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A REVIEW ON ETHOSOMES - AS NOVEL DRUG DELIVERY SYSTEM

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ABSTRACT

Ethosomal system is a lipid vesicular nanocarrier that holds a high concentration of alcohols. This nanocarrier is design to deliver drugs to the dermis and transdermally with diverse physicochemical characteristics Since its delivery in 1996, ethosomes have been exposed to subsequent research resulted in the addition of new components to the original formula, which ultimately to the improvement of novel ethosomal system types. These new transporters are arranged by means of an assortment of strategies and portrayed through various boundaries, including vesicular size, zeta potential, Entrapment Efficiency, and skin pervasion. The ethosomes adequacy in dermal/transdermal organization is assessed by means of clinical examinations as well as a large number of in vivo models. Topical preparations, such as gels, frequently contain ethosomal dispersions. Patches, and moisturizers, because of their solidness and comfort. An in-depth discussion of outline of ethosomal frameworks from the angle of ethosomal types, starting with traditional ethosomes before moving on to transethosomes and binary ethosomes. What's more, this work gives an extensive outline of the parts of the ethosomal framework and they're in addition to highlighting the various methods, contribution to the final properties of ethosomes s of planning and the normal dose structures utilized as ethosomes' vehicles.

Keywords: Ethosomes; Transethosomes; Ethanol; Cold method; Skin permeation

INTRODUCTION

Transdermal drug delivery system as compared to oral drug delivery system offers or provides better alternative for the drug to achieve greater therapeutic effect which could be one of the advantageous points for the drug to remain for prolonged period of time. The outermost layer of the skin is the stratum corneum

which causes the hurdle to deliver the dugs of high molecular weight. There are various strategies which improve the permeation of the drug through the skin such as iontophoresis, sonophoresis, micro needle and lipid vesicular system such as emulsions, micro emulsions, lipid drug delivery and ethosomes drug delivery. Ethosomes deliver the drug to the stratum corneum by eminent and self-reinforcing deformability. For better

drug delivery into the skin researchers have understood the properties of vesicular structure. The vesicles are important for their cellular communication and particle transformation. Major advances in finding vesicle derivatives, known as an Ethosomes. Ethosomes saturate through the skin layers all the more quickly and have essentially higher transdermal motion in contrast with customary liposomes. [1]

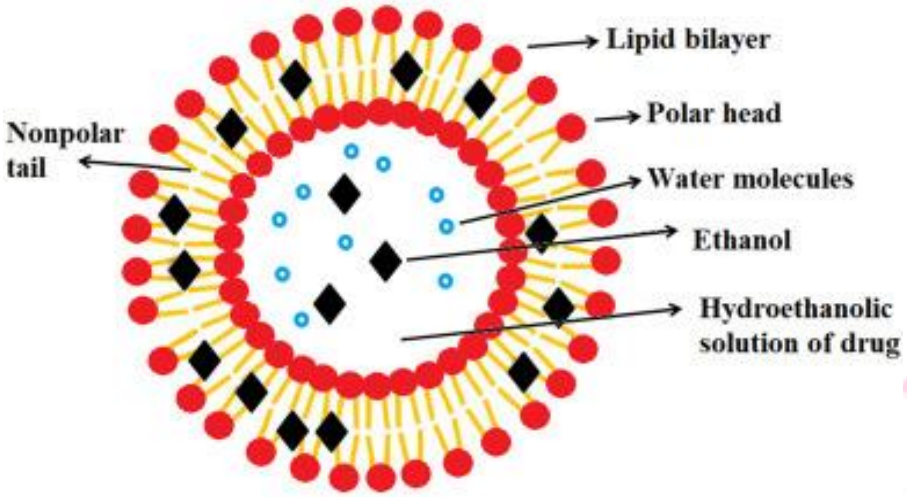

Figure. 1. Structure of Ethosomes

ETHOSOMES

A modified version of liposomes, which have shown to be effective transporters in the transdermal area, are ethosomes. Phospholipids, ethanol, and water are the major components of ethosomes, which are lipid vesicles. The ethanolic medication solution is contained in an aqueous core of ethosomes, and a lipid bilayer makes up the outer layer (Fig. 1). In order to deliver molecules (drugs, medicines, or active agents) to the deeper layers of the skin, the effect of ethanol fluidizing the phospholipid bilayers helps to the production of vesicles with a pliable shape. Ethosomes are stretchy phospholipid-based vesicles that contain between 20 and 45 percent ethanol and water. Ethanolic liposomes are called ethosomes. Ethosomes are non-invasive, flexible, pliable vesicular delivery systems that improve the distribution of active ingredients by allowing medications to reach deep skin layers and/or the systemic circulation. They are made up of phospholipids (phosphatidylcholine, phosphatidylserine, and phosphatidic acid), water, and a significant amount of ethanol. The high quantity of ethanol in ethosomes makes them special since ethanol is recognized for disrupting the organization of skin lipid bilayers. As a result, when ethanol is Incorporated into a vesicle membrane, the vesicle gains the potential to pierce the stratum corneum. Additionally, the lipid membrane is packed less firmly than in usual vesicles because of the high alcohol content. Although it is equally stable, it allows for a more pliable structure and enhances the ability of drugs to distribute via stratum lipids. [2]

Although the lipid membrane is less densely packed then traditional vesicles, it has comparable durability and increases medication dispersion in SC lipids. 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 and ethosomal carrier

presence various problems and opportunities for future study and development of innovative better therapeutics.

Ethaonolic 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%). [3]

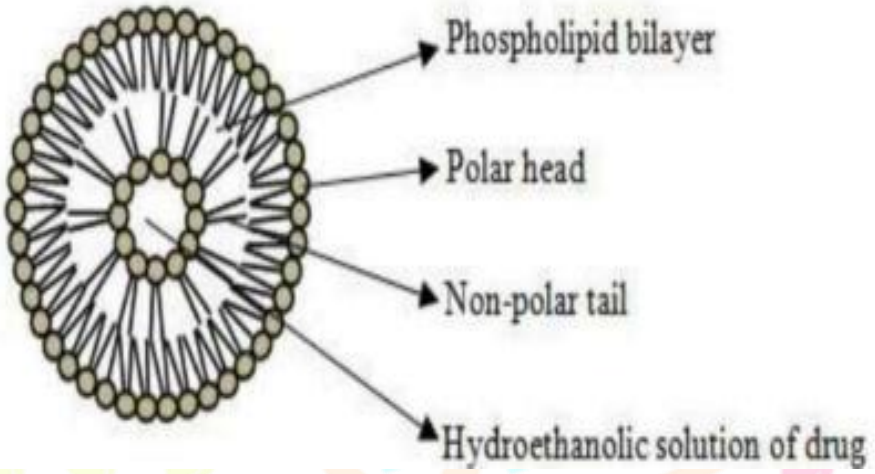

Figure. 2. Ethosomes

TYPES OF ETHOSOMES

The known ethosomal system could be arranged into three unmistakable sorts as per the parts integrated into their equation in particular, excustomary ethosomes, binary ethosomes, and transethosomes as displayed in Figure 3: Different types of ethosomal systems.

1.Traditional ethosomes conventional or classical ethosomes

They are the first evolved ethosomal framework that altered the liposomal structure through the fuse of a Classification of Ethosomal System. The known ethosomal system could be arranged into three unmistakable sorts as per the parts integrated into their equation in particular, excustomary ethosomes, binary ethosomes, and transethosomes as displayed in Figure-3: Different types of ethosomal systems. Traditional ethosomes conventional or old style ethosomes are the at first evolved ethosomal framework that altered the liposomal structure through the fuse of a generally high measure of ethanol, up to 45%, alongside phospholipids and water parts. The potential of traditional ethosomes was great. for transdermal medication conveyance when contrasted with conventional liposomes predominantly due with their more prominent entanglement effectiveness, more modest size, and negative surface charge. Moreover, the ethosomal framework uncovered more noteworthy solidness in correlation with the exemplary liposomes.

2.Binary Ethosomes

This type of ethosomal system was first described by Zhou et al. and included change of the conventional ethosomes by means of the expansion of various types of liquor. The double ethosomes have been

concentrated on in various examination that generally utilized propylene glycol/ethanol combination or isopropanol/ethanol combination.

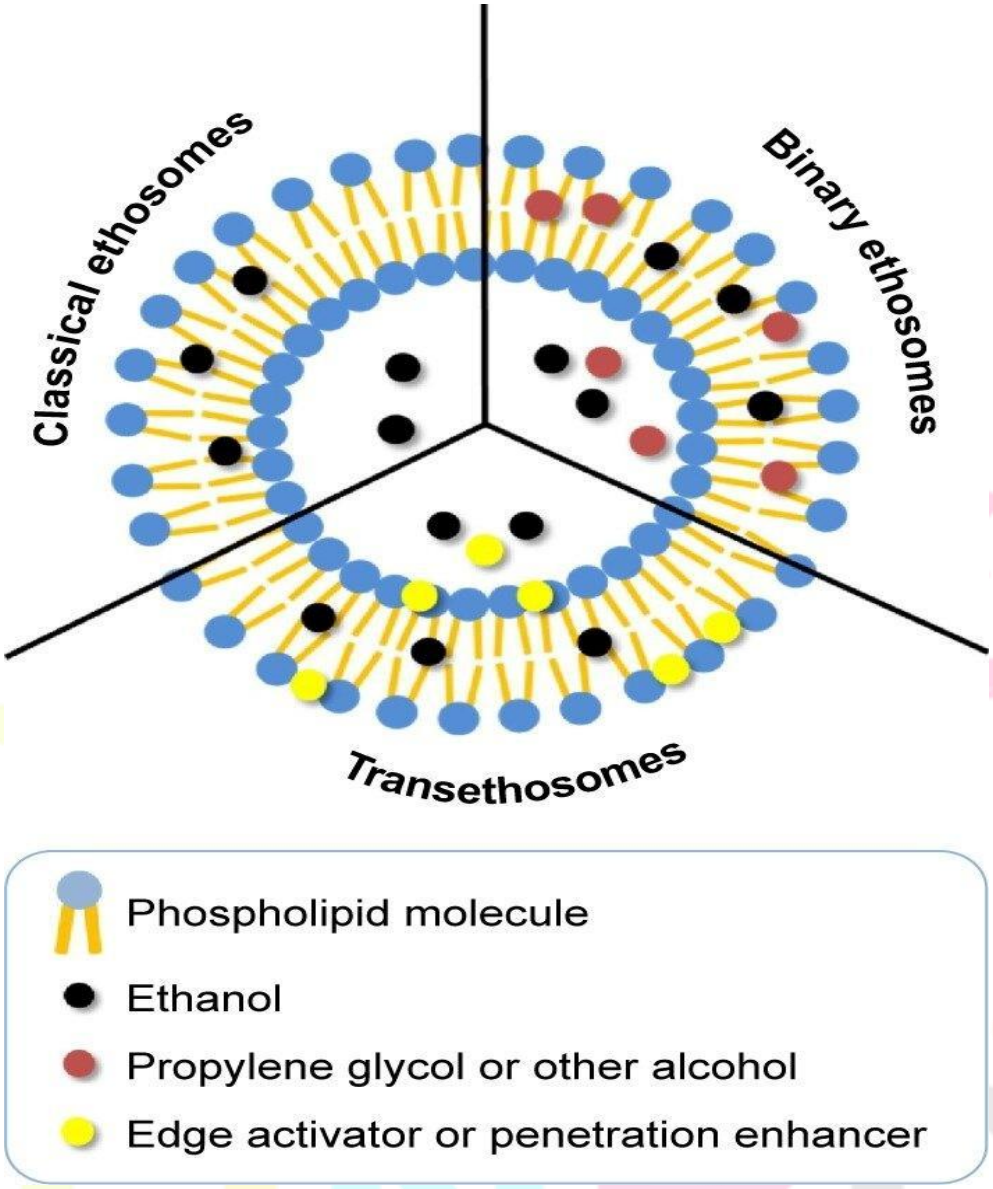

Figure. 3 Types of ethosomes

3.Transethosomes

Transethosomal system is the latest generation of ethosomes that was first described by Song et al. This framework has similar parts as customary ethosomes, however with the incorporation of a penetration enhancer or edge activator into the vesicular structure. The advancement of these vesicles was a preliminary to blend the advantages of customary ethosomes with transfersomes (versatile liposomes) into a solitary vesicular transporter that was demonstrated its huge prevalence over the work of art ethosomes as detailed by a few investigations. [4]

METHODS OF PREPARATION

Preparation of ethosomes grounds on quick and easy scale up techniques without requiring any complex pilot- and industrial-level instruments. Ethosomes preparation includes two simple "cold" and "hot" methods.

1.Cold method

This is one of the most commonly used ethosome preparation methods, consisting of two basic and simple setups. In the first setup, phospholipid and other lipid material is dissolved by intense stirring in ethanol at room temperature with the use of mixer such as Heidolph mixer with continuous addition of polyols such as propylene glycol etc. With constant stirring followed by heating at 30 0C in water bath. In the second setup, water is to be heated at 30 0C in a separate vessel, both mixtures (obtained from first and second setup) are to be blended together following 5 min stirring in a covered vessel. Using sonication or extrusion process, the vesicle size of ethosomal formulation can be reduced to desire extend. Finally, the formulation is stored under refrigeration.

2.Hot method

This method consists of dispersion of phospholipid in water by heating in a water bath at 40 0C until a formation of a colloidal solution. In a separate vessel, ethanol and propylene glycol are mixed and heated to 40 0C. If both mixtures exceed 400C the aqueous phase is added to the organic phase. Depending on their hydrophilic / hydrophobic properties the drug is dissolved in water or ethanol. Using probe sonication or extrusion process, the vesicle size of ethosomal formulation can be diminished to the extent of desire.

3.Classic mechanical dispersion method

Dissolve phospholipid in an organic solvent, or in a round bottom flask (RBF) mixture of organic solvents. Using a rotary vacuum evaporator above lipid transition temperature to remove the organic solvent to create a thin lipid film on the RBF wall; Traces of the solvent should be separated from the accumulated lipid film by leaving overnight in vacuum. Hydrate the lipid film with the drug's hydro ethanol solution by spinning the flask with or without periodic sonication at the correct temperature and eventually cool the resulting ethosomal suspension at room temperature. The formulation should be stored under refrigeration.

4.**The ethanol injection–sonication method**

In this process, the organic phase containing the dissolved phospholipid in ethanol is injected into the aqueous phase using a 200-flow syringe system38 µl / min, then homogenized for 5 minutes with an ultrasonic probe. [5]

CHARCTERISTICS OF ETHOSOMAL SYSTEM

Visualization of Vesicles by TEM and SEM:

The ethosome preparations' vesicular shape is evaluated by using. Microscope for transmission electrons (TEM). Tests are dried on carbon-covered matrix and adversely stained with fluid arrangement of phosphotungstic corrosive. After being dried, example is seen under the magnifying instrument at 10-100 k-overlay amplifications at a speeding up voltage of 100 Kv. The size also, state of the vesicles is seen in the Filtering Electron Microscopy (SEM). One drop of ethosomal suspension is mounted on a reasonable glass stub. It is then air dried and gold-plated with sodium aurothiomalate so that it can be seen under examining electron magnifying lens at 10,000 amplifications.

Size distribution and Vesicular Size: The size conveyance of ethosomal planning can be estimated in a multimodal mode, by Powerful Light Dissipating (DLS) strategy utilizing a mechanized Malvern Autosizer 5002 investigation framework. For vesicle size estimation, ethosomal arrangement is blended in with the medium.

Entrapment Efficiency:

Entrapment Efficiency of ethosomal vesicles can be determined by means of centrifugation. The vesicles were isolated in a rapid cooling rotator at 20,000 rpm for 90 minutes at a constant temperature of 4 °C [15]. The dregs and supernatant fluids were isolated measure of drug in the silt not set in stone by lysing the vesicles utilizing methanol. The effectiveness of entrapment may thus be still up in the air by the accompanying condition, Capture Proficiency = DE ⁄ DT x 100 Where, DE - Measure of medication in the ethosomal dregs DT - Hypothetical measure of medication used to set up the definition (equivalent to measure of medication in supernatant fluid and in the drugs)

Transition Temperature:

Vesicular lipids' Transition temperature (T) can be estimated in copy by DSC in an aluminum container at a warming under a constant nitrogen stream, at a rate of 10 °C per minute. Confocal Scanning Laser Microscopy (CSLM): The skin's mechanism and depth can be studied with CSLM. ethosomal preparation penetration the skin thickness can be optically scanned through the z axis at various intervals. of a confocal laser filtering magnifying instrument.

Surface Tension Measurement:

In an aqueous solution, the drug's surface tension activity can be estimated by the ring strategy in a Du Nouy ring tensiometer.

Phospholipid-ethanol interaction:

The Phospholipid-ethanol connection was concentrated by utilizing Differential Scanning and 31P-NMR with proton decoupling calorimetry.

Degree of deformability and Turbidity:

The Level of deformability of the ethosomal readiness can be performed by Expulsion Strategy and the turbidity of the arrangement can be performed by utilizing Nephalometer in vitro drug release study and Drug Deposition study: In vitro drug discharge study and Medication Testimony of ethosomal readiness can be performed by Franz dissemination cell with fake or natural film, Dialysis pack dispersion. [6]

COMPOSITION OF ETHOSOMES

Ethanol

Ethanol is an efficient penetration enhancer. It plays an important role in ethosomal systems by giving the vesicles special dimensional characteristics size, ζ-Potential, stability, prevention of clogging and increased permeability of the skin. Concentrations of ethanol in ethosomal systems have been reported to be ~10% 50%. Many researchers concluded that when the concentration of ethanol is increased, the size of the ethosomes would decrease. Increasing ethanol concentration above the optimum amount, however, would cause the bilayer to be leaky, leading to a small increase in vesicular size and a significant decrease in the efficacy of trapping, and would solubilize the vesicles by further raising the ethanol concentration. Vesicular load is an important parameter which can affect vesicular properties such as stability and skin vesicle interaction. The high concentration of ethanol in ethosomes has moved the vesicular load from positive to negative. Ethanol serves as a negative charge supplier for ethosomal surfaces, thereby preventing accumulation of the vesicular network as a result of electrostatic repulsion. In fact, ethanol had stabilizing effects, too. Ethanol also has a direct effect on the efficiency of trapping in ethosomal systems, and typically increasing concentrations in ethanol would increase the efficiency of trapping. [7]

Phospholipids

Phospholipids from different sources were used in formulation of the ethosomal scheme. The selection of phospholipid type and concentration for formulation are important factors during the production of ethosomal system since they will affect the scale, the effectiveness of the trapping, ζ -Potential vesicular properties, stability, and penetration. Highly negatively charged vesicles were produced by the incorporation of DPPG (1,2-dipalmitoyl sn-glycero-3-phosphatidylglycerol) in the ethosomal formulation, while cationic ethosomal vesicles were produced by using a cationic lipid, such as DOTAP (1,2 dioleoyl-3- tri methyl ammonium-propane [chloride salt]). In general, in an ethosomal formulation, the concentration range of phospholipids is 0.5%–5%. Rising phospholipid concentration can increase vesicular size marginally or moderately, but will greatly improve the efficiency of trapping. The relationship, however, is only valid until there is a certain concentration.

Cholesterol

Cholesterol is a stable steroid molecule, and its integration into ethosomal structures increases medication stability and clogging effectiveness. This avoids leakage and decreases permeability of the vesicles and vesicular fusion. Generally, it is used at a concentration of 3% but in some formulations, it was used up to 70% of the total phospholipid concentration in the formulation. Several studies have recorded that the vesicular size of ethosomal systems increased with cholesterol.

Dicetyl phosphate

Dicetyl phosphate is widely used to avoid vesicle aggregation and to improve formulation stability. It is used at concentrations between 8% and 20% of the total phospholipid concentration in the ethosomal formulation. However; the impact of dicetyl phosphate on other properties of the ethosomal system remain uncertain.

Propylene glycol

PG is a widely used penetration enhancer. This is used at a concentration range of 5%-20% in the preparation of binary ethosomes and has been found to influence the ethosomal properties of size, trapping capacity, permeation and stability. PG integration into ethosomal systems will result in more reduction of particle size relative to systems without PG. A substantial reduction in particle size was achieved from 103.7±0.9 nm to 76.3±0.5 nm when the PG concentration raise from 0% to 20 % v/v. It is suggested that PG enhances ethosome stability by increasing the viscosity and anti-hydrolysis property. [8]

Isopropyl alcohol

Dave et al studied the influence of IPA on the entrapment efficiency and skin permeation of a diclofenac-loaded ethosomal system. Three types of formulations have been prepared: classical ethosomes containing 40% ethanol, binary ethosomes containing approximately 20% IPA and 20% ethanol, and a vesicular system containing 40% IPA. The vesicular device containing 40 % IPA was found to have higher trapping performance (95 %) than the binary ethosomes (83.8 %).

Skin-penetrating and cell-entering peptide

Skin-penetrating and cell-entering peptide (SPACE) is a skin-penetration enhancer discovered by phage display and shown to deliver short RNA (sirna) and streptavidin to the skin after direct chemical conjugation. This penetration enhancer was incorporated in transethosomes for the delivery of hyaluronic acid.

Other alcohols

Along with ethanol, certain alcohols such as PG and IPA are also used in the preparation of binary ethosomes. efficiency, and change in the ζ-potential charge from negative to positive which lead to aggregation of the vesicles within 1 week. [9]

MECHANISM OF PENETRATION

Mechanism of ethosomal drug delivery remains a matter of debate, a combination of processes most likely contributes to the enhancing effect. At physiological temperature the stratum corneum lipid multilayer is tightly packed strongly conformationally ordered. The high concentrations of ethanol make ethosomes special because ethanol is responsible for disrupting the organization of skin lipid bilayer; thus can incorporated into vesicle membrane, vesicles are capable of penetrating stratum corneum. The lipid membrane also packed less tightly than traditional vesicle due to its high concentration of ethanol but has similar stability, enabling a more malevolent structure, giving it more flexibility and the ability to squeeze through small places such as openings created to disrupt the corneum lipid stratum. Ethanol interacts with lipid molecules in the area of the polar hard group, thereby reducing the rigidity of the corneum stratum lipids and increasing their fluidity. The intercalation of ethanol into the environment of the polar head group will result in an increased permeability of the membrane. The ethosomes itself can interact with stratum corneum barrier, in addition to the effect of ethanol on the structure of the stratum corneum. Although encapsulated drug remained predominantly on the skin surface in classic liposomes, the ethosomal system was shown to be highly effective carrier for increased drug delivery through the skin. The successful drug delivery shown along with the long term ethosomal stability makes this device a promising candidate for transdermal drug delivery.

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

Ethanol improves permeation through the skin. The mechanisms underlying its penetration-enhancing action are well understood. The major benefits of ethosomes over liposomes are improved drug penetration. 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 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. 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. [10]

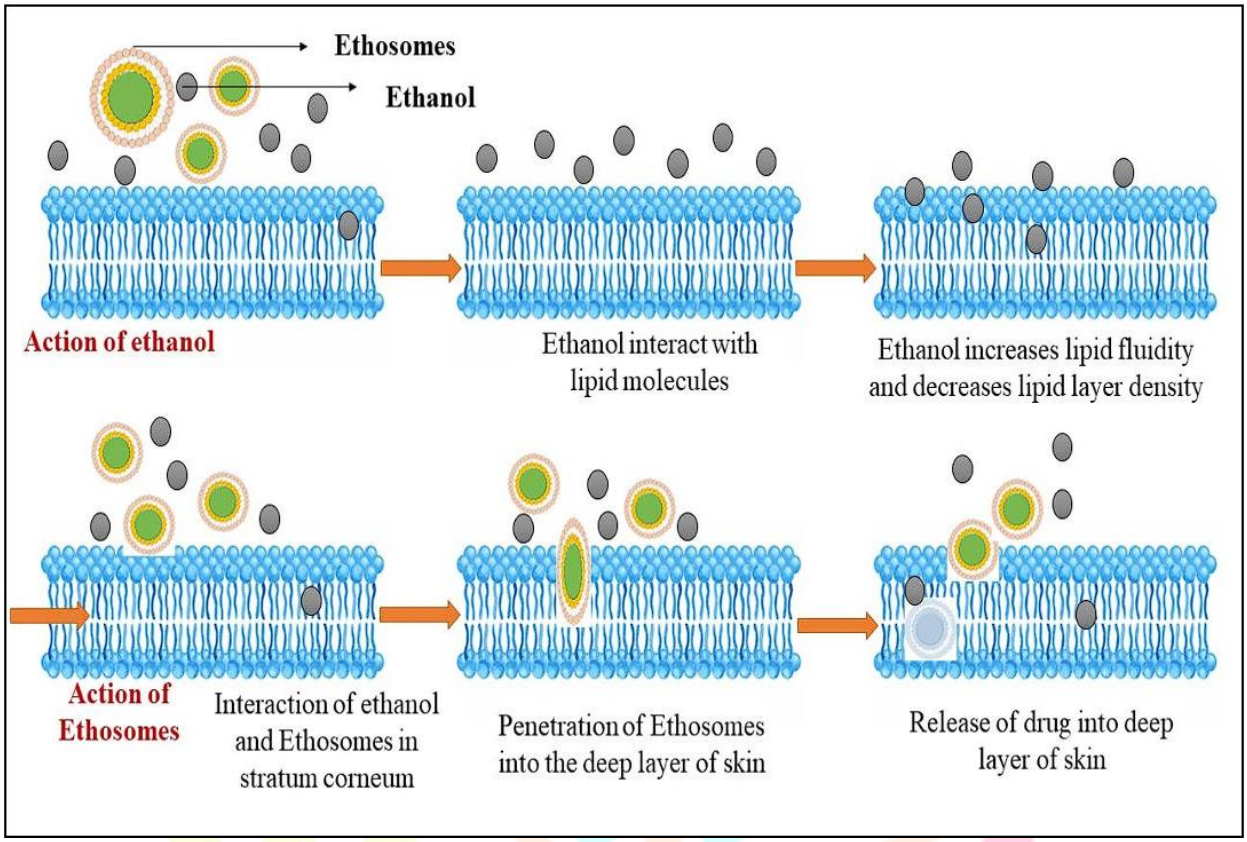

Figure-4. Mechanism for Skin Delivery of Ethosomal Systems.

APPLICATIONS OF ETHOSOMES

Hormone delivery

Oral hormone delivery is related to numerous issues, such as high first-pass metabolism, poor oral bioavailability and many dose-dependent side effects. In addition, oral hormonal preparations which depend heavily on patient compliance with these side effects. The risk of treatment failure is known to rise with every missed pill. Touitou et al. Revealed ability of ethosomes in hormonal delivery by performing a comparative analysis of transdermal delivery of testosterone loaded ethosomes (Testosome), as compared to transdermal testosterone patch through rabbit pinna skin, which showed approximately 30-times higher skin permeation of testosterone from ethosomal formulation.

Transcellular delivery

Ethosomes have been shown to be an effective penetration enhancer and carrier device for the transcellular delivery of various therapeutic agents in active clinical trials. In contrast, almost no fluorescence was observed when integrated in a hydroethanolic solution or classic liposomes. After 3 min of incubation, the intracellular existence of each of the three tested probes was evident.

Delivery of antibiotics

Topical antibiotic delivery is a safer option to improve the therapeutic efficacy of those drugs. Conventional oral therapy and other side effects cause many allergic reactions. [12]

Delivery of anti-parkinsonism agent

Dayan and Touitou prepared ethosomal formulations of the psychoactive drug trihexyphenidyl hydrochloride (THP) and contrasted their delivery from traditional liposomal formulations. THP is an antagonist of M1 muscarinic receptors and used to treat Parkinson's disease. The transdermal flux value of THP from ethosome

via the nude mouse skin was 87, 51 and 4.5 times higher than that of liposome, phosphate buffer, and hydro ethanol solution, respectively. After application of ethosomes, the amount of THP remaining in the skin at the end of 18 hrs. was substantially higher than after application of liposome or hydroethanolic (control) solution. Such findings revealed a greater potential for skin permeation of ethosomal-THP formulation and its use to help treat Parkinson disease.

Anti-viral drug delivery

Zidovudine is a potent antiviral agent that acts on the acquired immunodeficiency virus. Fast side effects link oral administration of zidovudine. So an appropriate zero-order delivery of zidovudine is needed to maintain the anti-AIDS effect predicted. It was concluded from various studies that ethosomes could increase the transdermal flux, prolong the release and pose an attractive route for sustained zidovudine delivery. Acyclovir is another anti-viral drug which is commonly used topically for Herpes labialis treatment. The traditional external formulation of the marketed acyclovir is associated with low skin penetration of hydrophilic acyclovir to the dermal layer resulting in inadequate therapeutic efficacy. Scientists have devised the acyclovir ethosomal formulation for dermal delivery to solve the problem associated with traditional topical acyclovir

Delivery of problematic drug molecules

It is difficult to transmit large biogenic molecules such as peptides or proteins orally, because they are fully degraded in the GI tract. Non-invasive protein delivery is a safer choice for addressing the oral delivery problems. Researchers have been investigating the effect of ethosomal insulin delivery in normal and diabetic SDI rats on reducing blood glucose levels in vivo. The result showed that insulin administered from this patch in both normal and diabetic rats induced a substantial decrease (up to 60 %) in BGL. At the other hand, an injection of insulin from a control formulation does not reduce the BGL

Cosmeceutical application of ethosomes

The benefit of applying ethosomes in cosmeceuticals is not only to enhance cosmetic chemicals 'stability and decrease skin irritation from irritating cosmetic chemicals, but also to enhance transdermal permeation, particularly in elastic types. Furthermore, the compositions and sizes of the vesicles are the key considerations that need to be addressed in order to achieve these benefits of the elastic vesicles for cosmeceuticals [12]

Table.1 Marketed product of 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.

Topical delivery of DNA

A lot of environmental pathogens are trying to get into the body through the skin and skin has developed into an outstanding defensive barrier that is both immunologically active and capable of expressing the gene. The important use of ethosomes on the basis of the above facts is to use them for the topical delivery of DNA molecules to express genes in skin cells. It has been proposed that ethosomes may be used as carriers for applications for gene therapy that require transient gene expression. The findings also suggested the ability to use ethosomes for successful transdermal immunization. Therefore, improved ethosomal skin permeation capacity opens the possibility of using these dosage types to deliver immunizing agents.

Pilosebaceous targeting

The percutaneous drug delivery of hair follicles and sebaceous glands is increasingly recognized as potentially significant elements. The interest in pilosebaceous units was directed to their use as depots for localized therapy, particularly for the treatment of follicle-related disorders such as acne or alopecia. In addition, extensive attention has also been paid to using the follicles as transportation shunts for systemic drug delivery. [13].

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. The incorporation of ethosomal systems in suitable vehicles such as gels, patches, & creams shows better skin permeation & therapeutics results. Ethosomal vesicles open new opportunities for development of novel formulation. 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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