



Ethosomes as Novel Drug Delivery Carrier-A Review

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1. Abstract:

Skin is the constitutional and largest organ of the human body and also manageable organ of human body. The outermost layer of the skin stratum corneum (SC) causes a barrier for high molecular weight drug and hydrophilic drugs. Trans Dermal Drug Delivery system (TDDS) are the dosage form which are self-reliant, distinct dosage form which reaches the system circulation when applied to the skin thus first pass metabolism. The objective of TDDS is to cross the stratum corneum (SC) for which various methods have been used to increase the penetration of the drugs into the skin this reaching the system circulation. Ethosomes are the most promising or pioneering novel drug delivery system. Ethosomes are the novel drug delivery system which contain high concentration of ethanol and water thus which improves the bioavailability and skin permeability. Ethosomes are the novel phospholipids carriers which enable the drugs to reach the blood circulation which are made up of phospholipids. This article focuses on advantages, disadvantages, preparation method, its dosage form such as gels, patches, and creams. Method of characterization parameters are highlighted such as vesicle size, zeta potential, size distribution etc. Ethosomes are innovative carriers for delivery of therapeutic agents.

Keywords: transdermal, skin permeability, ethosomes

2. Introduction:

Trans dermal drug delivery system as compared to oral drug delivery system offers or provides better alternative for the drug to achieve greater therapeutic effect which could be one of the advantageous point for the drug to remain for prolonged period of time.[1][2] The outermost layer of the skin is the stratum corneum which causes the hurdle to deliver the drugs of high molecular weight. There are various strategies which improve the permeation of the drug through the skin such as iontophoresis, sonophoresis, microneedle and lipid vesicular system such as emulsions, microemulsions, lipid drug delivery and ethosomes drug delivery. Ethosomes deliver the drug to the stratum corneum by eminent and self-reinforcing deformability.[3][4]. For better drug delivery into the skin researchers have understood the properties of vesicular structure. The vesicles are important for their cellular communication and particle transformation. Major advances in finding vesicle derivatives, known as an ethosomes.[5]

1.1 Ethosomes

Ethosomes were developed by Tavitoli with good attributes and high durability. Ethosomes are ethanolic liposomes. Ethosomes range into the size range of 200-300 nanometer. The size of ethosomes can be modified from ten to nm to microns. They are soft malleable vesicles which are used for enhanced delivery of active agents[6][7]. Vesicles keep the drug shielded from other removal systems which are able to release the right amount of drug by keeping the concentration for longer period of time. Ethosomes contain higher concentration of ethanol and water. Ethosomes system is composed of phospholipid (phosphatidylcholine, phosphatidylserine, phosphatic acid)[8]. Due to higher concentration of ethanol it makes ethosomes unique. Ethanol increases the flexibility and fluidity of lipid layer and loosens the tight junction of stratum corneum. Ethanol causes disturbance of skin lipid layer which easily passes into the vesicle membrane, it enhances the vesicles ability to penetrate stratum corneum. Ethosomal system are categorized by efficacy, safety and easiness[9][10]

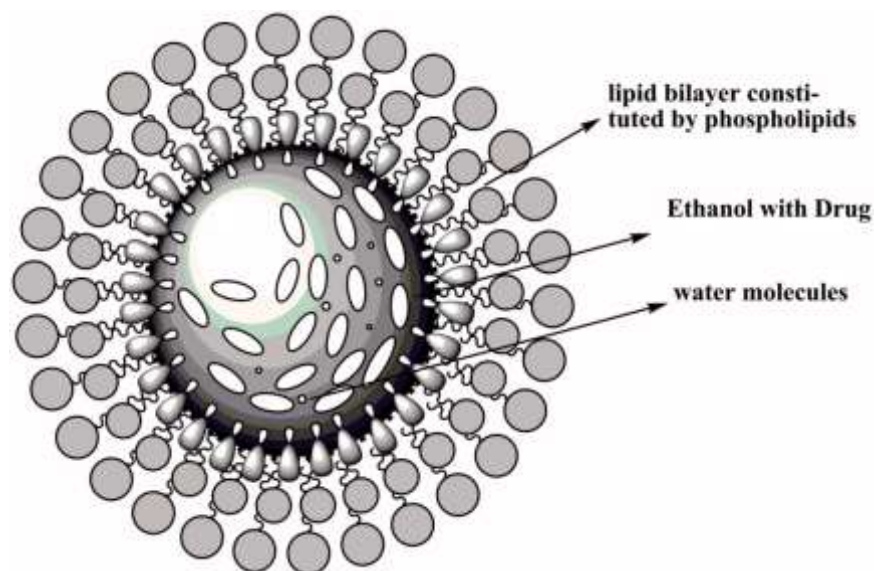


Fig 1. Structure of Ethosome[11]

1.1.1 Advantages of Ethosomes:[12, 13, 14]

1. 1.Ethosomes have excellent stability over longer periods.
2. 2.Ethosomes enhance the permeation of the drugs across the skin in an efficient manner which enables the drug to reach at the desired of the action.
3. 3.As ethanol is having amphiphilic nature,ethosomes can be encapsulated which enhance the delivery of both hydrophilic and lipophilic drugs across the skin.
4. 4.Alcohol in the ethosome act as preservative hence no need to add other preservative.
5. 5.Good patient compliance observed.
6. 6.Delivery of peptide and protein is possible.
7. 7.Easiest method for delivery of drug as compared to iontophoresis and phonophoresis.
8. 8.Ethosomes can be applied in various cosmetic field.

1.1.2. Disadvantages of ethosomes:[15-20]

1. 1.Ethosomes have higher concentration of ethanol due to which allergic reaction is observed if the patients are allergic to ethanol.
2. 2.Ethanol is inflammable, due to which proper care should be taken during its handling, preparation and storage.
3. 3.Chances of irritation to the skin due to excipients or due to other components of ethanol.
4. 4.Molecular size should be reasonable which is suitable for transdermal delivery.
5. 5.Drugs that require high blood level cannot be administered- limited to only potent molecules.
6. 6. Ethosomal administration have sustained drug delivery.
7. 7. Poor yield.
8. 8. May not be economical.

1.2 Composition of Ethosomes:

Ethosomes are vesicular carriers composed of phospholipids with various chemical structures like phosphatidylcholine(PC), hydrogenated phosphatidylcholine, phosphatic acid, phosphatidylglycerol(PG) and higher concentration of ethanol and water. Such a composition of ethosomes enables the delivery of the drug through the skin[21,22]. The ethanol content in the ethosome can be modulated which may be isopropyl alcohol. The ethanol content causes disturbance of lipid bilayer which enables to penetrate stratum corneum. The structure becomes more malleable and improves drug distribution through the stratum corneum. The preparation of ethosome can be combined with non-ionic surfactants, cationic lipids can also be added such as cocamide, citrimide etc. The concentration of non aqueous phase alcohol and glycol combination range between 22-70%[23,24]. Different additives employed in formulation of ethosomes are listed below in the given in the table:

Table no. 1 Different Additives Employed In Formulation Of Ethosomes[25-28]

Class of Polymer	Example	Uses
Phospholipid	Phosphatidylcholine, Phosphatidylserine	Emulsifier
1. Polyglycol	Polyethylene glycol, Polypropylene glycol	Skin Penetration Enhancer
2. Alcohol	Ethanol, Isopropyl Alcohol	To release the drug into deeper layer of skin.
3. Cholesterol	Cholesterol	Provide stability to vesicle membrane.
4. Vehicle	Carbopol 934	Gel forming agent

1.3 Ethosomal system types:

- a. Classical ethosomes:
are composed of phospholipids and contain high concentration of ethanol upto 45%. Classical ethosomes are spherical in shape and are smaller than classical liposomes. They carry negatively charged zeta potential. Entrapment efficiency is higher than classical liposomes. The drug entrapped in classical ethosomes ranges from 130Da to 24Da[29-32].
- b. Binary Ethosomes:
Binary ethosomes is composed of phospholipids. They were developed by another type of alcohol known as propylene glycol. The size of binary ethosomes is equal to or smaller than classical ethosomes. Entrapment efficiency is higher than classical ethosomes.[33,34,35]
- c. Transethosomes:
Transethosomes are composed with phospholipids and penetration enhancer. They have regular or irregular shape. Size of transethosomes depend on the concentration of penetration enhancer.[36-39]

1.4 Mechanism of drug penetration:

Stratum corneum have two pathways which comprises of intercellular and transcellular pathways. Drug is deliver into the skin by imposed vesicles. Vesicles deliver the drug into the deepest layer of skin. In ethosomes the size is affected by concentration of phospholipid and ethanol. Ethosome permeate into the skin through stratum corneum which is transcutaneous pathway and open hair follicles. The ethanol in the ethosome escalate the ethosome permeation. The transcutaneous allow the penetration of therapeutic agents[40,41]. This phenomenon is based on two effects.

1. Ethanol effect
2. Ethosomes effect

1. Ethanol effect:

The role of ethanol in the ethosome is that it act as penetration enhancer. It reduces the barrier resistance of stratum corneum. Ethanol penetrate into the intracellular lipids. It enhances the solubility of drug. As ethanol is volatile there is loss from formulation which influences the drug will flux across the membrane[42].

2. Ethosomes effect:

Ethosomes permeates into the intracellular lipids and hence decreases the density of lipid multilayer of cell membrane. The drug is being liberated into the deep layer of skin[41].

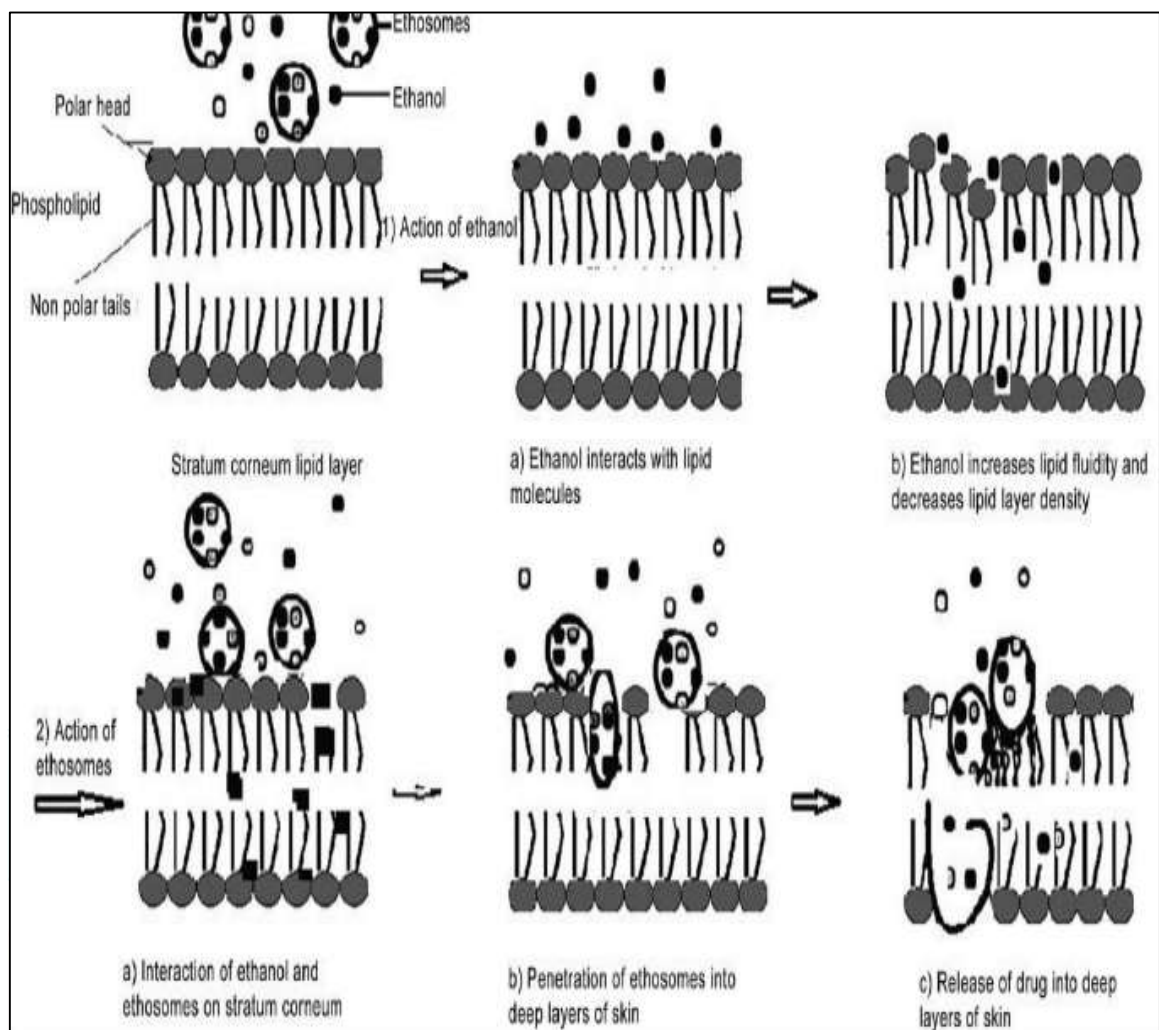


Fig 2. Mechanism of Ethosomes

1.5 Method of Preparation of Ethosomes:

Cold method :

This is the most common method for preparation of ethosomes. In this method in a covered vessel drug, phospholipid and ethanol are dissolved with stirring with the use of mixer. Glycol or propylene glycol is added during stirring. Then the mixture is heated in a water bath upto 30°C. In a separate vessel water is heated then added to the mixture. The size of ethosomal formulation can be decreased by sonication and extrusion method.[42,43]. The formulation is stored under refrigeration[44].

Hot method:

In this method colloidal solution is obtained by dispersing phospholipid in water which is heated in a water bath at 40°C. In a separate vessel ethanol and propylene glycol are mixed and heated at 40°C. Organic phase is added to aqueous phase. The drug is then dissolved in alcohol or water. The size of ethosomal formulation can be decreased by sonication and extrusion method[45].

Classic Mechanical Dispersion Method:

In a round bottom flask soya phosphatidylcholine is dissolved in a mixture of chloroform:ethanol. By using rotary vacuum evaporator the organic solvent are removed to form a thin film on the wall of the flask. Traces of solvent are removed by leaving the contents overnight. Hydration is done with different concentration of hydroethanolic mixture containing drug at suitable temperature[46,47]

1.6 Methods for Characterization of Ethosomes:

Table no. 2 Methods for Characterization of Ethosomes:[48,49,50]

Characterisation of Ethosomes	Technique
<ul style="list-style-type: none"> Vesicle shape Size Zeta Potential Transition Temperature Drug Content Drug Entrapment Surface Activity Measurement In vitro drug release study & drug deposition 	<p>Transmission Electron Microscope, Scanning Electron Microscope</p> <p>Tens of nanometer to microns.</p> <p>Zeta Meter</p> <p>Differential Scanning Calorimetry</p> <p>UV Spectrophotometer</p> <p>Ultra Centrifugation</p> <p>DuNouy Ring Tensiometer.</p> <p>Franc Diffusion Cell</p>

1.7 Evaluation of Ethosomes:[51-54]

1. Morphology of vesicle

The shape of vesicle can be determined by using two techniques Transmission electron microscope and Scanning electron microscope. The vesicles are stained by using aqueous solution. The vesicles are dried and observation is done by two methods TEM & SEM. Also, the vesicle size was studied by for SEM analysis, the animals ultra-thin sections were cut and mounted on stubs by using adhesive tapes and coated with gold palladium alloy. The thin section was observed under SEM.

2. Stability studies

Vesicles were stored at 5°C. After 180 days vesicle size, vesicle shape and zeta potential was observed.

3. Percent Entrapment Efficiency

The entrapment efficiency can be calculated by:

Ultracentrifugation

It contains two segments. Each segment contains preparation of vesicle. First segment is set overnight which is set at intended rpm and time. The other segment contains drug which is assayed by method HPLC to check the entrapment efficiency.

4. Vesicle- skin interaction study

The vesicle skin interaction study can be performed by fluorescence microscopy.

5. Skin permeation study

The abdominal skin was separated from underlying connective tissue. The skin was placed on aluminium foil. Temperature was maintained at 32°C. The effective permeation area of the diffusion cell and receptor cell volume was 1.0 cm² and 10 mL, respectively. Ethosomal formulations were applied to the skin, samples were withdrawn at 1,2,4,6,8,12&24 time interval. The samples were analysed by HPLC method.

1.8 Applications of Ethosomes:[55-56]

1. Delivery of antibiotics:
Some of the antibiotics causes several side effects and causes several allergic reactions. Ethosomes can be alternative drug delivery for delivery antibiotic deeper into the skin. Ethosomes penetrate through the epidermis and suppress the infection. Result shows that ethosomal formulation can be highly efficient[55].
2. Transdermal delivery of hormones:
Oral administration is associated with first pass metabolism. To overcome this problem ethosome transdermal delivery of hormone is the alternative[56].
3. Delivery of drug molecules:
Peptides or proteins are degraded in GIT. Formulating above molecule into ethosomes increases permeability and therapeutic efficacy[56].
4. In the treatment of Rheumatoid arthritis:
Significant increase in biological anti-inflammatory was observed which hence increases skin permeation and accumulation[56].
5. Cosmeceutical application of Ethosomes:
To increase stability of cosmetic chemicals and to decrease skin irritation.
6. In the treatment of herpetic infection.
5% acyclovir ethosomal preparation was compared to 5% acyclovir cream which showed improvement in herpetic infections.
7. Transcellular Delivery.
Better uptake of anti-HIV drug from ethosomes as compared to anyi-HIV therapy.
8. In the treatment of Anti- Parkinsons disease.
Dayan and Touitou prepared ethosomal formulation of psychoactive drug named trihexyphenidyl hydrochloride HCL (THP) which was compared to classical liposomes. THP is M1 receptor antagonist used in treatment of Parkinson disease. The results showed better skin permeation with ethosomal THP formulation.
9. Ethosomes as Anti-keratinizing agent .[56]
Ethosomes and liposomes of azelaic acid were prepared as topical vesicle . Result showed that ethosomes could be responsible for higher azelaic acid.

Marketed formulations based on Ethosomes:[57,58,59]

Table no.3 Marketed Products based on Ethosomal Formulations

Products	Narrative	Mechanism
Body shape (Maccabi-CARE)	Gel executive solidification, stretching the skin flexible and based on technology called Ethosome.	Deeper diffusion into the skin.
Supravir cream	For the treatment of herpes virus	Lipid perbutation
Noicellex	Topical anti-cellulite cream	Deeper diffusion into the cream
Cellutight EF	Increase metabolism and breakdown fats	Deeper penetration into the skin

3.Conclusion:

As mentioned above ethosomes improve the permeation of drugs through the skin. Ethosomes are soft, malleable vesicles and carrier for transportation of drugs. They enable the drugs to reach deeper into the skin hence reaching the systemic circulation. They are well known for safety and efficacy. Also some of the herbal extracts and phytochemicals have been successfully delivered in ethosomes. Ethosomes have been tested to deliver cationic drugs, proteins and peptides. Ethosomes have been proven excellent carriers for delivering the therapeutic agents.

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