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A REVIEW ON NOVELTRENDS IN VESICULAR CARRIER FOR ENHANCED TRANSDERMAL DELIVERY: ETHOSOMES

Pharmaceuticals

KEYWORDS: Transdermal drug delivery, ethosomes, noninvasive, ethanol, phospholipid.

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ABSTRACT

Skin acts as a major target as well as a principal barrier for topical/transdermal drug delivery. Despite the many advantages of this system, the major obstacle is the low diffusion rate of drugs across the stratum corneum. One simple and convenient approach is application of drugs in formulation with elastic vesicles or skin enhancers. Ethosomes are novel non-invasive ethanolic phospholipids came into existence from 1997 which acts as skin enhancers and carries the drug across stratum corneum and make them available in deeper layers of skin. The ethosomes can be prepared by hot method, Cold method and optimized method. The evaluation parameters of ethosomes include visualization, vesicle size and zeta potential, entrapment efficiency. Ethosomes have been found to be much more efficient at delivering drug to the skin than either liposomes or hydroalcoholic solution. The comprehension of this review is to illuminate the main aspects of ethosomes such as structure, composition, mechanism of penetration, advantages, available marketed products etc.

INTRODUCTION:

Transdermal drug delivery offers many advantages as compared to traditional drug delivery systems, including oral and parenteral drug delivery system. Skin is the largest human organ and consists of three functional layers: epidermis, dermis, and subcutis. It has a wide variety of functions. One major task of the skin is to protect the organism from water loss and mechanical, chemical, microbial and physical influences.[1] The protective properties are provided by the outermost layer (epidermis) of the skin (Engstrom et al 2000). 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.[2]To overcome the stratum corneum barrier, various mechanisms have been investigated, including use of chemical or physical enhancers, such as iontophoresis, sonophoresis, etc. Liposomes, niosomes, transferosomes and ethosomes also have the potential of overcoming the skin barrier and have been reported to enhance permeability of drug through the stratum corneum barrier. 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 (Elsayed et al 2006).

ETHOSOMES

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 [3](Verma and Fahr, 2004; Bhalaria et al 2009). 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 tens of nano meters to microns (μ) (Patel, 2007). Ethosomes are the modified forms of liposomes that are high in ethanol content (Figure 1). The ethosomal system is composed of phospholipid (Phosphatidylcholine, phosphatidyl serine, phosphatitidic acid), high concentration of alcohol (ethanol and isopropyl alcohol) and water[4]. 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 (Ceve 2004).

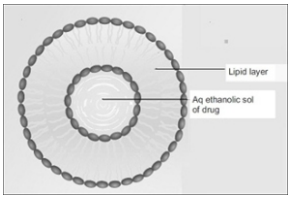


Fig. 1. Representation of ethosomes contents

Composition

The ethosomes are composed of hydroalcoholic or hydro/glycolic phospholipid in which the concentration of alcohol is relatively high. Typically, ethosomes may contain phospholipids with various chemical structures like phosphatidylcholine (PC), hydrogenated PC, phosphatidic acid (PA), phosphatidylserine (PS), phosphatidyl ethanolamine (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%.[5]

MECHANISM OF DRUG PENETRATION

The main advantage of ethosomes over liposomes is the increased permeation of the drug. The mechanism of the drug absorption from ethosomes is not clear. The drug absorption probably occurs in following two phases:

1. Ethanol effect
2. Ethosomes effect

1. ETHANNOL EFFECT

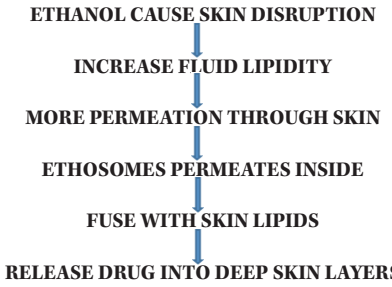
Ethanol acts as a penetration enhancer through the skin. The mechanism of its penetration enhancing effect is well known. Ethanol penetrates into intercellular lipids and increases the fluidity of cell membrane lipids and decrease the density of lipid multilayer of cell membrane.[6]

2. ETHOSOMES EFFECT

Increased cell membrane lipid fluidity caused by the ethanol of ethosomes results increased skin permiability So the ethosomes permeates very easily inside the deep skin layers, where it got fused with skin lipids and releases the drugs into deep layer of skin.[7]

MECHANISM OF ACTION

ETHOSOMES



Method 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 (Manosroi et al 2009).[8]

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 (Bhalaria et al 2009; Touitou, 1998). [8]

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 (Manosroi et al 2009). 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 hydro ethanolic mixture containing drug by rotating the RBF at suitable temperature (Dubey et al 2007).[9]

CHARACTERIZATION OF ETHOSOMES

Visualization of vesicles: Transmission electron microscopy (TEM) and scanning electron microscopy (SEM) [10]

Vesicle size and zeta potential: Dynamic light scattering (DLS) and photon correlation spectroscopy (PCS). Zeta potential is an important parameter that affects the aggregation of vesicles and depicts the physical stability of vesicular systems and it can be measured by Zeta meter [11]

Entrapment efficiency: Ultracentrifugation technique.[12]

Surface tension activity measurement Ring method in a Du Nouy ring tensiometer (Cevc, 2004).

Transition temperature Differential scanning calorimetry.[13]

Penetration and permeation studies Depth of penetration from ethosomes can be visualized by confocal laser scanning microscopy (CLSM).[14]

Stability of ethosomes: the ability of ethosomal formulations to retain the drug was checked by keeping the preparations at different temperatures, i.e. 25±2°C (room temperature), 37±2°C and 45±2°C for different periods of time. The stability of ethosomes can also be determined quantitatively by monitoring size and morphology of the vesicles using DLS and TEM (Toll et al 2004). Degree of deformability and turbidity.the degree of deformability of the ethosomal preparation can be performed by extrusion method and the turbidity of the preparation can be performed by using nephelometer.[15,16]

APPLICATIONS OF ETHOSOMES:

DRUG	RESULTS
Trihexyphenidyl hydrochloride[17]	Improved transdermal flux↓ Provide controlled release↓ Improved patient compliance
Insulin[18]	Significant decrease in blood glucose level ↓Provide control release ↓
Acyclovir[19]	Increase skin permeation↓ Improved in biological activity two to three times↓ Improved in Pharmacodynamic profile↓
NSAIDS (Diclofenac)[20]	Sel↓ective delivery of drug to desired side for prolong period of time
DNA	Better expression of genes↓ Selective targeting to dermal cells↓
Bacitracin[21]	Improved dermal deposition↓ Improved intracellular delivery↓ Increased bioavailability↓
Anti-HIV agents Zidovudine Lamivudine[22]	Improved transdermal flux↓ Improved in biological activity two to three times↓ Prolonging drug action↓ Reduced drug toxicity↓ Affected the normal histology of skin↓
Ammonium glycyrrhizinate[23]	Improved dermal deposition exhibiting sustained release↓ Improved biological anti-inflammatory activity↓

Table 1: applications of ethosomes

Factors affecting physical nature of ethosomes:

There are some factors such as hydration temperature, choice of surfactant, nature of membrane, nature of drug, etc., can affect significantly the physical nature of ethosomes. Hydration temperature Choice of main surfactant Nature of drug Nature of membrane additives Size reduction techniques Addition of kinetic energy

MARKETED FORMULATIONS OF ETHOSOMES:

Noicellex TM an anti – cellulite formulation of ethosome is currently marketed in Japan. Lipoduction TM another formulation is currently used in treatment of cellulite which contains pure grape seed extracts (antioxidant) is marketed in USA. Similarly Physonics is marketing anti - cellulite gel in London. Nanominox© containing monoxidil is used as hair tonic to promote hair growth is marketed by Sinere

CONCLUSION:

The main disadvantage of transdermal drug delivery is the poor penetration of most compounds into the human skin.it can be easily concluded that ethosomes can provide better skin permeation than other vesicular carriers like liposomes. They have potential ability to transport drugs such as hydrophilic, lipophilic, peptides, cationic drugs, proteins and peptides. Many researches are going on them to allow better control over drugs release in in-vivo, increasing their safety data and for effective therapy.

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