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ETHOSOMES: A REVOLUTIONARY TREND IN LIPID BASED VESICLES AND PARTICULATE CARRIERS FOR TRANSDERMAL DELIVERY OF DRUGS

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ABSTRACT

In recent years, transdermal drug delivery systems have acquired a lot of attention of researchers across the world. Encapsulation of the drug in ethanol-based lipid carrier like ethosomes has been widely recognized as one of the simple and convenient approach to accomplish the permeation of drug via skin. These are non-invasive particulate transporter that reaches drug in deep skin layers and the systemic circulation. Over the liposomes, ethosomes have higher penetration rate through the skin. The increased permeation of ethosomes is apparently due to the presence of ethanolic content in it. Basically, ethosomes are composed of phospholipids, ethanol and water. Ethosomes come up with a number of advantages including improved drug delivery, efficacy, patient compliance and easement. This review focuses on the various aspects of ethosomes likes excipients various method of preparation, characterization, applications, patent reports and future prospects.

Keywords *– Ethosomes, Particulate carrier, Vesicle, Transdermal.*

1. INTRODUCTION

There are number of various pharmaceutical drug delivery systems viz. tablets, transdermal, parenteral, emulsion, suspension, etc. [1-16]. Ethosomes (Fig. 1) are ethanolic liposomes. These are phospholipid nano-vesicles used for dermal and transdermal delivery of molecules [17-18]. These are soft, malleable lipid vesicles composed mainly of phospholipids, alcohol (ethanol or isopropyl alcohol) in relatively high concentration (20-45%) and water. This carrier presents interesting features correlated with its ability to permeate intact through the human skin due to its high deformability [19]. Phospholipids with various chemical structures like phosphatidyl choline, hydrogenated PC, phosphatidyl ethanolamine are used at concentrations ranging from 0.5-10%. The source of the phospholipids can be egg, soyabean, semi-synthetics, and synthetics. Some preferred phospholipids are soya phospholipids such as Lipoid S100, Phospholipon 90 (PL-90) [20].

High concentration of alcohol (20-45%) in the formulation provides soft, flexible characteristics and stability to the vesicles and it also disrupts lipid bilayers structure of the skin results in an increase in the membrane permeability [21]. Examples of alcohols, which can be used, include ethanol (commonly used) and isopropyl alcohol. Glycols can likewise be utilized in arrangements as an

infiltration enhancer. Among glycols propylene glycol and transcutol are for the most part use. For providing further stability to ethosomes vesicles cholesterol at concentrations ranging between about 0.1-1% can also be incorporated [22].

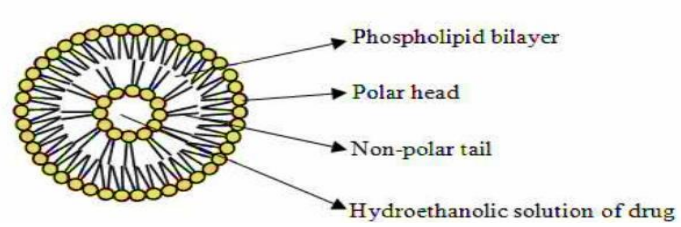

Fig. 1: Structure of ethosomes.

2. MERITS OF ETHOSOMAL DELIVERY SYSTEM [23-26]

- It contains safe raw materials in the formulation.
- It enhances the permeation of drug through skin for transdermal drug delivery.
- Ethosomal drug delivery system can be applied widely in Pharmaceutical, Veterinary, Cosmetic domains.
- The ethosomal drug is administrated in gel or cream formulation hence produces high patient compliance.
- Delivery of large molecules like peptides, protein molecules are feasible.
- The Ethosomal system is passive, non-invasive.
- Biodegradable system.

3. TYPES OF ETHOSOMAL SYSTEMS

3.1. Classical ethosomes

Traditional ethosomes are changed old style liposomes and are made out of phospholipids, a high grouping of ethanol up to 45% w/w, and water. Reported to be superior for transdermal drug delivery because they were smaller and had negative ζ-potential and higher entrapment efficiency [27].

3.2. Binary ethosomes

Binary ethosomes were developed by adding another types of alcohol Propylene Glycol (PG) and Isopropyl Alcohol (IPA) [28].

3.3. Transethosomes

These novel vesicles were developed in an attempt to combine the advantages of classical ethosomes and deformable liposomes (transfersomes) in one formula to produce transethosomes [29].

4. CONSTITUENTS OF ETHOSOMES [30-35]

- Ethosomes are mainly composed of phospholipids, water & ethanol.
- Typically, ethosomes may contain phospholipids like phosphatidylcholine, hydrogenated PC, phosphatidic acid, phosphatidylserine, phosphatidylethanolamine, phosphatidylglycerol, phosphatidylinositol, hydrogenated PC, ethanol or isopropyl alcohol, water and propylene glycol or transcutol.
- Some favored phospholipids are soya phospholipids like Phospholipon 90 (PL90). It is normally utilized in a scope of 0.5-10% w/w.
- Cholesterol at concentrations ranging between 0.1-1% also added.

- Non-ionic surfactants (PEG-alkyl ethers) can combine with phospholipids
- Cationic lipids like cocoamide, POE alkyl amines, dodecylamine, cetrimide added to concentration of the non-aqueous phase may range between 22%-70%. [26-27]

5. MECHANISM OF ACTION

In case of the enhanced potential for transdermal delivery of biologically active agents— loaded ethosomal carriers, the exact mechanism of skin permeability modulation remains somehow speculative [36]. Synergistic instrument between ethanol, vesicles and skin lipids exists, prompting an improved pervasion profile. The proposed system of ethosomal skin regulation lies in the association of ethanol with lipid particles in the polar head locale, bringing about a decrease of the progress temperature (Tm) of SC lipids, along these lines improving their smoothness and prompting a cluttered form [37-40]. This progress gives an expected site to delicate, pliant ethosomes to enter all the more effectively inside the skin layers. After effective application, the penetration improvement from ethosomes is a lot more prominent than would be normal from simply unadulterated ethanol, recommending a synergic instrument between ethanol, vesicles and skin lipids [41-42] (Fig. 2).

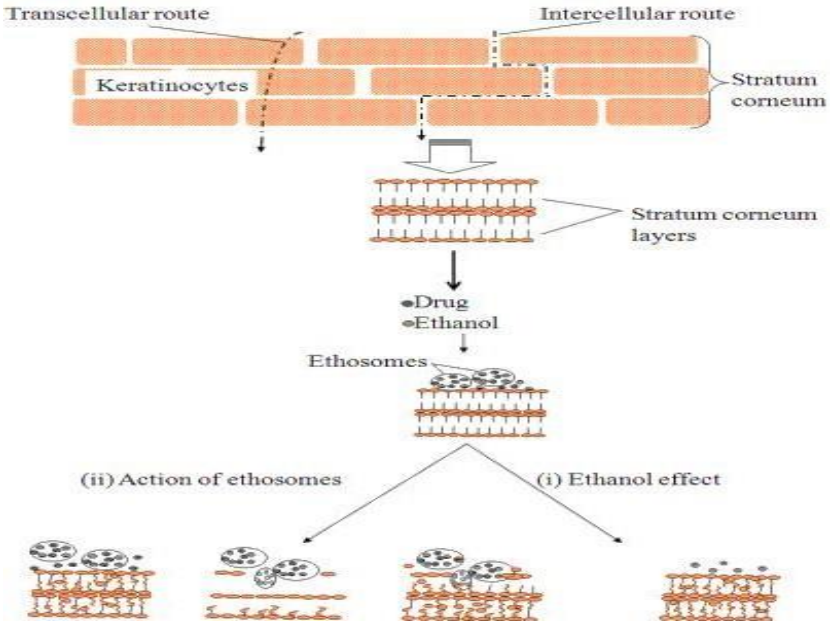

Fig. 2: Mechanism of skin penetration [53].

6. METHODS OF PREPARATION OF ETHOSOMES

6.1. Preparation by Cold method [43]

This is one of the most extensively used method.

- Initially, phospholipid is dissolved in ethanol by vigorous stirring in a covered vessel with continuous addition of polyols as propylene glycol in a water bath at 30°C.
- Water is heated up to 30°C in a separate vessel and slowly added in a fine stream to the above mixture.
- The vesicle size of ethosomal formulation can be reduced to desired one using sonication or extrusion method and stored under refrigeration.

6.2. Preparation by Hot method [44]

- In this, phospholipid is dispersed in water in a water bath at 40°C until a colloidal solution is obtained. In another vessel, ethanol and glycol are mixed and heated up to 40°C.

- As temperature of both mixtures reaches 40°C, the organic phase is added to the aqueous phase. Add drug dissolved in suitable solvent (in water or ethanol depending upon solubility)

7. CHARACTERIZATION STUDIES OF ETHOSOMES

7.1. Vesicle shape

Ethosomes can be easily visualized by using Transmission Electron Microscopy (TEM) and by Scanning Electron Microscopy [45].

7.2. Vesicle size and zeta potential

Particle size can be determined by Dynamic Light Scattering (DLS) and Photo Correlation Spectroscopy (PCS). Zeta potential can be measured by Zeta meter [46].

7.3. Transition temperature

The transition temperature of the vesicular lipid systems can be confirmed by using Differential Scanning Calorimetric (DSC) [47].

7.4. Drug entrapment

It can be me assured by the ultracentrifugation technique [48].

7.5. Drug content

This can be determined using UV spectrophotometer. This can also be quantified by modified high performance liquid chromatographic method [49].

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 [50].

7.7. Stability studies

The solidness of vesicles can be controlled by asses sing the size and construction of the vesicles after some time. Mean size is measured by DLS and structure changes are observed by TEM [51].

7.8. 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) [52].

8. EVALUATION TESTS

Following tests are performed for the evaluation of ethosomes [53-56].

- Filter membrane-vesicle interaction
- Skin Permeation Studies
- Stability Study
- Vesicle-Skin Interaction Study by TEM and SEM
- Vesicle-Skin Interaction Study by Fluorescence Microscopy
- Drug Uptake Studies
- Statistical analysis

9. DETERMINATION OF DRUG CONTENTS

There are various methods of analytical methods commonly used for various pharmaceutical formulations. These methods include UV-spectroscopy, HPTLC, HPLC, gas chromatography, etc. [57-81].

Table 1: Marketed formulation of ethosomes [53].

S. N.	Product	Manufacturer	Uses
1.	Cellutight EF	Hampden Health, USA	To increase metabolism and break down fat.
2.	Decorin cream	Genome Cosmetics,Pennsylvania, US	Anti-aging cream
3.	Nanominox	Sinere, Germany	First minoxidil-loaded ethosomes product hair growth promoter
4.	Noicellex	Novel Therapeutic Technologies, Israel	Topical anti-cellulite cream
5.	Skin genuity	Physonics, Nottingham, UK	Powerful cellulite buster that reduces orange peel.
6.	Supravir cream	Trima, Israel	Formulation of acyclovir for thetreatment of herpes virus.

10. DISCUSSION AND CONCLUSION

Ethosomes are phospholipids vesicles which include ethanol to increase elasticity. Ethosomes are soft, malleable vesicles tailored for enhanced delivery of active agents, which makes them a promising contender for future transdermal drug delivery product. Enhanced delivery of bioactive molecules through the skin and cellular membranes by means of an ethosomal carrier unlocks an abundance of challenges and window of opportunities. Enhanced delivery of synthetic and herbal drug molecules through the skin and cellular membranes by means of an ethosomal carrier opens tremendous possibilities & opportunities for the research and future upcoming development of novel refined therapies.

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