ETHOSOMES: A NOVEL TRANSDERMAL DRUG DELIVERY SYSTEM

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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. Several methods have been tried to increase the permeation rate of drugs temporarily. One simple and convenient approach is application of drugs in formulation with elastic vesicles or skin enhancers. Vesicular system is one of the most convenient methods for transdermal delivery of active substances and in that ethosomes are most useful vesicular systems. Ethosomal carriers are systems containing soft vesicles, composed of hydroalcoholic or hydro/glycolic phospholipid in which the concentration of alcohols is relatively high. The high concentration of ethanol brings increase in fluidity of lipids hence increase in permeability of the skin and improves the drug penetration. Ethosomal formulation may contain many drugs such as acyclovir, salbutamol, Insulin, cyclosporine, fluconazole, minoxidil, etc. These are prepared by hot method and cold methods. The size of Ethosomal formulation can be decreased by sonication and extrusion method. The high concentration of ethanol makes the ethosomes unique and useful for transcellular delivery, delivery of hormones, anti-arthritis, anti-HIV etc. Thus, it can be a logical conclusion that ethosomal formulation possesses promising future in effective dermal/transdermal delivery of bioactive agents.

Key Words: Stratum Corneum (SC), Liposome, Classic Liposomes, Ethosomes, Ethanol, Phospholipid, Vesicles, Transdermal Drug Delivery.
INTRODUCTION

TO TDDS TDDS are defined as self-contained, discrete dosage forms which when applied to the intact skin, deliver the drug through the skin, at a controlled rate to the systemic circulation. For transdermal delivery of drugs, stratum corneum is the main barrier for permeation of drug. Now-a-days liposomes, niosomes, transferosomes and ethosomes (vesicular and non-invasive drug delivery) are used to increase the permeation of drug through the stratum corneum. One of the major advances in vesicle research was the finding that some modified vesicles possessed properties that allowed them to successfully deliver drugs in deeper layers of skin. Transdermal delivery is important because it is a non-invasive procedure for drug delivery. Further, problem of drug degradation by digestive enzymes after oral administration and discomfort associated with parenteral drug administration can be avoided. It is the most preferred route for systemic delivery of drugs to pediatric, geriatric and patients having dysphasia. Hence, transdermal dosage forms enjoy being the most patient compliant mode of drug delivery.

INTRODUCTION TO ETHOSOMES

These are lipid vesicle containing phospholipids, alcohol in relatively high concentration and water. Ethosomes are soft vesicles made of phospholipids and ethanol and water. Ethosomes can entrap drug molecules various physic chemical characteristics i.e. of hydrophilic, lipophilic, or amphiphlic. The size range of ethosomes may vary from 10 nanometers to microns.

Composition of ethosomes: Ethosomes are vesicle carrier comprises of hydro alcoholic or hydro alcoholic glycolic phospholipid in which the concentration of alcohols or their combination is relatively high. Ethosomes may contain phospholipid with various chemical structures like phosphotidyl choline (PC), Hydrogenated phosphotidyl choline (HPC), Phosphatic acid, Phosphatidyserine,Phosphatidylethanolamine (PE) Phosphatidylglycerol (PPG) Phosphatidylinositol (PI), Alcohol, water and propylenrglycol. Drug delivery can be
modulated by altering alcohol: water or alcohol- polyol water ratio some preferred phospholipids are soya phospholipids such as phospholipon90 (PL-90). It is usually employed in range of 0.5-10% w/w cholesterol at concentration ranges between 0.1 to 1% can also be used, include ethanol and isopropyl alcohol. Among glycols, propylene glycol and from suite are generally used in addition, nonionic surfactants can be combined with the phospholipids in these preparations. Cationic lipids like cocoamide, POE alkyl amines, dodecylamine, cetrimide etc.

The concentration of alcohol in the final product may range from 20 to 50%. The concentration of nonaqueous phase may range between 22 to 70%.

PERMIATION THROUGH SKIN
The major problem associated with the dermal delivery system is the excellent barrier property of the skin. This resides in the outermost layer, the stratum cornea. This unique membrane is only some 20 um thick but has evolved to provide a layer that prevents us from losing excessive amounts of water and limits the ingress of chemicals with which come in to contact. The precise mechanisms by which drugs permeate the stratum corneum are still under debate but there is substantial evidence that the route of permeation is a tortuous one following the intercellular channels. The diffusion path length is between 300 and 500um rather than the 20 um suggested by the thickness of the stratum corneum. However, the tortuosity alone cannot account for the impermeability of the skin. The intercellular channels contain a complex milieu of lipids that are structured into ordered bilayer arrays. It is the combination of the nature of these and the tortuous route that is responsible. A diffusing drug has to cross, sequentially, repeated bilayers and therefore encounters a series of lipophilic and hydrophilic domains.

Advantages
1. Delivery of large molecules is possible (peptides, protein molecule)
2. It contains nontoxic 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. High patient compliance. The ethosomal drug is administered in semisolid form hence producing higher patient compliance.
7. It is passive, noninvasive and is available for immediate commercialization.

DISADVANTAGES
1. May not be economical. Poor yield
2. Drugs that require high blood levels cannot be administered – limited only to potent molecules, those requiring a daily dose of 10mg or less.
3. In case if shell locking is ineffective then the ethosomes may coalescence and fall apart on transfer into water.
4. Loss of product during transfer from organic to water media

MECHANISM OF PENETRATION
The advantages of ethosomes over liposomes are the increased permeation of the drugs. 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

**Ethanol effect:** it acts as a penetration enhancer through the skin. The mechanism of its penetration enhancer effect is well known. It penetrates in to intercellular lipids and increases the fluidity of cell membranes lipids and decrease the density of lipid multilayer of cell membrane.

**Ethosomes effect:** Increased cell membrane lipid fluidity caused by the ethanol of ethosomes results increased skin permeability. In the case of ethosomes encapsulating drugs, the higher positive zeta potential imparted by the drug can improve skin attachment of the vesicles. While encapsulated drug in classic liposomes remained primarily at the surface of the skin the ethosomal system was showed to be highly efficient carrier for enhanced drug delivery through the skin due to increased fluidity of the lipids.
METHOD OF PREPARATION: There are two methods which can be used for the formulation and preparation of ethosomes. These methods are very simple and convenient and do not involve any sophisticated instrument or complicated process. Ethosomes can be formulated by following methods³⁹.

1. Hot method.
2. Cold method.

COLD METHOD

1. Phospholipid + ethanol + glycol + drug
   vigorously stirred

2. Heated to 300°C

3. Preheated water added to above mixture, stirred

4. Desired vesicle size obtained on sonication

5. Finally refrigerated
HOT METHOD

![Flowchart](image)

METHODS OF CHARACTERIZATION

- **Visualization:** Visualization of ethosomes can be done using transmission electron microscopy (TEM) and by scanning electron microscopy (SEM). Visualization by electron microscopy reveals an ethosomal formulation exhibited vesicular structure 300-400 nm in diameter.

- **Scanning electron microscopy (SEM)**
  Different lipid types might influence the surface morphology or shape of the particles (Cortesi et al. 2002). Solid lipid microparticle suspensions were deposited on metallic stubs then placed in liquid nitrogen and dried under vacuum. The freeze-dried microparticles were coated uniformly with gold. It is characterized for morphology and surface properties using a scanning electron microscope.

- **Entrapment Efficiency**
  The entrapment efficiency of drug by ethosomes can be measured by the ultracentrifugation technique[32]. The chemical nature of the lipid is an important factor in determining the EE of drug in the SLM because lipid which forms highly crystalline particles with a perfect lattice lead to drug expulsion (Westesen et al. 1997). On the other hand, the imperfection (lattice defects) of the lipid structure could offer space to accommodate the drug. The percentage EE ranged from 80.7–95.7%. The lost or unentrapped drug could be due to the solubility of the drug in the water–poloxamer phase. Schwarz and Mehnert (1999) also reported a reduction in drugentrapment in the presence of poloxamer. Dayan and Tootou [33] have shown that
entrapment efficiency of trihexyphenidyl hydrochloride increased from 36% for liposomes to 75% for ethosomes.

- **Differential scanning calorimetry (DSC):**
  Transition temperature (Tm) of the vesicular lipid systems was determined by using the Mettler DSC 60 computerized with Mettler Toledo star software system (Mettler, Switzerland). The transition temperature was measured by using the aluminium crucibles at a heating rate 10 degree/minute. Within a temperature range from 20°C-300°C.

- **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) [34]. The size of ethosomes ranges between tens of nanometers to microns and is influenced by the composition of the formulation.

  Zeta potential is an important and useful indicator of particle surface charge, which can be used to predict and control the stability. In general, particles could be dispersed stably when the absolute value of zeta potential was above 30mV due to the electric repulsion between particles (Mu¨ller et al. 2001).

- **Drug Content**
  Drug can be quantified by a modified high performance liquid chromatographic method.

- **Surface Tension Activity Measurement**
  The surface tension activity of drug in aqueous solution can be measured by the ring method in a Du Nouy ring tensiometer.

- **Vesicle Stability**
  The stability of vesicles 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.

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

- **Penetration and Permeation Studies**
Depth of penetration from ethosomes can be visualized by confocal laser scanning microscopy

CONCLUSION

New and alternative drug delivery systems are currently the focus of many research activities. Efficacy, safety and convenience of use are important factors that need to be considered when developing alternate drug delivery systems. In recent years, the transdermal route of drug delivery has evolved considerably and it now competes with oral treatment. Most of the device-induced transdermal drug delivery techniques are still in the early stages of commercialization. All device-induced transdermal delivery techniques have a common concern regarding the safety of use, and skin reactions arising due to perturbing the stratum corneum – even though it is only temporary. Ethosomal carrier opens new challenges and opportunities for the development of novel improved therapies.

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