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Ethosomes: A Novel Tool for Herbal Drug Delivery

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ABSTRACT

Phytomedicines are used worldwide by human being from ancient times. Herbal drugs are becoming more popular in the modern world for their application to cure variety of diseases with less toxic effects and better therapeutic effects. However these medicines suffer from certain limitation such as toxicity, stability issues, poor bioavailability and patient compliance. To minimize these problems various novel drug delivery systems (NDDS) such as phytosomes, ethosomes, transfersomes, herbal transdermal patches, nanoparticles and biphasic emulsions are used nowadays. Novel drug delivery system is valuable in delivering the bioactive at controlled rate and delivery of bioactive at the target that reduces the adverse effects with the increase in bioavailability of the bioactives. Ethosomes are lipid based elastic vesicles containing phospholipids, alcohol (ethanol and isopropyl alcohol) in relatively high concentration and water. High concentration of ethanol enhances the topical drug delivery and prolongs the physical stability of ethosomes with respect to liposomes. It has been shown that the physicochemical characteristics of ethosomes allow this vesicular carrier to transport active substances more efficaciously through the stratum corneum into the deeper layers of the skin than conventional liposomes. Ethosomes entrap drug molecule with various physicochemical characteristics i.e. of hydrophilic, lipophilic, or amphiphilic. Ethosomes possess many advantages when compared with transdermal or dermal drug delivery system. Large molecules like proteins, peptide molecule is possible, increased skin permeation, non toxic, in comparison to oral drug delivery system as it eliminates gastrointestinal interference & first pass metabolism of drug. Herbal ethosome technology has been effectively used to enhance bioavailability of many popular herbs including *Sophora alopecuroides*, *Cannabis sativa*, *Glycyrrhiza glabra* etc. can be developed for various diseases.

INTRODUCTION

Ethosome are lipid vesicles containing phospholipids, alcohol (ethanol or isopropyl alcohol) in relatively high concentration in water. This lipidic vesicular system containing ethanol has been developed by Touitou. Ethosomes were reported to improve the skin delivery of various drugs. Ethosomes have also been prepared by adding penetration enhancers such as propylene glycol and showed enhanced penetration efficacy. The presence of age- activator agents (i.e. ethanol and sodium cholate) in lipid bilayers noticeably improves carrier penetration through the stratum corneum, allowing an efficacious local and systemic delivery of both hydrophobic and hydrophilic compounds. Ethosomes have been proved to be a good delivery carrier in transdermal field and its enhancement effect has been widely recognized. In ethosomal composition, various additives used are phospholipids, polyglycol, alcohol, cholesterol, dye and vehicle [1-4].

Ethosomes have higher penetration rate through the skin as compared to liposome and hence these can be used widely in place of liposomes. Ethosomes are the slight modification of well established drug carrier liposome. Unlike liposomes, which are mainly known for the delivery of drugs to the outer layers of skin, ethosomes have been shown to enhance permeation of drug through the stratum corneum barrier. The main reason suggested to be responsible for deeper distribution and penetration in the skin was might be due to the synergistic effects of combination of phospholipids and high concentration of ethanol in ethosomes [5-9].

Synthetic drugs have a disadvantage of adverse or toxic effects whereas herbal drugs are always since ancient times they are believed to be safe with no adverse effects [10].

Certain limitations of herbal medicines and phytochemicals such as instability in highly acidic pH, pre-systemic metabolism in liver, solubility and absorption problems, can lead to drug levels below therapeutic concentration in the plasma, resulting in less or no therapeutic effects. Also, most of the plant actives such as glycosides, tannins, flavonoids, etc. are polar molecules and are poorly absorbed due to large molecular size – which limits the absorption via passive diffusion, and poor lipid solubility – which severely limits their ability to cross the lipid-rich biological membranes. These limitations lead to reduced bioavailability and hence, low therapeutic index of plant actives. Incorporation of novel drug delivery technology to plant actives minimizes the pre-

systemic metabolism, degradation of drug in the gastrointestinal tract, distribution / accumulation of drug in the non targeted tissues and organs, and hence reduces the side effects and improves the therapeutic efficacy and ultimately, the patient compliance [11-17].

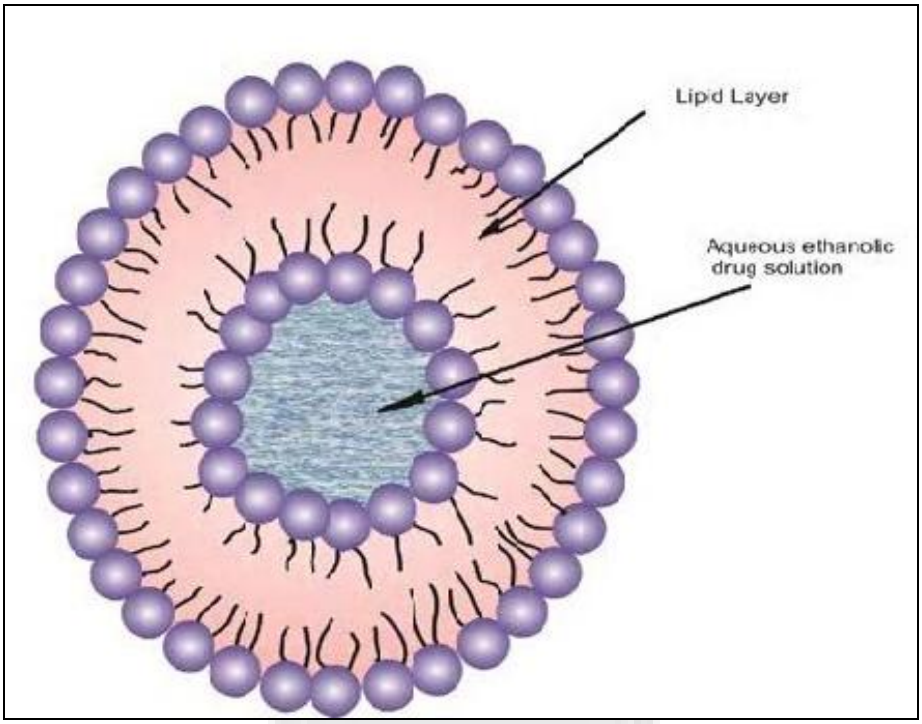

Figure 1: Structure of Ethosome

ANATOMY OF THE SKIN

Human skin is an effective, selective barrier to chemical permeation, although the skin as a route for delivery can offer many advantages, including avoidance of first-pass metabolism, lower fluctuations in plasma drug levels, targeting of the active ingredient for a local effect, and good patient compliance. Water soluble molecules and drugs are normally not able to cross the skin as the skin is a natural barrier to water. The stratum corneum is composed of insoluble bundled keratins surrounded by a cell envelope, stabilized by cross-linked proteins and covalently bound lipids as shown in Figure 2.

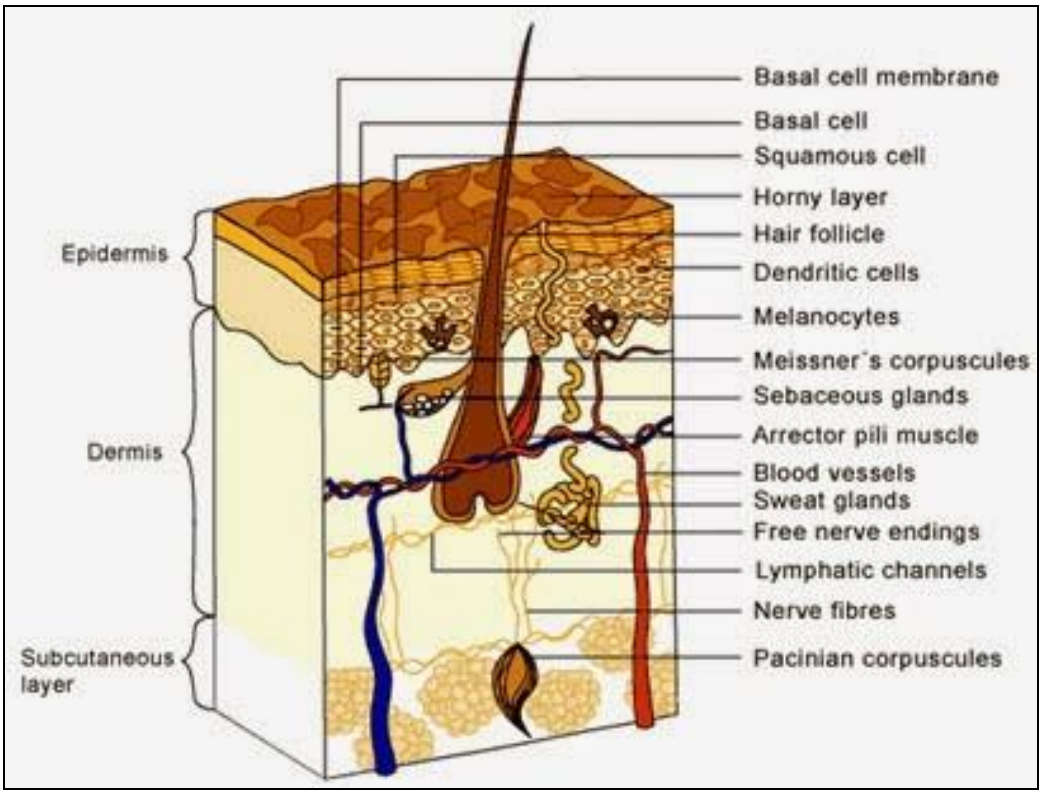

Figure 2: Anatomy of Skin

In general, the epidermis (specifically the stratum corneum) provides the major control element; most small, water-soluble, and non-electrolytes diffuse into the systemic circulation a thousand times more rapidly when the horny layer is present. Thus, to maximize the flux of the drug, the barrier hindrance is reduced by various approaches. Several technological advances have been made in the recent decades to overcome skin barrier properties. Examples include physical means such as iontophoresis, sonophoresis, microneedles, and chemical means, using penetration enhancers and biochemical means, such as, liposomal vesicles and enzyme inhibition. The physical means like iontophoresis, microneedles, and sonophoresis are relatively complicated to use, and will affect patient compliance. The use of chemical enhancers such as surfactants and organic solvents induce irritation, cause damage, and reduce skin barrier function, therefore, it is desirable to deliver the therapeutic agents that maintain the normal skin barrier function without the aid of a chemical enhancer. One such approach is the use of vesicular systems. In the past decade, topical delivery of drugs by liposomal formulation has evoked considerable interest. Deformable liposomes and transferosomes were the first generation of elastic vesicles introduced by Ceve and Blume, in 1992, and were reported to penetrate intact skin while carrying a

therapeutic concentration of drugs, when applied under non occluded conditions. The drug, encapsulated in lipid vesicles, prepared from phospholipids and nonionic surfactants is known to be transported into and across the skin. The lipids present in the skin contribute to the barrier properties of the skin and prevent the systemic absorption of drugs. Due to the amphiphilic nature, lipid vesicles may serve as non-toxic penetration enhancers for drugs. In addition, the vesicles can be used for encapsulating hydrophilic and lipophilic as well as low and high molecular weight drugs. Therefore, these lipid rich vesicles are hypothesized to carry a significant quantity of drugs across the skin, thus enhancing the systemic absorption of drugs. The use of lipid vesicles in the delivery system for skin treatment has attracted increasing attention in recent years, however, it is generally agreed that classic liposomes are of little or no value as carriers for drug delivery, because they do not penetrate the skin deeply, but rather remain confined to the upper layer of the stratum corneum; only specifically designed vesicles are shown to enhance permeation into the stratum corneum barrier. It has been investigated and reported that lipid vesicular systems embodying ethanol in relatively high concentrations, called ethosomes, are very efficient at enhancing the skin permeation of a number of drugs [18-20].

ADVANTAGES OF ETHOSOMAL DRUG DELIVERY

In comparison to other transdermal & dermal delivery systems,

- Ethosomes are enhanced permeation of drug through skin for transdermal and dermal delivery.
- Ethosomes are platform for the delivery of large and diverse group of drugs (peptides, protein molecules).
- Ethosome composition is safe and the components are approved for pharmaceutical and cosmetic use.
- Low risk profile- The technology has no large-scale drug development risk since the toxicological profiles of the ethosomal components are well documented in the scientific literature.
- High patient compliance- The ethosomal drug is administrated in semisolid form (gel or cream), producing high patient compliance. In contrast, iontophoresis and phonophoresis are relatively complicated to use which will affect high market attractiveness for products with proprietary technology.

- Relatively simple to manufacture with no complicated technical investments required for production of Ethosomes.
- Ethosomal system is passive, non-invasive and is available for immediate commercialization.
- Various applications in pharmaceutical, veterinary, cosmetic field.[10,13,14,21-25]

DISADVANTAGES

- Very poor yield so may not be economical.
- Skin irritation or dermatitis may occur in some patients due to penetration enhancer or the excipients used.
- Loss of product during transfer from organic to water media.
- It is limited only to potent molecules, those requiring a daily dose of long or less.
- The molecular size of the drug should be reasonable that it should be absorbed percutaneously [10,19,21,26].

ETHOSOMES COMPOSITION

Ethosomes are composed of hydro alcoholic (or) hydro alcoholic glycolic phospholipid in which alcohol combinations are high. Ethosomes contain phospholipid with various chemical structures like phosphotdylcholine, hydrogenated phosphotdylcholine, phosphatidic acid, phosphotidyl serine, phosphatidylethanolamine, phosphatidyl glycerol, water, propylene, such a composition enables delivery of high concentration of active ingredients through skin, drug delivery can be modulated by altering alcohol. Some preferred phospholipids are soya phospholipids such as phospholipon90 (0.5-10% w/w), cholesterol (0.1-1%), glycols, propylene glycol are generally used. Non ionic surfactants can be combined with phospholipids in these preparations. The concentration of the non aqueous phase (alcohol and glycol combination) may range between 22 to 70% [27-33].

Table 1: Different Additives Employed In Formulation of Ethosomes [1,21,22,29]

Class	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 Fluorescene Isothiocynate (FITC) 6- Carboxy fluorescence	For characterization study
Vehicle	Carbopol 934	As a gel former

INFLUENCE OF HIGH ALCOHOL CONTENT

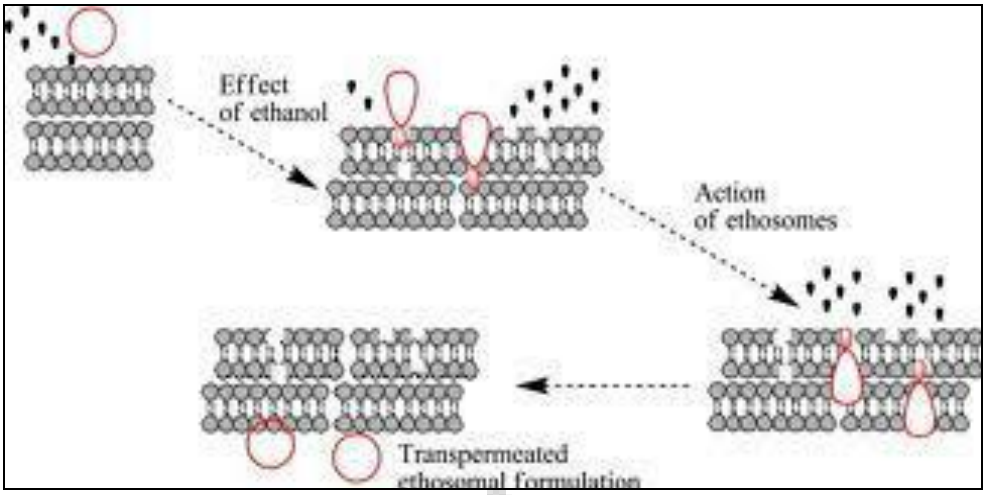

Figure 3: Influence of high alcohol on skin

Ethanol is efficient permeation enhancer and is present in quite high concentration (20-25%) in ethosomes. The synergistic effect of combination of relatively high concentration of ethanol (20-25%) in vesicular form in ethosomes was suggested to be the main reason for their better skin permeation ability. The high concentration of ethanol (20-25%) in ethosomal formulation could disturb the skin lipid bilayer organization. When integrated to the vesicles to permeate the stratum corneum due to high ethanol concentration, the ethosomal lipid membrane was packed less tightly than conventional vesicle. Ethosomes squeeze through small openings created in the disturbed stratum corneum layer. The vesicular nature of ethosomal formulation could be modified by varying the ratio of components and chemical structure of the phospholipids.[21,31,34]

MECHANISM OF DRUG PENETRATION

1. Ethanol 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.

2. Ethosomes Effect: Increased cell membrane lipid fluidity caused by the ethanol of ethosomes results increased skin permeability. 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 skin4-6 [6,8,21-24,28,29,35].

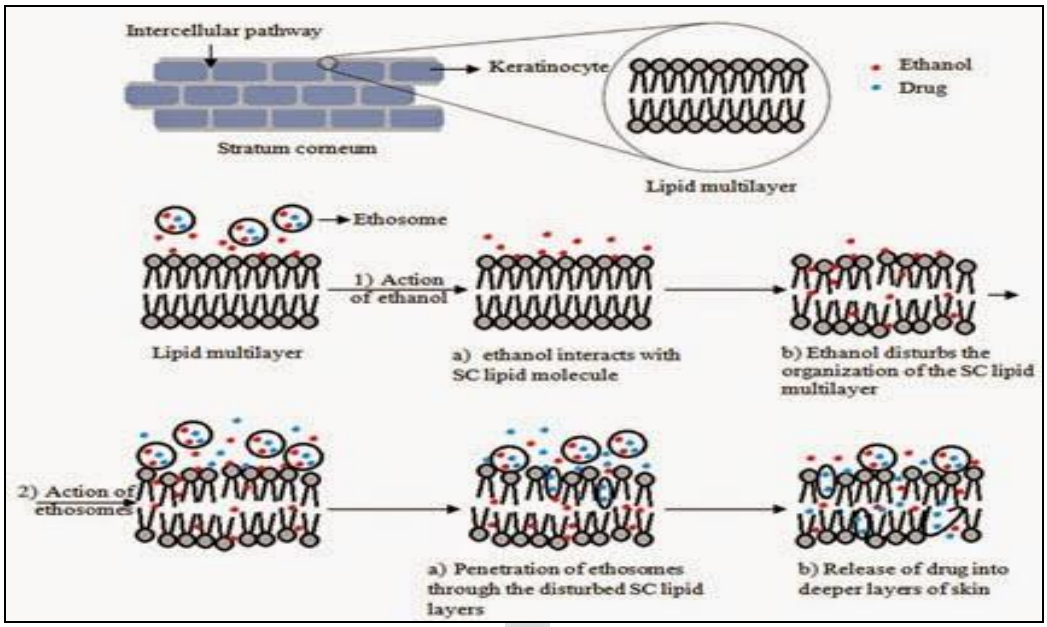

Figure 4: Mechanism of Drug Permeation

CHARACTERIZATION OF ETHOSOMES

Table 2: Methods for the Characterization of Ethosomal Formulation [7,10,21,22,36,37]

Parameters	**Methods**
Vesicle shape (morphology)	Transmission electron microscopy, Scanning electron microscopy
Entrapment efficiency	Mini column centrifugation method, Fluorescence Spectrophotometry
Vesicle size and size distribution	Dynamic light scattering method
Vesicle Skin interaction study	Confocal laser scanning microscopy, Fluorescence microscopy Transmission electron microscopy, Eosin-Hematoxylin staining
Phospholipid-ethanol interaction	31P NMR Differential scanning calorimeter
Degree of deformability	Extrusion method
Zeta potential	Zeta meter
Turbidity	Nephalometer
In vitro drug release study	Franz diffusion cell with artificial or biological membrane, Dialysis bag diffusion
Drug deposition study	Franz diffusion cell
Stability study	Dynamic light scattering method Transmission electron microscopy

FORMUATION OF HERBAL ETHOSOME [38-42]

Table 3: Formulations of Herbal Ethosomes

Botanical	Formulation	Biological activity	Active ingredient	Drawback of traditional dose	Application of emulsion formulation	Method of preparation
Glycyrrhiza glabra	Amonium Glycyrrhizinate Ethosomes	Anti inflammatory	Glycrrhizic Acid	Poor permeability	Increases of *in vitro* percutaneous permeation and significantly enhanced anti inflammatory activity	Solvent dispersion method
Tripterygium wilfordi	Triptolide	Anti inflammatory	Diterpene Triepoxide	Poor water solubility and toxicity	high entrapment efficiency, good percutaneous permeability	combining filming rehydration method ultrasonic method
Podophyllum hexandrum	Podophyllotoxin	Purgative, antirheumatic, antiviral and antitumor	Etoposide and Teniposide	Slow pharmacological action	Higher entrapment efficiency and enhance its therapeutic effect	solvent dispersion method
Sesbania grandiflora	Sesbania ethosome	Anti-microbial	leucocyanidin and cyaniding	Poor permeability	Enhance Transdermal permeation	solvent dispersion method
Sophora alopecuroides	Sophora ethosome	Antiendotoxic, anticancer, and antiinflammatory	Sophocarpine, matrine, oxymatrine, sophoridine,	low percutaneous penetration and bitter taste	Enhance drug deliver and stability	transmembrane pH gradient active loading method
Sophora flavescens	Matrine ethosome	Cardioprotective, Antiinflammatory	Matrine and oxymatrine alkaloid	Lower bioavailability	Improve precutaneous permeation	Solvent dispersion method

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