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Ethosomes in Transdermal and Topical Drug Delivery: A Review

Bhavana S N[1], Lakshmi Radhika G[2], Bharath B H[3], Hemanth S N[4], Venkanagouda Shridharagouda Agasimundin[5]

[1,2,3,4,5] Department of Pharmaceutics, SJM College of Pharmacy, SJM Campus, Chitradurga, Karnataka, India

ABSTRACT: The skin is one of the most extensive and readily accessible organs of the human body, and its use as a route for drug delivery offers numerous advantages over traditional drug delivery systems. These advantages include lower fluctuations in plasma drug levels, avoidance of gastrointestinal disturbances and first-pass metabolism, as well as improved patient compliance. Transdermal drug delivery systems (TDDS) are defined as self-contained, discrete dosage forms that, when applied to intact skin, deliver of drugs at the controlled rate to the systemic circulation Ethosomes, developed from Touitou et al. in 1997, are novel lipid carriers composed of ethanol, phospholipids and water. These ethosomes are designed as non-invasive drug carrier system that can permeate the skin, fuse with cell membrane lipids, and release the drug. Ethosomes can be formulated using either hot or cold methods. Evaluation parameters for ethosomes include size, shape, drug content and zeta potential. Ethosomes have been successfully evaluated for the delivery of various drugs, including cyclosporine a insulin and salbutamol. Overall, ethosomes hold great potential as an important drug delivery tool in the future.

KEYWORDS: Drug delivery, Ethosomes, Lipid carriers, Skin permeation, Transdermal.

INTRODUCTION

The skin is one of the most extensive and accessible organs of the human body, and as a route for drug delivery, it offers several advantages over traditional systems, including reduced fluctuations in plasma drug levels, avoidance of gastrointestinal disturbances and first-pass metabolism, and improved patient compliance.[1] The stratum corneum, the outer most layer of skin, acts as a primary barrier aganist drug penetration, restricting the bioavailability of medications applied topically. Consequently, it is essential to explore and compare different delivery carriers that can overcome this natural skin barrier for effective systemic drug delivery.[2]

Transdermal drug delivery systems (TDDS) are defined as self-contained, discrete dosage forms which, when applied to intact skin, deliver the drug(s), through the skin, at a controlled rate to systemic circulation.[3] The transdermal route is considered a promising method for both local and systemic drug delivery. Compared to traditional pharmaceutical forms, transdermal drug delivery systems (TDDS) provide numerous benefits, including bypassing first-pass metabolism, offering sustained drug release, reducing the frequency of doses, minimizing side effects, and enhancing patient compliance.[4]Transdermal drug delivery is gaining significance due to non-invansive method of administration. It overcomes several limitations of oral drug delivery, such as degradation of drug by digestive enzymes, irritation of the gastrointestinal mucosa and the first-pass effect. Additionally, due to the pain associated with the parenteral route, patients prefer the transdermal route. As a result, transdermal dosage forms are considered the most patient-compliant mode of drug delivey.[5]

Ethosomes were developed by Touitou et al., 1997 as additional novel lipid carriers composed of ethanol, phospholipids and water. Ethosomes are designed as non-invasive drug carrier system.[6] Touitou (1996) had discovered that ethosomes are lipid vesicular systems embodying ethanol in relatively high concentration.[4]Ethosomes are a novel carrier system used for the delivery of drugs with low penetration through biological membranes, particularly the skin. Ethosomes are a slight modification of the well-established liposome drug carrier.[7]

Ethosomes are soft, malleable vesicles primarily composed of phospholipids, a relatively high concentration of ethanol, and water. These vesicles serve as a novel vesicular carrier for enhanced delivery to and through the skin.[1] The size of ethosomes can be adjusted from tens to micron to nanometers. Due to their high deformability, ethosomes demonstrate an exceptional ability to permeate intact skin. The high ethanol concentration in ethosomes is what makes them unique, as ethanol disrupts the lipids bilayer organization. When incorporated into vesicle membrane, ethonal enhances the vesicle's ability to penetrate the stratum corneum. A Additionally, the high ethanol content causes the lipid membrane to be less tightly packed than in conventional vesicles, resulting in a more flexible structure. This improves drug distribution within the stratum corneum lipids. Compared to classical liposomes,

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which primarily deliver drugs to the outer layer of the skin, ethosomes significantly enhance drug permeation through the stratum corneum barrier.[8]

Ethosomes are a novel type of liposome carrier known for their high deformability, entrapment efficiency and enhanced percutaneous permeability through the stratum corneum. Compared to conventional liposomes they offer a more stable structure, promoting better drug absorption, storage in skin cells and mobility to target cells. Ethosomes provide prolonged durg action, are non-virulent and improve therapeutic efficacy through gradual release. They avoid the frist-pass effect and gastrointestinal degradation, ensuring drug stability at the target site while reducing toxicity, adverse reaction and administration frequency, ultimately enhancing patient compliance and clinical outcomes.[9]

ETHOSOMES COMPOSITION

The ethosomal system is composed of phospholipids, ethanol, and water. The phospholipids used in the formulation can have diverse chemical structures, including phosphatidyl choline (PC), hydrogenated phosphatidyl choline, phosphatidyl ethanolamine (PE), phosphatidyl glycerol (PPG), phosphatidyl inositol (PI), and others. The proportion of the non-aqueous phase typically ranges from 22% to 70%. Ethanol or isopropyl alcohol can serve as the alcohol component. For characterization purposes, dyes or amphiphilic fluorescent probes, such as D-289, Rhodamine 123, Fluorescein Isothiocyanate (FITC), and 6-carboxyfluorescein, are frequently incorporated into ethosomes.[1]

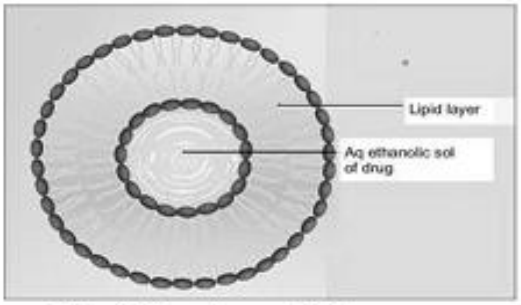

Fig.: 2 Structure of Ethosomes:

HOW do ethosomes work?

Vesicle, ethanol and skin lipids work together in a complementary way to enhance the function of ethosomes. Compared to liposomes, ethosomes have a stronger interaction with skin lipids leading to better distribution of active ingredients. Ethanol affects the lipid moleculesin the stratum corneum by lowering a transition temperature of the lipids in the head group region. This reduces the lipid multilayer density and increases fluidity, allowing the drug to penetrate deeper into the skin. Additionally, ethanol helps make the vesicles smoother and more flexible, aiding in their deeper penetration into the epidermis.[2]

MECHANISM

The main advantage of ethosomes over liposomes lies in their enhanced drug permeation. However, the precise mechanism of drug absorption from ethosomes remains unclear. Drug absorption is likely to occur in two distinct phases:

1.Ethanol effect
2.Ethosomes effect

1.Ethanol effect: Ethanol acts as a penetration enhancer through the skin. Ethanol penetrates into intracellular lipids and increases the fluidity of cell membrane lipids and decreases the density of lipid multi-layer of cell membrane.[5]

2.Ethosome effect: Increased cell membrane lipid fluidity caused by the ethanol of ethosomes results in increased skin permeability. So, the ethosome permeates very easily inside the deeper skin layer where it got fused with skin lipids and releases the drug into deeper layer of skin.[5]

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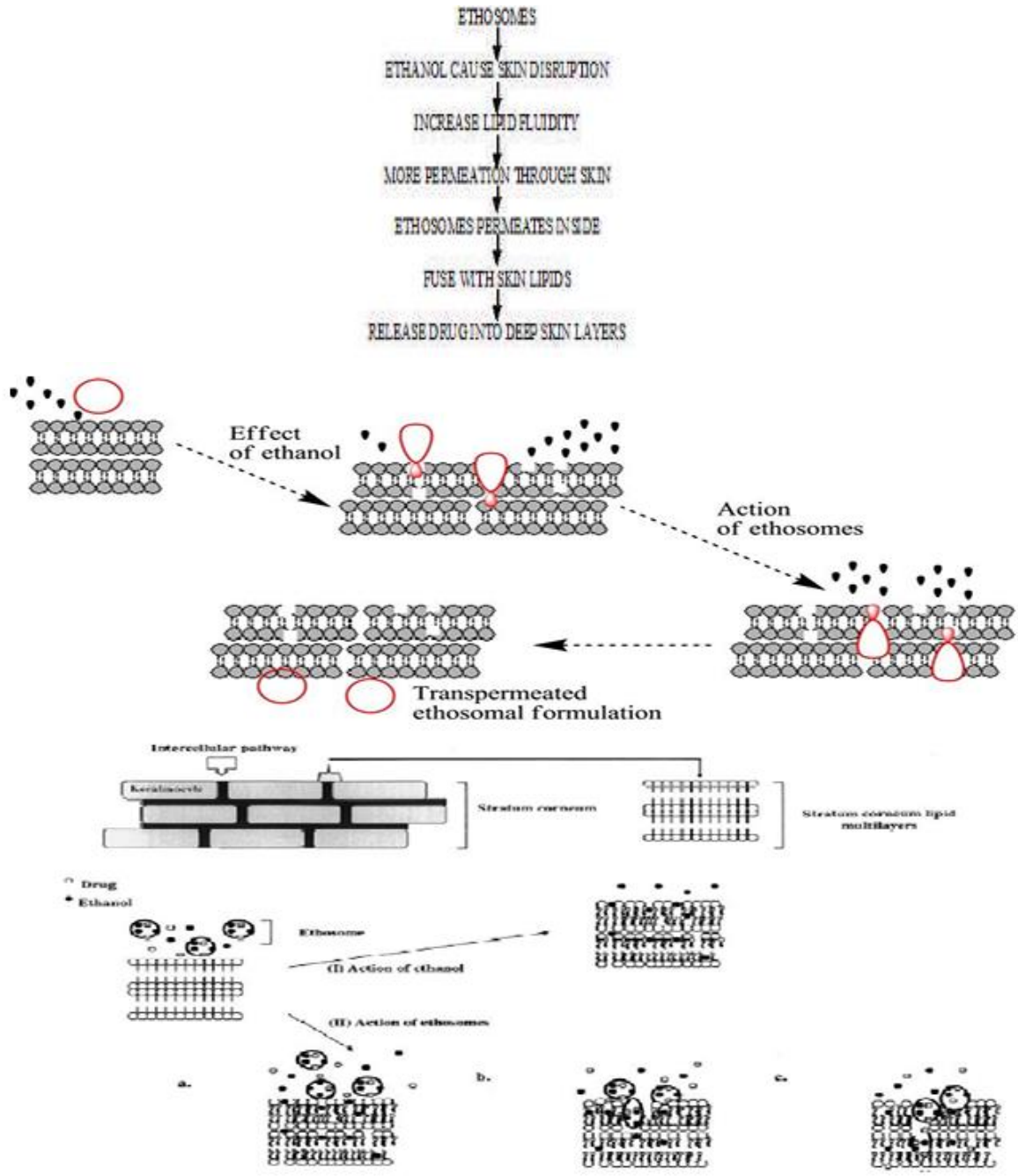

Fig. 3: Mechanism of Ethosomes

METHODS OF PREPARATIONS OF ETHOSOMES

Ethosomal formulation may be prepared by hot, cold and Classic Mechanical Dispersion method as described below. Both the methods are convenient, do not require any sophisticated equipment and are easy to scale up at industrial level.

1. Cold method:

In this method phospholipids, drug and other lipid materials are dissolved in ethanol in a covered vessel at room temperature by vigorous stirring with the use of mixture. Propylene glycol or other polyol is added during stirring. The mixture is heated at 300ºC in a water bath. The water is heated to 300ºC in a separate vessel is added to the mixture, which is then stirred for 5 min in a covered

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vessel. The vessel size of ethosomal formulation can be decreased to the desired extent using probe sonication or extrusion method. finally the formulation is stored under refrigeration[5]

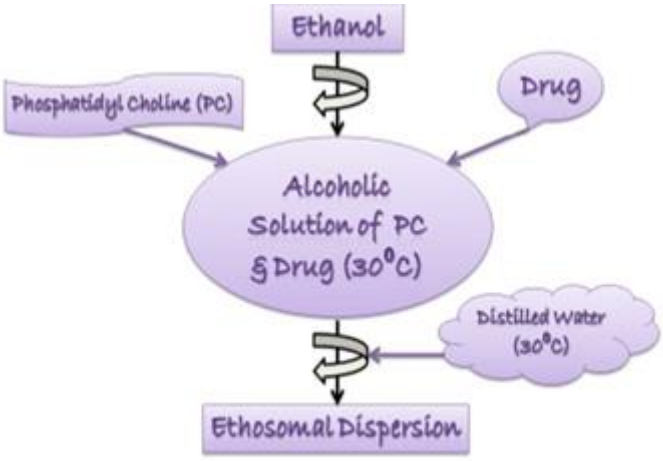

Fig.1: Preparation of Ethosomes by Cold Method

2. **Hot method:**

In this method phospholipid is dispersed in water by heating in a water bath at 400 ºC until a colloidal solution is obtained. In a separate vessel ethanol and propylene gly0col are mixed and heated to 400 ºC. Once the mixture reaches 400 ºC the organic phase is added to the aqueous one. The drug is dissolved in water or ethanol depending on its hydrophilic or hydrophilic properties. The vesical size of ethosomal formulation can be decreased to the desire extent using probe sonication or extrusion method.[5]

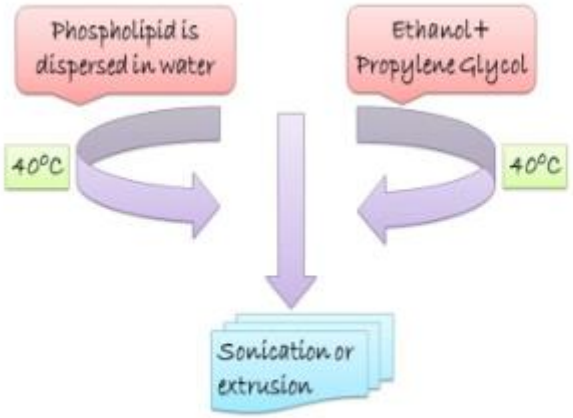

Fig.2: Preparation of Ethosomes by Hot Method

3. **Classic Mechanical Dispersion Method:**

Soya phosphatidylcholine is dissolved in a mixture of chloroform: methanol (3:1) in round bottom flask. The organic solvent are removed using rotary vacuum evaporator above lipid transition temperature to form of a thin lipid film on wall of the flask. Finally traces of solvent mixture are removed from the deposited lipid film by leaving the contents under vacuum overnight. Hydration is done with different concentration of hydroethanolic mixture containing drug by rotating the flask at suitable temperature.[6]

Advantages:

1. Ethosomes are non-invasive and passive delivery systems made from safe, non-toxic ingredients in their formulation.
2. Its composition is safe and are used in the cosmetic and pharmaceutical use.
3. Transport a variety of molecules with diverse physicochemical characteristics including peptides other large molecules as well as both hydrophilic and lipophilic compounds.

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4. They are administered in semi solid dosage form and has good patient compliance
5. Ethosomes offers a platform for delivering a wide range of drugs from various therapeutic classes.[10]

Disadvantages:

1. Ethosomes may clump together and gets precipitated with poor shells and are not economical.
2. Adhesive will not stick to all kinds of skin
3. Due to the enhancers and excipients used in the drug delivery system, dermatitis and skin irritation have occurred.
4. Product loss occurs when ethsomes are transferred from organic to aqueous phase.
5. Administration of ethosomes did not achieve rapid bolus type drug input.
6. They were designed for sustained and slow drug delivery.[10]

Applications

1. Numerous trails have shown that Ethosomes are an effective treatment for viral and microbial skin infections. Animal models of deep skin infections were used to develop and test the efficacy of bacitracin and erythromycin ethosomal system.
2. When produced,ammonium glycyrrhizinate ethosomes were demonstrated to have an anti-inflammatory effect on the skin of human volunteer subjects.
3. When tested *in-vivo* on rabbits ,ethosomal patches for treating androgen insufficiency in males and menopausal symptoms in women demonstrated significantly better results.
4. Research suggest that ethosomal may exhibit analgesic, antipyretic and effective properties in treating erectile dysfunction.
5. Research has also indicated that ethosomes could be used to transport DNA molecules topically, enabling skin cell to express specific genes.[2]

EVALUATION

1.Vesicle Shape

Ethosomes can be easily visualized by using transmission electron microscopy (TEM) and by scanning electron microscopy (SEM).[7]

2.Vesicle Size and Zeta Potential

Particle size of the ethosomes can be determined by dynamic light scattering (DLS) and photon correlation spectroscopy (PCS). Zeta potential of the formulation can be measured by Zeta meter. [7]

3.Transition Temperature

The transition temperature of the vesicular lipid system can be determined by using differential by scanning calorimetry (DSC). [7]

4.Drug Entrapment

The entrapment efficiency of ethosomes can be measured by the ultracentrifugation technique.[7]

5.Drug Content

Drug content of the ethosomes can be determined using UV Spectro photometer. This can also be quantified by a modified high performance liquid chromatographic method.[7]

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]

7.Stability Studies

The stability of vesicles can be determined by assessing the size and structure of the vesicles over time. Mean size is measured by DLS and structure changes are observed by TEM.[7]

8.Skin Permeation Studies

The ability of the ethosomal preparation to penetrate into skin layers can be determined by using confocal laser scanning micros copy (CLSM). [7]

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CONCLUSION

Ethosomes a represent an advanced and promising drug delivery system, providing several benefits such as increased drug stability, enhanced skin penetration and improved therapeutic efficacy. Their ability to carry both hydrophilic and lipophilic drugs opens up new opportunities in the transdermal delivery of a wide range of medications. However, further research and development are required to fully understand their long-term stability, safety and performance in clinical applications.

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