



Ethosome: A Novel Approach to Enhance Drug Permeation

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ABSTRACT

Skin offers an excellent barrier to molecular transport. Except for highly lipophilic, low molecular weight drugs SC is the most fearsome barrier to the passage of most of the drugs. Various approaches have been made for increased drug delivery into the body through the intact skin including using lipid vesicles like liposome, niosomes etc. Classic liposomes do not deeply penetrate the skin hence they are of little or no value as carriers for transdermal drug delivery. One of the major advances in vesicle research is the finding that some specially designed vesicles possessed properties that allowed them to successfully deliver drugs in deeper layer of skin. Ethosome is one of the specially designed lipid carrier recently developed.

Keywords: Ethosomes, liposomes, stratum corneum (SC).

INTRODUCTION

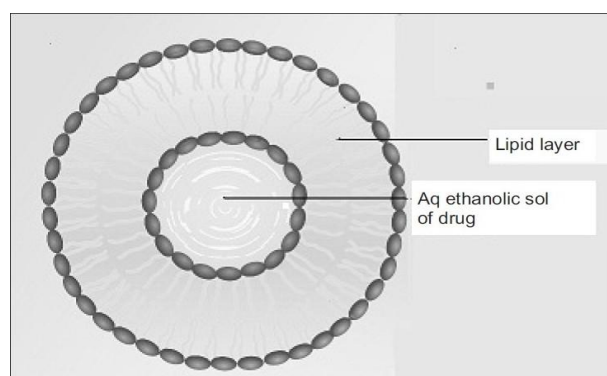
As compared to traditional drug delivery systems transdermal delivery of drugs through the skin to the systemic circulation offers many advantages such as transdermal drug delivery system (TDDS) showed promising lead to comparison to oral drug delivery system because it eliminates GI interferences and first pass metabolism of the drug however the most disadvantage of TDDS is it encounters the barrier properties of the Stratum Corneum.^{1,3,4}

Varied mechanisms are investigated, together with use of chemical or physical enhancers, iontophoresis, sonophoresis, etc to enhance the penetration of drug through the skin. Vesicular systems like liposomes, niosomes, transferosomes and ethosomes even have been reportable to increase permeability of medication through the percutaneous barrier. The permeability of the skin enhanced by penetration enhancer, so that the drugs can cross through the skin easily. Classic liposomes are known mainly to deliver drugs to the outer layers of the skin, unlike classic liposomes ethosomes can enhance penetration through the stratum corneum barrier. Ethosomes penetrate faster through the skin layers and possess considerably higher percutaneous flux as compared to classic liposomes.³

ETHOSOME

"Ethosomes are ethanolic liposomes". Ethosomes are noninvasive soft, malleable vesicular delivery carriers that enable drugs to reach the deep skin layers and/or the systemic circulation and enhanced the delivery of active agents. They're composed of phospholipids, (phosphatidylcholine, phosphatidylserine, phosphatidic acid), high concentration of ethyl alcohol (ethanol) and water. As ethanol is known for its disturbance of skin lipid bilayer organization, the high concentration of ethanol

makes the ethosomes unique; therefore, when integrated into a vesicle membrane, ethanol gives ability to the vesicle to penetrate the stratum corneum. Also, due to their high alcohol concentration, the lipid membrane is packed less tightly than typical vesicles. However it has equivalent stability, permitting an additional malleable structure and improves drug distribution ability in stratum lipids.^{5,6,7} Within the pharmaceutical, biotechnology, veterinary, cosmetic, and nutraceutical markets the Ethosomes were found to be suitable for various applications. These soft vesicles are often modulated from tens of nanometers to microns.^{6,8}



ETHANOL- AS PENETRATION ENHANCER

Chemical penetration enhancers are those substances that reversibly reduce the barrier resistance of the stratum corneum. Among them one of the most commonly used penetration enhancer is ethanol. A number of mechanisms have been proposed for penetration enhancing action of ethanol. To enhance the solubility of the drug, ethanol can be included in the formulation, as a solvent. Poorly soluble permeants are prone to depletion in the donor vehicle hence this is particularly important for them. Ethanol will rapidly evaporate at skin temperature since it is a relatively volatile solvent. Ethanol loss from a formulation result in

the supersaturation of the drug which will influence the drug flux across the membrane. In addition, ethanol facilitates improved drug partitioning by altering the solubility properties of the stratum corneum. To reinforce the percutaneous delivery of levonorgestrel, corticosteroid and 5-fluorouracil across gnawing animal skin, ethyl alcohol has been used in vitro and oestrogen across human skin in-vivo. It has been reported that the enhancement effect of ethanol was concentration dependent. Once work the impact of ethyl alcohol on skin water content it's been over that formulations containing high levels of alcohol were capable of dehydrating the skin, which can justify the concentration dependant action of ethanol.^{9,10,11}

INFLUENCE OF HIGH ALCOHOL CONTENT

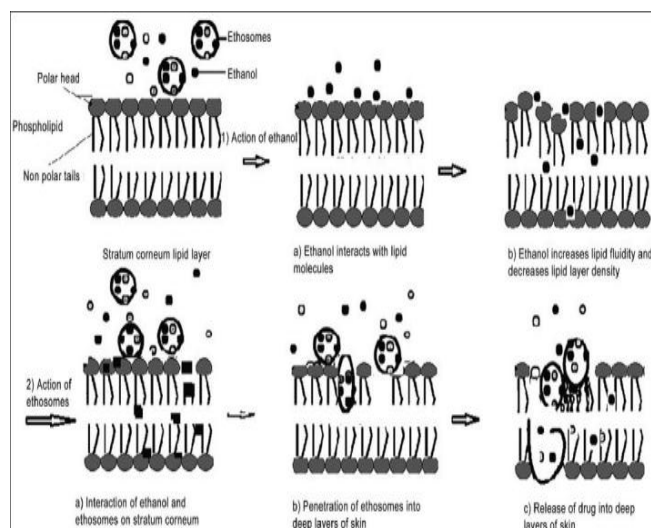
Ethanol is an efficient penetration enhancer. Ethanol is present in 20-50% in ethosomes. However, because of the interlock impact of ethyl alcohol on supermolecule (lipid) bilayers, it absolutely was usually believed that vesicles couldn't be with high concentration of ethyl alcohol. Touitou investigated and discovered supermolecule sac systems contain ethyl alcohol in comparatively high concentration and named them ethosomes. Liposomes and ethosomes are differ in their composition.

The main reason behind the suggestion of the synergistic impact of combination of comparatively high concentration of ethyl alcohol (20-50%) in sac type in ethosomes was their higher skin penetration ability. The skin lipid bilayer organization can be disturbed by the high concentration of ethanol (20-50%) in ethosomal formulation. Therefore, it could give an ability to the vesicles to penetrate the stratum corneum, when integrated into a vesicle membrane. Furthermore, the ethosomal lipid membrane was packed less tightly but possessed equivalent stability as that of conventional vesicles due to high ethanol concentration. This allowed a softer and malleable structure giving more freedom and stability to its membrane, which could squeeze through small openings created in the disturbed stratum corneum lipids. In addition, by varying the ratio of components and chemical structure of the phospholipids, the vesicular nature of ethosomal formulations could be modified. The flexibility of ethosomes for general delivery is clear from the reports of increased delivery of quite an few medication like Zovirax, minoxidil, triphexyphenidyl, androgenic hormone, cannabidol and zidovudine.^{9,12}

MECHANISM OF DRUG PENETRATION

➤ Ethanol effect: Ethanol acts as a penetration enhancer and penetrates into intercellular lipids, which enhances the fluidity of cell membrane lipids and reduces the density of lipid multilayer of cell membrane.

➤ Ethosomes effect: Inflated cytomembrane lipid fluidity followed by the ethyl alcohol effect that is gift within the ethosome leads to associate degree inflated skin porosity. As a results of this, ethosomes penetrates terribly simply within the deep skin layers, wherever it got amalgamate with skin lipids and releases the medication into deep layer of skin.^{5,13,14}



Advantages

1. Delivery of large and diverse group of drugs (peptides, protein molecules) are possible.
2. Safe composition, with non-toxic components.
3. Components are approved for pharmaceutical and cosmetic use.
4. High patient compliance.
5. Simple technique as compared to Iontophoresis and Phonophoresis.
6. Passive, noninvasive and is available for immediate commercialization.
7. Wide range of application in Pharmaceutical, Veterinary, Cosmetic field.
8. More penetration through skin as compared to conventional forms.^{3,15,13}

Disadvantages

1. Ethosomal administration is n't a way to attain speedy bolus sort drug input, rather it always designed to supply slow, sustained drug delivery.
2. The molecular size of the drug ought to be cheap that it ought to be absorbed percutaneously.
3. Adhesive may not adhere well to all types of skin.
4. May not be economical.
5. Poor yield.

6. Skin irritation or dermatitis due to excipients and enhancers of drug delivery systems.

7. Just in case if shell protection is ineffective then the ethosomes could coalesce and fall aside on transfer into water.

8. Loss of product during transfer from organic to water media.²

METHODS OF PREPARATION OF ETHOSOMES

Ethosomes can be prepared by three very simple and convenient methods that is;

1. Cold method
2. Hot method
3. Classic Mechanical Dispersion Method

1. Cold Method

In a covered vessel at room temperature phospholipid, drug and other lipid materials are dissolved in ethanol by vigorous stirring with the use of mixer. During stirring propylene glycol or other polyol is added. At 30⁰C, in a water bath the mixture is heated. In a separate vessel water is heated to 30⁰C and is added to the mixture, which is then stirred for 5 min in a covered vessel. Using sonication or extrusion method vesicle size of ethosomal formulation can be decreased to desire extend. The formulation is stored under refrigerator finally.^{3,16,17}

2. Hot method

At 40⁰C phospholipid is dispersed in water by heating in a water bath until a colloidal solution is obtained. Ethanol and propylene glycol are mixed in a separate vessel and heated to 40⁰C. The organic phase is added to the aqueous phase, once both mixtures reach 40⁰C. Depending on hydrophilic/ hydrophobic property of the drug it is dissolved in water or ethanol. Using probe sonication or extrusion method the vesicle size of ethosomal formulation can be decreased to the desire extent.^{3,16,18}

3. Classic Mechanical Dispersion Method

Soya phosphatidylcholine is dissolved in a mixture of ethanol:chloroform (1:3) in round bottom flask. The organic solvents 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 completed with totally different concentration of hydroethanolic mixture containing drug by rotating the flask at appropriate temperature.¹⁶

VARIOUS METHODS OF CHARACTERIZATION OF ETHOSOMES

1. Surface morphology: For vesicular shape and surface morphology studies Transmission Electron Microscope (TEM) and Scanning electron microscope (SEM) can be

used. Using phosphotungstic acid as negative stain, TEM can be performed.

2. Vesicle size and size distribution: Ethosome size and size distribution can be done by dynamic light scattering method (DLS) using computerized inspection system.

3. Entrapment efficiency: By ultracentrifugation technique, mini column centrifugation method and fluorescence spectrophotometry the ability of ethosomes to efficiently entrap lipophilic and hydrophilic drugs can be measured.

4. Glass transition temperature: By using differential scanning calorimetry (DSC).

the glass transition temperature of the vesicular lipid systems can be determined.

5. surface tension activity measurement: By Du Nouy ring tensiometer surface physical phenomenon activity of ethosomes are often measured in solution.

6. Turbidity: It can be measured by nephelometer.

7. Vesicle skin interaction study: Vesicle skin interaction study can be done by examining under transmission electron microscopy or confocal laser scanning microscope (CSLM) or fluorescence microscope or eosin – hematoxylin staining. For microscopy ethosomes ought to be loaded with visible radiation marker like rhodamine123.

8. Degree of deformability or Elasticity measurement: The elasticity of ethosome vesicle membrane can be determined by extrusion technique. The ethosomal formulation are extruded through filter membrane (pore diameter 50 nm) using stainless steel filter holder of diameter 25 nm, by applying a pressure of 2.5 bar.

9. Zeta potential: Zeta potential can be measured by zeta meter or dynamic light scattering method (DLS).¹

APPLICATIONS

1. Pilosebaceous targeting

In the percutaneous drug delivery hair follicles and greasy glands are more and more being recognized, as doubtless important components. Moreover, substantial attentions are been targeted on exploiting the follicles as transport shunts for general drug delivery. Rogaine is employed locally on the scalp for the treatment of phalacrosis, which may be a lipid soluble drug, by pilosebaceous delivery. Interest in oil gland units has been directed towards their use as depots for localized medical aid, notably for the treatment of follicle-related disorders such as acne or alopecia.

2. Transcellular Delivery

Touitou et al., in their study incontestible higher living thing uptake of antibiotic drug, desoxyribonucleic acid and E-Mycin victimization CLSM and FACS techniques in several cell lines. Higher cellular uptake of anti-HIV drug ZDV and nucleoside reverse transcriptase inhibitor in MT-



2 cell line from ethosomes as compared to the marketed formulation urged ethosomes to be a sexy clinical different for anti-HIV medical aid.

3. Delivery of problematic drug molecules

Oral delivery of enormous biogenic molecules such as peptides or proteins and hormone is troublesome as a result of they're utterly degraded within the GIT tract hence percutaneous delivery maybe a higher different. However typical percutaneous formulation of biogenic molecules such as peptides or macromolecule and hormone has poor penetration. Formulating these on top of molecules into ethosomes considerably increase penetration and therapeutic effectuality.

4. Transdermal Delivery of Hormones

Oral administration of hormones is related to issues like high first pass metabolism, low oral bioavailability and several other doses dependent side effects. The danger of failure of treatment is thought to extend with every pill incomprehensible .

5. Delivery of Anti-Arthritis Drug

Topical delivery of anti-arthritis drug may be a higher choice for its site-specific delivery and overcomes the matter related to typical oral medical aid.

6. Delivery of Antibiotics

Topical delivery of antibiotics may be a better option for increasing the therapeutic effectuality of these agents. Typical oral medical aid causes many aversions along with many side effects. Ethosomes penetrate quickly through the stratum and convey considerable quantity of medication into the deeper layer of skin than conventional forms and suppress infection at their root. Based on this Godin and Touitou ready-antibiotic drug and E-Mycin loaded ethosomal formulation for dermal delivery. Antibiotic loaded formulation of ethosomes are extremely economical. Also it would overcome the issues related to typical medical aid.

7. Cosmeceutical Applications of Ethosomes

The advantage of applying ethosomes in cosmeceuticals isn't solely to extend the steadiness of the cosmetic chemicals and reduce skin irritation from the irritating cosmetic chemicals, however conjointly for percutaneous sweetening, particularly within the elastic forms. However, the compositions and sizes of the vesicles are the most factors to be thought of to get these blessings of the elastic vesicles for cosmeceuticals applications.

8. Topical delivery of DNA

Many environmental pathogens conceive to enter the body through the skin. Skin so, has evolved into a wonderful protecting barrier, that is additionally immunologically active and ready to categorical the cistron. On the premise of on top of facts another necessary application of ethosomes is to use them for

topical delivery of deoxyribonucleic acid molecules to specific genes in skin cells. Touitou et al. in their study ethosomal formulation was prepared by encapsulating the GFP-CMV driven transfecting construct. This formulation was applied for 48hrs on the dorsal skin of 5-week male CD1 nude mice. After 48th hour, treated skin was removed. Penetration of inexperienced fluorescent macromolecule (GFP) formulation was determined by CLSM. And expression of genes in skin cells. It absolutely was urged that ethosomes might be used as carriers for cistron medical aid applications that need transient expression of genes. These results conjointly showed the chance of victimization ethosomes for effective percutaneous protection. Gupta et al. recently reported immunization potential using transfersomal formulation. Immunizing agents can be deliver using ethosomes because of its high skin penetration ability.

MARKETED PRODUCTS OF ETHOSOME ³

S.No	Name of product	Uses	Manufacturer
1	Supravir cream	For the treatment of herpes virus	Trima, Israel
2	Noicellex	Topical anti-cellulite cream	Novel Therapeutic Technologies, Israel
3	Skin genuity	Powerful cellulite buster, reduces orange peel	Physonics, Nottingham, UK
4	Decorin cream	Anti-aging cream, treating, repairing, and delaying the visible aging signs of the skin including wrinkle lines, sagging, age spots, loss of elasticity, and hyper pigmentation	Genome Cosmetics, Pennsylvania, US
5	Nanominox	First minoxidil containing product, which uses ethosomes. Contains 4% Minoxidil, well-known hair growth promoter that must be metabolized by sulfation to the active compound.	Sinere, Germany
6	Cellutight EF	Topical cellulite cream, contains a powerful combination of ingredients to increase metabolism and break down fat.	Hampden Health, USA

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