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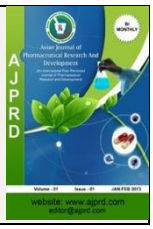

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Review Article

Ethosomal Drug Delivery System: A Newer Approach

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A B S T R A C T

The transdermal drug delivery system is a technique that provides advantages over conventional administration routes such as intravenous ororal route. Ethosomes are non-invasive delivery carriers that enables drugs to reach the deep skin layers and the systemic circulation. Ethosomal systems are conceptually sophisticated, they are simple in their preparation, safe for use a combination that can highly expand their application. Ethosomes are soft, malleable vesicles tailored for enhanced delivery of active agents. The size range of ethosomes may vary from tens of nanometres (nm) to microns (µm). Ethosomes formulation are convenient for use & harmlessness to skin.

Keywords: Ethosomes, Non- Invasive, Ethosomal carrier, Ethanol.

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INTRODUCTION:

The objective of transdermal drug delivery system is to cross the stratum corneum. Various methods have been used for the penetration rate of drugs. TDDS is going importance due to its non-invasive procedure for administration. Despite the challenges, TDD offers several unique advantages including relatively large & Ethosomes are the most pioneering vesicular system with eminent level of ethanol present in it which ensures better Penetration of drugs in to deeper part of skin[1]. To Improve the permeation of drug through the skin various mechanisms are reported like iontophoresis, sonophoresis, etc niosome, liposomes, & Ethosomes etc. Ethosomes are ethanolic liposomes. The vesicles have been well known for their importance in cellular communication and particle transportation for many years. Ethosomes are lipid vesicles containing phospholipids, alcohol (Ethanol & Isopropyl alcohol) in relatively high concentration and water. Ethosomal drug delivery system can be applied widely in pharmaceutical veterinary[2,3]. The size range of ethosomes may vary from tens of nanometres (nm) to microns (µm). Ethosomes formulation are convenient for use & harmlessness to skin. Ethosomes are composed of phospholipid, alcohol, polyglycol and water.

Table: 1. Additives used in Ethosomes Formulation[4]

Type	Use	Example.
Alcohol	Act as permeation enhancers	Ethanol, Isopropyl alcohol
Phospholipid	Preparation of vesicles	Egg phosphatidyl choline, soya Phosphatidyl choline, Distearyl Phosphatidyl choline.
Polyglycol	Permeation enhancer	Propylene glycol
Cholesterol	Providing stability to the vesicles	Cholesterol
Dyes	For Characterization study	Fluorescence isothiocyanate, 6- carboxy fluorescence
Vehicle	Gel Forming	Carbopol D934

The high concentration of ethanol directs its exclusivity where the lipid membrane is packed less tightly than conventional. It has equivalent stability in which ethanol has proven to increase the drug distribution in the stratum corneum ad also has malleable structure. Ethanol increases the flexibility and fluidity of lipid and loosens the tight junction of stratum corneum by interacting with the polar head region of lipid molecules which reduces the melting point of lipid which thereby increases the permeability of skin and also the penetration of disorganized lipid bilayers. Ethanol concentration is also responsible for stearic stabilization because of its negative charge which leads to deeper drug penetration in skin with high transdermal flux. Since incorporation of high ethanol concentration confers a negative charge to the liposomes which causes the size of vesicles to decrease, and that in turn eventually leads to enhanced bioavailability of therapeutic agents[5,6].

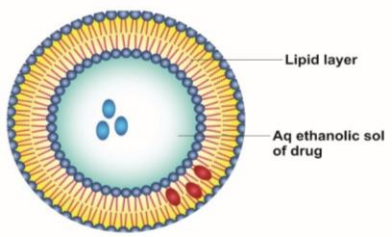

Figure: 1 Ethosomes Formulation

Advantages of Ethosomal drug delivery system:

1. Transportation of active moieties by ethosomes in the skin layer have more importance than conventional liposomes on the basis of retention in the skin layer.
2. The synergistic effect of combination of relatively high concentration of ethanol (20-50%) in vesicular form in ethosomes was suggested to be the main reason for their better skin permeation ability.
3. Ethosomes are passive, non-invasive & available for immediate commercialization[7].
4. This is the type of formulation which is used for the delivery of peptide protein molecules.
5. Ethosomes are simplest method for delivery of drug molecules instead of phonophoresis & iontophoresis.
6. Ethosomal drug is administered in semisolid form (Gel or Cream), producing high patient compliance.
7. 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.

Disadvantages of Ethosomal drug delivery system:

1. Ethosomal formulations may not be economical.
2. The molecular size of the drug should be reasonable that it should be adsorbed percutaneously.
3. Skin irritation or dermatitis due to excipients & enhancers of drug delivery system.
4. Loss of product during transfer from organic to water media[8].
5. Yield will be very poor.
6. Adhesives may not be suitable for all types of skin[9].
7. Product wastage from while transferring organic media to water media[10,11].

Ethosomal system types:

On the basis of their composition ethosomes are classified in to different types.

1. Classical ethosomes:

Ethosomes are prepared by the modification in liposomal formulations. They contain the of high concentration of ethanol (45% w/w), phospholipids and water. These ethosomes were considered to be higher to liposomes for percutaneous delivery due to their smaller size and better entrapment efficiency[12-14]. Classical ethosomes are the variation of classical liposomes. The molecular weights of drugs caught in traditional ethosomes ranged from 130.077 Da to 24 kda. Were encapsulated in such type of ethosomes[15-16].

2. Binary Ethosomes:

Binary ethosomes were developed by adding another type of alcohol to the classical ethosomes. Like PG & IPA. etc.

3. Tansethosomes:

Tansethosomes are the new generation of ethosomal systems & were first reported in 2012 by song *et al*[17]. This ethosomal system includes the basic components of classical ethosomes and an additional compound such as a penetration enhancer or an edge activator (surfactant) in its formula. In an attempt to combine the advantages of classical ethosomes with deformable liposomes (transfersomes) in one formula to generate transethosomes, these novel vesicles were formed. Transethosomes with molecular weights ranging from 130.077 Da to 200–325 kda.

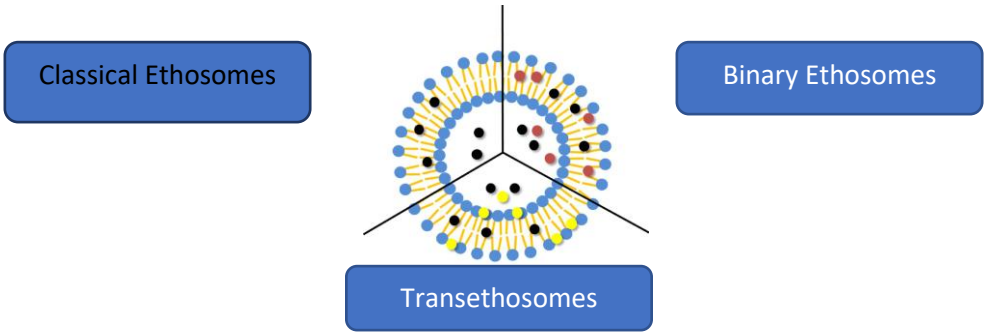

Figure 2: Classifiaction of Ethosomes

Table: 2 Comparison of different types of Ethosomes on the basis of various parameters.

Parameter	Composition	Morphology	Size	ζ-Potential	Entrapment efficiency	Skin Permeation	Stability
Classical ethosomes	1. Phospholipids 2. Ethanol 3. Stabilizer 4. Charge inducer 5. Water 6. Drug/agent	Spherical	Smaller than the Classical liposomes	Negatively Charge	Higher than Classical Liposomes	Higher than classical liposomes	Stable than liposomes
Binary Ethosomes	1. Phospholipids 2. Ethanol 3. Propylene Glycol 4. Charge inducer 5. Water 6. Drug/Agent	Spherical	Equal to or smaller than Classical Liposomes	Negatively Charge	Higher than classical Liposomes	Equal to or higher than classical ethosomes	Stable than liposomes
Transethosomes	1. Phospholipids 2. Ethanol 3. Edge Activator 4. Charge inducer 5. Water 6. Drug/agent	Regular	Based upon Conc.	Penetration enhancer	Positively or negatively Charged	Higher than Liposomes	No particular trend

Method of Formulation:

Ethosomal Preparation various methods. These methods do not require any sophisticated equipment & easy to scale up at industrial level.

Cold Method

In this method Phospholipids, drug and other lipid materials are dissolved in ethanol in a covered vessel at room temperature by vigorous stirring with the use of mixer.PG or other polyol is added during stirring. This mixture is heated to 30^0C in a water bath. The water heated to 30^0C in a separate vessel is added to the mixture, which is then stirred for 5 min in a covered vessel. The vesicle size of ethosomal formulation can be decreased to the desire extent using probe sonication or extrusion method. Finally, the formulation is stored under refrigeration[18,19].

Hot Method

In this method phospholipid is dispersed in water by heating in a water bath at 40^0C until a colloidal solution is obtained. In a separate vessel ethanol and propylene glycol are mixed and heated to40°C. Once both mixtures reach 40°C,t he 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 desire extent using probe sonication or extrusion method[20].

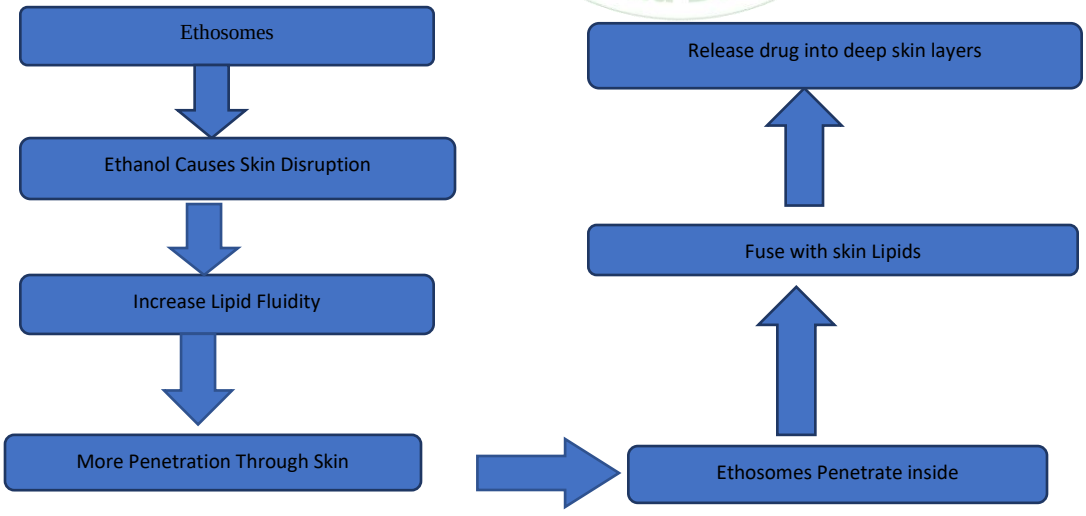

Figure: 3 Mechansim of Ethosomes through skin.

Evaluation of Ethosmal Formulation:

Vesicle size & Zeta Potential

Dynamic light scattering (DLS) & Photon correlation spectroscopy are the two-methods used in assessing the particle size & zeta Potential[21]. For vesicles size

determination ethosomal preparation is mixed with the suitable medium.

Vesicle shape

Transmission electron microscopy (TEM) and Scanning electronic microscopy (SEM) are used to characterize the surface morphology of the ethosomal vesicles[22]. Prior to analysis, mount the ethosomes onto double sided tape that has previously been secured on copper stubs and coated with platinum, then analysed at different magnifications. The size and shape of the vesicles are observed in the Scanning Electron Microscopy (SEM). One drop of ethosomal suspension is mounted on a clear glass stub. It is then air dried and gold coated using sodium aurothiomalate to visualize under scanning electron microscope at 10,000 magnifications.

Entrapment Efficiency

Ultracentrifugation is the widely used technique to measure the entrapment efficiency of ethosomes. The vesicles are separated in a high-speed cooling centrifuge at 20,000 rpm for 90 minutes in the temperature maintained at 4°C.Separate the sediment and supernatant liquids determine the amount of drug in the sediment by lysing the vesicles usingmethanol[23]. From this, determine the entrapment efficiency by the following equation,

Entrapment efficiency = DE/DT x 100 Where,

DE - Amount of drug in the ethosomal sediment

DT - Theoretical amount of drug used to prepare the

formulation (Equal to amount of drug in supernatant liquid

and in the sediment).

Transition Temperature: -

The Transition temperature (T) of vesicular lipids can be measured in duplicate by DSC in an aluminium pan at a heating rate of 10°C per min, under a constant nitrogen stream[24].

Confocal Scanning Laser Microscopy (CSLM):-

CSLM can be used to investigate depth and mechanism of skin penetration of ethosomal preparation. The skin thickness can be optically scanned at different increments through the z-axis of a confocal laser scanning microscope[25].

Drug Content: -

Drug content of the ethosomes can be determined using UV spectrophotometer. This can also be quantified by a modified high-performance liquid chromatographic method[26].

Surface Tension Measurement

Du Nouy ring tensiometer is used. Ring method is used to know the surface tension activity of drug in aqueous solution[27].

Degree of deformability and Turbidity: -

The Degree of deformability of the ethosomal preparation can be performed by Extrusion Method and the turbidity of the preparation can be performed by usingNephalometer[28].

Stability studies

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. The ability of ethosomal preparation to retain the drug can be checked by keeping the preparation at different temperatures, i.e., 25 ±2°C & 37±2°C & 45±2°C for different periods of time (1,20,40,60,80 & 120 days) The ethosomal preparations were kept in sealed vials (10ml capacity) after flushing with nitrogen.

***In vitro* drug release study**

In vitro drug release study of ethosomal preparation can be performed by Franz diffusion cell with artificial or biological membrane, Dialysis bag diffusion[29].

Therapeutics applications of Ethosomes:

Ethosomes are mainly used in transdermal delivery system Ethosome are mainly used as replacement of liposomes. Oral administration of hormones is associated with problems like high first pass metabolism, low oral bioavailability and several doses dependent side effects. Which can be rectified by Ethosomal formulation.

- Improved Skin deposition containing antibiotics.
- Targeting to the dermal cells & Improved dermal deposition.
- Improved intracellular delivery & increased bioavailability of bacitracin.
- Improved pharmacodynamic profile of Anti- HIV agents.
- Selectively delivery of NSAID of drug to desired side for prolonged period of time.
- Increase the biological activity two or three times & skin permeation of Acyclovir.
- Erythromycin containing Ethosomal formulation is used for better cellular uptake.
- In treatment of genetic disorder by using DNA in ethosomal formulation.
- Acyclovir containing formulation used in treatment of Herpes labialis.
- Enalapril maleate containing ethosomes used in treatment of hypertension to reduce major side effects in oral delivery.

CONCLUSION:

Ethosomes are novel vesicular transdermal drug delivery system. Ethosomes are characterized by simple method of preparation. Ethosomes have been tested to encapsulate hydrophilic drugs, cationic drugs, proteins and peptides. The incorporation of ethosomal systems in suitable vehicles such as gels, patches, & creams shows better skin-permeation & therapeutics results. Ethosomal vesicles open new opportunities for development of novel formulation.

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