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A COMPREHENSIVE REVIEW ON ETHOSOMAL GEL

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ABSTRACT

Ethosomal systems are newer lipid vesicular carriers that have been around for 20 years, but over that period they have grown significantly as a means of transdermal drug delivery. They have a sizable amount of ethanol in them. These nanocarriers carry medicinal substances with various physicochemical qualities throughout the skin and deep skin layers. Since they were created in 1996, ethosomes have undergone substantial investigation; new substances have been added to their original composition, creating new varieties of ethosomal systems. These innovative carriers, which can be added to gels, patches, and lotions, are prepared using several novel methods. In addition to clinical trials, many in vivo models are employed to assess the effectiveness of dermal/transdermal administration. This review focuses on different generation of ethosomes and their comparison with other conventional liposomes.

KEY WORDS: *Ethosomes, Transdermal drug delivery, Lipid vesicular systems,*

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. [1] 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 drug. [2] 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. [3] **.**

The development of liposomes heralded a new era in drug delivery research, and a variety of vesicular systems have subsequently been created [4]. 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 [5].

The development of modified versions of liposomes was prompted by their lower size, lower entrapment efficiency, and negative zeta potential. Novel modified lipid carriers called ethosomes are made of ethanol, phospholipids, and water. In addition to phospholipids and water, which have been suggested to have improved vesicular properties and skin penetration, ethanol is present in quite high amounts in ethosomes [6]. Ethosomes, are again divided into binary, classical, and transethosomes based on their contents like alcohol, have quickly emerged as an unique drug delivery system [[7], [8], [9], [10]].

Ethosomes

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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) [13, 14].

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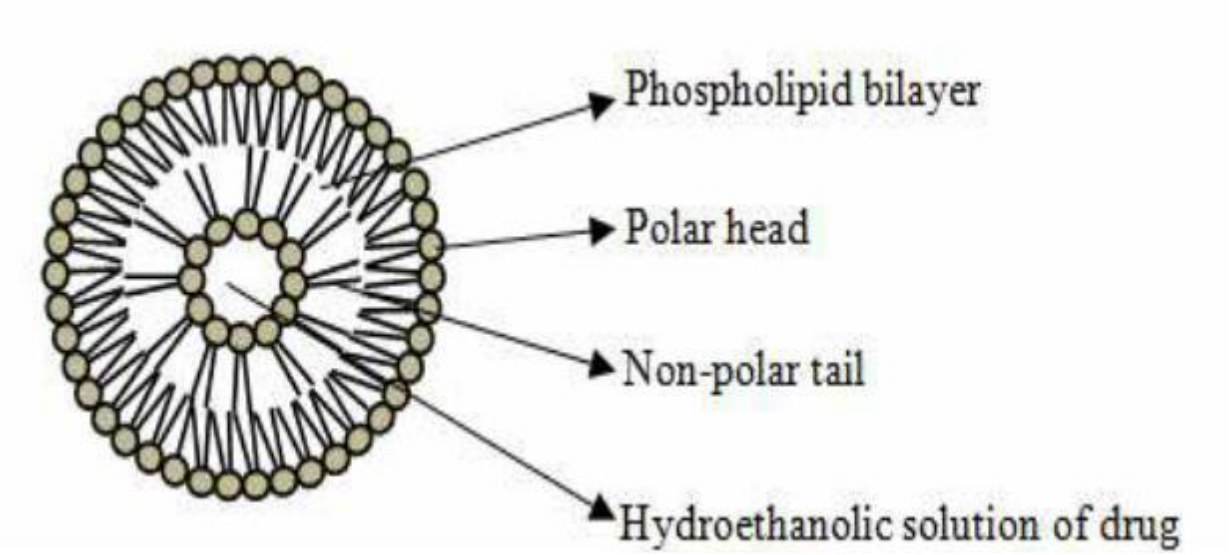

Fig 1- Structure of Ethosome

Composition of Ethosomes

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

Types of Ethosomal system

- **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. [15, 16]

- **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.[17]

- **Transethosomes**

Transethosomes 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 transethosomes [18].

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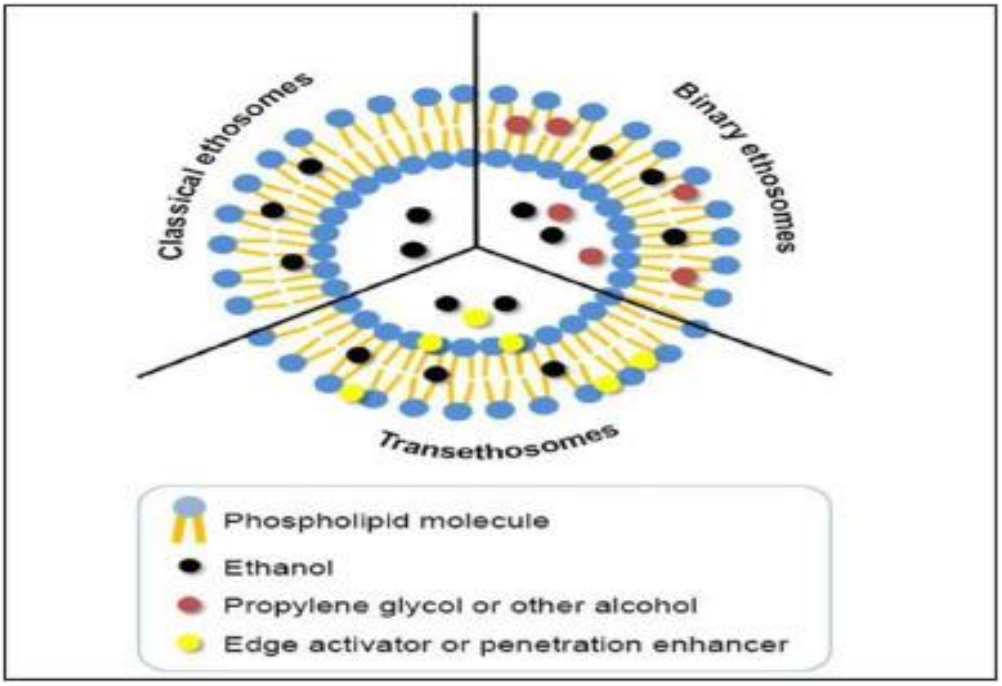

Fig 2- Classification of Ethosomes

Methods for preparation of Ethosomes-

The hot approach and the cold method are two often employed techniques needed to create ethosomes.

- **Cold method**

At room temperature, with vigorous shaking, the ethanol is dissolved in the phospholipids, medicine, and other lipid components. The jar is then heated to 30 °C. This is widely used and is referred to as the "cold approach. In another beaker, water is heated to 30 °C before being introduced and continuously swirled into the initial mixture. Vesicles start to emerge after 5 min of churning. It's important to keep produced vesicles cold [19].

- **Hot method**

The hot procedure entails combining the medication with ethanol and propylene glycol. At 40 °C, phospholipid dispersion in water is created. This dispersion is combined with a previously produced mixture. Size reduction is next accomplished by sonication or extrusion after this final combination is heated to 30 °C [20].

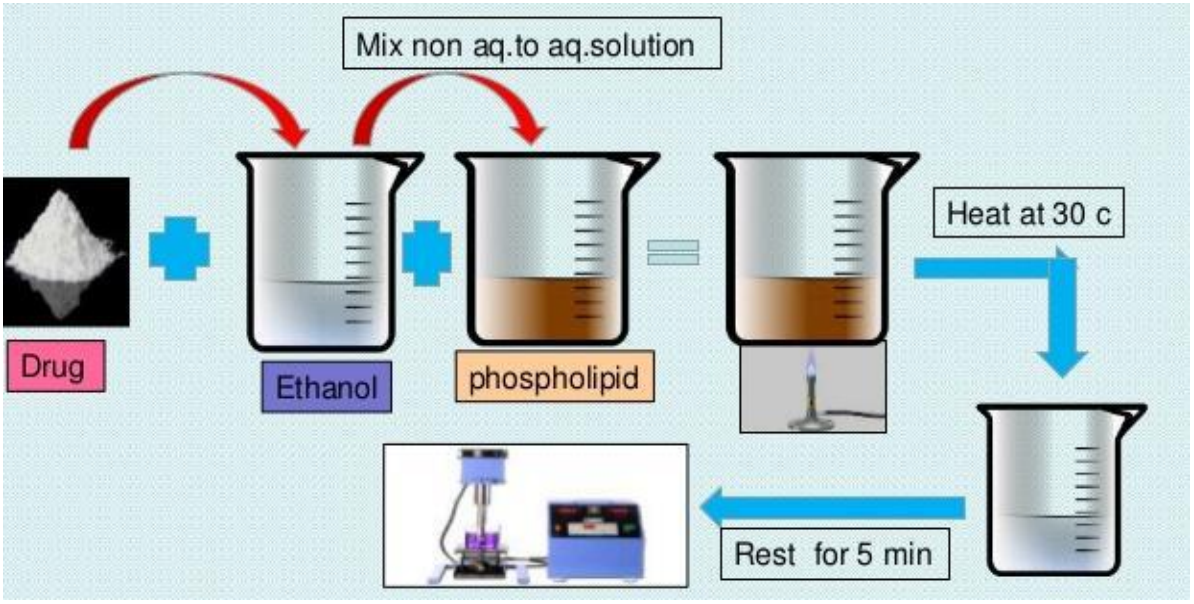

Fig 3- Method of preperation of Ethosomes

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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 [21, 22]

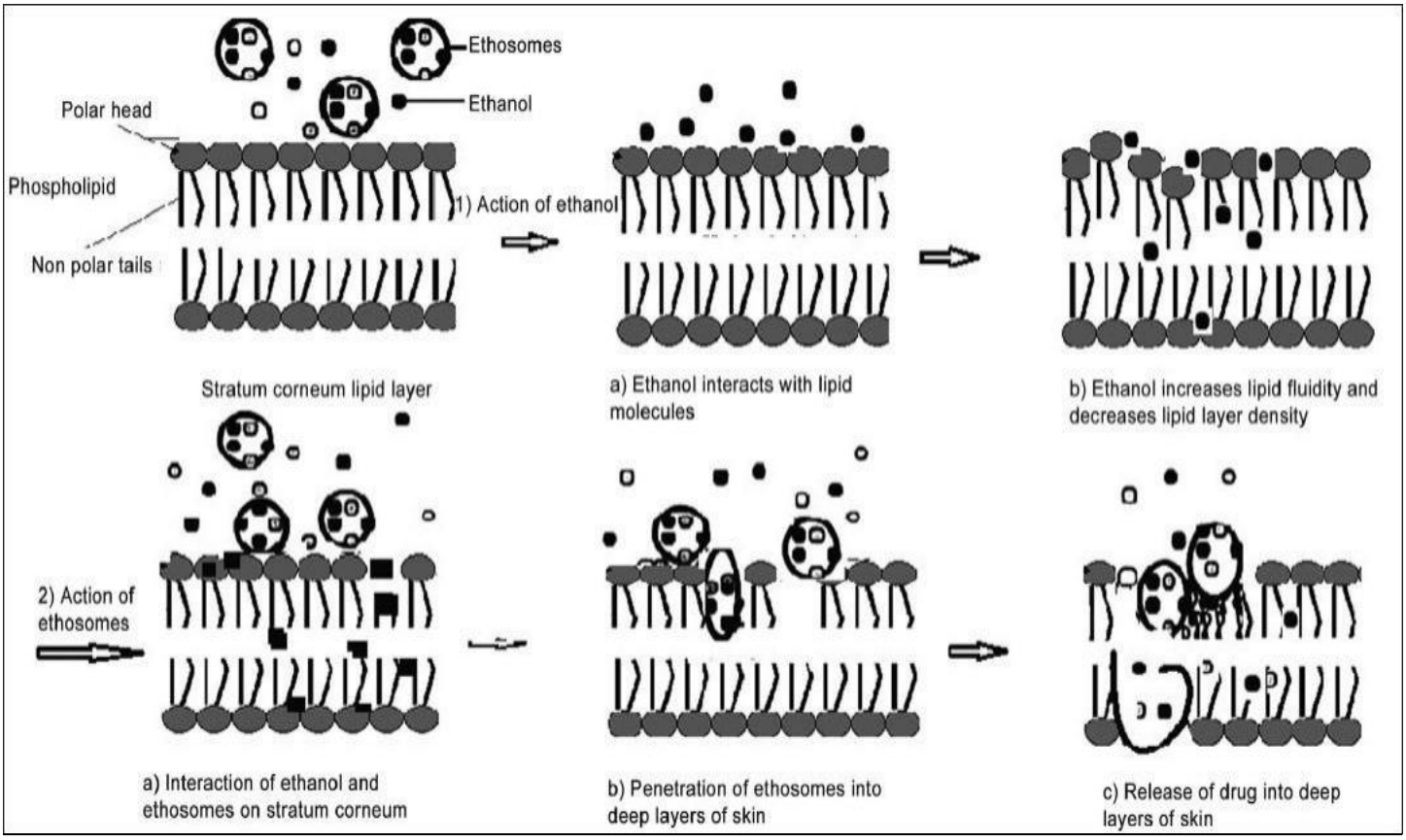

Fig 4- Mechanism of ethosomal drug penetration through skin

Applications of Ethosomes-

- 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 [23].
- 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.

Advantages Of Ethosomal Drug Delivery [24, 25, 26]

- 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.

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- Permeation enhancer used in the formulation increase the permeability of the skin so that the drugs easily cross the skin.

Limitations of ethosomal drug delivery

- Increased levels are needed. Only powerful compounds with a daily intake of 10 mg or less are allowed [27, 28].
- Instead of offering moderate, continuous medication delivery, it is often intended as a method of achieving quick bolus type drug input.
- Sufficient solubility of the medicine to penetrate cutaneous microcirculation and enter the systemic circulation in both lipophilic and watery conditions.
- The drug's molecular size needs to be appropriate for percutaneous absorption.
- Not all varieties of skin will adhere to adhesive as well.
- It might not be cost-effective.
- A low yield.
- Dermatitis or skin irritation brought on by excipients and enhancers used in medication delivery systems.

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 srcretagogues. 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 [29] .
- 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 tomuscle and synovial fluid is desirable [30] .
- 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. Bhale 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 [31].
- 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 ethsomes 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 [32] .
- 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 [33].

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

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promising drug carrier in future for not only topical treatment of local and systemic disorders, but also for the cosmetic and cosmeceutical field.

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