Ethosomes: A New Era in Transdermal Drug Delivery System

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Abstract: Ethosomes are drug carriers that enable drugs to reach the deep skin layers and/or the systemic circulation. Even though ethosomal systems are theoretically complicated, they are simple in their preparation, safe for use in a combination that can highly expand their application. Ethosomes are malleable, soft vesicles designed for enhanced delivery of active ingredients. As they have unique structure, ethosomes are able to encapsulate the highly lipophilic molecules like cannabinoids, testosterone and minoxidil, as well as cationic drugs such as propranolol, trihexaphenidyl, Cyclosporine, insulin, salbutamol etc and able to deliver through the skin. Ethosomes have a number of benefits including enhancing patient compliance and comfort improving the drug's efficacy, and reducing the total cost of treatment. Ethosomal drug delivery is the enhanced system of delivery of bioactive molecules through the skin and cellular membranes by means of a carrier which will opens a number of opportunities and challenges for the researcher and for the future development of novel drug carrier system.

Keywords: Transdermal drug delivery, Ethosomes, NDDS, Lipid vesicles, structured vesicles

INTRODUCTION

Transdermal drug delivery is an attractive alternative to oral delivery of drugs and is an alternative to hypodermic injection. From ancient period of time people have placed substances on the skin for therapeutic effects and now in advanced era, a variety of topical formulations have been developed to treat local symptoms. The first transdermal model for drug delivery is transdermal patch which delivers scopolamine to treat motion sickness was approved for use in the United States in 1979.In next decade, nicotine patches became the first transdermal blockbuster, raising the profile of transdermal delivery in medicine and for the regular use. In this new era of novel drug delivery, there are 19 transdermal delivery systems for such drugs as hormone replacement therapy and in combination patches containing more than one drug for

contraception and iontophoretic and ultrasonic delivery systems for analgesia. Harmones like estradiol, fentanyl, lidocaine and testosterone also delivered through patches. Transdermal delivery has a number of benefits compared with the oral route. The important key factor in use of transdermal delivery is to avoid significant first-pass effect of the liver that can prematurely metabolize drugs. Transdermal delivery is a better option for the hypodermic injections, which are painful and needle re-use has the risk of disease transmission, especially in developing countries. Another key factor of transdermal systems is they are noninvasive and can be self-administered. Also they. These systems are inexpensive. The drugs pliable to the administration through transdermal route are the main constrains and have wide scope in that area.

Ethosomes: The ethosome word is derived from the word "*Somes*" means the cell like structure of novel drug delivery system. There are different types of somes like Ethosomes, Colloidosomes Phytosomes, Niosomes, Liposomes, Cubosomes etc. Ethosomes are non-invasive carriers that enable drugs to reach the deep skin layers and/or the systemic circulation. The ethosomes are composed of different ingredients like phospholipids, alcohol (ethanol and isopropyl alcohol) in comparatively high concentration and water. Ethosomes are malleable vesicles, soft and poised mainly of phospholipids, ethanol (relatively high concentration) and water. These "soft vesicles" plays a novel role in vesicular carrier for boosted delivery through the skin. The size of ethosomes vesicles varies from 10 nm to few microns. Ethosomes also contain phospholipids like liposomes; however, they contain higher levels of alcohol. A mechanism of action these transporters in improving permeation is depends on the alcohol content as penetration enhancers as well as disruption of intercellular lipid structure of SC by the phospholipids in their content.

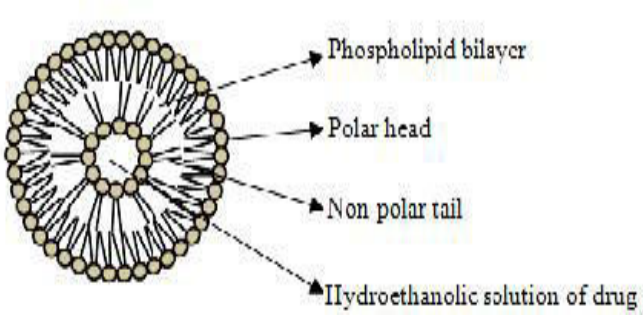

Fig 1: Structure of Ethosomes

METHODS OF PREPARATION

The Ethosomes are prepared by using a different additives which will be the best suited with the drug and its properties. Two conventional methods used for the preparation of Ethosomes are Cold method and hot method. Other methods are also used for Ethosome preparation like Classic mechanical dispersion method and transmembrane pH gradient active loading method. Most commonly used method is cold method.

Table 1: Ingredients used in formulation of Ethosomes:

Sr. No.	Class	Example	Uses
1.	Phospholipids	Soya phosphatidylcholine, phosphatidylcholine, phosphatidylcholine Distearyl Diplamityl	Vesicles former
2.	Cholesterol	Cholesterol	Gives stability to vesicle membrane
3.	Polyglycol	Propylene glycol, Transcutol RTM	Enhance skin penetration
4.	Alcohol	Ethanol, Isopropyl alcohol	Gives the softness for vesicle membrane and enhance penetration
5.	Dye	Rhodamine-123, Rhodamine red, Fluorescene Isothiocynate (FITC), 6-Carboxy fluorescence	Characterization
6.	Vehicle	Carbopol 934	As gel forming agent

1. Cold method: Take Ethanol and dissolve phospholipid in a covered vessel at room temperature with vigorous stirring. Propylene glycol or other polyol is added during stirring. Heat this mixture at 30^0C in a water bath. Heat the water up to 30^0C in a separate vessel and add to the above mixture slowly in a fine stream. The drug can be dissolved either in ethanol or in water depending on the hydrophobic / hydrophilic properties of drug or ingredients. Stir the mixture for another 5 min and cool the resultant suspension of ethosome at room temperature. Sonicate the formulation to get desired vesicle size of Ethosomes or extrusion method is also used. Formulation should be stored under refrigeration.

2. Hot method: Phospholipids are dispersed in water. Colloidal solution is formed by heating in a water bath at 40^0C. In a separate vessel mix glycols with ethanol and heat this mixture up to 40^0C. At a same temperature add the organic phase to the aqueous phase. Stir the mixture for another 5 min and cool the suspension at room temperature. The drug can be dissolved either in ethanol or in water depending on the hydrophobic/ hydrophilic properties it bears. Sonication or extrusion method is used to get desired vesicle size.

3. Classic mechanical dispersion method: In RBF (Round Bottom Flask) take Organic solvent or a mixture of organic solvents and dissolve Phospholipid. Organic solvent is removed by using a rotary vacuum evaporator above lipid transition temperature so as to form a thin lipid film on the wall of the RBF. Keep the contents under vacuum overnight to remove the traces of the deposited solvent from lipid film. Hydrate the lipid film with hydro-ethanolic solution of drug by rotating the flask at suitable temperature with or without intermittent sonication. Cool the resultant ethosomal suspension at room temperature. The formulation should be stored under refrigeration.

DRUG PENETRATION THROUGH ETHOSOMES: However, the process of ethosomal drug delivery remains a matter of guesswork; it is likely to be a combination of processes of the penetration enhancement. The stratum corneum lipid multilayer remains densely packed at physiological temperature, and are in highly conformational order. The unique property of Ethosomes is characterized by high concentration of ethanol, which causes disturbance in normal nature for skin lipid bilayer organization. As drug gets incorporated into a vesicle membrane, disturbance in lipid nature give an ability to penetrate the stratum corneum. Higher concentration of ethanol, keeps the lipid membranes less tightly packed than in conventional vesicles but has equivalent stability, allowing a more flexible structure that gives it more freedom and ability to penetrate through small places, openings created by disturbing the stratum corneum lipid. Ethanol has its own property to interact with lipid molecules in the polar head group region which reduce stringency of the stratum corneum lipids layer and fluidity is increased. Membrane permeability is increased by introducing ethanol into the polar head group environment.

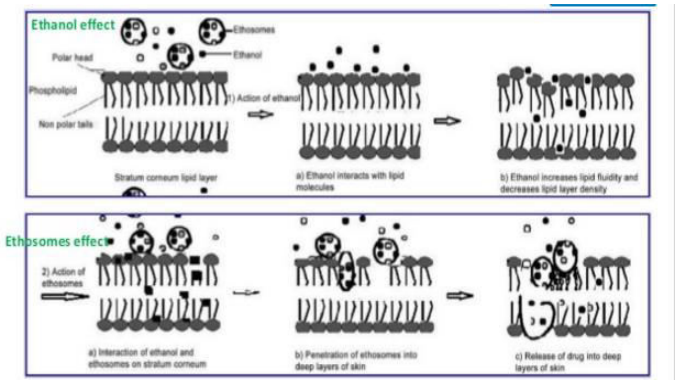

Fig 3: Mechanism of drug penetration through Ethosome

CHARACTERIZATION OF ETHOSOMES: The different methods for the characterization of ethosomes are as follows,

1. **Physical Characterization:** Motic Image Plus software is used for physical characterization. Formations of the desired Ethosomes are determined in economic way by using this method. Primary particle size evaluation also done for the formulation. Appropriate sizing and further evaluation and should be done using Malvern Zetasizer.

2. **Visualization:** Ethosomes are visualized by using transmission electron microscopy (TEM) and scanning electron microscopy (SEM).
3. **Vesicle size and Zeta potential:** Particle size and zeta potential of the ethosomes can be done by computerized inspection system and photon correlation spectroscopy (PCS) and dynamic light scattering (DLS) .
4. **Entrapment Efficiency:** Ultracentrifugation technique is used to measure the entrapment efficiency of drug entrapped in Ethosomes.
5. **Transition Temperature:** The transition temperature of the vesicular lipid systems formed in ethosomes can be determined by using differential scanning calorimetry (DSC).
6. **Surface Tension Activity Measurement:** Du Nouy ring tensiometer is used to determine the surface tension activity of drug in aqueous solution by ring method.
7. **Vesicle Stability:** The stability of ethosome is depend upon the shape, structure and size of vesicle. Stability 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.
8. **Drug Content:** Modified High Performance Liquid Chromatographic (HPLC) method is used to determine the drug content in Ethosome.
9. **Penetration and Permeation Studies:** Confocal laser scanning microscopy (CLSM) is used to visualize the depth of drug penetration from Ethosomes.

ADVANTAGES OF ETHOSOMAL DRUG DELIVERY:

When compared to other transdermal & dermal delivery systems;

1. Enhanced permeation of drug through skin for transdermal and dermal delivery than other transdermal drug delivery.
2. Large and diverse group of drugs (peptides, protein molecules) can be delivered.
3. Formulation is safe and the components are approved for pharmaceutical and cosmetic use.
4. Ethosomes have high patient compliance as drug is administrated in semisolid form (gel or cream). As in Iontophoresis and Phonophoresis are complicated to use and have less patient compliance.
5. Simple method of production and less investments is required for formulation of Ethosomes.
6. High market attractiveness of products.

7. Passive system of drug delivery, non-invasive and is available for immediate commercialization.
8. Various applications in cosmetic field pharmaceutical, veterinary.

STABILITY OF ETHOSOMES:

Ethosomes have great stability as compared to conventional pharmaceutical liposomes. Larger vesicles are formed in liposomes on storage. The fusion and breakage of liposome vesicles on storage describes an important problem of drug leakage from the vesicles. Due to the absence of electrostatic repulsion there is a tendency of neutral liposomes to aggregate, whereas in ethosomes, ethanol grounds a modification of the net charge of the system which imparts negative charge to the ethosomal system and gives the some degree of steric stabilization, which results in increased stability of vesicles against agglomeration and prevent the drug leakage from vesicles. Entrapment efficiency is increases by increasing the concentration of ethanol from 20 to 45% by an upsurge in the fluidity of the membranes. An extra increase in the ethanol concentration (>45%) lose the stability of the vesicles and possibly makes the vesicle membrane leaky, results in to a decline in entrapment efficiency.

APPLICATIONS OF ETHOSOMES:

Ethosomes have various applications in different field and can be used for many purposes in drug delivery. Ethosomes are the best replacement of liposomes. Transdermal route of drug delivery is mainly preferred for ethosomal preparation as they have better penetration capability as compared to other transdermal delivery systems. Ethosomes are used to deliver Hydrophilic as well as impermeable drugs through the skin. Various drugs have been proved therapeutically active when given with ethosomal carrier.

CONCLUSION

Ethosomal transdermal drug delivery system is one of the successful advanced techniques to deliver drug through skin. Major side effects of the various drugs like cardiac arrest, gastric irritation or ulceration and drugs which are given for local action in a particular part can be delivered through Ethosomal drug delivery system which minimizes the side effects as well as gives better penetration is observed as compared to other transdermal drug delivery systems. Ethosomes is a novel idea which completes the requirement of patient and gives better compliance and it shall be useful for the delivery of various drugs for systemic as well as local drug delivery.

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