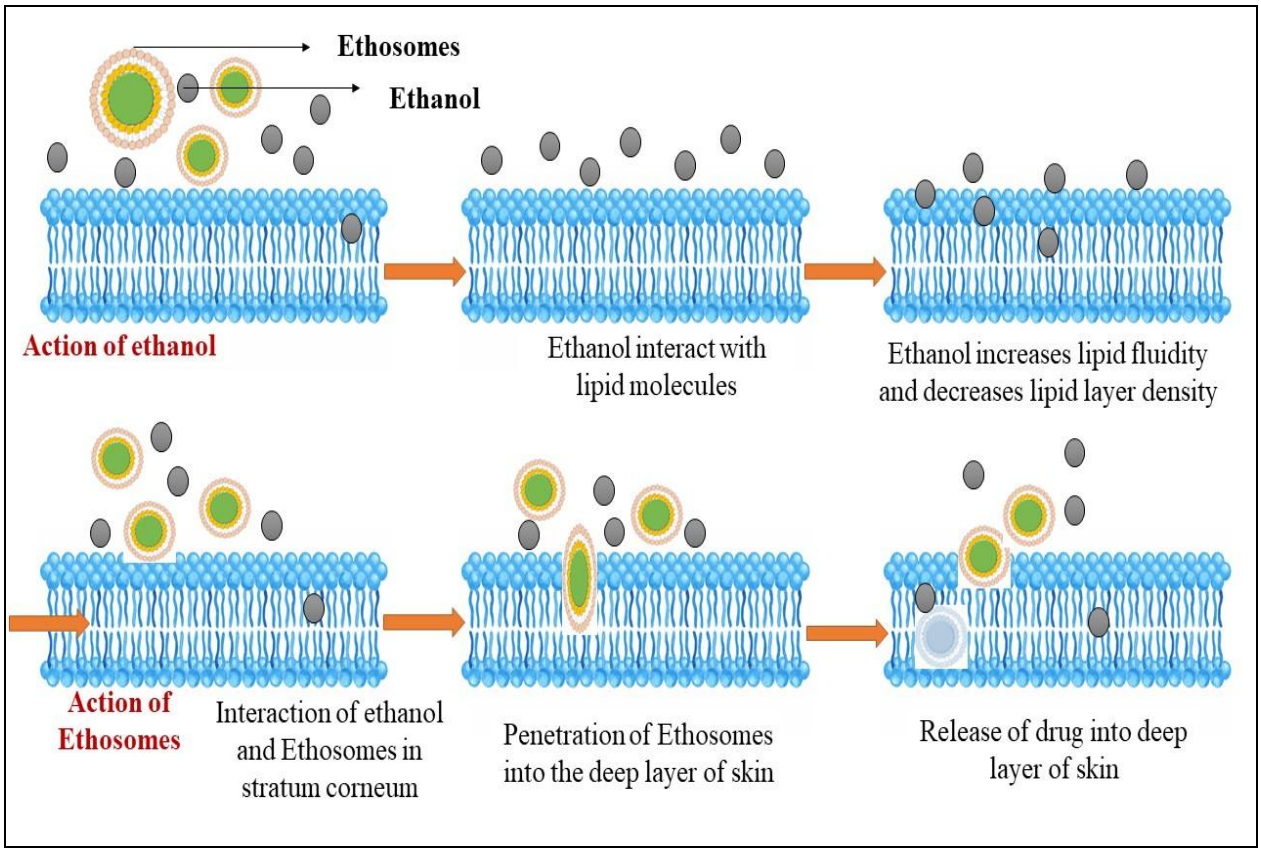

Figure 3: Proposed Mechanism for Skin Delivery of Ethosomal Systems.

Following topical application, ethosomes significantly improve penetration compared to pure ethanol, implying a synergistic process involving ethanol, vesicles, and skin lipids. In general, ethanol, aqueous ethanol, or ethanolic phospholipid solutions are more potent permeability enhancers than ethanol. It is suggested that ethosomes may operate as drug penetration enhancers and drug transporters across the SC (Hashem et al.,2011). Ethanol may increase the drug's solubility in the vehicle, disrupt the structure of the SC lipid bilayer, and increase its lipid fluidity. The subsequent mixing of phospholipids with intercellular SC lipids was found to improve skin permeability (Cortesi et al.,2009) (Chen et al., 2010) (Patel et al., 2009).

Advantages and Limitation of Ethosomal Drug Delivery

- In comparison to other transdermal & dermal delivery systems, Ethosomal drug delivery systems contain several advantages.
- Few advantages are; enhanced permeation of drug through skin for transdermal drug delivery.
- High patient compliance: The ethosomal drug is administrated in semisolid form (gel or cream) hence producing high patient compliance. Delivery of large molecules (peptides, protein molecules) is possible.
- Simple method for drug delivery in comparison to Iontophoresis and Phonophoresis and other complicated methods.
- Ethosomal drug delivery system can be applied widely in Pharmaceutical, Veterinary, Cosmetic fields. It contains non-toxic raw material in formulation.
- The Ethosomal system is passive, non-invasive and is available for immediate commercialization (Garg et al., 2017).

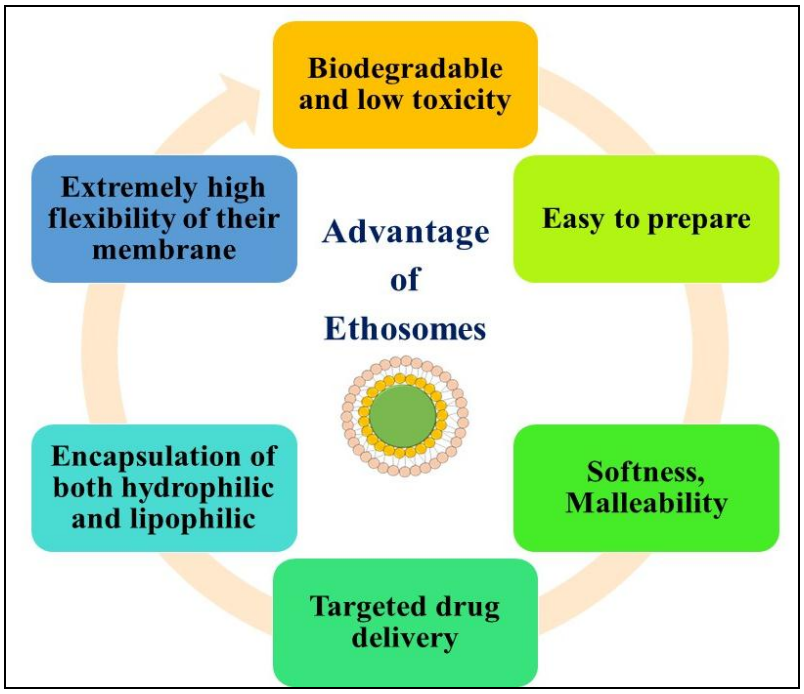

Figure 4: Advantage and Limitation of ethosomes.

1.5 Disadvantages of Ethosomal Drug Delivery

- They required High blood levels cannot be administered – limited only to potent molecules, those requiring a daily dose of 10mg or less.
- Adequate solubility of the drug in both lipophilic and aqueous environments to reach dermal microcirculation and gain access to the systemic circulation, in case if shell locking is ineffective then the ethosomes may coalescence and fall apart on transfer into water, Loss of product during transfer from organic to water media.
- May not be economical.
- Poor yield.
- The molecular size of the drug should be reasonable that it should be absorbed percutaneously.
- Adhesive may not adhere well to all types of skin.
- Ethosomal administration is not a means to achieve rapid bolus type drug input, rather it usually designed to offer slow, sustained drug delivery, Skin irritation or dermatitis due to excipients and enhancers of drug delivery systems, The main advantage of ethosomes over liposomes is the increased permeation of the drug (Jain et al., 2015) (Touitou and Godin; 2007) (Zhong;2012) (Kumar et al.,2016) (Ramadon et al.,2017) (Shahwal et al., 2011).

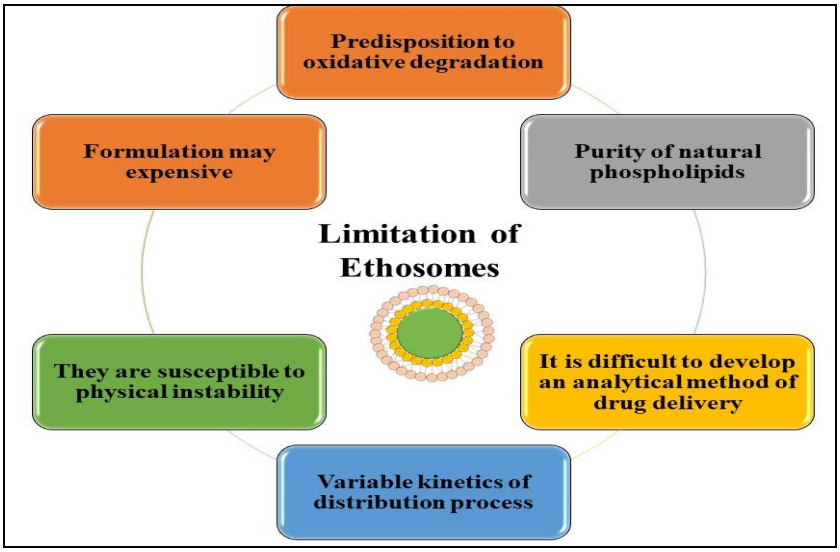

Figure 5: Limitation of ethosomes.

1.6 Methods of preparation of Ethosomes

Ethosomes preparation grounds on simple and easy scale up techniques without entailment of any sophisticated instruments at both pilot and industrial levels. Basic methods used for preparation of these vesicular carriers are as follows:

1. Cold method
2. Hot method

1. Cold Method

This is the most often used method for preparing ethosomal formulation. In this approach, phospholipids, drugs, and other lipid components are dissolved in ethanol in a covered jar at room temperature using a mixer and rapid agitation. During the stirring process, propylene glycol or another polyol is introduced. In a water bath, this mixture is heated to 300 degrees Celsius. Water heated to 300°C in a separate vessel is added to the mixture, which is then agitated in a covered vessel for 5 minutes. The ethosomal formulation's vesicle size can be reduced to the desired extent through sonication (Šentjurc et al.,1999) or extrusion (Touitou et al., 1998). After that, the formulation is refrigerated (Kaplun-Frischoff and Touitou;1997).

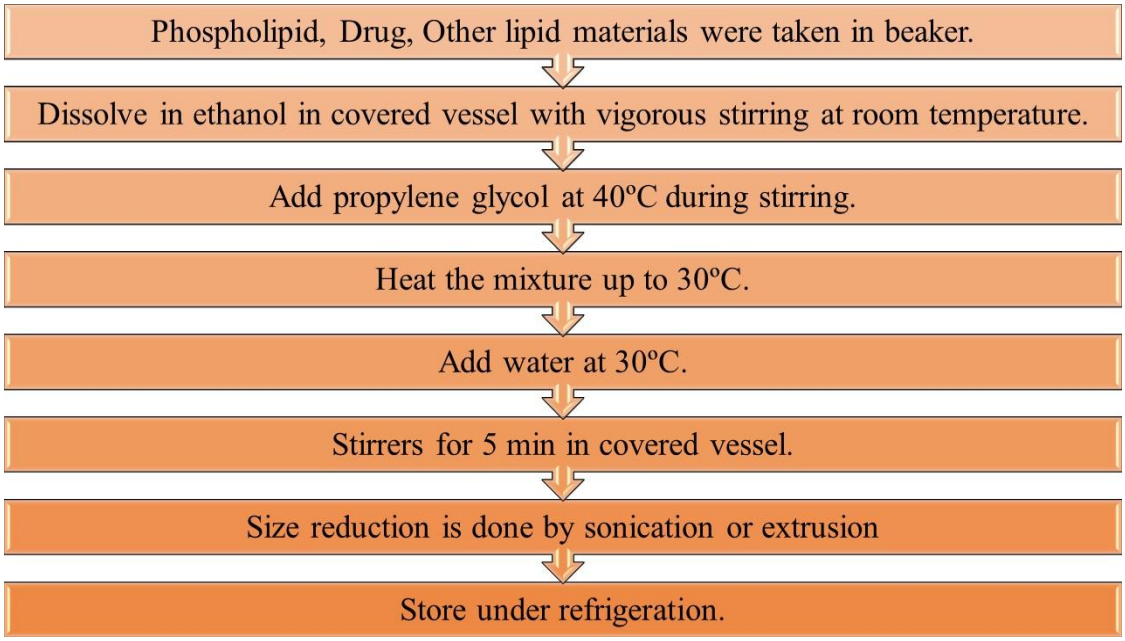

Figure 6: Cold Method for the Preparation of Ethosomes.

2. Hot method

When both combinations reach 400 degrees Celsius, the organic phase are introduced to the aqueous one. Depending on its hydrophilic/hydrophobic qualities, the medication gets dissolved in water or ethanol. The ethosomal formulation's vesicle size can be reduced to the desired extent by probe sonication or extrusion (Rao et al.,2008). This technique disperses phospholipid in water by heating it in a water bath at 400°C until a colloidal solution is formed. In a separate tank, ethanol

and propylene glycol are combined and heated to 400 degrees Celsius.

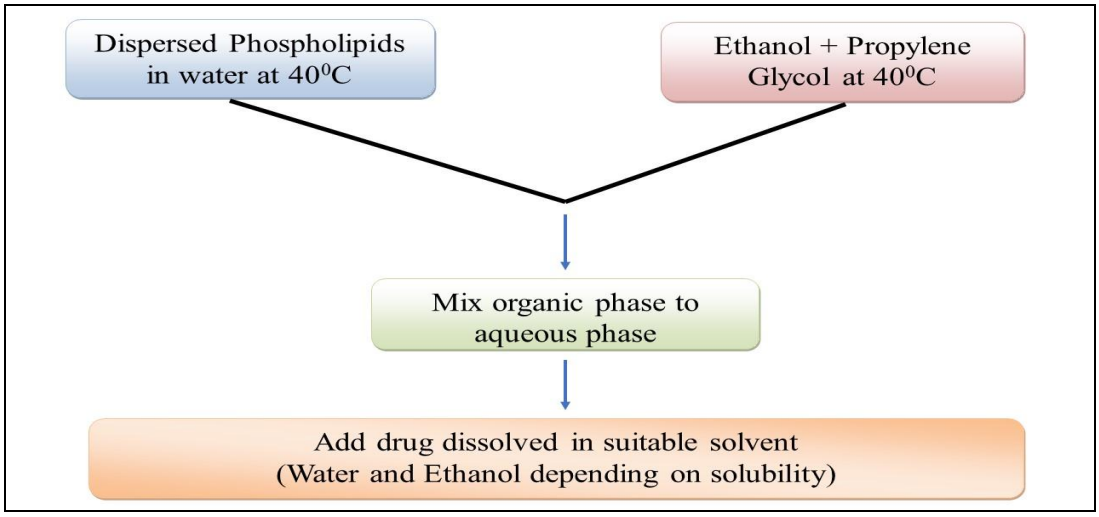

Figure 7: Hot Method for the Preparation of Ethosomes.

1.7 Method of Characterizations of Ethosomal Formulation

1. **Vesicle shape:** Ethosomes can be seen using transmission electron microscopy (TEM) and scanning electron microscopy (SEM). Electron microscopy reveals an ethosomal formulation with a vesicular structure 300-400 nm in diameter. The vesicles appear flexible, as evidenced by their irregular spherical form.
2. **Vesicle size and Zeta potential:** Dynamic light scattering (DLS) using a computerized inspection system and photon correlation spectroscopy can be used to detect particle size and zeta potential (PCS).
3. **Drug entrapment:** The ultracentrifugation technique may be used to assess the entrapment effectiveness of ethosomes.
4. **Transition Temperature:** Differential scanning Calorimetry may be used to estimate the transition temperature of vesicular lipid systems.
5. **Drug content:** The drug content of the ethosomes may be determined using a UV spectrophotometer. This might also be quantified using a modified high performance liquid chromatographic approach.
6. **Surface tension measurement:** The surface tension activity of drug in aqueous solution can be measured by the ring method in a Du Nouy ring tensiometer.
7. **Stability studies:** The stability of vesicles can be measured by analyzing their size and structure over time. DLS measures mean size, and TEM determines structural changes.
8. **Skin permeation studies:** The ability of the ethosomal preparation to penetrate into the skin layers can be determined by using confocal laser scanning microscopy (CLSM)

Table 2: Characterization of ethosomes (El Maghraby et al., 2000) (Fry et al., 1978) (Patel;1990) (Cevc et al.,1995) (Van den Bergh et al., 1997) (Toll et al., 2004) (Agarwal et al., 2019).

S.No.	Parameters	Methods	Importance
1.	Size and shape	SEM, TEM, DLS	Determine skin penetration
2.	Entrapment efficiency	Ultracentrifugation	Suitability of method
3.	Zeta potential	Zeta Meter	Stability of vesicles
4.	Drug content	UV, HPLC	Important in deciding the amount of vesicle preparation to be used
5.	Invitro dissolution	Franz diffusion cell	Determine the drug release rate from Vesicle
6.	Skin permeation	CLSM	Determines rate of drug transport through skin
7.	Stability studies	SEM, TEM, HPLC	To determine the shelf life of vesicle Formulation

1.8 Evaluation of Ethosome (Celia et al., 2011) (Groison et al., 2011)

1. Filter Membrane-Vesicle Interaction Study by Scanning Electron Microscopy It involves application of vesicle suspension (0.2 mL) to filter membrane having a pore size of 50 nm and placing it in diffusion cells. The upper side of the filter was exposed to the air, whereas the lower side was in contact with phosphate buffer

saline solution, (having pH 6.5). The filters were removed after 1 hour and were prepared for SEM studies by fixation at 4°C in Karnovsky's fixative overnight followed by dehydration with graded ethanol solutions (30%, 50%, 70%, 90%, 95%, and 100% v/v in water). Finally, filters were coated with gold and examined in SEM (Leica, Bensheim, Germany).

2. Skin Permeation Studies The hair of test animals (rats) was carefully trimmed short (<2 mm) with a pair of scissors, and the abdominal skin was separated from the underlying connective tissue with a scalpel. The excised skin was placed on aluminums foil, and the dermal side of the skin was gently teased off for any adhering fat and/or subcutaneous tissue. The effective permeation area of the diffusion cell and receptor cell volume was 1.0 cm2 and 10 mL, respectively. The temperature was maintained at 32°C ± 1°C. The receptor compartment contained phosphate buffer saline solution (10 mL of pH 6.5). Excised skin was mounted between the donor and the receptor compartment. Ethosomal formulation (1.0 mL) was applied to the epidermal surface of skin. Samples (0.5 mL) were withdrawn through the sampling port of the diffusion cell at 1, 2, 4, 8, 12-, 16-, 20- & 24-hour time intervals and analyzed by high performance liquid chromatography assay.

3. Stability Study: Stability of the vesicles was determined by storing the vesicles at 4°C ± 0.5°C. Vesicle size, zeta potential, and entrapment efficiency of the vesicles was measured after 180 days using the method described earlier.

4. Vesicle-Skin Interaction Study by TEM and SEM: From animals' ultra-thin sections were cut (Ultra cut, Vienna, Austria), collected on forever coated grids and examined under transmission electron microscope. For SEM analysis, the sections of skin after dehydration were mounted on stubs 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.

5. Vesicle-Skin Interaction Study by Fluorescence Microscopy: Fluorescence microscopy was carried according to the protocol used for TEM and SEM study. Paraffin blocks are used, were made, 5-µm thick sections were cut using microtome (Erma optical works, Tokyo, Japan) and examined under a fluorescence micro– Cytotoxicity Assay MT-2 cells (Lymphoid cell lines) were propagated in Dulbecco's modified Eagle medium (HIMEDIA, Mumbai, India) containing 10% fetal calf serum, 100 U/mL penicillin, 100 mg/mL streptomycin, and 2 mmol/L glutamine at 37°C under a 5% CO2 atmosphere. Cytotoxicity was expressed as the cytotoxic dose 50 (CD50) that induced a 50% reduction of absorbance at 540nm.

6. Drug Uptake Studies: The uptake of drug into MT-2 cells (1×106 cells/mL) was performed in 24-well plates (Corning Inc) in which 100 µl RPMI medium was added. Cells were incubated with 100 µl of the drug solution in phosphate buffer saline solution (pH 7.4), ethosomal formulation, or marketed formulation, and then drug uptake was determined by analyzing the drug content by HPLC assay**.**

7. HPLC Assay: The amount of drug permeated in the receptor compartment during in vitro skin permeation experiments and in MT-2 cell was determined by HPLC assay using methanol: distilled water: acetonitrile (70:20:10 vol/vol) mixture as mobile phase delivered at 1 mL/min by LC 10-AT vp pump (Shimadzu, Kyoto, Japan). A twenty-micro liter injection was eluted in C-18 column (4.6×150 mm, Luna, 54, Shimadzu) at room temperature. The column eluent was monitored at 271 nm using SPDM10A vp diode array UV detector. The coefficient of variance (CV) for standard curve ranged from 1.0% to 2.3%, and the squared correlation coefficient was 0.9968.

8. Statistical Analysis: Statistical significance of all the data generated was tested by employing ANOVA followed by student zed range test. A confidence limit of $P < .05$ was fixed for interpretation of the results using the software PRISM (Graph Pad, Version 2.01, and San Diego, CA).

1.9 Therapeutics application of Ethosomes

Ethosomes can also be used for many purposes in drug delivery. Ethosomes are mainly used as replacement of liposomes. Mainly the transdermal route of drug delivery is preferred. Ethosomes can be used for the transdermal delivery of hydrophilic and impermeable drugs through the skin. Various drugs have been used with ethosomal carrier (Cevc and Blume; 2001) (Talegaonkar et al., 2006).[75,76]

1. Pilosebaceous targeting: Hair follicles and sebaceous glands are becoming more recognised as potentially important components in percutaneous medication administration. Furthermore, much emphasis has been placed on using the follicles as transport shunts for systemic medication administration. Minoxidil is a lipid-soluble medication that is used topically to the scalp to cure baldness via pilosebaceous administration. Interest in pilosebaceous units has been directed towards their use as depots for localized therapy, particularly for the treatment of follicle-related disorders such as acne or alopecia (Soni et al.,1992)

2. Transcellular Delivery: (Touitou et al.,1994) used CLSM and FACS methods to demonstrate improved intracellular absorption of Bacitracin, DNA, and erythromycin in various cell lines. Better cellular absorption of anti-HIV drugs Zidovudine and Lamivudine by ethosomes compared to the marketed formulation revealed that ethosomes might be a promising therapeutic option for anti-HIV therapy.

3. Delivery of problematic drug molecules: Oral delivery of large biogenic molecules such as peptides or proteins and insulin is difficult because they are completely degraded in the GIT tract hence transdermal delivery is a better alternative. But conventional transdermal formulation of biogenic molecules such as peptides or protein and insulin has poor permeation. Formulating these above molecules into ethosomes

significantly increase permeation and therapeutic efficacy (Pandey et al.,2014)

4. In the treatment herpetic infection 5% acyclovir ethosomal preparation compared herpetic infections**.**

5. Transdermal Delivery of Hormones: Hormone delivery via mouth is linked with issues such as rapid first pass metabolism, limited oral bioavailability, and a variety of dose-dependent adverse effects**.** The risk of failure of treatment is known to increase with each pill missed.

6. Delivery of Anti-Arthritis Drug: Topical anti-arthritis medication administration is a superior choice for site-specific delivery and avoids the problems associated with standard oral treatment.

7. Delivery of Antibiotics: Topical delivery of antibiotics is a better choice for increasing the therapeutic efficacy of these agents. Conventional oral therapy causes several allergic reactions along with several side effects. Conventional external preparations possess low permeability to deep skin layers and sub dermal tissues. Ethosomes can circumvent this problem by delivering sufficient quantity of antibiotic into deeper layers of skin. Ethosomes penetrate rapidly through the epidermis and bring appreciable amount of drugs into the deeper layer of skin and suppress infection at their root. With this purpose in mind Godin and Touitou prepared Bacitracin and erythromycin loaded ethosomal formulation for dermal and intracellular delivery. The results of this study showed that the ethosomal formulation of antibiotic could be highly efficient and would overcome the problems associated with conventional therapy (Manosroi et al., 2015)

8. Cosmeceutical Applications of Ethosomes: The benefit of using ethosomes in cosmeceuticals is that they not only boost the stability of cosmetic chemicals and reduce skin irritation from irritating cosmetic chemicals, but they also improve transdermal penetration, especially in elastic forms. However, the compositions and sizes of the vesicles are the most important aspects to consider in order reaping the benefits of elastic vesicles for cosmeceutical applications (Agrawala and Ritschel ;1988)

9. Topical delivery of DNA: Many environmental pathogens attempt to enter the body through the skin. Skin therefore, has evolved into an excellent protective barrier, which is also immunologically active and able to express the gene. On the basis of above facts another important application of ethosomes is to use them for topical delivery of DNA molecules to express genes in skin cells. Touitou et al. in their study encapsulated the GFP-CMVdriven transfecting construct into ethosomal formulation. They applied this formulation to the dorsal skin of 5-week male CD1 nude mice for 48 hr. After 48 hr., treated skin was removed and penetration of green fluorescent protein (GFP) formulation was observed by CLSM. It was observed that topically applied ethosomes-GFP-CMV-driven transfecting construct enabled efficient delivery and expression of genes in skin cells. It was suggested that ethosomes could be used as carriers for gene therapy applications that require transient expression of genes. These results also showed the possibility of using ethosomes for effective transdermal immunization. Gupta et al. recently reported immunization potential using transfersomal formulation. Hence, better skin permeation ability of ethosomes opens the possibility of using these dosage forms for delivery of immunizing agents (Higo;2007) (Nair and Nair;2015) (Shabreen oghal and Sangeetha ;2020)

10. Marketed Product of Ethosomes (Ita ;2016) (Jondhalekar et al., 2017) (Singh et al.,2019) [85-87]: In 2000, the ethosomes technology began to Commercialize. There are only two companies which developed ethosomes products (Table 3).

Table 3: Marketed Products Based on Ethosomal Drug Delivery System.

S.No.	Name of product	Manufacturer	Uses
1.	Decorin cream	Genome Cosmetics, Pennsylvania, US	Anti-aging cream, treating, repairing, and delaying the visible aging signs of the skin including wrinkle lines, sagging, age spots, loss of elasticity, and hyper pigmentation
2.	Noicellex	Novel Therapeutic Technologies, Israel	Topical anti-cellulite cream
3.	Skin genuity	Physonics, Nottingham, UK	Powerful cellulite buster, reduces orange peel
4.	Supravir cream	Trima, Israel	For the treatment of herpes virus
5.	Cellutight EF	Hampden Health,USA	Topical cellulite cream, contains a powerful combination of ingredients to increase metabolism and break down fat
6.	Nanominox	Sinere, Germany	First Minoxidil containing product, which uses ethosomes. Contains 4% Minoxidil, well-known hair growth promoter that must be metabolized by sulfation to the active compound.

CONCLUSION

It is easy to deduce that ethosomes penetrate the skin better than liposomes. When compared to transdermal and dermal administration systems, ethosomes offered more benefits. They are noninvasive drug delivery carriers that allow drugs to reach deep skin layers before being delivered into the systemic circulation. It transports large molecules like peptides and protein molecules. Ethosomes are distinguished by their ease of manufacture, safety, and efficacy, and they may be modified for increased skin permeability of active medicines. The fundamental limiting element of transdermal drug delivery systems, the epidermal barrier, may be significantly overcome using ethosomes. Topically applied ethosomes can enhance the residence duration of pharmaceuticals or cosmetic chemicals in the stratum corneum and epidermis and inhibit systemic absorption of drugs or cosmetic chemicals; these features allow them to penetrate readily into the deeper layers of the skin and circulation. Ethosomal carrier introduces new problems and potential for the creation of innovative and better therapeutics. Furthermore, study in this field will allow for improved regulation of medication release in vivo as well as long-term safety data, making the therapy more successful.

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Conflict of interest

The authors confirm that this article content has no conflict of interest.

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