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A REVIEW ON ETHOSOMAL DRUG DELIVERY SYSTEM

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ABSTRACT
Transdermal drug delivery is a dosage form that is applied topically to the skin layer (epidermis) which helps to deliver the drug into the skin layer before entering the systemic circulation. Ethosomes are soft, and flexible vesicles which helps in rapid drug absorption. Ethosomes have better pharmaceutical properties than the conventional liposomes such as room temperature stability, and improved compatibility with the Stratum Corneum barrier. Ethosomes are non-toxic in nature and can be used in the preparation of cosmeceutical and it has better drug absorption to the skin. The mechanism of ethosomes is mainly occurred due to increased lipid fluidity within the cell membrane caused by the ethanol in ethosome. As a result, skin permeability is increased. The most widely used application for ethosomal formulation is to transport the DNA topically into the skin layer for gene expression and hence ethosomes are used in the delivering the vaccines by transdermal route. Ethosomal preparations have promising future in delivering bioactive substances via transdermal distribution. The discovery of ethosomes and vesicle derivatives was a crucial breakthrough in vesicle research. Ethosomes are preferred because they are non-irritant to the GIT tract and avoid first-pass metabolism.

KEYWORDS: Ethosomes, Transdermal, Lipid-based vesicles, Delivery systems.

INTRODUCTION
Ethosomes are preferred because they don't cause any irritation to the GIT tract and first-pass metabolism; transdermal drug delivery systems (TDDS) have shown promising outcomes compared to oral drug delivery systems. Main disadvantage of TDDS is that the drug might interact with the Stratum Corneum barrier, meaning that only lipophilic drugs with molecular weight less than 500Da can cross the Stratum Corneum barrier. Chemical and physical enhancers, including iontophoresis, sonophoresis, and other similar methods, have all been studied to promote drug permeation through the skin layer (Epidermis). Drug permeation across the Stratum Corneum barrier has also been observed to be increased by liposomes, niosomes, transferosomes, and ethosomes. Permeation enhancers like alcohols (Ethanol, Isopropyl Alcohol) increases the rate of permeation in the skin, allows the drugs to pass through the skin more efficiently. Ethosomes penetrate the skin layers faster and have a higher transdermal flow than traditional liposomes. Ethosomes have demonstrated excellent percutaneous medication delivery efficacy as a lipid carrier. They also have better pharmaceutical properties than conventional liposomes, such as room temp stability, high trap performance, and improved compatibility with the Stratum Corneum (SC), allowing for even more effective penetration of lipophilic and hydrophilic drugs into the skin's deep layers through the SC. The role of ethosomes in transdermal penetration and their effects on the skin are unknown. Some of the critical techniques used to study the transdermal process include Attenuated Total Reflectance (ATR-FTIR), Differential Scanning Calorimetry (DSC) and other microscopic techniques like TEM, Raman, Scanning Electronic Microscope (SEM) and various surface analysis techniques like XPS, and Electron Spin Resonance (ESR).

History
The development of liposomes heralded a new era in drug delivery research, and a variety of vesicular systems have subsequently been created. Cevc and Blume also discovered transferosomes, which are malleable or elastic liposomes, in 1992. Transferosomes were then followed by the ground-breaking work of Touitou et al. which resulted in the discovery of a unique lipid vesicular system known as ethosomes.[1-3]

Advantages and Disadvantages of ethosomes[4-5]

Advantages

1. Large molecules such as peptides and protein molecules can be delivered.
2. It is made up of non-toxic raw materials.
3. Increased drug absorption through the skin
4. Its composition can be used for preparation of pharmaceuticals and cosmetics
5. It has a low-risk profile
6. Patient compliance is high.
7. Ethosomes can be directly marketed due to its non-invasive properties
8. Ethosome systems is used in various industries including pharmaceuticals, biotechnologies, cosmetics, nutraceuticals and veterinary medicines.
9. Compared to iontophoresis, phosphophoresis, and other complex processes, this is a simple drug delivery approach

Disadvantages

1. Rather than a fast bolus-type drug intake, ethosomal administration is designed to provide continuous, sustained pharmaceutical distribution.
2. Effective drug solubility in lipophilic and aqueous media for cutaneous micro-circulation and systemic circulation.
3. The drug's molecular size must be adequate for percutaneous absorption
4. Adhesive might not stick to all skin types.
5. It might not be cost-effective.
6. Allergy responses to ethanol or other ethosomal components can be identified.
7. Ethosomal carriers, in contrast to other carriers (solid lipid nanoparticles, polymeric nanoparticles, and so on), are only required for transdermal administration.
8. Because ethanol is flammable, more caution should be exercised when planning, applying, transporting, and storing it.
9. Loss of product is observed during the phase transition from organic to water medium.

Types of ethosomes

1. Classical ethosomes

Classical ethosomes are a modification of classical liposomes and are composed of phospholipids, a high concentration of ethanol up to 45% w/w, and water. Classical ethosomes were reported to be superior over classical liposomes for transdermal drug delivery because they were smaller and had negative ζ-potential and higher entrapment efficiency. Moreover, classical ethosomes showed better skin permeation and stability profiles compared to classical liposomes. The molecular weights of drugs entrapped in classical ethosomes have ranged from 130.077 Da to 24 kDa.9,10.[6-8]

2. Binary ethosomes

Binary ethosomes were introduced by Zhou et al.11 Basically, they were developed by adding another type of alcohol to the classical ethosomes. The most commonly used alcohols in binary ethosomes are propylene glycol (PG) and isopropyl alcohol (IPA).[9-13]

3. Transethosomes

Transethosomes are the new generation of ethosomal systems and were first reported by Song et al in 2012.17 This ethosomal system contains the basic components of classical ethosomes and an additional compound, such as a penetration enhancer or an edge activator (Surfactant) in their formula. These novel vesicles were developed in an attempt to combine the advantages of classical ethosomes and deformable liposomes (Transfersomes) in one formula to produce transethosomes. Many researchers have reported superior properties of transethosomes over classical ethosomes.17–30 Different types of edge activators and penetration enhancers have been investigated to produce ethosomal systems with better characteristics. Transethosomes were reported to entrap drugs with molecular weights ranging from 130.077 Da to 200–325 kDa.[14-15]

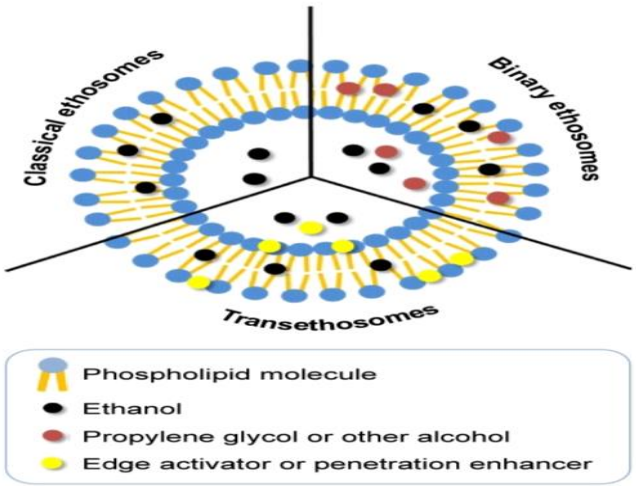

Figure 1: Systematic representation of types of ethosomes.

Composition of ethosomes

Ethosomes comprise several main components, as seen in Fig.1.

Ethosomes mainly comprises of ethanol (10-50%), water and phospholipids (such as phosphatidylcholine which helps in the formation of bilayer lipid vesicles).

It consists of non-aqueous phase (22-70%). The alcohol that is used in the composition can be ethyl or isopropyl alcohol.

Ethosomes is hydroalcoholic in nature due to the high alcohol content caused by the mixture of alcohols.

Ethanol and isopropyl alcohol are examples of alcohols that can be employed. Propylene glycol (05-20%) and transcutol are the most often utilized glycols.

Non-ionic surfactants like polyethylene glycol can be combined with the phospholipids (1-5%) for the formulation of ethosomes.[16-17]

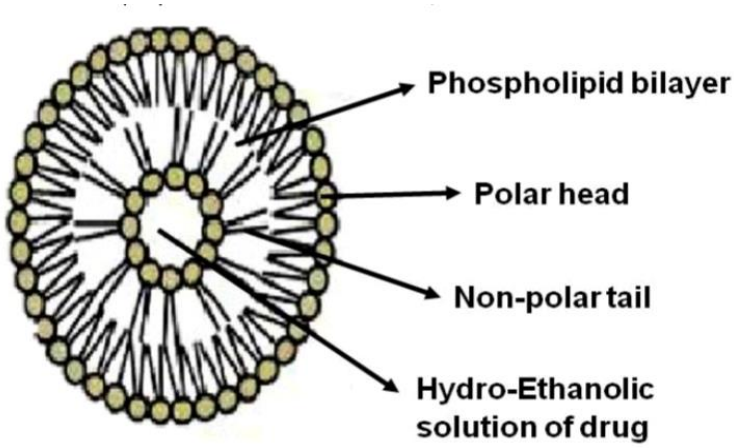

Figure 2: Representation of composition of ethosomes.

METHODOLOGY

1. The classical cold method

This is the simplest and most widely used method for the preparation of ethosomal systems, and if required it could be done under nitrogen protection. It was introduced by Touitou in 1996, and involves the preparation of the organic phase and aqueous phase separately. The organic phase is obtained by dissolving the phospholipids (in addition to surfactants or penetration enhancer for transethosomes) in ethanol or mixture of solvents (ethanol/PG) for the preparation of binary ethosomes, at room temperature, or at 30°C.6 The aqueous phase used is either water, buffer solution or normal saline solution. The aqueous phase is added to the organic phase in a fine stream, dropwise, or using a syringe pump at a constant rate of 175 or 200 µL/min. The mixture is stirred at a speed of 700–2,000 rpm, using an overhead81 or magnetic stirrer. The mixing is done for 5–30 minutes to obtain the required ethosomal suspension. The drug to be incorporated in the ethosomal system will be dissolved in either the aqueous or the organic phase, depending on its physicochemical properties. Figure 3 presents the preparation steps of an ethosomal system using the classical cold method.[18-19]

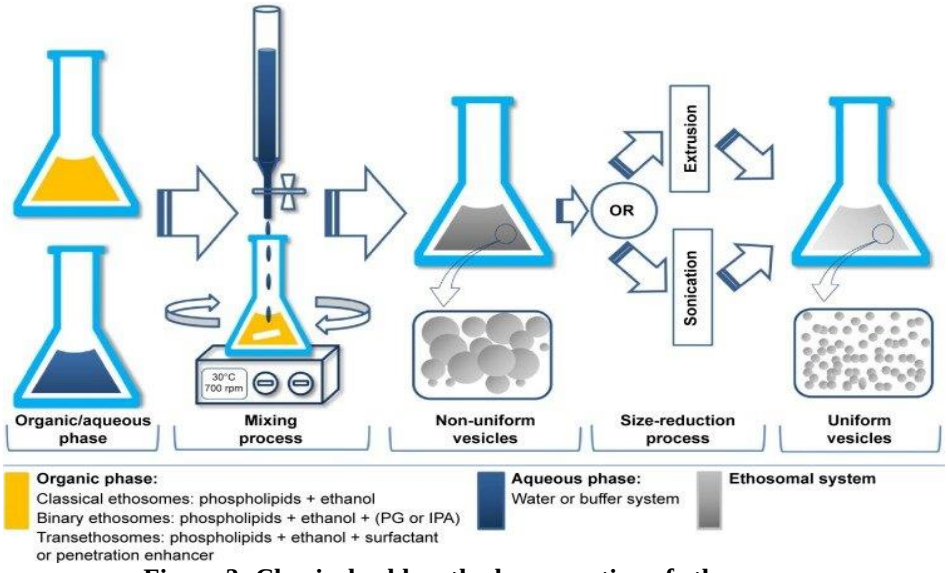

Figure 3: Classical cold method preparation of ethosomes.

2. The hot method

This method was first described by the inventor of ethosomes in 1996.5 In one vessel, phospholipid is dispersed in water and then placed in a water bath at 40°C until a colloidal suspension is obtained. In another vessel, ethanol is heated to 40°C and then added dropwise to the phospholipid dispersion under continuous mixing using a mechanical or magnetic stirrer.84 The drug is dissolved in either the organic or aqueous phase, based on its hydrophilic/hydrophobic properties.[20-21]

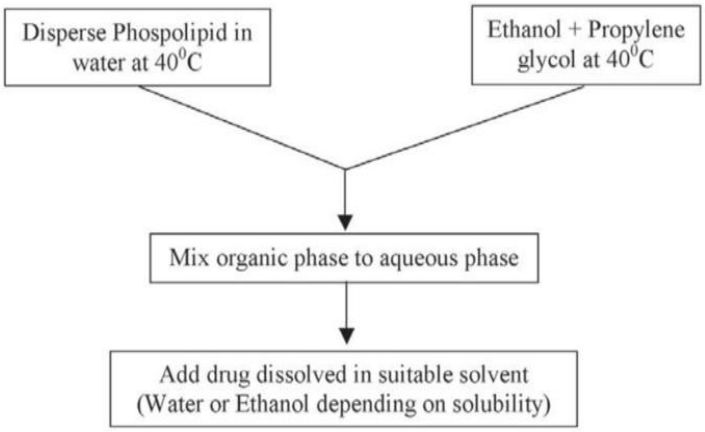

Figure 4: The hot method of preparation of ethosomes.

3. The ethanol injection–sonication method

In this method, the organic phase containing the dissolved phospholipid in ethanol is injected to the aqueous phase, using a syringe system, 38 at a flow rate of 200 µL/min, then homogenized with an ultrasonic probe for 5 minutes.[22]

4. The reverse-phase evaporation method

This is the least used method and specially designed to produce large unilamellar vesicles. The organic phase is prepared by dissolving the phospholipid in diethyl ether and then mixing it with the aqueous phase at a ratio of 3:1 v/v in an ultrasonic bath at 0°C for 5 minutes to form a water-in oil emulsion. The organic solvent is removed under reduced pressure to produce a gel, which turns into a colloidal dispersion upon vigorous mechanical agitation.[23]

Evaluation of ethosomes

Study of interactions between Vesicle and Filter Membrane by Using SEM

In this method, coating of filter membrane is done by using a suitable vesicular suspension (0.5 mL). Then the coated filter membrane is placed in Franz diffusion cell apparatus. After placing filter membrane in the Franz Diffusion cell apparatus, top portion of the filter membrane was open and exposed to air and bottom portion of the filter membrane was suspended in phosphate buffer (pH 6.5) and keep it for 1 hour. Later, the filters were removed and sample preparations is done for SEM analysis. The sample preparation for SEM analysis is done by a reagent called Karnovsky's fixative reagent at 04°C and also ethanol graded solutions is used for sample preparation. Later, the filters were analysed by SEM.[24-25]

Permeability studies

In skin permeability studies, rodent animals are used like rats or guinea pigs. In this method, the hair follicles of the rodent animals are carefully trimmed (2mm). Now with the help of scalpel, the abdomen epidermis was separated and from that the connective tissue was extracted. The removed skin was kept on a sheet of aluminium foil. Slowly remove the dermal side. The temperature is maintained at 32 degrees Celsius plus or minus 1 degree Celsius. 10 mL saline solution was kept in the receptor compartment. The donor and receptor compartments were partitioned by excise skin. The ethosomal formulation was applied to the skin's epidermal surface (1.0 mL). High-performance chromatography test was performed to evaluate samples (0.5 mL). Collect the samples respectively with time-intervals: 2,4,6,8,12,16,20,24 hours accordingly.[26]

Stability study

Storing the vesicles at cool temperature (04°C). The various stability studies of ethosomes includes, entrapment efficiency, vesicular size and zeta potential.[27]

Drug content studies

Drug content studies can be conducted by using HPLC method to determine the amount of drug uptake.[28]

HPLC Assay

It is an invitro permeation assay which measures the amount of drug permeated in the receptor compartment and assay is conducted by using HPLC method. In this method methanol: distilled water: acetonitrile is used as mobile phase and ratio of mobile phase is 70:20:10 vol/vol. Flow rate of mobile phase pass through the

column is at 1ml/min. Column used in this method is octadecylsilane(C-18).[29-30]

Statistics data analysis

Ethosomes can also be evaluated by various statistical method, one of the methods that is widely used is the ANOVA technique which preferably used to examine the statistical data. Obtained, followed by a studentized ranged test. The results were interpreted using PRISM statistical software.[31-32]

Applications

Ethosomes have been shown in numerous trials to be an effective treatment for viral and microbial skin infections. Animal models of deep skin infections were used to create and test the efficacy of the bacitracin and erythromycin ethosomal systems.

When manufactured, ammonium glycyrrhizinate ethosomes were shown to have an anti-inflammatory impact on the skin of human volunteer subjects.

When tested in vivo on rabbits, ethosomal patches in treating androgen insufficiency in males and menopausal symptoms in women have sufficiently demonstrated better results.

Research suggests that ethosomes may have analgesic, antipyretic, and efficacious effects against erectile dysfunction.

Research has also indicated that ethosomes might be utilised to topically transport DNA molecules for skin cells to express certain genes.[33]

CONCLUSION

Ethosomes have been proven as an emerging and effective carrier system over two decades. Their ability to provide effective therapeutic effect, topically and systemically through skin have made them an appealing and novel carrier system over time. Profound investigation has also resulted in the development of a new generation of ethosomal systems known as Transethosomes. Over classical ethosomes these transethosomes have better skin permeation and systemic circulation. Continuous research has been carried on ethosomal systems and research supports that these carriers along with penetration enhancers could be proven effective as vehicles for delivering drug in form of gels, patches and creams. More detailed studies however are needed to further work on the stability of the ethosomal system.

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