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ETHOSOMES - A NOVEL VESICULAR TRANSDERMAL DRUG CARRIER

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ABSTRACT

Transdermal drug delivery system is emerging as one of the most prominent route in drug delivery. It has given a path for easy administration of drugs with increased patient compliance. The skin is the major route for transdermal drug delivery, it present a way for drugs to reach systemic circulation without exposing them to gastric acids and first pass metabolism, but the main disadvantage of skin is the low diffusion of drugs through stratum corneum, which acts as barrier for drug delivery. Ethosomes are novel non-invasive ethanolic phospholipids came into existence from 1997 which acts as skin enhancers and carries the drug across stratum corneum and make them available in deeper layers of skin. The insight of this review is to enlighten the main aspects such as structure and composition of stratum corneum, mechanism of penetration, advantages, applications and available marketed products etc.

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INTRODUCTION

The stratum corneum is the outermost layer of the skin that acts as the barrier and maintains the connection between internal organs and external environment. The drug is passed from the surface of the skin into stratum corneum by involving percutaneous absorption under the influence of concentration gradient. By this mechanism the drug get diffused through stratum corneum, which act as the rate determining step in percutaneous absorption. Various drug delivery systems are used for the delivery of drug through stratum corneum.[1] One of such delivery is transdermal drug delivery system which shows efficient results when compared to oral drug delivery as it eliminates gastric acid contact, increased patient compliance, extended duration of activity, minimizing side effects, improving physiological and pharmacological response, avoiding the fluctuation of drugs and first pass metabolism. Lipophilic drugs having molecular weight < 500 Da can pass through the barrier easily, [2, 3] but the hydrophilic drugs show very less or low permeation. To improve the process of penetration of drugs through strartum corneum, investigations presented usage of physical or chemical permeation enhancers such as iontophoresis, sonophoresis, liposomes, niosomes, transferosomes and ethosomes etc. Permeation enhancers increases the permeability of the skin so that the drug can easily enter into skin and can cross statum corneum. [4,5] shown in figure 1. There are different pathways by which the drug penetrates through the skin but the TDDS mainly involves passive diffusion. Different pathways are shown in figure 2. [6]

ETHOSOMES

Ethosomes are the novel vesicular drug carriers that carry the drug with low solubility across the

biological membrane through skin. Ethosomes are the slighter modified form of liposomes with higher concentration of phospholipids, alcohol (ethanol, isopropyl alcohol) and water.[7] The size range of ethosomes may vary from tens of nanometers to microns (μ).[8] They are the permeation enhancers, increases the permeability of the skin so the drug can cross the skin barriers easily and has the capability entrap drug molecule with various physicochemical characteristics i.e. of hydrophilic, lipophilic, or amphiphilic. [9] Structure of ethosome is shown in fig 3.

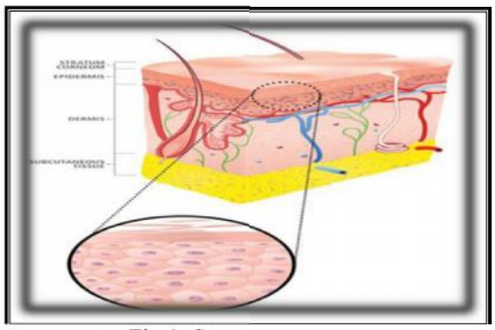

Fig 1: Stratum corneum

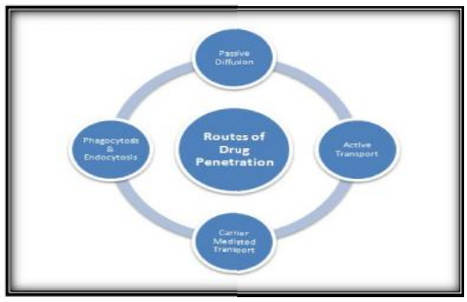

Fig 2: Main routes of drug penetration

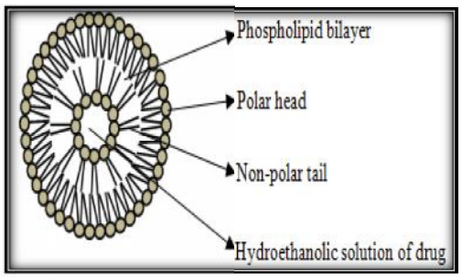

Fig 3:- Structure of ethosome

COMPOSITION OF ETHOSOMES

Ethosomes consists of hydro glycolic or hydro alcoholic phospholipids in which the concentration of alcohols and their combination is relatively high. Chemical structure of ethosmes may contain phospholipids like phosphotidylcholine (PC), hydrogenated PC, phosphotidylserine (PS), phosphotidic acid (PA), phosphotidylethanolamine (PEA), phosphotidylinositol(PI), phosphotidylglycerol (PG), alcohols, glycols and water. The concentration of non aqueous phases may ranges between 22 to 70%. [10]

MECHANISM OF DRUG PENETRATION

Mechanism of drug absorption from ethosomes may occurs in following two phases.

1. Ethanol effect
2. Ethosomal effect

1.Ethanol effect

Ethanol acts as penetration enhancer that penetrates into intercellular lipids and increases the fluidity of cell membrane lipids by decreasing the density of lipid layer in the cell membrane.[12]

2. Ethosomal effect

Due to ethanol effect, ethosomes can permeate easily into deeper layers of skin where it fuses with lipid layers of cell membrane and releases the drug into deeper layers of skin. [10]

ADVANTAGES OF ETHOSOMAL DRUG DELIVERY [13, 14]

1. Ethosomes enhances the permeation of drug through deeper layers of skin.
2. Ethosomes acts as a platform for protein and peptide drug delivery.
3. The components of ethosomes accede to use in cosmetics and pharmaceutical formulations.
4. Toxicological profiles of ethosomes prove that, low risk profile enhances the formulation development.
5. Ethosomes can be administered as semisolid dosage forms, which shows improved patient compliance.
6. Easy to manufacture and available for immediate commercialization.
7. Ethosomes improve skin delivery under occlusive and non-occlusive conditions.

DISADVANTAGES OF ETHOSOMAL DRUG DELIVERY [15, 16]

1. Poor practical yield.
2. Ethosomes with poor shells may clump together and leads to precipitation.
3. Transfer of ethosomes from organic to aqueous layer leads to loss of product.

MANUFACTURE OF ETHOSOMES

Ethosomes can be prepared by hot method, cold method and other methods.

Hot method:

Transfer the drug to a mixture of propylene glycol and ethanol and mix them (Mixture 1). Disperse phospholipids in water and heat to 40^0c (Mixture 2). Incorporate mixture 2 in mixture 1 and mix up thoroughly for five minutes at 40^0c. The preparation is sonicated three times for every five minutes alternatively at 40^0c. Then the preparation is homogenized using high pressure homogenizer at 15000 psi to get ethosomes. The above process is shown in fig 4. [6]

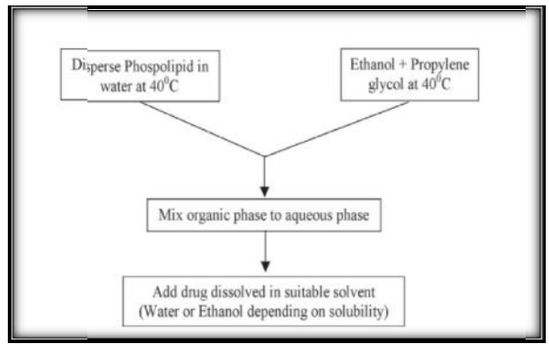

Fig 4:- Manufacture of ethosomes by using Hot method

Cold method:

Drug, phospholipids and other materials were transferred to a beaker containing ethanol and stir them vigorously at 30^0c. Water kept at 30^0c is added to the above mixture and mixed for five minutes. Vesicle size

of ethosomes can be decreased by sonication and the final mixture is stored under refrigeration. The above process is shown in fig 5. [6]

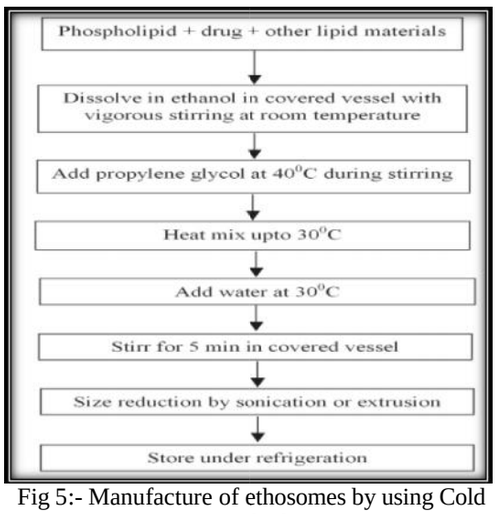

Fig 5:- Manufacture of ethosomes by using Cold method

Other Methods

Other methods include mechanical dispersion method, injection method and classic method.

Mechanical dispersion method

Dissolve soya phosphotidylcholine in a mixture of chloroform and methanol in 3:1 ratio and transfer it to a round bottom flask. Rotary vacuum evaporator is used to remove the organic solvents to form a thin lipid film on the walls of the flask. Solvent mixture if any is removed under vacuum leaving overnight. Lipid film is hydrated by rotating the flask at definite temperatures with different concentrations of hydroethanolic mixtures containing drug. [19, 20]

Injection method

In this method different concentrations of lecithin, ethanol, isopropyl alcohol, propylene glycol etc were used to prepare ethosomes. Drug with phospholipids is dissolved in ethanol and propylene glycol and the mixture was kept at 30^{0}c. Slowly distilled water is added to the above mixture in a fine stream with constant stirring at 700 rpm in a closed vessel for 5 minutes. After cooling to 4^{0}c the above mixture is subjected to sonication three times for every five minutes alternatively. [11]

Classic method

Drug along with phospholipid is dissolved in ethanol and kept at 30^{0}c. To the above mixture double distilled water is added as a fine stream with constant stirring at 700rpm in a closed vessel. Then the product is homogenized by passing through a polycarbonate membrane using hand extruder three times for every five minutes alternatively. [18]

CHARACTERIZATION OF ETHOSOMES [21-27]

a. Surface morphology of ethosomes is determined by SEM (Scanning Electron Microscope) and TEM (Transmission Electron Microscopy).
b. Particle size and zeta potential of ethosomes can be determined by DLS (Dynamic Light Scattering) and PCS (Photon Correlation Spectroscopy).
c. Ultra-centrifugation technique is used to determine entrapment efficiency of drug by ethosomes.
d. The transition temperature of the vesicular lipid systems can be determined by using differential scanning calorimetry.
e. The surface tension activity of drug in aqueous solution can be measured by using ring tensiometer.
f. The stability of vesicles can be determined by assessing the size and structure of the vesicles over time.
g. Permeation of ethosomes can be visualized by confocal laser scanning.
h. Drug content of ethosomes can be determined using UV spectrophotometer and modified high performance liquid chromatographic method.

EVALUATION OF ETHOSOMES

Morphology of ethosomes

Morphological characterization of ethosomes was done by taking scanning electron microscpe . The samples were air dried and gold coated using sodium aurothiomalate to 200 Aº thickness prior to microscopy with an accelerating voltage of 20 KV and the photographs were taken within the range of 7000x – 12000x magnifications.[12]

Entrapment Efficiency

Percentage entrapment efficiency was calculated using following formula,

Percentage entrapment efficiency = AQ / TQ × 100

Where AQ is the actual drug content and TQ is the theoretical quantity of drug present in ethosomes. [28]

Skin permeation studies

The hair on the abdominal skin of rats was carefully trimmed and the abdominal skin was separated from connective tissue with a scalpel. Excised skin was place on aluminium foil and dermal skin was gently teased off for adhering fats or subcutaneous tissue. Effective permeation area was taken as 1 cm with 2 to 10 ml receptor cell volume and the temperature was maintained at 32^{0}c±1^{0}c. Receptor compartment was filled with 10 ml phosphate buffer with pH 6.5. Excised skin was mounted between receptor and donor compartments and 1 ml formulation was applied to epidermal surface of the skin. 0.5 ml samples were withdrawn at definite time intervals through a sampling port and analyzed by spectrophotometry or high performance liquid chromatography. [12]

Stability studies

Ethosomal preparations were kept in sealed vials after flushing with nitrogen and the stability study was conducted as per ICH guidelines for the period of three months at various accelerated temperature and humidity conditions of 25°C/60%RH, 40°C/70%RH, 60°C/80%RH. Drug retentive behaviour and morphology studies were conducted throughout the above period. [29]

APPLICATIONS OF ETHOSOMES

Pilosebaceous Targeting:

Pilosebaceous targeting have been use for localized therapy, particularly for the treatment of follicle related disorders such as acne or alopecia. Ethosomal formulation of minoxidil a lipid soluble drug used for baldness accumulate into nude mice skin two to seven fold higher and thus can be use for pilosebaceous targeting for better clinical efficacy. [4, 31]

Transdermal Delivery:

Since ethosomes enhance permeability of drug through stratum corneum, it can be use for administration of drugs having poor skin permeation, low oral bioavailability, first pass metabolism and dose dependent side effect. Touitou et al reported that the

skin permeation of testosterone from ethosomal formulation is nearly 30 times higher than the marketed transdermal patch of testosterone (Testosterone Patch, Alza). They also concluded that effective permeation area of ethosomal testosterone formulation was 10 times less than required when compared to commercial gel formulation. [31-33]

Delivery of HIV drugs:

An effective antiretroviral therapy is required on a long term basis and is associated with strong side effects.[53] Adequate zero order delivery of zidovudine, Lamivudine a potent antiviral agent is required to maintain expected anti- AIDS effect. Subheet Jain et al reported that ethosomal formulation of the above drugs prolong the release with increased transdermal flux. [54] Formulation of acyclovir show high therapeutic efficiency with shorter healing time and higher percentage of abortive lesions.

Delivery of problematic drug molecules:

Oral delivery of large biogenic molecules such as peptides or proteins and insulin is difficult because they are completely degraded in the GIT hence transdermal delivery is a better alternative. But conventional transdermal formulation of biogenic molecules such as peptides or protein and insulin has poor permeation. Formulating these above molecules into ethosomes significantly increase permeation and therapeutic efficacy. [55]

MARKETED FORMULATIONS

Noicellex TM an anti – cellulite formulation of ethosome is currently marketed in Japan. Lipoduction TM another formulation is currently used in treatment of cellulite which contains pure grape seed extracts (antioxidant) is marketed in USA. Similarly Physonics is marketing anti -cellulite gel in London. Nanominox© containing monoxidil is used as hair tonic to promote hair growth is marketed by Sinere.

Table 1: Different additives employed in the formulation of ethosomes [11]

CLASS	EXAMPLE	USE
Phospholipids	Soya phosphatidyl choline Egg phosphatidyl choline Dipalmityl phosphatidyl choline Distearyl phosphatidyl Choline	Vesicles forming component
Polyglycols	Propylene glycol	As a skin penetration enhancer
Alcohols	Ethanol Isopropyl alcohol	For providing the softness to vesicle membrane and 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 gel former

Table 2: Various applications of ethosomes

Sl.No	DRUGS	RESULTS
1	**Anti-viral agents** Zidovudine [34] Lamivudine [35] Stavudine [36]	Prolonged drug action, reduced drug toxicity. Control release for prolonged period of time. Improved biological anti-inflammatory activity, sustained effect
2	**NSAIDS** Diclofenac[37] Aceclofenac	Selective and prolong delivery of drug to desired site. Superior to the marketed gel for the topical administration
3	Acyclovir [38]	Increased skin permeation and biological activity two to three times.
4	Topical Photodynamic Therapy[39] (PDT) (5- aminolevulinic acid)	Greater penetration ability than that of liposomes, More entrapment efficiency
5	Trihexyphenidyl Hydrochloride [40]	Higher entrapment capacity, improved tansdermal flux, improved patient compliance
6	Antibiotic[41] (Erythrmycin) (Cannabidol)	Complete inhibition of infection, prolonged drug action. Improved skin deposition and biological activity
7	Pilosebaceous targeting [4] (Minoxidil)	High penetration into deep layers of the skin.
8	Ammonium[42] Glycrrhizinate	Improved biological anti-inflammatory activity, sustained effect.
9	Salbutamol sulphate[43]	Controlled release rate, enhanced skin permeation.
10	Propranolol[44]	Better skin permeation.
11	Testosterone[45]	Significantly higher permeation into the skin increased systemically delivery
12	Finasteride[46]	Enhanced percutaneous absorption.
13	Bacitracin[47]	Reduced drug toxicity.
14	Methotrexate[48] (MTX)	Enhanced transdermal flux, lower lag time, higher entrapment efficiency and better stability profile.
15	Gold Nanopartical[49]	Gold nanopartical in ethosomes shows enhancement of pharmacological efficacy in transdermal and dermal delivery systems.

16	Azelaic acid[50]	Used in treatment of acne ,ethosomes improves the sustained release
17	Alfuzosin hydrochloride (AH)[51]	Increased penetrability
18	Tacrolimus[52]	Used for the therapy of atopic dermatitis (AD) or psoriasis. Insure adequate topical delivery of the drug into deeper skin layers and increased stability.

CONCLUSION

Ethosomes are versatile vesicular carriers that open a new path for improvised therapies. So from the above stated applications and advantages they can be considered as better carriers than liposomes to enhance the permeation of drugs through the skin. They have potential ability to transport drugs such as hydrophilic, lipophilic, cationic drugs, proteins and peptides. Many researches are going on to allow better control over drug release in in-vivo, increasing their safety and effective therapy.

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