ETHOSOMAL GEL: A REVIEW

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ABSTRACT
Ethosomal systems are lipid vesicular carriers which containing high percentage of ethanol. These nanocarriers are formulated to overcome the limitations associated with conventional oral therapy. Which deliver drugs into deep skin layers. Different preparation techniques are used in the preparation of these nanocarriers. For patient compliance and stability, ethosomal dispersions are incorporated in to gels, patches, and creams. This publication gives a detailed review on the effects of ethosomes, constituents, mechanism of drug penetration, formulation methods, evaluation and examples for drugs used in ethosomal systems.

KEY WORDS: Ethosomes, Transdermal drug delivery, Lipid vesicular systems, Gel.

INTRODUCTION
The oral drug delivery system has overcome a number of limitations such as degradation of drug, GI irritation and first pass metabolism effect. Due to the above reason the transdermal route is most prefer by the patient there for research the ethosome carrier moiety for the transdermal drug delivery system. Ethosomal vesicles used for delivery of drugs to reach the deep skin layers and or the systemic circulation and are the advanced forms of liposomes that are high in ethanol content. They can incorporate hydrophilic and hydrophobic drugs to enhance the accumulation of drugs. Ethosomal drug is administered in semisolid form (gel or cream) hence producing high patient compliance. The most widely used gel- forming agents used in ethosomal systems are carbopol and hydroxypropyl methycellulose. These polymers have been shown to be compatible with ethosomal systems, providing the required viscosity and bioadhesive properties.

ETHOSOMES
Ethosomes (Fig. 1) are system containing soft vesicles, composed of hydro alcoholic or hydro/ glycolic phospholipids, water, alcohol (ethanol and isopropyl alcohol) in relatively high concentration. This high concentration of ethanol makes the ethosomal system unique. The range of ethanol in final product will be 20 % - 30 %. The size of ethosomes will be in the range of tens of nanometers to microns (μ).

Fig.1: Structure of ethosome
ETHOSOMES COMPOSITION

<table>
<thead>
<tr>
<th>Class</th>
<th>Example</th>
<th>Uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phospholipid</td>
<td>Soya phosphatidyl choline, Egg phosphatidyl choline, Dipalmityl phosphatidyl choline, Distearyl phosphatidyl choline</td>
<td>Vesicles forming agent</td>
</tr>
<tr>
<td>Polyglycol</td>
<td>Propylene glycol, Transcutol RTM</td>
<td>As a skin permeation enhancer</td>
</tr>
<tr>
<td>Alcohol</td>
<td>Ethanol, Propyl alcohol</td>
<td>For providing softness for vesicle membrane</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>Cholesterol</td>
<td>For providing the stability to vesicle membrane</td>
</tr>
<tr>
<td>Dye</td>
<td>Rhodamine-123, Rhodamine red, Flurescene, Isothiocynate (FITC), 6-Carboxy flurescene</td>
<td>For characterization study</td>
</tr>
<tr>
<td>Vehicle</td>
<td>Carbopol D 934</td>
<td>As a gel former</td>
</tr>
</tbody>
</table>

TYPES OF ETHOSOMAL SYSTEMS

![Fig: 2 Schematic representation of different types of ethosomal systems]

**Classical ethosomes**
Classical ethosomes are composed of phospholipids, water, and high concentration of ethanol (40%). Because of small size, negative zeta potential and higher entrapment efficiency classical ethosomes were superior over classical liposomes. Drugs having molecular weight ranging from 130.077 Da to 24 k Da can be entrapped in classical ethosomes. Classical ethosomes also shows better skin permeation and stability profiles than classical liposomes. [6, 7]

**Binary ethosomes**
Binary ethosomes can be prepared by adding another type of alcohol to the classical ethosomes. Propylene glycol (PG) and isopropyl alcohol (IPA) are the most commonly used alcohols in binary ethosomes. [8]

**Tranethosomes**
Tranethosomes are the new form of ethosomal systems. In their formula it contain basic components from classical ethosomes and a penetration enhancer or an edge activator (surfactant). These novel vesicles were developed to combine the advantages of classical ethosomes and transfersomes in one formula to produce tranethosomes. [9]

**MECHANISAM OF DRUG PENETRATION**
In ethosomal formulations both ethanol and phospholipids together enhance the skin permeation of the drugs. The mechanism of the drug absorption probably occurs by two phases. The first phase of the mechanism is due to the “ethanol effect”. In this incorporation of ethanol in to intercellular lipids, fluidizes the lipid bilayers and decreasing the density of skin lipids. This is followed by the “ethosome effect”, in
this the increased cell membrane fluidity by the ethanol will increase the skin permeability, because of this ethosomes permeate very easily in to the deep skin layers where it fused with the skin lipid and release the therapeutic agents into the deep skin layers.\(^{[10,11]}\)

![Fig. 3: Mechanism of ethosomal drug penetration through skin](image)

**ADVANTAGES OF ETHOSOMAL DRUG DELIVERY\(^{[12,13,14]}\)**

- Increased skin permeation of the drug
- Large molecules like proteins, peptide molecule is possible.
- Good patient compliance.
- Compared with Iontophoresis and phonophoresis, ethosomes are simple method of drug delivery.
- It can be widely applied in cosmetic, veterinary, herbal drug technology.
- It can entrap all types of drug molecules i.e. hydrophilic, lipophilic or amphiphilic.
- Permeation enhancer used in the formulation increase the permeability of the skin so that the drugs easily cross the skin.

**METHOD OF PREPARATION OF ETHOSOME AND ETHOSOMAL GEL**

**Cold method:** In this method, phospholipid and drug dissolved in ethanol in a covered vessel at room temperature by vigorous stirring. During stirring propylene glycol was added. This mixture was heated to 30°C in water bath. The water was heated to 30°C in a separate vessel. And was added to the center of the vessel, the mixture was stirred for 5min at 700 rpm in a covered vessel. The size reduction of ethosomal formulation can be done by sonication or extrusion method and finally the formulation stored under refrigerator.\(^{[15]}\)

![Fig. 4: Mechanism of ethosomal drug penetration through skin](image)

**Hot method:** In this method, the phospholipid is dissolved in water by heating in a water bath at 40°C until a colloidal solution is obtained. In a separate vessel ethanol and propylene glycol are mixed and heated to 40°C. Once both the mixtures reaches the 40°C, the organic phase is added to the aqueous phase. The drug is
dissolved in water depending on their hydrophilic/hydrophobic character. The vesicle size of the ethosomal formulation can be decreased by using sonication or extrusion method.\[16\]

**Method of preparation of ethosomal gel**

In the preparation of ethosomal gel first we go for the preparation of gel base, Carbopol 934 is commonly used gel former and at low concentration it forms good consistency transparent gel. It will be prepared by dispersing carbopol 934 in hot distilled water in which glycerol was previously added. To this accurately weighed quantity of methyl paraben and propyl paraben was added. Then the mixture will be neutralized by triethanolamine. Then the ethosomal formulation was slowly added in carbopol 934 gel base with gentle stirring. Finally, we get the ethosomal gel.\[17\]

**DRUGS FORMULATED AS ETHOSOMAL GEL**

Ethosomal carrier opens a new challenges and opportunities for the development of novel improved therapies. Ethosomal drug delivery system has been applied to many drugs some of which are mentioned below:

- Gliclazide is an oral antihyperglycemic agent used for the treatment of non insulin dependent diabetes mellitus (NIDDM). It belongs to the sulfonylurea class of insulin secretagogues. A research is conducted by Lamsal et.al, (2015) on the topic Formulation and evaluation of gliclazide ethosomes as a novel drug carrier. In this shows that, oral administration of gliclazide has number of limitations. The major one is low bioavailability and poor water solubility. Thus ethosomes were found to be a better option for transdermal drug delivery of gliclazide. Preparation of ethosomes done by cold. And one ethosomal formulation were prepared and evaluated for different parameters. On the basis of different parameters like vesicle shape, entrapment efficiency, Vesicle size the best formulation was selected. This was further incorporated in to gel using carbopol 934. The result shows the potential of ethosomes of being a safe and very efficient drug carrier for systemic as well as topical delivery of drug.\[18\]

- A research study conducted by Sujitha et. al, (2014) on the topic Formulation and evaluation of piroxicam loaded ethosomal gel for transdermal delivery. This research study, was in aim to formulate and evaluate the ethosomes containing piroxicam by using phospholipid, ethanol, propylene glycol and distilled water. The ethosomes will be prepared by cold method. The studies show the potential of ethosomal vesicles and gel formulation to treat rheumatic disease where facilitated penetration of the drug in to muscle and synovial fluid is desirable.\[19\]

- A novel ethosomal system has been developed for transdermal delivery. Etodolac is generally given by oral route but it shows several limitations like gastric ulceration, first pass metabolism etc. To overcome these problems, alternative transdermal route has been selected. Bhole et. al, (2013) conducted a research study on the topic Formulation and evaluation of ethosomes for transdermal delivery of Etodolac. This study clearly shows that the permeability of ethosomes of etodolac is increased by using ethanol in the formulation. In this work the ethosomes were prepared by hot method and evaluated. The prepared ethosomes were characterized for vesicle shape, vesicle size, and entrapment efficiency. Ethosomal gel was evaluated for in vitro drug release, spreadability, pH studies. Thus, the prepared ethosomes was proved to be effective carrier for transdermal drug delivery.\[20\]

- In another research work conducted by Sowjanya et. al, (2013) on the topic Development and in vitro evaluation of gel containing ethosomes entrapped with sulphasalazine. In this study Sulfasalazine is a non steroidal anti-inflammatory drug having half life 5 to 7 h and used for the treatment of rheumatoid arthritis. The oral use of sulfasalazine is not recommended as it requires frequent administration. For this reason transdermal route is a better option for drug delivery. In this work ethosomes of sulfasalazine were prepared by hot method. The best formulation had showed no significant change in vesicle size, entrapment efficiency, drug release after stability studies\[21\]

- The research work carried out by Indora et. al, (2015) on the topic Design, development and evaluation of fluconazole for topical fungal infection. Fluconazole is used for the treatment of local and systemic fungal infection. But there are several problems associated with oral up take of fluconazole that are low bioavailability, first pass metabolism, side effects and can be overcome by incorporating it in to ethosomes. The preparation of ethosomes done by cold method and evaluated and study the effect of different concentrations of phospholipid and ethanol on drug entrapment efficiency to obtain an optimized formulation, calculate the percentage drug release and study kinetic model complying with the formulation.\[22\]

**CONCLUSION**

As mentioned above, numerous studies have been published showing that ethosomes can substantially improve the permeation of drugs through the stratum corneum and thereby their efficacy. The main disadvantage of transdermal drug delivery system i.e. epidermal barrier can be overcome by ethosomes to significant extent. The incorporation of ethosomal systems in suitable vehicle such as gels represents an important step to get better skin-permeation and therapeutic results. Thus ethosomes can become a promising drug carrier in future for not only topical treatment of local and systemic disorders, but also for the cosmetic and cosmeceutical field.
REFERENCE


