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ETHOSOMES: A CURRENT TECHNOLOGY FOR DRUG DELIVERY VIA TOPICAL ROUTE

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ABSTRACT

Ethosomes are phospholipid-based elastic nanovesicles containing a high content of ethanol(20-45%). Ethosomal systems are much more efficient in delivering substances to the skin in the terms of quantityand depth, than either conventional liposomes or hydroalcoholic solutions.Ethosomes used mainly for transdermal delivery of drugs. Enhanced delivery of bioactivemolecules through the skin and cellular membranes by means of an ethosomal carrier opens numerous challengesand opportunities for the research and future development of novel improved therapies.

INTRODUCTION:

Continuous intravenous infusion is recognized as a superior mode of drug administration notonly to bypass hepatic first-pass metabolism, but also to maintain a constant and prolongeddrug level in the body. To provide continuous drug infusion through an intact skin, several transdermal [1] therapeuticsystems have been developed for topical application onto the intact skin surface to control thedelivery of drug and its subsequent permeation through the skin tissue. The intensity of interests in the potential biomedical applications of transdermal controlleddrug administration is demonstrated in the increasing research activities in a number of healthcare institutions in the development of various types of transdermal therapeutic systems forlong term continuous infusion of therapeutic agents, including antihypertensive, anti-anginal,anti-histamine, anti-inflammatory, analgesic, anti-arthritic steroidal, and contraceptive drugs. To improve the permeation ofdrugs through the skin various mechanisms have beeninvestigated, including use of chemical or physical enhancers,such as iontophoresis, sonophoresis, etc. Liposomes, niosomes,transferosomes and ethosomes also have been reported toenhance

permeability of drug through the stratum corneumbarrier. Permeation enhancers increase the permeability ofthe skin, so that the drugs can cross through the skin easily.Unlike classic liposomes that are known mainly to deliverdrugs to the outer layers of skin, ethosomes can enhance permeation through the stratum corneum barrier **[2]**.Ethosomes permeate through the skin layers more rapidlyand possess significantly higher transdermal flux incomparison to conventional liposomes.Ethosomes are lipid vesicles containing phospholipids,alcohol (ethanol and isopropyl alcohol) in relatively highconcentration and water. Ethosomes are soft vesicles made ofphospholipids and ethanol (in higher quantity) and water.Ethosomes [3] are defined as noninvasive delivery carriers that enable drugs to reach deep into the skin layers or systemic circulation. These are soft, malleable vesicles tailored for enhanced delivery of active agents. The vesicles have been well known for their importance in cellular communication and for many years. Vesicles would also allow controlling the release rate of drug over an extended time, keeping the drug shielded from immune response or other removal systems and thus be able to release just the right amount of drug and keep that concentration constant for longer period of time.

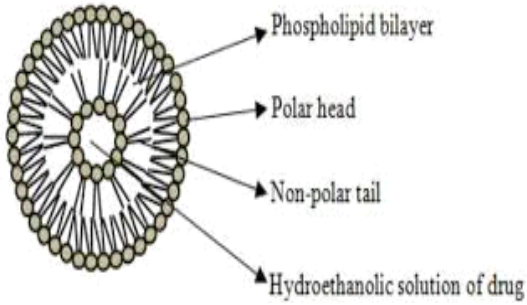

Figure 1: Structure of ethosome

Structure of Skin:

The skin is a multi-layered structure [4] made up of stratum corneum (SC), the outermost layer, under which lies the epidermis and dermis. Stratum corneum is the outermost layer of the epidermis. It consists of 10 to 25 layers of dead, elongated, fully keratinized corneocytes, which are embedded in a matrix of lipid bilayers. It has been shown that the stratum corneum is the main barrier to penetration through the skin. When a topical formulation is placed on the skin, the active drug is required to penetrate through the stratum corneum into the viable tissue. The limiting factor for these processes is the slow diffusion through the dead horny layer of skin. Stratum corneum behaves as a hydrophobic membrane. Within these layers of skin are interspersed fibroblasts, hair follicles and sweat glands that originate in the dermis blood supply.

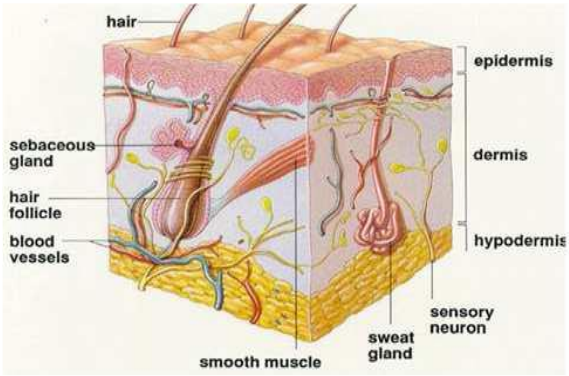

Figure 2: Structure of skin

To overcome the stratum corneum barrier, various mechanisms have been investigated, including use of chemical or physical enhancers such as iontophoresis, sonophoresis, etc. Liposomes [5], niosomes, transferosomes and ethosomesalso have the potential of overcoming the skin barrier and have been reported to enhance permeability of drug through the stratum corneum barrier.Ethosomes are ethanolic liposomes.

Types of ethosomal systems

Classical ethosomes: Classical ethosomes are a modification of classical liposomes and are composed of phospholipids, a high concentration of ethanol up to 45% w/w, and

water. Classical ethosomes were reported to be superior over classical liposomes for transdermal drug delivery because they were smaller and had negative ζ-potential and higher entrapment efficiency. Moreover, classical ethosomes showed better skin permeation and stability profiles compared to classical liposomes.

Binary ethosomes: Binary ethosomes were developed by adding another type of alcohol to the classical ethosomes. The most commonly used alcohols in binary ethosomes are propylene glycol (PG) and isopropyl alcohol (IPA).

Transethosomes: This ethosomal system contains the basic components of classical ethosomes and an additional compound, such as a penetration enhancer or an edge activator (surfactant) in their formula. 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.

Advantages of ethosomal drug delivery [5, 6]

1. Delivery of large molecules (peptides, protein molecules) is possible.
2. It contains non-toxic raw material in formulation.
3. Enhanced permeation of drug through skin for transdermal drug delivery.
4. It can be applied widely in pharmaceutical, veterinary, cosmetic fields.
5. It has high patient compliance.
6. The ethosomal system is passive, and non-invasive in nature.

Disadvantages of ethosomal drug delivery [7, 8]

1. It is limited only to potent molecules, those requiring a daily dose of 10mg or less.
2. It is not a means to achieve rapid bolus type drug input, rather it usually designed to offer slow, sustained drug delivery.
3. The molecular size of the drug should be reasonable that it should be absorbed percutaneously.
4. Adhesive may not adhere well to all types of skin.
5. It may not be economical as well as giving poor yield.
6. Skin irritation or dermatitis due to excipients and enhancers of drug delivery systems.

Composition of ethosomes [9, 10]:

They are composed mainly of phospholipids, high concentration of ethanol and water. The ethosomes are vesicular carrier comprise 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). Drug delivery can be modulated by altering alcohol: water or alcohol-polyol: water ratio.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 to concentration of the nonaqueous phase

(alcohol and glycol combination) may range between 22 to 70%.

Methods of preparation of ethosomes [11, 12]

Ethosomes can be prepared by two very simple and convenient methods such as cold method and hot method.

- **Cold Method** :

In this method phospholipid, drug and other lipid materials are dissolved in ethanol in a covered vessel at room temperature by vigorous stirring with the use of mixer. Propylene glycol or other polyol is added during stirring. This mixture is heated to 30^0C in a water bath. The water heated to 30^0C in a separate vessel is added to the mixture, which is then stirred for 5 min in a covered vessel. The vesicle size of ethosomal formulation can be decreased to desire extend using sonicationor extrusion method. Finally, the formulation is stored under refrigera

- **Hot method**

In this method phospholipid is dispersed in water by heating in a water bath at 40^0C until a colloidal solution is obtained. In a separate vessel ethanol and propylene glycol are mixed and heated to 40^0C. Once both mixtures reach 40^0C, 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 desire extent using probe sonication or extrusion method.

Characterisation of ethosomes [13-14]

1. **Vesicle shape**: Transmission Electron Microscopy (TEM) And scanningelectronic Microscopy (SEM) are used to characterize the surface morphology of the ethosomal vesicles.
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).
3. **Entrapment Efficiency**: Ultracentrifugation technique is used to measure the entrapment efficiency of ethosomes. The vesicles are separated in a high speed cooling centrifuge at 20,000 rpm for 90 minutes maintaining the temperature at 4°C.Separate the sediment and Supernatant liquids. Determine the amount of drug in the sediment by lysing the vesicles usingmethanol. The entrapment efficiency by the following equation

Entrapment efficiency$= \frac{De}{Dt} \times 100$(1)

De - Amount of drug in the ethosomal sediment Dt - Theoretical amount of drug used to prepare the formulation (Equal to amount of drug in supernatant liquid and in the sediment)

4. **Transition Temperature:** The transition temperature of the vesicular lipid systems can be determined by using differential scanning calorimetry.

5.Drug content:

Drug content of the ethosomes can be determined using UV spectrophotometer. This can also be quantified by a modified high performance liquid chromatographic method.

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.Stability studies:

The ability of ethosomal formulations to retain the drug was checked by keeping the preparations at different temperatures, *i.e.*25±2°C, 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.

Table 1: Composition of ethosomes

S.No	Materials	Examples	Uses
1	Phospholipid	Soya Phosphatidyl Choline Egg Phosphatidyl Choline Dipalmitylphosphatidyl Choline Distearylphosphatidyl Choline	Vesicles Forming Component
2	Polyglycol	Propylene Glycol TranscutolRtm	As A Skin Penetration Enhancer
3	Alcohol	Ethanol Isopropyl Alcohol	For Providing The Softness For Vesicle Membrane As A Penetration Enhancer
4	Cholesterol	Cholesterol	For Providing The Stability To Vesicle Membrane
5	Dye	Rhodamine-123 Rhodamine Red Fluorescenisothiocynate (Fitc) 6- Carboxy Fluorescence	Rhodamine-123 Rhodamine Red Fluorescenisothiocynate (Fitc) 6- Carboxy Fluorescence
6	Vehicle	Carbopol 934	As A Gel Former

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).

Application of ethosomes [15, 16]

1. **Treatment of microbial and viral skin infections:** Ethosomal systems containing antibiotic drugs have beeninvestigated in the treatment of various skin infections.Bacitracin and erythromycin ethosomal systems were formulatedand tested for their efficiency in animal modelsof deep skin infections.
2. **Anti-inflammatory ethosomal systems [17, 18]:** Ammonium glycyrrhizinate (AG) ethosome was testedby Paolino and colleagues for the treatment ofinflammatory-based skin diseases on human volunteerswith methyl-nicotinate chemically induced erythema.Results showed that AG ethosomes induced a significant reduction in the intensity and the duration of erythemawith respect to the other formulations.
3. **Ethosomal systems for menopausal syndromes [19]:** Ethosomal compositions have been tested for their efficiency in the treatment of androgen deficiency associated with menopause in men and menopausal syndromes in women. A testosterone ethosomal patch system, Testosome, was designed for the treatment of androgendeficiency in men.
4. **Management of erectile dysfunction:** In an in-office pilot clinical study, carried out among menwith episodes of erectile dysfunction, patients we retreated with ethosomal prostaglandin E1 (PGE1_ systemsapplied on the glans penis. The patients were asked toevaluate their ability to have sexual intercourse by scoringthe erectile response, in addition to erection assessment by a physician.
5. **Analgesic and antipyretic ethosomal systems:** A recent study

investigated the *in vivo* analgesic andantipyretic therapeutic effects of transdermal ethosomalibuprofen in two animal models, the Brewer's yeastinduced fever rat and tail flick nociception mice.

6. **Topical delivery of DNA:** Ethosomes is to use them for topical delivery of DNA molecules to express genes in skin cells. It was suggested that ethosomes could be used as carriers for gene therapy applications that require transient expression of genes.

CONCLUSION:

Ethosomes are soft, malleable vesicle and potenial carrier for transportation of drugs giving improved therapies. These are characterised by simplicity in their preparation, saftey and efficacy and can be tailored for enchanced skin permeation of active drugs. It can be easily concluded that ethosomes can provide better skin permeation than liposomes. The main limiting factor of transdermal drug delivery system i.e. epidermal barrier can be overcome by ethosomes to significant extent.

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