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ETHOSOMES AS NOVEL DRUG DELIVERY CARRIERS – A REVIEW

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Abstarct:
To provide continuous drug infusion through an intact skin, several transdermal therapeutic systems have been developed for topical application onto the intact skin surface to control the delivery of drug and its subsequent permeation through the skin tissue. Transdermal route is promising alternative to drug delivery for systemic effect. Ethosomes are the ethanolic phospholipid vesicles which are used mainly for transdermal delivery of drugs. Ethosomes have higher penetration rate through the skin as compared to liposomes hence these can be used widely in place of liposomes. Ethosomes have become an area of research interest, because of its enhanced skin permeation, improved drug delivery, increased drug entrapment efficiency etc.

Key words: *Ethosomes, Phospholipids, Transdermal, Skin permeation*

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INTRODUCTION:

Transdermal drug delivery offers many advantages as compared to conventional drug delivery systems, including oral and parenteral drug delivery system. Transdermal route is one of the better alternative to achieve constant plasma levels for prolonged periods of time, which additionally could be advantageous because of less frequent dosing regimens [1]. Advantages claimed are increased patient acceptability, avoidance of first pass metabolism, predictable and extended duration of activity, minimizing side effects and utility of short half life drugs, improving physiological and pharmacological response, avoiding the fluctuation in drug levels. The barrier function govern by stratum coneum is main problem for delivery of drugs across the skin. The stratum corneum consists of corneocytes surrounded by lipid layers, which play an essential role in the barrier properties of the stratum corneum [3-4]. In order to increase the number of drugs administered via transdermal route, novel drug delivery systems have to be designed. These systems include use of physical means, such as iontophoresis, sonophoresis, microneedles, etc. and chemical means like penetration enhancers (surfactants and organic solvents) and biochemical means using liposomes, niosomes, transferosomes and ethosomes also have been reported to enhance permeability of drug through the stratum corneum[5].

The vesicles have been well known for their importance in cellular communication and particle transportation for many years. Researchers have understood the properties of vesicles structure for use in better drug delivery within their cavities, which would to tag the vesicle for cell specificity. One of the major advances in vesicle research was the finding a vesicle derivatives, known as an ethosomes[6].

Ethosomes

They are mainly used for the delivery of drugs through transdermal route. Drug can be entrapped in ethosomes which have various physicochemical characteristics i.e. hydrophilic, lipophilic, or amphiphilic [7,8]. Ethosomes are soft, malleable vesicles used for delivery of drugs to reach the deep skin layers and/or the systemic circulation. The size range of ethosomes may vary from nano meters to microns (μ) [9]. Ethosomes are the modified forms of liposomes that are high in ethanol content . The ethosomal system is composed of phospholipid (Phosphatidylcholine, phosphatidylserine, phosphatitidic acid), high concentration of alcohol (ethanol and isopropyl alcohol) and water. The high concentration of ethanol makes ethosomes unique because ethanol causes disturbance of skin lipid bilayer organization, hence when incorporated into a vesicle membrane, it enhances the vesicles' ability to penetrate the stratum corneum [10].

Composition of Ethosomes:[11,12]

The ethosomes are vesicular carrier comprised of hydroalcoholic or hydro/alcoholic/glycolic phospholipid in which the concentration of alcohols or their combination is relatively high. Typically, ethosomes may contain phospholipids with various chemical structures like 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). Such a composition enables delivery of high concentration of active ingredients through skin. Drug delivery can be modulated by altering alcohol: water or alcohol-polyol: water ratio. Some preferred phospholipids are soya phospholipids such as Phospholipon 90 (PL-90). It is usually employed in a range of 0.5-10% w/w. Cholesterol at concentrations ranging between 0.1-1% can also be added to the preparation. Examples of alcohols, which can be used, include ethanol and isopropyl alcohol. Among glycols, propylene glycol and Transcutol are generally used. In addition, non-ionic surfactants (PEG-alkyl ethers) can be combined with the phospholipids in these preparations. Cationic lipids like cocoamide, POE alkyl amines, dodecylamine, cetrimide etc. can be added too. The concentration of alcohol in the final product may range from 20 to 50%. The concentration of the non-aqueous phase (alcohol and glycol combination) may range between 22 to 70%. Table 1.

Table 1: Different Additives Employed In Formulation of Ethosomes

Class of Polymer	Example	Uses
Phospholipid	Soya phosphatidyl choline Egg phosphatidyl choline Dipalmityl phosphatidyl choline Distearyl phosphatidyl choline	Vesicles forming component
Polyglycol	Propylene glycol Transcutol RTM	As a skin penetration enhancer
Alcohol	Ethanol, Isopropyl alcohol	For providing the softness for vesicle membrane As a penetration enhancer
Cholesterol	Cholesterol	For providing the stability to vesicle membrane
Dye	Rhodamine-123 Rhodamine red Fluorence (FITC) 6-Carboxy fluorescence	For Characterization study
Vehicle	Carbopol 934	Gel forming agent

METHODS OF PREPARATION:

Cold method

This is the most common method utilized for the preparation of ethosomal formulation. In this method, phospholipid, drug and other lipid materials is mixed. Propylene glycol or other polyol is added during stirring. This mixture is heated to 300°C in a water bath. The water heated to 300°C in a separate vessel is added to the mixture, which is then stirred for 5 min in a covered vessel. The vesicle sizes can be decreased to desire extend using sonication or extrusion method. Finally, formulation is stored under refrigeration[13].

Hot method

In this method, phospholipid is dispersed in water by heating in a water bath at 400°C until a colloidal solution is obtained. In a separate vessel ethanol and propylene glycol are mixed and heated to 400°C. Once both mixtures reach 400°C, the organic phase is added to the aqueous one. The drug is dissolved in water or ethanol depending on its hydrophilic/hydrophobic properties. The vesicle size of ethosomal formulation can be decreased to the desired extent using probe sonication or extrusion method [14,15].

Classic method

The phospholipid and drug are dissolved in ethanol and heated to 30°C±1°C in a water bath. Double distilled water is added in a fine stream to the lipid mixture, with constant stirring at 700 rpm, in a closed vessel. The resulting vesicle suspension is homogenized by passing through a polycarbonate membrane using a hand extruder for three cycles[13].

Mechanical dispersion method

Soya phosphotidylcholine is dissolved in a mixture of chloroform: methanol in round bottom flask (RBF). The organic solvents are removed using rotary vacuum evaporator above lipid transition temperature to form a thin lipid film on wall of the RBF. 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 RBF at suitable temperature [16].

Characterizations of Ethosomes

1. **Visualization**

Visualization of ethosomes can be done using transmission electron microscopy (TEM) and by scanning electron microscopy (SEM) [17].

2. **Vesicle size and Zeta potential**

Particle size and zeta potential can be determined by dynamic light scattering (DLS) using a computerized inspection system and photon correlation spectroscopy (PCS)[18].

3. **Differential scanning calorimertry (DSC)**

Transition temperature (Tm) of the vesicular lipid systems was determined by using the Mettler DSC 60 computerized with Mettler Toledo star software system (Mettler, Switzerland).The transition temperature was measured by using the aluminium crucibles at a heating rate 10 degree/minute, within a temperature range from 20˚C–300˚C [19,20].

4. **Surface Tension Activity Measurement**

The surface tension activity of drug in aqueous solution can be measured by the ring method in a Du Nouy ring tensiometer [19,20].

5. **Entrapment Efficiency**

The entrapment efficiency of drug by ethosomes can be measured by the ultra centrifugation technique[20].

6. **Penetration and Permeation Studies**

Depth of penetration from ethosomes can be visualized by confocal laser scanning[17]

7. **Vesicle Stability**

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[17,19,20].

8. **In vitro drug release study and Drug Deposition study**

In vitro drug release study and Drug Deposition of ethosomal preparation can be performed by Franz diffusion cell with artificial or biological membrane, Dialysis bag diffusion.

Advantages of ethosomal drug delivery

1. In comparison to other transdermal & dermal delivery systems
2. Enhanced permeation of drug through skin for transdermal drug delivery.
3. Delivery of large molecules (peptides, protein molecules) is possible.
4. It contains non- toxic raw material in formulation.
5. High patient compliance- The ethosomal drug is administrated in semisolid form (gel or cream) hence producing high patient compliance.
6. The Ethosomal system is passive, non-invasive and is available for immediate commercialization.
7. Ethosomal drug delivery system can be applied widely in Pharmaceutical, Veterinary, Cosmetic fields.
8. Simple method for drug delivery in comparison to iontophoresis and phosphophoresis and other complicated methods.

Applications of Ethosomes

1. Delivery of Anti-Viral Drugs
2. Topical Delivery of DNA
3. Transdermal Delivery of Hormones
4. Delivery of anti-parkinsonism agent
5. Transcellular Delivery
6. Delivery of Anti-Arthritis Drug
7. Delivery of Antibiotics

CONCLUSION:

The main limiting factor of transdermal drug delivery system i.e. epidermal barrier can be overcome by ethosomes to significant extent. The ethosomes have more advantages when compared to transdermal and dermal delivery. Ethosomes are the non invasive drug delivery carriers that enable drugs to reach the deep layers of skin and delivering to the systemic circulation. It delivers large molecules such as peptides, protein molecules. Ethosomal drug delivery is aimple method for drug delivery in comparison to Iontophoresis and Phonophoresis and other complicated methods. High patient compliance as it is administrated in semisolid form (gel or cream) and also finds various application in Pharmaceutical, Veterinary, Cosmetic field.

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