A SUMMARIZE OF TRANSDERMAL APPLICATION OF DRUGS WITH ETHOSOMES

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ABSTRACT:

Ethosomes are non-invasive delivery devices that allow drugs to reach the deeper layers of the skin and the systemic circulation. Although ethosomal systems are conceptually advanced, their preparation is a simple and safe combination that can greatly expand their application. Ethosomes are soft, malleable vesicles adapted to improve the transport of active substances. Due to their unique structure, Ethosomes are able to encapsulate and carry through the skin very lipophilic molecules such as cannabinoids, testosterone and minoxidil, as well as cationic drugs such as propranolol, trihexaphenidyl, cyclosporine, insulin, salbutamol. Enhanced transport of bioactive molecules through the skin and cell membranes by an ethosomal carrier opens up many challenges and opportunities for research and further development of new, improved therapies. Ethosomes are gaining popularity in the design of drug delivery systems for topical and transdermal use because they can reach deep skin layers and systemic circulation. Although conceptually advanced, Ethosomes are easy to make and safe to use. Although very efficient, Ethosomes offer the potential for expanding applications. The purpose of the review is to give an in-depth overview of the properties and preparation of Ethosomes, followed by a characterization and list of drugs encapsulated in Ethosomes over the last 15 years.

Keywords: Ethosomes, Malleable iron vesicles, Ethosomes carriers and Transdermal patches.

1.0. INTRODUCTION

Transdermal medicine delivery is becoming more and more popular because it is a non-invasive method of administration. Many of the drawbacks of oral medication delivery are addressed by transdermal drug delivery, including first-pass action, gastrointestinal mucosal irritation, and drug breakdown by digestive enzymes. Patients strongly prefer the transdermal route, partly because of the discomfort during administration that comes with the parenteral route. Therefore, the most patient-compliant method of drug delivery is transdermal dosage forms. [1, 2] Some issues should be considered while creating transdermal

dosage forms. The outermost layer of the skin, known as the stratum conium (SC), is layered with the dermis and epidermis. Interspersed across these skin layers are sweat glands, hair follicles, and fibroblasts that are derived from the dermis blood supply. [3]

1.1. TRANSDERMAL DRUG DELIVERY IS NECESSARY.

Despite these difficulties, TDD has a number of special benefits, such as being comparatively vast and easily accessible. Surface area for absorption, application simplicity and therapy termination. Furthermore, the development of safer penetration enhancers, vesicular carriers, and improved drug delivery technologies has rekindled interest in building transdermal delivery systems for medications previously believed to be unsuitable for TDD. Permeation of drugs and skin [4,5] The structural and biochemical aspects of human skin, as well as those traits that contribute to both the pace at which drugs enter the body through the epidermis and the barrier's function,

1.2. ETHOSOMES

Hydro alcoholic or hydro alcoholic/glycolic phospholipids comprise the Ethosomes, which are vesicular carriers. It has a significantly high alcohol content, or mix of alcohols. Phospholipids with different chemical structures, such as phosphatidylcholine (PC), hydrogenated PC, phosphatidic acid (PA), phosphatidylserine (PS), phosphatidylethanolamine (PE), phosphatidylglycerol (PPG), phosphatidylinositol (PI), hydrogenated PC, alcohol (ethanol or isopropyl alcohol), water, and propylene glycol (or other glycols), may be present in the Ethosomes. [6] Skin distribution of a high concentration of active substances is made possible by this combination. Alcoholic substitution: water or alcohol. Drug delivery is changed by the polyol/water ratio. Typically, phospholipids in the range of 0.5–10% w/w are employed, such as phospholipid 90 (PL-90), which is derived from soy. It is also possible to employ cholesterol in the preparation process to boost the stability of Ethosomes at concentrations ranging from 0.1 to 1%. The most commonly used alcohols are ethanol and isopropyl alcohol, and the most commonly used glycols are propylene glycol and transcutol. Furthermore, in these preparations, non-ionic surfactants (PEG-alkyl ethers) are occasionally employed with the phospholipids. Cocoamide, POE alkyl amines, dodecyl amine, cetrimide, and other cationic lipids may also be added. The finished product may have between 20 and 50% alcohol content. The non-aqueous phase's content, which is the mixture of alcohol and glycol, can be anywhere from 22 to 70%. [7,8]

1.3. Types of ethosomal systems

There are three types of ethosomal systems based on their composition.

1.3.1. Classic Ethosomes:

Classic Ethosomes are modified Ethosomes composed of phospholipids, water and a high ethanol content of up to 45% (w/v). Due to their small size, negative zeta potential and higher entrapment efficiency, classical Ethosomes were found to be superior to classical liposomes.

Drugs with molecular weights ranging from 130.077 Da to 24 kDa are ideal for closed classical Ethosomes. Classic Ethosomes also have a better skin permeability and stability profile than classic liposomes [9]

1.3.2. Binary Ethosomes:

Binary Ethosomes were introduced by Zhou et al. basically; they were developed by adding another type of alcohol to the classic Ethosomes. The most commonly used alcohols in binary Ethosomes are propylene glycol (PG) and isopropyl alcohol (IPA) [10]

1.3.3. TransEthosomes:

TransEthosomes are a new form of Ethosomes systems and were developed to combine the advantages of classical Ethosomes and transfersomes at the same time. time the formula. . In its composition, it contains basic components such as classic Ethosomes and penetration enhancer or edge activator (surfactant) [11]

1.4. Techniques for Preparing Ethosomes

The preparation of ethosomal formulation can be done either way, as explained below: hot or cold. Both approaches are

1.4.1. THE COLD METHOD

This approach involves dissolving phospholipids, drugs, and other lipid compounds in ethanol in a covered jar at room temperature by using a mixer and vigorous stirring. Stirring adds propylene glycol or another polyol. In a water bath, this combination is heated to 300 °C. After adding the water that has been heated to 300 °C in a different vessel, the mixture is covered and agitated for five minutes. Probe sonication or extrusion methods can be used to reduce the ethosomal formulation's vesicle size to the desired degree. The formulation is then refrigerated for storage.
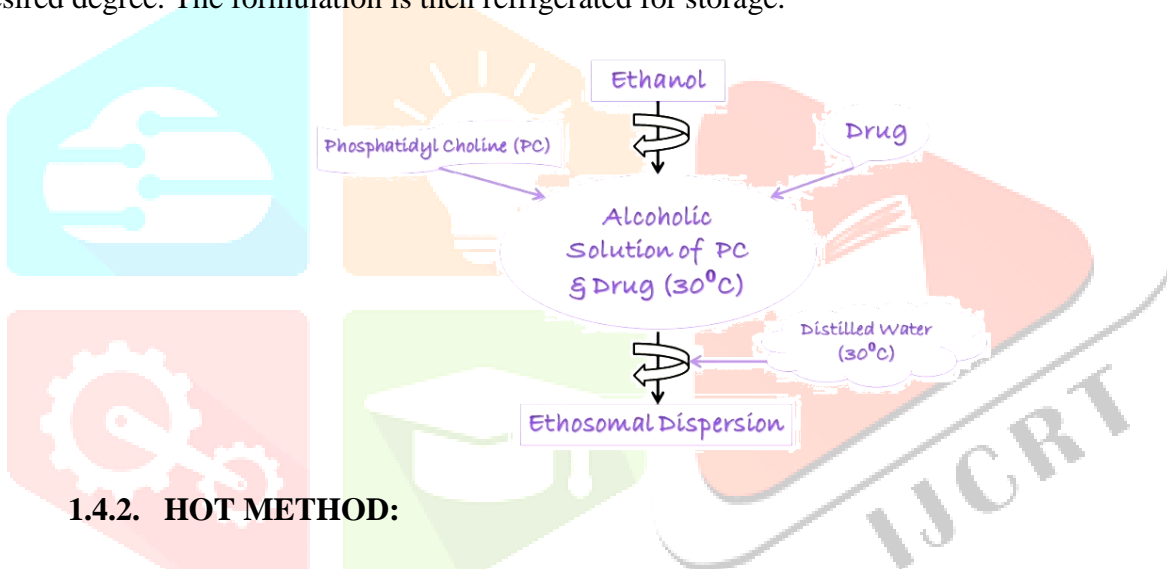
1.4.2. HOT METHOD:

This technique produces a colloidal solution by heating phospholipid in a water bath at 400 degrees Celsius. 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 400 °C. 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. [12]
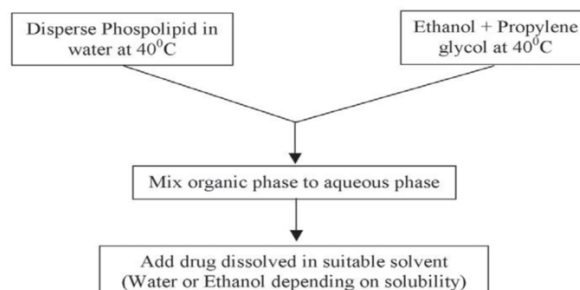
1.5. SKIN CARRIAGE FROM THE ETHOSOMAL FRAMEWORK

The primary benefit of Ethosomes over liposomes is the expanded pervasiveness of the medication. It is unclear how the drug is taken in from Ethosomes. The medication retention most likely happens in the following two stages: 1. Effect of ethanol 2. Ethosomes impact 1. Ethanol impact Ethanol goes about as an infiltration enhancer through the skin. The component of its infiltration-improving impact is notable. Ethanol infiltrates into intercellular lipids, expands the smoothness of cell layer lipids, and diminishes the thickness of the lipid multi-facet of the cell layer. 2. Ethosomes impact Expanded cell film lipid smoothness brought about by the ethanol of Ethosomes results in expanded skin porousness. So the Ethosomes saturate effectively inside the profound skin layers, where they get melded with skin lipids and deliver the medications into the profound layer of skin [13, 14]

1.6. CHARACTERIZATION OF ETHOSOMES

Vesicle shape Transmission electron microscopy (TEM) and checking electronic microscopy (SEM) are utilized to describe the surface morphology of the ethosomal vesicles. Prior to investigation, mount the Ethosomes onto two-sided tape that has recently been gotten on copper hits and covered with platinum, then, at that point, examine them at various amplifications. Vesicle size and Zeta potential Dynamic light dissipating (DLS) utilizing a modernized investigation framework and photon relationship spectroscopy (computers) are the two techniques utilized in surveying the molecule size and zeta capability of arranged Ethosomes. Entrapment Effectiveness Ultracentrifugation is the most widely utilized method to gauge the ensnarement effectiveness of Ethosomes. The vesicles are isolated in a high-velocity cooling rotator at 20,000 rpm for an hour and a half, and the temperature is kept at 4°C. Separate the silt and supernatant fluids. Determine the amount of medication in the silt by lysing the vesicles with methanol. From this, determine the entanglement effectiveness of the accompanying condition. Entanglement effectiveness = DE / DT x 100 Where, DE: Measure of medication in the ethosomal silt DT: Hypothetical measure of medication used to set up the detailing (equivalent to measure of medication in the supernatant fluid; furthermore, in the residue) [15]

Characterization of Ethosomes

1.6.1. Visualization:

Imaging of Ethosomes can be done using transmission electron microscopy (TEM) and scanning electron microscopy (SEM).

1.6.2. Vesicle size and zeta potential:

It can be detected by dynamic light scattering (DLS) and photon correlation spectroscopy (PCS). Zeta potential of the Ethosomes suspension can be measured with a Zeta meter [16]

1.6.3. pH measurement:

The pH of the preparation was measured with a pH meter by immersing the glass electrode completely in the semi-solid compound to cover it electrode [17]

1.6.4. Transition temperature:

The transition temperature of vesicular lipid systems can be determined by differential scanning calorimetry (DSC) [18]

1.6.5. Drug entrapment:

The efficiency of entrapment can be measured. Ultracentrifugation technique [19]

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1.6.6. Drug concentration:

The amount of drug can be determined by a modified high-performance liquid chromatography method and a UV spectrophotometer.

1.6.7. Surface tension measurement:

Du Novy ring tension meter is a ring method used to measure drug surface tension.

1.6.8. Skin penetration studies:

The ability of an ethosomal formulation to penetrate the skin layers can be determined by confocal laser scanning microscopy (CLSM).

1.6.9. Stability Measurements:

Ethosomes stability was determined by TEM imaging and DLS size at various times after vesicle preparation [20]

1.6.10. Evaluation Tests:

Using the filter membrane-vesicle interaction method(0.2 ml) was applied to a filter membrane with a pore size of 50 nm and placed in the diffusion cells. The upper side of the filter was exposed to air, while the lower side was exposed to PBS (phosphate buffered salt) (pH 6.5). Filters were removed after 1 h and prepared for SEM studies by fixing overnight at 4u00b0C in a Karnovskyu2019s fixative, followed by stepwise dehydration with ethanol solutions (30%, 50%, 70%, 90%, 95% and 100% by volume) water). Finally, the filters were coated with gold and examined in SEM (Leica, Bensheim, Germany).

1.6.11. TEM and SEM bladder-skin interaction study:

Animals were cut in ultrathin sections (Ultracut, Vienna, Austria), collected on formware-coated grids, and examined by transmission electron microscopy. For SEM analysis, the skin sections were taped to trikes after drying and coated with gold palladium alloy using a fine-coating ion sputtering device. Sections were examined with a scanning electron microscope.

1.6.12. Bladder-skin interaction study using fluorescence microscopy:

Fluorescence microscopy was performed according to the protocol used in the TEM and SEM study. Paraffin blocks were used, prepared; 5–03 billion cm thick sections were cut with a microtome (Erma optical Works, Tokyo, Japan) and examined in a fluorescence microcytotoxicity assay. MT-2 cells (lymphoid cell lines) were grown in Dulbecco's modified Eagle medium (HIMEDIA, Mumbai, India). Contains 10% fetal calf serum, 100 U/mL penicillin, 100 mg/mL streptomycin, and 2 mmol/L L-glutamine at 37 u00b0C in 5% CO2C. Cytotoxicity was expressed as the cytotoxic dose 50 (CD50) causing a 50% decrease in absorbance at 540 nm.

1.6.13. Skin Penetration Studies:

The hair of the test animals (rats) was carefully cut with scissors (andlt;2 mm) and the abdominal skin was separated from the underlying connective tissue with a scalpel. The excised skin was placed on aluminum foil and the dermal side of the skin was carefully removed for any attached adipose tissue and/or subcutaneous tissue. The effective penetration area of the diffusion cell and receptor cell was 1.0 cm2 and 10 ml, respectively. The temperature was maintained at 32u00b0C u00b1 1u00b0C. The receiver chamber contained phosphate-buffered saline (10 ml pH 6.5). Excised skin was fixed between the donor and receiver chamber.

The ethosomal preparation (1.0 ml) was applied to the epidermal surface of the skin. Samples (0.5 mL) were taken through diffusion chamber sample ports 1, 2, 4, 8, 12, 16, 20 and amp; every 24 hours and analyzed by HPLC [21]

1.6.14. Drug uptake study:

Drug uptake into MT-2 cells (1u00d7106 cells/ml) was performed in 24-well plates (Corning Inc) after each 100 u RP03b was added environment. . Cells were incubated with 100 µL of drug solution in PBS (pH 7.4), ethosomal preparation or marketed preparation, and then drug uptake was determined by analyzing drug content by HPLC analysis.

1.6.15. HPLC analysis:

The amount of drug penetration into the receptor compartment in in vitro skin penetration experiments and MT-2 cells was determined by HPLC analysis using methanol:distilled water: acetonitrile (70:20:10 v/ v).) mixture as mobile phase delivered at 1 ml/min by LC 10AT vp pump (Shimadzu, Kyoto, Japan)[22]

1.7. Advantages of ethosomal drug delivery

Compared to other transdermal & transdermal delivery systems

- Improved transdermal drug permeability for transdermal delivery.
- Possible delivery of large molecules (peptides, protein molecules).
- Contains non-toxic raw materials.
- High patient compliance Ethosomal system is passive, non-invasive and available for immediate commercialization.
- Ethosomal drug delivery system can be widely applied in pharmaceutical, veterinary and cosmetic fields.
- A simple method of drug administration compared to iontophoresis and phosphoresis and other complex methods.

1.8. Disadvantages of TDDS:
- It cannot deliver drugs in pulsatile.
- It cannot develop if the drug or formulation irritates the skin.
- Possibility of local irritation at the site of use.
- Long-term commitment is difficult[23]

2.0. MECHANISM OF PENETRATION

The component of the entrance of the Ethosomes into and through the skin isn't yet totally explained. Two concurrent instruments of activity have been proposed: ethanol has a fluidization impact on the ethosomal lipids, and ethanol has a fluidization impact on the layer corneum lipids. (Figure 2) In light of the utilization of ethanol in the arrangement of the Ethosomes, the deformability of the pre-arranged vesicles is expanding. Additionally, it is anticipated that the high alcohol content will partially extract the stratum corneum lipids. These cycles are responsible for the expanding bury and intracellular porousness of Ethosomes. The super-deformable vesicles can fashion ways in the disorganized layer of the corneum and, lastly, discharge drugs into the more profound layers of the skin. As a result, it is reasonable to anticipate the formation of a path through the skin, which will make it possible for the Ethosomes and the cells from the deepest layers of the skin to fuse. The stream graph of the entrance of Ethosomes is as portrayed in Figure 1. Fig. 1: Composition of Ethosomes Fig. 2. Mechanism of Penetration[24]
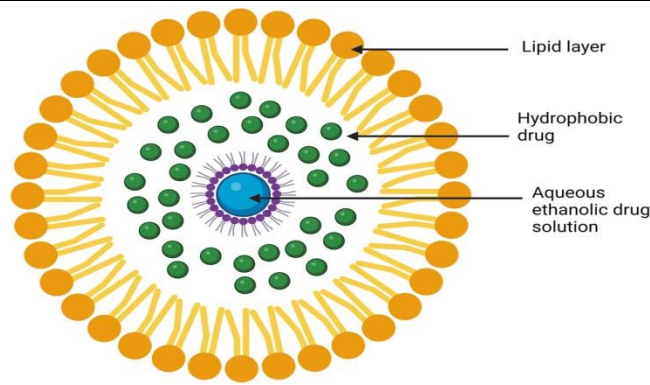
"Fig" 1:.Composition of Ethosomes
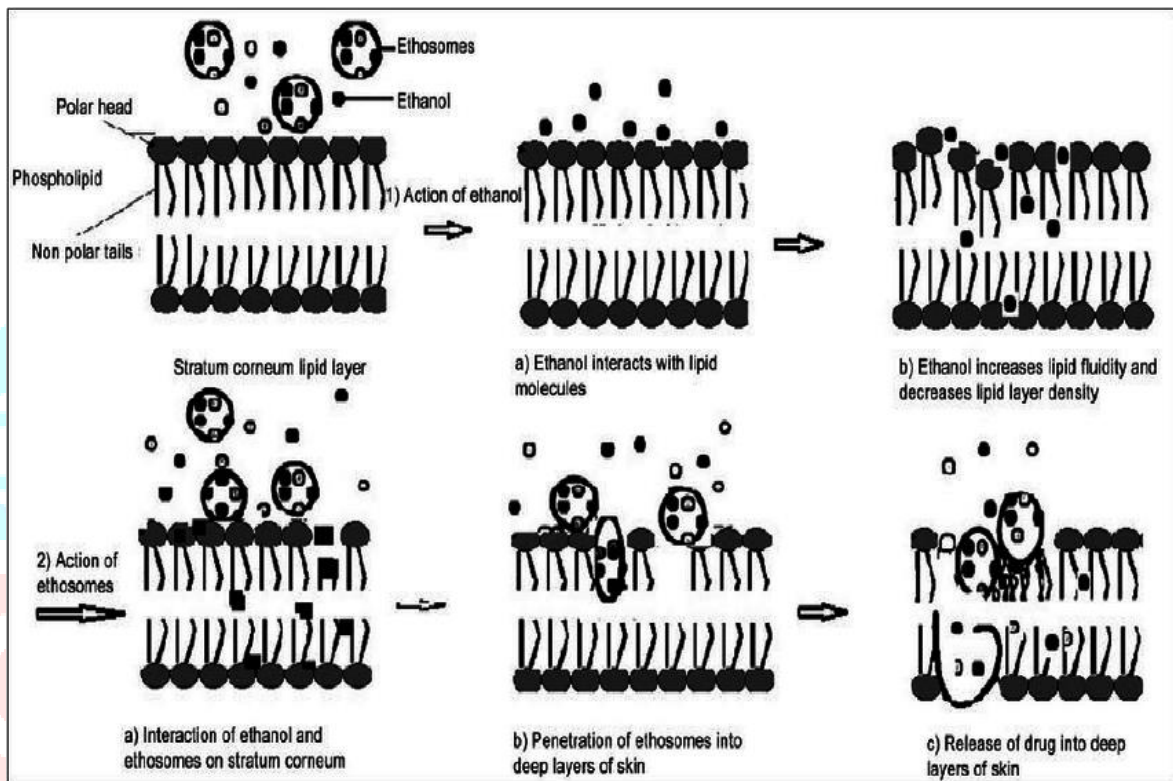
"Fig" 2 : Mechanism of Penetration

3.0.   CONCLUSION

Ethosomes have started another region of vesicular examination for transdermal medication conveyance. Ethosomes are characterized by straightforwardness in their planning, wellbeing, and viability and can be custom-made for enhanced skin penetration of dynamic medications. Ethosomes are capable of significantly overcoming the epidermal barrier, which is the primary limitation of the transdermal drug delivery system. Ethosomes have been tried to embody hydrophilic medications, cationic medications, proteins, and peptides. As a result, ethosomal formulations have a bright future for efficient bioactive agent transdermal delivery.

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