Review Article

An Overview of Ethosomes as Novel Vesicular Carrier: Its Principle, Preparation and Applications

Snehal Raut*, Priti Koli, Harshad Desai, Sardar Shelake, Nilesh Chougule
Ashokrao Mane Institute of Pharmacy, Ambap, Tal. Hatkanangale, Dist. Kolhapur, State Maharashtra, 416112, India.
***Corresponding author's E-mail:** sraut0725@gmail.com

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ABSTRACT

Ethosomes are a novel vesicular system that has emerged in the realm of pharmaceutical technology, where pharmaceuticals are entrapped to improve therapeutic efficacy. Ethosomes are made up of phospholipid, alcohol, polyglycol, and other substances. water Ethanol improves skin penetration and helps the medication go into the body deeper skin layers. Ethosomes are frequently employed instead of liposomes because they provide better medication delivery, penetration, and other benefits. Ethosomes are soft, pliable vesicles that can be employed both topically and systemically. Ethosome carriers have a lot of potential in terms of drug development and research. The major goal of this review is to provide comprehensive information on Ethosomes.

Keywords: Ethanol, Ethosomes, Skin Penetration, skin, liposomes.

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INTRODUCTION

Transdermal drug delivery systems are self-contained, discrete dosage forms that, when combined, comprise a Transdermal drug delivery system. When applied to healthy skin, the medicine is delivered to the body at a controlled rate. circulatory system One of the largest and Lower variations in plasma drug levels, avoidance of gastronomical disturbances and first-pass drug metabolisms, and good patient satisfaction All of these benefits come from leveraging the human body and skin as a drug delivery system. [1]

Over standard medication delivery systems, this technology has an advantage. The skin is one of the most easily accessible organs. The transdermal drug delivery technology is superior to oral drug delivery systems. (TDDS) demonstrated promising results since it removes gastrointestinal interferences and first pass drug metabolism. However, the fundamental disadvantage of TDDS is that it encounters the barrier. Various solutions have been investigated in order to enhance the entry of medications through the skin, including the use of chemical or biological agents Iontophoresis and sonophoresis are examples of physical enhancers etc. Throughout the last several decades, researchers have devised many techniques to weaken or break the skin barrier and transport medications into the body through the skin barrier and deliver drugs into the body through the intact skin. suspension such as liposomes, niosomes and microemulsions, have also been proposed as low risk drug carriers, but they don't add much to a transdermal medication delivery system because they don't penetrate the skin deeply and instead stay on the top layers.[2]

ETHOSOMES

Ethosomes are ethanolic liposome Drugs that can penetrate deep into the epidermal layers and/or the systemic circulation. These are malleable, squishy vesicles that help spread active ingredients more effectively. Systemic circulation using non invasive delivery carriers are known as ethosomes. These are soft, pliable vesicles designed to distribute active substances more effectively.

Vesicles are well-known for their role in cellular communication and particle transport. Vesicles would also enable for more precise control of medicine release rates over extended periods of time. keeping the medicine safe from immunological reaction and other clearance processes over time being able to release just the right amount of drug and keep that concentration constant for longer periods of time.[3] Ethosomes are a slightly modified version of the well-known drug carrier liposome. Ethosomes are lipid vesicles containing phospholipids, alcohol (ethanol and isopropyl alcohol), and other substances. Alcohol, as well as a large amount of water. Ethosomes are delicate vesicles that store genetic material. phospholipids, ethanol (at greater quantities), and water are some of the substances that can be found in the body. Ethosomes can be tens of thousands of years old. The size ranges from nanometers (nm) to microns Ethosomes have a faster penetration rate into the skin layers and have a greater protein content increased transdermal flur.[4]

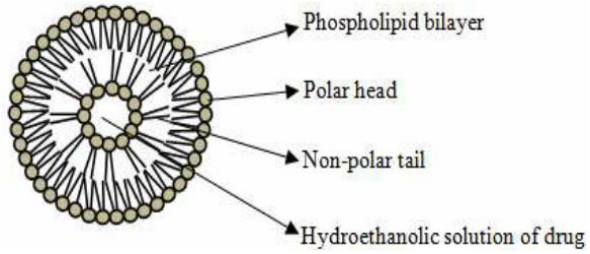

Figure 1: Structure of ethosome

Advantages of ethosomal drug delivery

Ethosomal drug delivery systems have various advantages over other transdermal and dermal administration technologies.

The following are a few advantages:

1. Large molecules (peptides, protein molecules) can be delivered.

2. The composition contains non-toxic raw materials

3. In the pharmaceutical, veterinary, and cosmetic industries, ethosomal drug delivery technology offers a wide range of applications

4. This is a simple operation in comparison to Iontophoresis and other medication delivery modalities.[5]

Disadvantages of ethosomal drug delivery

1. Ethosomal administration is not a means to achieve rapid bolus type drug input, rather it usually designed to offer slow, sustained drug delivery

2. The molecular size of the medicine must be tiny enough to pass through the skin.

3. Limited production.

4. Excipients and enhancers in drug delivery systems cause skin irritation or dermatitis. Enhancers in drug delivery systems cause skin irritation or dermatitis.[6]

ETHOSOMAL COMPOSITION

Ethosomes are vesicular carriers made up of hydroalcoholic or hydro/alcoholic/glycolic phospholipids with a high alcohol content or mixture of alcohols.

Ethosomes frequently contain phosphatidyl choline and other phospholipids with differing chemical configurations (PC), Phosphatidic acid (PA), phosphatidyl serine (PS), phosphatidyl choline (PC), phosphatidyl glycerol (PPG), phosphatidyl linositol (PI), hydrogenated ethanolamine (HEA), alcohol (ethanol or isopropyl alcohol), water, and propylene glycol (or other glycols). This type of formulation allows for the administration of large concentrations of active substances through the skin.[7]

The ratio of alcohol to water or alcohol-polyol to water can be changed to control drug delivery. Soya phospholipids, such as Phospholipon 90, are among of the most desired phospholipids (PL-90). It's commonly used at a concentration of 0.5-10 % W/W Cholesterol, in amounts ranging from 0.1 to 1 %, can also be added to the mixture.

Alcohols such as ethanol and isopropyl alcohol are examples of alcohols that can be used. The alcohol and glycol mixture in the non-aqueous phase can have a wide variety of concentrations.[8]

DRUG PENETRATION MECHANISM

In terms of drug permeability, ethosomes have a major advantage over liposomes. The process by which drugs are absorbed from Ethosomes is unknown. The absorption of drugs as following two phases are most likely to occur.[9]

1. Ethanol's impact
2. Ethosomes effect

1. Ethanol effect

Ethanol serves as a skin penetration enhancer Its penetration-enhancing mechanism is widely understood. Ethanol penetrates intercellular lipids, increasing the fluidity of cell membrane lipids and lowering the density of the cell membrane's lipid multilayer.

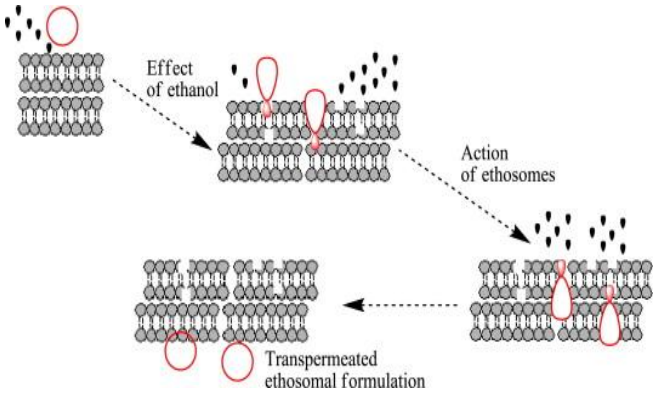

Figure 2: Ethanol's Effect

2. Ethosome effect:

Ethosome influence Increased skin permeability is induced by increased cell membrane lipid fluidity caused by the ethanol of ethosomes. As a result, ethosomes can easily penetrate deep skin layers, combining with skin lipids to release drugs into deeper skin layers.[10]

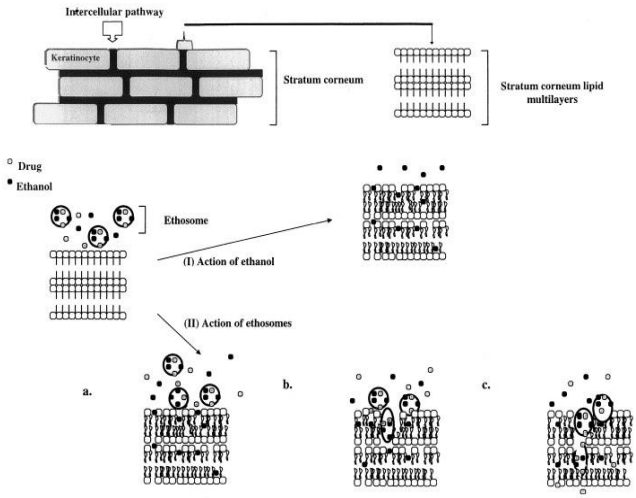

Figure 3: Proposed Mechanism for skin delivery of Ethosomal system

METHOD OF PREPARATION OF ETHOSOMES

Ethosomes can be made using two extremely easy and practical methods:[11]

1. Cold procedure

2. Hot technique

1. Cold process

This is the most widely used method for the preparation of ethosomal formulation.

Phospholipids, pharmaceuticals, and other lipid molecules are dissolved in ethanol in a covered vessel at room temperature using a mixer and fast agitation. During the stirring process, propylene glycol or another polyol is introduced. The temperature of this mixture is raised to 30 degrees Celsius. In a bath of water In a separate vessel, heat the water to 30 degrees Celsius. It is then swirled in a covered saucepan for 5 minutes. Using ethosomal formulation, the vesicle size can be reduced to the desired level method of sonication or extrusion finally, the mixture is kept refrigerated.

2. Procedure in a hot

To disseminate phospholipid, this procedure includes heating it in water. Bath at 40 °C until a colloidal solution forms. In a separate vessel, ethanol and propylene glycol are mixed and heated to 40 °C. Once both phases have achieved 40 °C, the organic phase is added to the aqueous phase. The drug is classified as hydrophilic or hydrophobic based on it hydrophilic/hydrophobic properties. Dissolved in ethanol or water a probe can be used to reduce the size of ethosomal formulation vesicles to the appropriate size method of sonication or extrusion[12].

METHOD OF CHARACTERIZATIONS OF ETHOSOMAL FORMULATION

1. Vesicle form

Ethosomes can be visualised using both transmission electron microscopy (TEM) and scanning electron microscopy (SEM). (SEM) Electron microscope analysis revealed an ethosomal formulation with vesicular structure. The diameter is between 300 and 400 nanometers.

2. Zeta potential and vesicle size

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. Interception of drugs

The trapping's effectiveness technique of ultra centrifugation can be used to measure ethosomes.

4. Changeover the temperature

The temperature at which vesicular lipid systems change can be Differential scanning calorimetry was used to determine this.

5. Drug content

The chemical make-up of the medication A UV spectrophotometer can be used to determine the drug content in ethosomes. This can also be quantified by a modified high performance liquid chromatographic method

6. Surface tension measurement

A drug's surface tension activity in watery In a Du Nouy ring tensiometer, the answer can be calculated using the ring method.

7. Stability studies

Vesicles' size and shape can be measured over time to determine their stability. DLS is used to determine meansize, while TEM is used to observe structural changes.

8. Permeation of the skin research

The ethosomal preparation's ability to A confocal laser can be used to examine infiltration into the epidermal layers. Scannable microscopy (CLSM).[13,14]

ETHOSOME EVALUATION

1. Filter membrane-vesicle interaction study by scanning electron microscopy

Scanning Electron Microscopy Study of Filter Membrane-Vesicle Interaction It entails the use of vesicle suspension (0.2 mL) to a 50 nm pore size filter membrane and inserting it in diffusion cells. The The filter's upper side was exposed to the air, while the lower side was in touch with it. phosphate buffered saline solution (having pH 6.5). After 1 hour, the filters were removed. Fixation at 4 °C in Karnovsky's fixative for SEM experiments took an hour. overnight, followed by dehydration with graded ethanol solutions (30 %, 50 %, 70 %, 90 %, and 100 % ethanol). In water, 95 percent and 100 percent V/V). Finally, gold-coated filters were inspected in a scanning electron microscope. (Bensheim, Germany: Leica)[15]

2. Skin permeation experiment

The test animals' hair was carefully trimmed short (the excised skin was placed on aluminium foil, and any clinging fat or subcutaneous tissue was gently plucked from the dermal side of the skin). The effective permeability area of the diffusion cell and the volume of the receptor cell were both 1.0 cm2. and ten milliliters, respectively. The temperature was kept at 32 °C minus 1 °C. The recipient Phosphatebuffer saline solution was in the compartment (10 mL of pH 6.5). Between the donor and receptor compartments, skin was extracted and implanted. Ethosomal A 1.0 mL formulation was applied to the epidermal surface of the skin. At 1, 2, 4, 8, 12, 16, and 18, samples (0.5 mL) were taken from the diffusion cell's sample port. as well as 24 hours. The results were determined using high-performance liquid chromatography. At 20 and 24 hour intervals, samples were taken. the outcomes were reviewed using time

intervals, and a test for high-performance liquid chromatography[16]

3. Stability analysis

The vesicles' stability was tested by storing them at 4 °C + 0.5 °C. The vesicles' size, zeta potential, and vesicle entrapment efficiency were all measured. After 180 days, repeat the technique mentioned before.

4. TEM and Sem analysis of vesicle-skin interaction

Ultra-thin slices of animals were taken. gathered on form var coated grids and inspected under a microscope (Ultracut, Vienna, Austria). electron microscope, transmission. The slices of skin following SEM analysis dehydration were adhered on stubs with adhesive tape and then gold-coated. alloy of palladium assay. The sections were examined using a scanning electron microscope.[17]

5. Fluorescence microscopy study of vesicle-skin interaction

Fluorescence microscopy was performed using the same methodology as the TEM and SEM experiments. To make the cuts, the microtome was used. Pieces cut from paraffin blocks that are 5 meters thick. (Tokyo, Japan: Erma optical works) and analysed using a fluorescence microscope Cytotoxicity In this experiment, MT-2 cells (T-lymphoid cell lines) were grown in Dulbecco's medium. 10 percent foetal calf serum, 100 percent modified Eagle medium (HIMEDIA, Mumbai, India) At 37 °C, 2 mmol/L Lglutamine, U/mL penicillin, 100 mg/mL streptomycin, and U/mL penicillin at 100 mg/mL streptomycin at 100 mg/mL streptomycin at 100 mg/mL streptomycin at 100 mg/mL strepto CO_2 atmosphere. The cytotoxic dosage 50 (CD50) was used to measure toxicity. At 540nm, there was a 50 % drop in absorbance.[18]

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 µ L RPMI medium was added. Cells had been Phosphate buffered saline solution (100 L) was used to treat the animals (pH 7.4), ethosomal formulation, or marketed formulation, and drug absorption was measured using HPLC assay.

7. HPLC analysis

During *In vitro* skin permeation studies and *In vivo* skin permeation assays, an HPLC assay using methanol was employed to assess the amount of drug permeated in the receptor compartment. The MT-2 cell is a type of cell that is found in the human body. The mobile phase is a 70:20:10 vol/vol combination of distilled water and acetonitrile supplied at 1 mL/min by the LC 10-AT vp pump (Shimadzu, Kyoto, Japan). At ambient temperature, a twenty-microliter injection was eluted in a C-18 column (4.6150 mm, Luna, 54, Shimadzu). The column eluent was monitoredat 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 0.99688.[19,20]

8. Statistical analysis

Statistical significance of all the data generated was tested by employing ANOVA followed by studentized range test.A confidence limit of $P < .05$ was fixed for interpretation of the results using the software PRISM (GraphPad, Version2.01, San Diego,CA)

APPLICATIONS OF ETHOSOMES

1. Antiviral drug distribution

Zidovudine is a powerful antiviral medication that targets the AIDS virus.

Zidovudine has a lot of negative side effects when used orally. to keep up with An appropriate zero-order distribution of zidovudine is required to provide the intended anti-AIDS effect necessary. Jai et al found that ethosomes might boost the transdermal flux, extend the release, and provide an appealing route for zidovudine delivery. Acyclovir is another antiviral medication that is often used topically to treat Herpes labialis. The conventional marketed acyclovir external formulation is associated with poor skin penetration of hydrophilic acyclovir to dermal layer resulting in weak therapeutic efficiency. [21]

2. Topical delivery of DNA

Delivery of DNA to the skin Many environmental diseases aim to enter the body through the skin. As a result, skin has evolved into a very effective protective barrier that is also highly permeable. capable of expressing genes and immunologically active. An additional intriguing application Based on the foregoing results, the goal of ethosomes is to employ them for current DNA. molecule delivery in skin cells to express genes. Touitou et al. encapsulated the GFP-CMV-driven transfecting construct in ethosomal DNA for their study. This mixture was applied to the dorsal skin of 5-week male CD-1 nude mice for 48 hours. After the treated skin was removed after 48 hours, CLSM was used to observe the penetration of the green fluorescent protein (GFP) formulation. Gupta and colleagues A transfersomal formulation with immunogenic potential was recently described. As a result, ethosomes' improved skin penetration ability opens up the option of employing these dosage forms to administer immunising drugs.[22]

3. Transdermal delivery of hormone

Oral administration of hormones is associated with issues such as high first-pass metabolism, low oral bioavailability, and various dose-dependent adverse effects. They discovered roughly 30-fold greater skin penetration of testosterone from an ethosomal formulation compared to a commercial formulation.[23]

4. Delivery of anti-parkinsonism agent

An ethosomal formulation of the psychoactive substance trihexyphenidyl hydrochloride (THP) was compared to a normal liposomal formulation by Dayan and Touitou. THP is an antagonist of M1 muscarinic receptors that is used to treat Parkinson's disease. The findings suggested that the ethosomal-THP formulation had a higher skin penetration capacity and could be used to better control Parkinson's disease.[24,25]

5. Transcellular delivery

Communication Using CLSM and FACS methods, Touitou et al. observed higher intracellular uptake of bacitracin. Different cell lines were exposed to DNA and erythromycin. Ethosomes showed better cellular absorption than the commercial product. In the MT-2 cell line of the anti-HIV medications zidovudine and lamivudine, implying that Ethosomes could be a promising anti-HIV treatment approach in the clinic.[26]

6. Delivery of anti-arthritis drugs

Topical anti-arthritis drug delivery is a better option for site-specific delivery and avoids the drawbacks of oral therapy. Delivery of Anti-Arthritis Drugs Topical anti-arthritis drug delivery is a better option for site-specific delivery and avoids the drawbacks of oral therapy. Encapsulating CBD in ethosomes greatly improved its skin penetration, accumulation, and thus biological activity, according to the finding.

7. Problematic drug molecule delivery

Large biogenic molecules like peptides and proteins are difficult to administer orally since they are totally destroyed in the GI tract. Non-invasive protein administration is a preferable strategy for overcoming the limitations associated with oral protein delivery. Dkeidek and Touitou investigated the effects of diabetes in normal and diabetic SDI rats. The efficacy of ethosomal insulin injection on lowering blood glucose levels (BGL) in diabetic patients vivo. A control formulation of insulin, on the other hand, was unable to reduce BGL levels. Paolino et al. looked at the use of ethosomes for ammonium glycyrrhizinate distribution through the skin. Glycyrrhizinate Glabra produces ammonium glycyrrhizinate, a naturally occurring triterpene that can be used to treat a number of inflammatory skin diseases.[27,28]

8. Delivery of antibiotic

Antibiotics can be given in a variety of ways. Antibiotics that are used topically have higher therapeutic efficacy. Oral therapy used in the past has resulted in a number of allergic reactions as well as a number of side effects. The use of external preparations with minimal permeability to deep skin layers and subdermal tissues is common. Ethosomes swiftly penetrate the epidermis, delivering a large number of drugs to the skin's deeper layers and controlling infection at the source. The findings of this investigation revealed that an ethosomal antibiotic formulation could be highly effective and eliminate the complications associated with traditional Therapy.[29, 30, 31]

CONCLUSION

The key limiting aspect of any formulation is targeting medications to a specific site, which can be overcome to a large amount via ethosomes. When compared to other medication delivery technologies such as transdermal and dermal delivery, ethosomes have more advantages. Ethosomes are non-invasive drug delivery vehicles that allow drugs to penetrate deep layers of the skin before being distributed throughout the body. It transports big molecules like peptides and proteins. In comparison to Iontophoresis, Phonophoresis, and other sophisticated drug delivery systems, this is a simple procedure. It has a high patient compliance rate because it is administered. Because it is delivered in a semisolid form (gel or cream) and has a wide variety of medicinal applications, it has a good patient compliance rate. industries, Veterinary, Cosmetic field. So overall the Ethosomes having good future scope in targeted drug delivery system.

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