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ETHOSOMES: The Promising Carriers for the Transdermal Delivery of Drugs

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Abstract: *Transdermal drug delivery route is widely used as compared to oral route because Transdermal drug delivery avoids GIT degradation and first pass metabolism of drugs. To improve penetration of drug through skin, the drug is encapsulated in ethanol based liposomes i.e ethosomes. Ethosomes are made up of phospholipid, ethanol and water. Ethosome offers many important advantages such as enhanced drug delivery, safety, patient compliance and comfort. The main purpose of this review article is to provide full information about ethosomes.*

Keyword*: Ethosomes, Ethanol, Transdermal, Topical, Vesicles.*

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I. Introduction

Transdermal drug delivery is a painless way of systemic drug delivery by applying the medication formulation to safe and intact skin[1,2]. The delivery of transdermal drugs has many advantages over other traditional drug delivery routes[3,4]. It can provide a non invasive alternative to parenteral pathways, while avoiding problems such as needle phobia[1,5]. The large surface area of the skin and the ease of access provide many opportunities for transdermal absorption on the body[2,5]. It can improve patient compliance by lowering dose levels and is also ideal for patients who are unconscious or vomiting or self administered[6]. Transdermal drug delivery avoids first pass metabolism and therefore increases bioavailability[7-9]. The main negative feature of drug delivery through the skin is the barrier properties of the skin stratum corneum, which is that only lipophilic drugs with molecular weight below 500 Daltons will move through stratum corneum[10,11]. Numerous mechanisms have been explored to overcome this problems, including the use of chemical or physical enhancers including ionophoresis, sonophoresis etc[12]. liposomes, niosomes, transfersomes and ethosomes also have the capacity to bypass the skin barriers, and increase drug permeability through the stratum corneum barrier[13,14].

II. Ethosomes

"Ethosomes are vesicles of ethanol". Ethosomes are modified types of phospholipid containing liposome carriers with high ethanol and water concentrations. Ethosomes are non invasive delivery carriers capable of delivering the medicines to deep skin layers and systemic circulation[15,16]. These are soft malleable vesicles that are designed to increase the delivery of active agents[17]. Ethosomes have become revolutionary liposome carriers with high deformability, high entrapment capacity and strong transdermal permeation levels in drug delivery systems that make them ideal for transdermal administration[18]. These vesicles allow the drug to be released over a longer period of time, keep the drug safe against immune response or other body removal mechanisms and thus be able to release the right amount of drug and retain this constant concentration for longer period of time[19]. Compared to conventional liposomes or hydro-ethanolic solution, ethosomes due to their soft and flexible nature may penetrate the skin and improve the delivery of different active agents to deeper layers of skin or improved systemic circulation[20]. It is possible to modulate the size of ethosomes vesicles from tens of nanometers to microns[21-23].

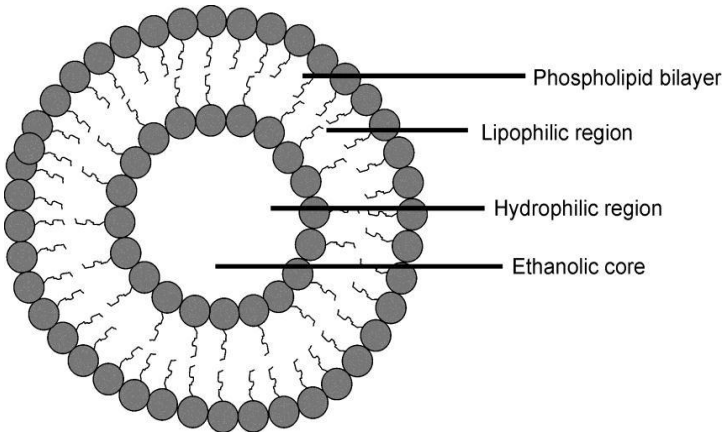

Figure No.1: Structure of ethosome

III. Types Of Ethosomes

1.) Classical Ethosomes

Classical ethosomes consist of phospholipids, water and high ethanol concentration. Classical ethosomes are better than conventional liposomes because of small size, negative zeta potential and higher entrapment efficiency.[24-26]

2.) Binary Ethosomes

Binary ethosomes are formed by introducing another form of alcohol such as propylene glycol and isopropyl alcohol etc to the classical ethosomes[27,28].

3.) ***Transethosomes***

Transethosomes are a new form of ethosomal system and have been designed to combine the advantages of classical ethosomes and transfersomes in a single formula. In their structure, they contain basic components such as that of classical ethosomes and a penetration enhancer or an edge activator[29-32].

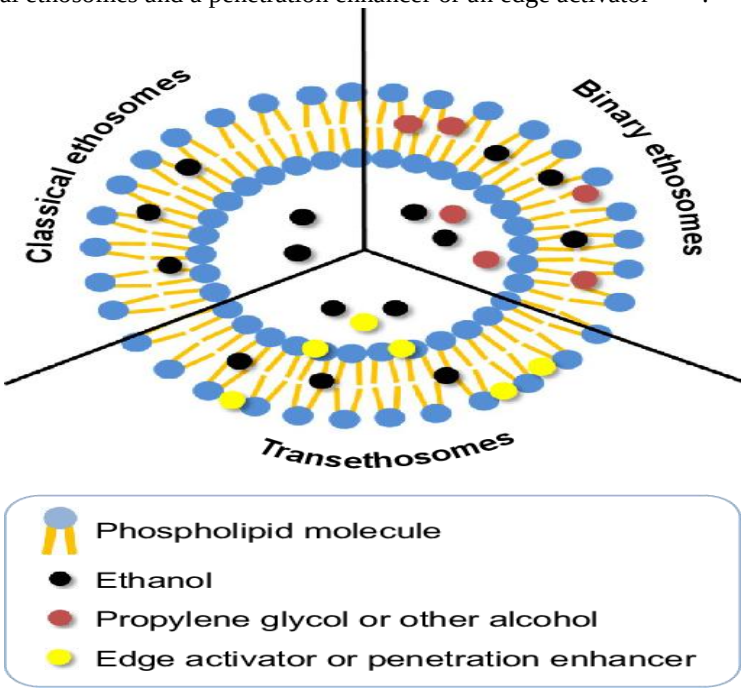

Figure No.2: Types of Ethosomes

IV. Advantages Of Ethosomes[33,34]

- Better drug permeation for topical and transdermal delivery compared to liposomes.
- It is easy to transmit macromolecules (proteins and peptides) through the skin.

- Ethosomal medication is delivered in a semi-solid (Gel or cream) form, resulting in increased patient compliance.
- It is formulated by using skin and body friendly and non toxic materials.
- The ethosomal delivery is passive, non-invasive and able for immediate commercialization.
- Ethosomal drug delivery system can be widely used in medical, vaterinary and cosmetic applications.
- Relatively easy to manufacture without the complicated technological investment required for ethosomes production.

COMPOSITION OF ETHOSOMES[35,36]

S.No	Materials	Examples	Uses
1	Phospholipid	Soya phosphatidyl choline Egg phosphatidyl choline Dipalmityl phosphatidyl choline Distearyl phosphatidyl choline	Vesicles forming component
2	Polyglycol	Propylene glycol	As a skin penitration enhancer
3	Alcohol	Ethanol Isopropyl alcohol	For providing the softness for vesicle membrane As a penetration enhancer
4	Cholesterol	Cholesterol	For providing the stability to vesicle membrane
5	Dye	Rhodamine – 123 Rhodamine red 6 – carboxy fluorescence	For characterization study
6	Vehicle	Carbopol 934	As a gel former

V. Mechanism Of Drug Penetration

Ethanol effect*:* ethanol functions as an enhancer of the skin's penitration. The mechanism of the enhancing effect of its absorption is well understood. Ethanol penetrates into intercellular lipids and raises cell membrane lipid fluidity and decreases cell membrane lipid density.

Ethosome effect*:* improved cell membrane lipid fluidity due to ethosome ethanol results in increased skin permeability. Therefore, ethosomes permeate very quickly within deep skin layer, where they are combined with skin lipids and release drugs into deep layers of skin.[37,38]

VI. Methods of Preparation

1. Cold method

One of the most commonly used methods for ethosome prepration is the cold method. First phospholipid is dissolved by vigorous stirring in ethanol at room temprature and polyols like propylene glycol etc are continuously added with regular stirring accompanied by 30ºC heating on water bath. Then in a separate vessel, water is heated at 30ºC, both mixtures are mixed together followed by 5 minutes of stirring in a covered vessel. By using sonication process, the size of ethosomal formulation can be reduced to desired extent.[39,40]

2. Hot method

In hot method, phospholipid is added in water by heating at 40ºC on a water bath until a colloidal solution is obtained (Aqueous phase). Ethanol and propylene glycol are correctly mixed in another vessel and heated up to 40ºC (Organic phase). The organic phase is added to the aqueous phase under constant stirring. By using sonication process, the size of ethosomal formulation can be reduced to desired extent.[41,42]

3. Classic mechanical dispersion method

This method dissolves phospholipid in an organic solvent or a mixture of organic solvents in a round bottom flask. The organic solvent is extracted with a rotating vaccum evaporator to create a thin film of lipids on the RBF surface. Traces of the solvent are separated from the accumulated lipid film by leaving the contents under vaccum overnight. By rotating the flask at the appropriate temperature, lipid film is hydrated with the drug's hydro-ethanolic solution. Eventually, at room temprature, cool the resulting ethosomal suspension[43].

VII. Characterization Of Ethosomes[44,45]

- ***Vesicle shape***

With transmission electron microscopy (TEM) and Scanning electron microscopy (SEM), ethosomes can be easily visualized.

- ***Vesicle size and zeta potential***

With the help of dynamic light scattering (DLS) and photo correlation on spectroscopy (PCS), the vesicle size of ethosomes can be determined. The zeta potential of formulation can be measured with the help of zeta sizer.

- ***Transition temperature***

By using differential scanning calorimetry (DSC), the transition temprature of the vesicular lipid systems can be determined.

- ***Entrapment efficiency***

The entrapment efficiency of ethosomal formulation can be measured by using ultracentrifugation and membrane dialysis techniques.

- ***Drug content***

Drug content of ethosomes can be determined by using UV Spectrophotometer and HPLC techniques.

- ***Stability studies***

Through measuring the size and shape of the vesicles over time, the stability of vesicles can be determined. Mean size is determined through DLS and changes in structure are detected by TEM.

- ***Skin permeation studies***

Confocal laser scanning microscopy (CLSM) can be used to assess the ability of ethosomal preparation to penetrate the skin layers.

Table: characterization of ethosomes

S.No	Parameter	Importance	Method
1	Size and shape	Skin penetration	SEM, TEM, DLS
2	Zeta potential	Vesicle stability	Zeta meter
3	Entrapment efficiency	Suitability	Ultracentrifugation
4	Drug content	Amount of drug	UV, HPLC
5	Invitro dissolution	Release rate	Franz diffusion cell
6	Skin permeation	Rate drug movement	CLSM

VIII. Therapeutic Application Of Ethosomes

Ethosomes can be used in the delivery of drugs for many purposes. Many drugs have been used with ethosomal carrier. Some applications of ethosomes are following:-

1. Pilosebaceous targeting

Large populations of the world are suffering from hair disorders such as seborrhea, excessive hair loss, and acne in the current years. Therefore, for effective treatment of pilosebaceous disorders, selective delivery of the specific drug to hair follicles is very important. Minoxidil is a lipophilic drug that is used topically on the scalp to treat hair loss. Minoxidil ethosomes were prepared and evaluated in vivo in hairless rats to investigate minoxidil targeting to pilosebaceous units via ethosomes. The results showed that minoxidil was located in the pilosebaceous units, indicating higher minoxidil delivery using ethosomal carriers.[46]

2. Transdermal delivery of hormones

Oral hormones administration is associated with issues such as first pass metabolism, poor oral bioavailability and side effects depending on several dosage. Along with these problems oral hormonal preparations has low patient compliance. So, therefore hormonal preparations can be administered in ethosomal delivery[47]

3. ***Delivery of anti-arthritis drug***

Topical delivery of Anti-Arthritis medication is a better option for site specific delivery and overcomes traditional oral therapy related problems[42].

4. ***Delivery of problematic drug molecules***

The oral delivery of large biomolecules such as proteins or peptides and insulin is difficult because they are fully degraded in the GIT tract. Therefore, transdermal delivery is a better alternative. But there is low permeation of traditional transdermal formulation of biomolecules including peptides or proteins and insulin. Formulating these molecule into ethosomes increases permeation and therapeutic effect[10,48]

5. ***Delivery of antibiotics***

Topical antibiotic delivery is a better option to increase these agent's therapeutic efficacy. Conventional oral treatment induces numerous allergic reactions along with several side effects. Conventional external formulations have poor permeability to deep skin layers and subdermal tissues. Ethosomes can solve this issue by delivering enough antibiotics into deeper skin layers. Ethosomes easily penetrate the epidermis and carry large quantities of drugs into the deeper layer of the skin and kill infection at its core. Ethosomal formulations loaded with bacitracin and erythromycin for dermal and intracellular delivery was formulated by godin and touitou. The results of this study showed that antibiotic ethosomal formulation could be highly effective and overcome the problems associated with traditional therapy[10]

6. Transcellular delivery

Better cellular absorption of Anti-HIV medication zidovudine and lamivudine from ethosomes in the MT-2 cell line relative to the marketed formulations, indicates that ethosomes be an enticing therapeutic option for Anti-HIV treatment.[49]

7. Topical delivery of DNA

Ethosomes can be used for the application of gene therapy. Ethosomal formulation has been shown to achieve better intracellular processing of DNA, better delivery and expression of genes in skin cells. Scientists have recently reported the potential for immunization via transfersomal formulation. Greater skin penetration capacity of ethosomes allows for the use of these kinds of dosage forms to deliver immunizing agents.[50]

ETHOSOMES IN COSMECEUTICALS

The benefit of the use of ethosomes in cosmetics is not only to increase the stability of cosmetic chemicals and reduce irritation of the skin due to irritating cosmetics, but also to improve transdermal permeation, especially in elastic types. The important factors to be considered in order to achieve these benefits of elastic vesicles for cosmeceutical application are composition and sizes of vesicles.[51]

Marketed products based on ethosomal drug delivery system[52,53]

Name of product	Uses	Manufacturer
Celltight EF	Topical cellulite cream	Hampden health, USA
Supravir cream	Used for herpes viral infection treatment	Trima, Germany
Decorin cream	Anti-Aging cream	Genome cosmetics, technologies, Israel
Skin genuity	Powerful cellulite buster	Physonics Nottingham, U.K
Nanominox	Hair growth promoter	Sinere, Germany
Noicellex	Topical anti-cellulite cream	Novel therapeutic technologies, Israel

Patents on ethosomal drug delivery system[54]

S.No	Title	Patent no.	Year
1	Chinese medicinal ethosome herpes gel patch for treating zoster	CN103536700(A)	2014
2	Leflunomide ethosome composition and its prepration method	CN103800277	2014
3	Ethosome gel film coating agent with multiple wound repair effects	CN103893394(A)	2014
4	Bullatacin ethosome gel	CN102552147(A)	2012
5	Daptomycin ethosome prepration	CN103006562(A)	2013
6	Ethosome prepration of male hormone medicaments	CN102406605(A)	2012
7	Lidocaine ethosomes	CN102813624(A)	2012
8	Paclitaxel ethosome gel	CN102579323(A)	2012
9	Progesterone ethosome	CN102397255(A)	2012
10	Acyclovir ethosomes	CN102133183(A)	2011

IX. Conclusion

Ethosomes are soft and flexible vesicles of ethanol with simple method of prepration, safety and efficacy. These are Non-Invasive delivery carriers capable of delivering the drug to deep skin layers and systemic circulation. Ethosomes have high deformability, high entrapment capacity, and better transdermal permeation. Therefore, ethosomes can become a successful drug carrier in the future not only for topical treatment of local and systemic diseases, but also for the cosmetic and pharmaceutical fields.

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