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ETHOSOME: A NOVEL VESICULAR DRUG DELIVERY SYSTEM

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ABSTRACT

Vesicular system improves therapeutic efficacies of drug by controlling and sustained action. Ethosome transport drug to the deep skin layers or systemic circulation. Ethosomes are novel carrier system used for delivery of drugs having low penetration through the biological membrane mainly skin. Ethosomes have higher penetration rate through the skin as compared to liposomes hence these can be used widely in place of liposomes. Although, the exact mechanism for better permeation into deeper skin layers from ethosomes is still not clear. The synergistic effects of combination of phospholipids and high concentration of ethanol in Vesicular formulations have been suggested to be responsible for deeper distribution and penetration in the skin lipid bilayers. The size range of ethosomes may vary from tens of nanometers to microns. This review focused on ethosome, its method of preparation, mechanism of action, its characterization and applications.

KEYWORDS: Vesicular system, Ehosomes, Liposomes, Phospholipids.

INTRODUCTION

In the past few decades, considerable attention has been focused on the development of novel drug delivery system (NDDS). The NDDS should ideally fulfill two prerequisites: Firstly, it should deliver the drug at rate directed by the needs of the body, over the period of treatment, secondly; it should channel the active entity to the site of action.[1] Conventional dosage forms including prolonged release dosage forms are unable to meet none of these. Novel drug delivery attempts to either sustain drug action at a predetermined rate, or by maintaining a

relatively constant, effective drug level in the body with concomitant minimization of undesirable side effects. It can also localize drug action by spatial placement of controlled release systems adjacent to or in diseased tissue or organ; or target drug action by using carriers or chemical derivatization to deliver drug to particular target cell type.[1, 2]

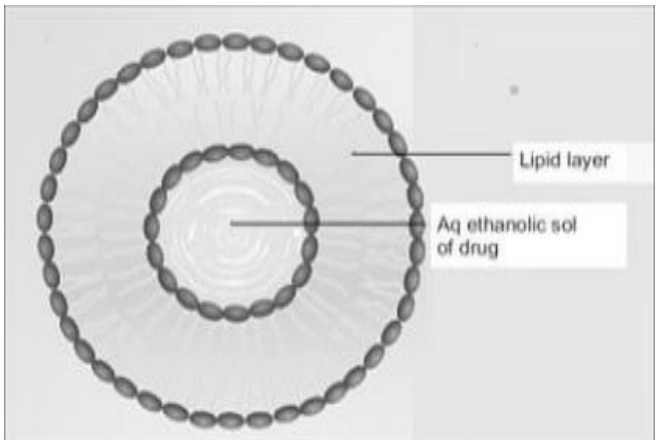
Novel vesicular drug delivery systems aim to deliver the drug at the rate directed by the need of body during the period of treatment, and channel the active entity to the site of action. Biologic origin of these vesicles was first reported in 1965 by ÂBinghamÊ and has been given the name ÂBinghambodiesÊ. A number of novel vesicular drug delivery system have been emerged encompassing various routes of administration to achieve targeted and controlled drug delivery.[2] Targeted drug delivery is a mode of delivering the therapeutic agent the tissue of interest while reducing the relative concentration of therapeutic agent in remaining tissue which improves the therapeutic efficacy and reduces side effects. Drug targeting means delivery of the drug to receptor, organ or any other specific part of the body to which one wishes to deliver the entire drug.[3] Now-a-days number of carriers are utilized to deliver the drug at target site, these include immunoglobulins, serum proteins, synthetic polymers, microspheres, niosomes, liposomes, erythrocytes etc. Among different carriers vesicular drug delivery are found to me more renowned.[4] These systems have also been used to improve the therapeutic index, stability, solubility of drug molecules.[2-5] One of the major advances in vesicle research was finding a vesicle derivative, known as Ethosomes.[6]

ETHOSOMES

Ethosomes are non-invasive delivery carriers that enable the drug to reach the deep skin layers and/or the systemic circulation. These are soft, malleable vesicles tailored for enhanced delivery of active agent. They are mainly composed of phospholipids (phosphatidlycholine, phosphatidyl serine, phosphatidic acid), high concentration of ethanol and water. The high concentration of ethanol makes the ethosomes unique, as ethanol is known for its disturbance of skin lipid bilayer organization therefore, when integrated into a vesicle membrane it gives the ability to the vesicle to penetrate the stratum corneum. Also because of their high ethanol concentration, the lipid membrane is packed less tightly than conventional vesicles but has equivalent stability, allowing a more malleable structure and improves drug distribution ability in stratum corneum lipid.[7,8]

The size range of ethosomes may vary from tens of micrometers to microns (μ).[9] Ethosomes are slight modification of well established drug carrier liposomes.[10] Unlike the classic

liposomes,[11,12] that are known mainly to deliver drugs to the outer layer of the skin, ethosomes can enhance permeation through stratum corneum barier.[13,14] Ethosomes can entrap drug molecule with various physicochemical charachterstics i.e of hydrophilic, lipophilic or amphiphilic.[15]



"Fig. 1" Representation of ethosomes contents

COMPOSITION

Ethosomal drug delivery can be modulated by altering alcohol: water or alcohol: polyol: water ratio. Ethosomes are vesicular carriers comprising of hydro alcoholic or hydro/alcoholic/glycolic phospholipid in which concentration of alcohols or their combination is relatively high (Friend et al 1988). The various types of additives used in ethosomes preparations are represented in the following table[16]:

Table 1: Different additives employed in formulation of ethosomes

Additives	Uses	Examples
Phospholipid	Vesicles forming component	Soya phosphatidyl choline,egg phosphatidy choline etc.
Polyglycol	Skin penetration enhancer	Propylene glycol,transcutol
Cholestrol	Stabilizer	Cholestrol
Alcohol	For providing the softness for vesicle membrane as a penetration enhancer	Ethanol,isopropyl alcohol
Vehicle	As a gel former	Carbopol 934
Dye	For characterization study	6-Carboxy Fluroscence, Rhodamine-123 etc.

MECHANISM OF DRUG PENETRATION

The mechanism of drug absorption from ethosomes is not clear. The drug absorption probably occurs in following two phases- ethanol effect and ethosomes effect.

Ethanol effect

Ethanol acts as a penetration enhancer through the skin. The mechanism of its penetration enhancing effect is well known. Ethanol penetrates into intracellular lipids and increases the fluidity of cell membrane lipids and decreases the density of lipid multilayer of cell membrane.[16] Ethanol interacts with lipid molecules in the polar hard group region, resulting in a reducing the rigidity of the stratum corneum lipids, increasing their fluidity. The interaction of ethanol into the polar head group environment can result in an increase in the membrane permeability. In addition to the effect of ethanol on stratum corneum structure, the ethosome itself may interact with the stratum corneum barrier.[17]

Ethosome effect

Increased cell membrane lipid fluidity caused by the ethanol of ethosomes results increased skin permeability. So, the ethosomes penetrates very easily inside the deep skin layers, where it gets fused with skin lipids and releases the drugs into deep layer of skin. [16] In the case of ethosome encapsulating drugs, the higher positive zeta potential imparted by the drug can improve skin attachment of the vesicles. [17]

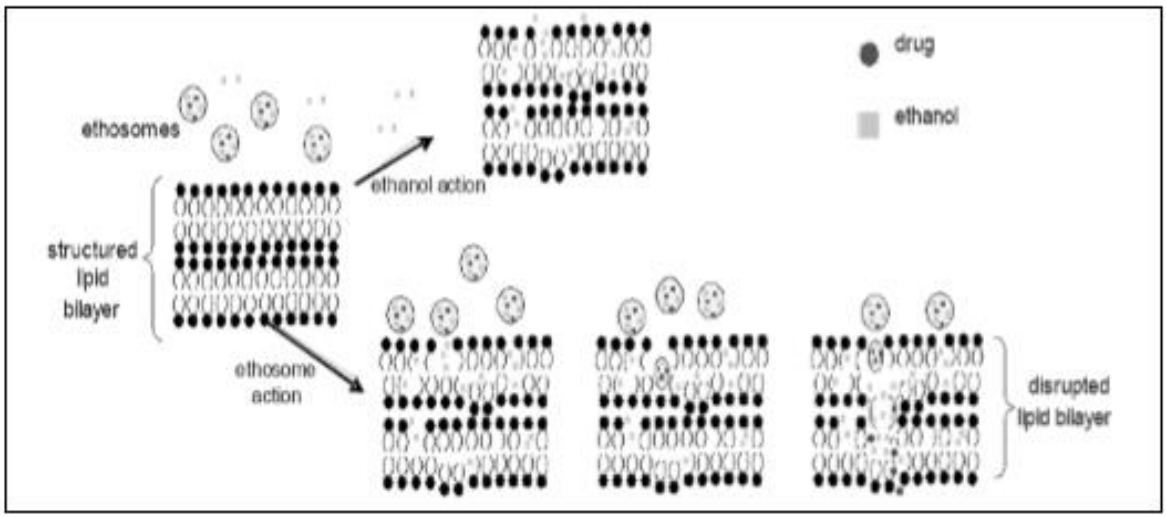


Fig 2. Mechanism of action of ethosome

METHODS OF PREPARATION

There are four methods which can be used for the formation and preparation of ethasomes.

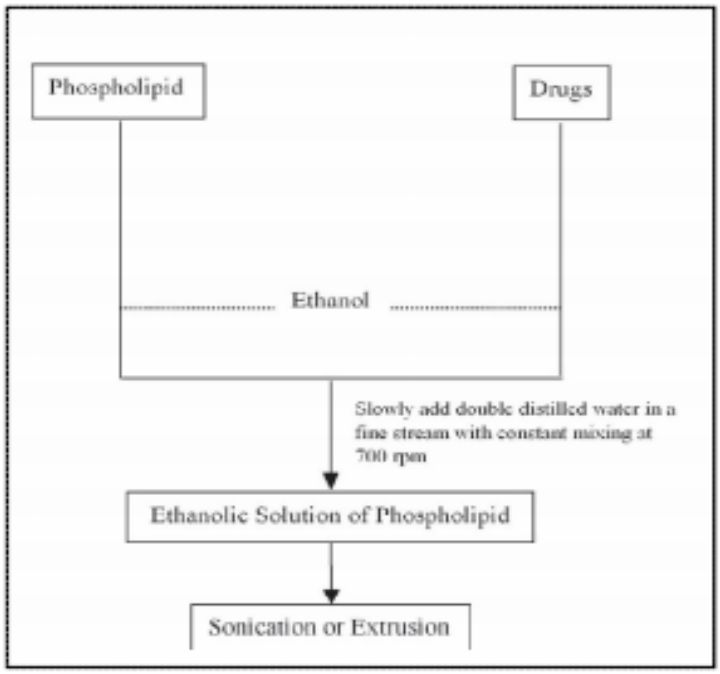
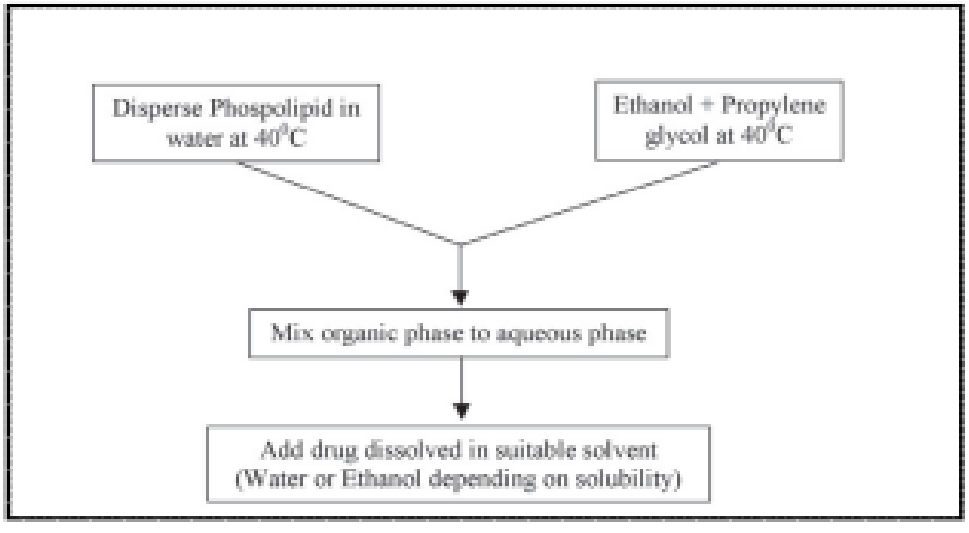


Fig 3. General method of preparation of ethosomes

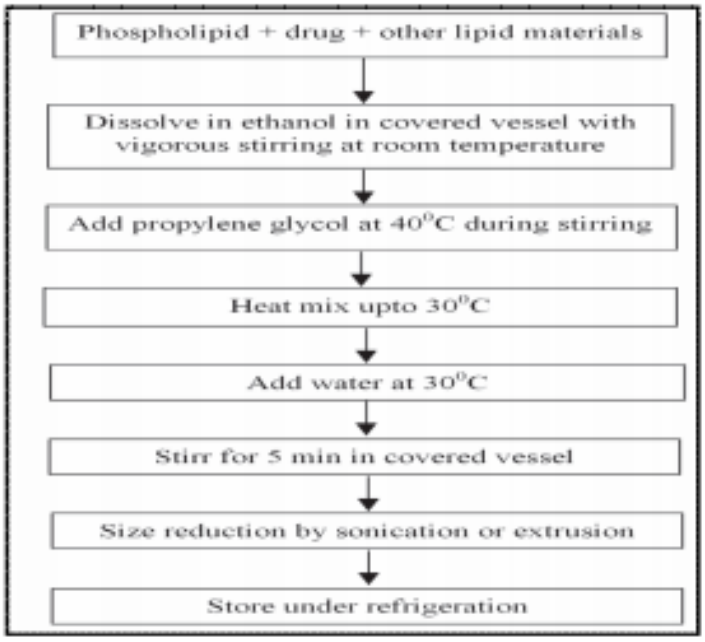
Hot method

In this method, phospholipid is dispersed in water by heating in a water bath at 40 ^{o} C until a colloidal solution is obtained. In a separate vessel ethanol and propylene glycol are mixed and heated to 40^{o} C. Once both mixtures reach 40 ^{o} C, the organic phase is added to the aqueous one. The drug is dissolved in water or ethanol depending on its hydrophilic/hydrophobic properties. The vesicle size of ethosomal formulation can be decreased to the desired extent using probe sonication or extrusion method.[16]



Cold method

This is the most common method utilized for the preparation of ethosomal formulation. In this method, phospholipid, drug and other lipid materials is mixed. Propylene glycol or other polyol is added during stirring. This mixture is heated to 30 ^{o} C in a water bath. The water heated to 30 ^{o} C in a separate vessel is added to the mixture, which is then stirred for 5 min in a covered vessel. The vesicle sizes can be decreased to desired extend using sonication or extrution method. [16]



Classic method

The phospholipid ad drug are dissolved in ethanol and heated to 30 ^{o} C in a water bath. Double distilled water is added in a fine stream to the lipid mixture, with constant at 700 rpm, in a closed vessel. The resulting vesicle suspension is homogenized by passing through a polycarbonate membrane using a hand extruder for three cycles.[16]

Mechanical dispersion method

Soya phosphotidylcholine is dissolved in as mixture of chloroform: methanol in round bottom flask (RBF).the organic solvents are removed using rotary vacuum evaporator above lipid transition temperature to form a thin lipid film on a wall of the RBF. Finally, traces of solvent mixture are removed from the deposited lipid film by leaving the contents under vacuum overnight. Hydration is done with different concentration of hydroethanolic mixture containing drug by rotating the RBF at suitable temperature.[16]

ADVANTAGES OF ETHOSOME

- Enhanced permeation of drug through skin for transdermal drug delivery.
- Delivery of large molecules (peptides, protein molecules) is possible.
- It contains non toxic raw materials in formulation.
- High patient compliance – the ethosomal drug is administered in semisolid form (gel or cream) hence producing high patient compliance.
- The ethosomal system is passive non- invasive and is available for immediate commercialization.
- Ethosomal drug delivery system can be applied widely in pharmaceutical, veternary, cosmetic fields.
- Simple method for drug delivery in comparison to iontophoresis and other complicated methods.[18]
- Better stability and solubility of many drugs as compared to conventional vesicles.
- Relatively smaller size as compared to conventional vesicles.[19]

IDEAL DRUG CHARACTERISTICS FOR ETHOSOME:[19,20]

Low dose

Short biological half life

Higher dosing frequency

Less oral bioavailability

High lipophilicity.[20]

CHARACTERIZATION OF ETHOSOMES:[17,18]

1) Vesicular characterization- Particle size, shape and zeta potential can be measure by using transmission electron microscopy (TEM), Scanning electron microscopy (SEM), Dynamic light scattering (DLS) and Photon correlation spectroscopy (PCS).[18,19,20]

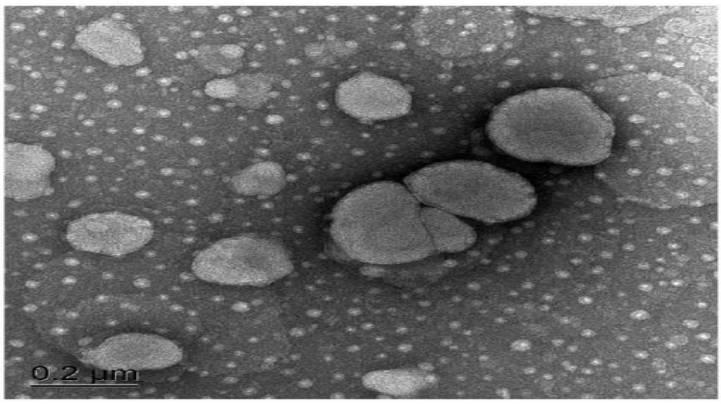


Fig 4. TEM image of ethosome[21]

2) Entraptment efficiency- It can be measured by ultracentrifugation technique.[18, 19]

3) Transition temperature- Transition temperature of vesicular lipid system can be measured by differential scanning calorimetry.[18]

4) Surface tension activity measurement- It can be measure by the ring method in a Du Nouy ring tensiometer.[18]

5) Vesicle stability- It depends on size, structure of vesicles. Structure and shape changes observe using TEM.[18]

6) Drug content- It can be done by using UV spectrophotometry and High performance liquid chromatography.[18,20]

7) Penetration study- It can be done by using confocal laser scanning microscopy (CLSM).[18]

8) Permeation study- It can be done by incorporating ethosome into gel. Diffusion studies of gel must be done using franz diffusion cell.[18,19]

9) Phospholipid-ethanol interaction- It can be done by using differential scanning calorimetry and P^{31} NMR.

APPLICATION OF ETHOSOME

1) Transdermal delivery of hormones

Oral delivery of hormones causes certain side effects like low bioavailability, first pass metabolism, failure of treatment if one dose is missed out.

Eg. Marketed testosterone patch (Testoderm patch, Alza) compared with testosterone Ethosomes, It was observed that Ethosomes give 30 times higher skin permeation, It improves skin permeation and bioavailability of testosterone. [16 ,17, 22]

2) Transcellular delivery

Transcellular delivery of ethosome in swiss albino mice 3T3 fibroblast has been investigated and results shows that the ethosomal carrier was not toxic to the cultured cell.[16 ,17, 23]

3) Treatment of Parkinson disease

Eg. Psychotic drug trihexyphenidyl.HCl (THP) used in treatment of parkinsons disease. Its ethosomal preparation compared with liposomal preparation. THP ethosomal preparation visualized under SEM and TEM, it consist of small phospholipid vesicles. Transdermal flux of THP Ethosomes was 4-5 times higher than liposomes. This shows THP Ethosomes can be use for better management of Parkinson disease.[16, 17, 24]

4) Delivery of anti-arthritis drug

Most of the anti-arthrits drugs are given by transdermal route. Oral formulation is associated with many problems such as low bioavailability, first pass metabolism and GIT degradation.[16 ,17]

5) Pilosebaceous targeting

Pilosebaceous units has been used for the treatment of follicle related disorder such as acne or alopecia. Minoxidil ethosome is used topically on scalp for treatment of baldness. It shows better permeation than conventional formulation. It shows better clinical efficacy .[16, 17, 25]

Eg. Cannabinol ethosomal preparation. It shows significant increase in biological anti-inflammatory activity. [16, 17, 26]

6) Delivery of proteins and peptides

Proteins and peptides are completely degraded in GIT. Transdermal delivery is one of the best option for delivery if protein and peptide.

Eg. Effect of ethosomal insulin delivery in lowering blood glucose level in vivo in normal and diabetic rats have been investigated. [16 ,17]

7) Delivery of antibiotics

Oral administration of antibiotic causes allergic reaction and several side effect. Hence topical delivery is the best option for its delivery. Ethosome penetrate rapidly through skin and deliver large amount of drug into deeper layer of skin.

Eg. Preparation of bacitracin and erythromycin loaded ethosomal formulation. [16, 17, 27]

8) Delivery of antiviral drugs

Eg. Zidovudine ethosomal formulation was prepared to overcome side effects associated with oral administration of zidovudine. [16, 28]

9) In cosmetics

It increases stability of cosmetics and also decreases skin irritation. It is used in topical administration of antioxidant. [16 , 17]

Table 2: Marketed products based on ethosomal drug delivery system

Name of product	Uses	Manufacturer
Cellutight EF	Topical cellulite cream, contains a powerful combination of ingredients to increase metabolism and break down fat	Hampden Health, USA
Decorin cream	Anti-aging cream, treating, repairing, and delaying the visible aging signs of skin including wrinkle lines, sagging, age spots, loss of elasticity and hyperpigmentation.	Genome cosmetics, Pennsylvania, US
Nanominox	First minoxidil containing product, which uses ethosomes. Contains 4% minoxidil, well known hair growth promoter.	Sinere, Germany
Noicellex	Topical anti-cellulite cream	Novel therapeutic technologies, Israel.
Skin genity	Powerful cellulite buster, reduces orange peel	Physonics, Nottingham,Uk
Supravir cream	For the treatment of herpes virus,	Trima, Israel

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