Ethosomal Drug Delivery System and Its Application in Treating Alopecia Areata: A Review

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Abstract: **Alopecia areata, an autoimmune condition characterized by patchy hair loss, affects approximately 2% of the global population, both male and female, with its prevalence on the rise. Present treatments for alopecia areata are insufficient as they fail to directly target hair follicles, are time-consuming, expensive, and prone to recurrence. Hence, a newer ethosomal formulation with an increased permeability and bioavailability of the therapeutic drug, improved targeting, stability, and prolonged drug retention will be an effective therapy. This study aims to expand on the concept of ethosomes, detailing their preparation method, penetration mechanism, composition, and their application in the treatment of alopecia.**

Keywords: Ethosomal Drug delivery, Alopecia areata, Hair loss, Nano delivery, Drug penetration

I. INTRODUCTION

The skin, our body's largest and most easily accessible organ, emerges as a promising approach for delivering medications systemically. With multiple layers, skin serves as a protective barrier against external substances. The outermost layer of the skin, the stratum corneum, is particularly formidable, significantly restricting the penetration of drugs and thereby limiting the effectiveness of transdermal medication delivery.[1]

Ethosomes composed of a phospholipid monolayer and ethanol, have shown promising characteristics such as enhanced drug penetration by increasing cell membrane fluidity and permeability. Furthermore, ethosomes exhibit superior characteristics such as stability at room temperature, high encapsulation efficiency, and enhanced compatibility with the stratum corneum, thus facilitating the effective penetration of both hydrophilic and lipophilic drugs into the deeper layers of the skin.

To overcome this barrier, specialized carriers are necessary to facilitate the transport of medication molecules with varied physicochemical properties at target sites. Unlike traditional liposomes, and other lipid-based formulations, ethosomes have distinctive structural features, modes of application, and mechanisms of action. Ethosomes, characterized by their non-invasive nature and ease of self-administration, offer numerous advantages over other traditional delivery systems. These include preventing first pass metabolism, ensuring controlled drug release, reducing dosage frequency, and promoting patient adherence.[2,3]

Alopecia, as an autoimmune condition, requires ongoing treatment for long-lasting results. Many existing medications fall short in delivering effective therapy. Consequently, employing a nano formulated ethosomal drug delivery system directly on the scalp enables penetration of drug directly into hair follicles, facilitating the desired therapeutic effects.

In summary, ethosomes represent a promising vesicular drug delivery system for percutaneous administration, offering several significant advantages over traditional liposomes. Their unique properties make them highly effective in delivering medications through the skin, potentially revolutionizing transdermal drug delivery methods.

II. MATERIALS AND METHODS:

This review consolidates information gathered from various research papers and review articles, providing an overview of ethosomal drug delivery system. It explores concepts of ethosomal preparation methods, mechanisms of penetration, composition, and their use in treatment of alopecia areata.

III. DISCUSSION:

3.1 What are Ethosomes?

Ethosomes are lipid vesicles primarily comprised of phospholipids, ethanol with a relatively higher concentration and water. Ethosomes are a modified form of liposomes, exhibiting modifications that make them effective carriers in transdermal applications. They possess an aqueous core containing an ethanolic solution of drugs, surrounded by a lipid bilayer.[4] The presence of ethanol fluidizes the phospholipid bilayers, resulting in vesicles with a flexible structure, facilitating the delivery of active agents to deeper skin layers.[7] Unlike liposomes, that exhibits instability and low permeability in transdermal formulations, ethosomes offer improved stability and enhanced permeation across the skin.[8,9] Consequently, ethosomes were developed to overcome these limitations and enhance drug permeation.[5,6]

Ethosomes vary in size from nanometers to microns, and they demonstrate higher transdermal flux and skin permeability compared to other vesicular systems. Classification of ethosomal systems is based on their composition, with three main types identified are:

1) Classical ethosomes: Classical ethosomes are modified ethosomes, composed of phospholipids, water, and high concentration of ethanol typically ranging up to 45 %w/v. Classical ethosomes offer superior characteristics in comparison to classical liposomes such as negative zeta potential, entrapment efficiency, better skin permeation and stability profiles and smaller size.[10,13,14]

2) Binary ethosomes: Binary ethosomes are obtained when another type of alcohol is added to the classical ethosomes. Propylene glycol and isopropyl alcohol are the most used alcohols in binary ethosomes. [11,13,14]

3) Transethosomes: Transethosomes are the newer form developed to aim at combining the benefits of classical ethosomes and transfersomes into a singular formulation. They are composed of penetration enhancers or surfactants in addition to the basic components of classical ethosomes. [12]

3.2 Method of penetration:

The precise method of ethosomal administration is still up for question, yet the proposed mechanism is as follows. The topmost layer of the skin, the stratum corneum is densely packed with lipid layers. Ethosomes, which contain a high concentration of ethanol, cause disorganization of this outer lipid bilayer, allowing them to pass through narrow passages and then disrupt the stratum corneum. Further, the ethanol is entrapped into a vesicle that passes to the deeper layer of the skin allowing the drug to reach the hair shafts.

The drug absorption probably occurs in the following two phases:

1. **Ethanol effect:** Ethanol acts as a penetration enhancer, thus enhancing the effect through the mechanism of penetration is well understood. Ethanol penetrates intercellular lipids and increases the fluidity of cell membrane lipids and decreases the density of lipid multilayer of cell membrane.[15]

2. **Ethosomes effect:** Increase in cell membrane lipid fluidity caused by the ethanol in ethosomes results in increased skin permeability. So, the ethosomes permeates very easily inside the deep skin layers, it gets fused with skin lipids and releases the drugs into deep layer of skin. [16]

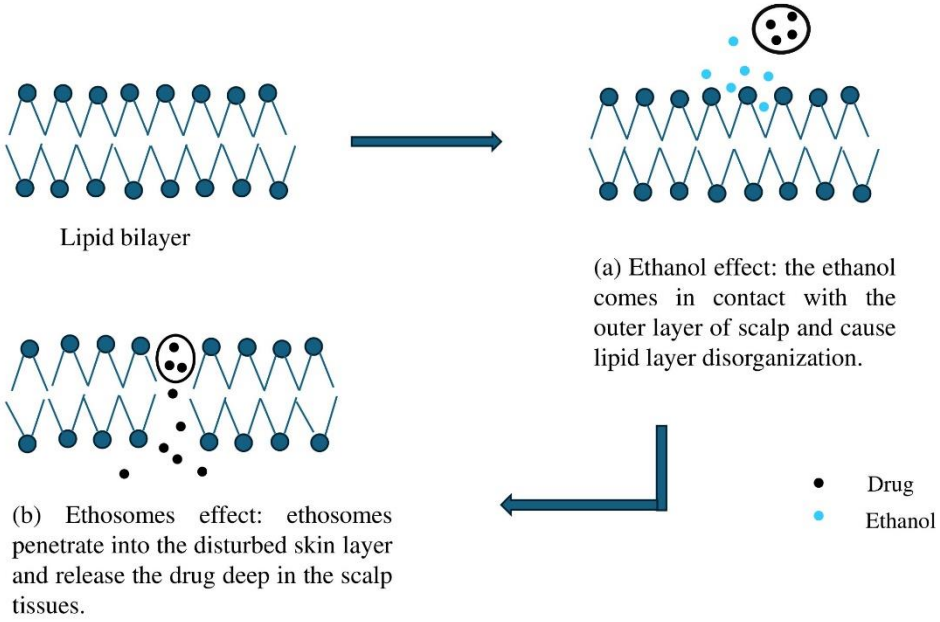

Figure 1: Method of penetration of ethosomes into the layers of scalp

3.3 Method of preparation:

1. **Hot method**: First, the phospholipid is dispersed in water by heating in a water bath at 40^0C. Simultaneously, ethanol and propylene glycol are mixed in separate vessels and heated up to 40^0C. Once both the mixtures reach 40^0C, the organic phase is introduced into the aqueous one. Depending on the hydrophilic/ hydrophobic nature of the drug, is dissolved in water or ethanol.[17] The desired size of vesicles can be achieved by sonication, and/or extrusion.[18]

2. **Cold method:** This is the most common method utilized for the preparation of ethosomal formulation. Here, phospholipid, drug and other lipid materials are dissolved in ethanol by heating in a water bath at 30°C. Propylene glycol or another polyol is added to the mixture and is heated to 30^0C in a water bath. Then, the water is heated in a separate vessel to 30^0C and is added to the above mixture, which is then stirred for 5 min in a covered vessel. The desired size of vesicles can be achieved by sonication, and/or extrusion.[19,6]

3. **Vortex/sonication method edge**: It is a simple, yet effective technique used for ethosomal preparation. This method involves introducing phospholipids and edge activators into a phosphate buffer by vigorous shaking and vertexing to ensure an even distribution of the components. By adjusting the duration and intensity of sonication, and the size of the vesicles is tailored accordingly. This method is versatile and can be used to prepare a wide range of drugs, both hydrophilic and hydrophobic. Further, it is also cost-effective and can be easily scaled up for large-scale production.[20]

4. **Rotary film evaporation:** This technique involves dispersing phospholipids into an organic solvent, which is then evaporated using a rotary evaporator. This process leaves a thin film of lipids around the inner walls of the flask. The lipid film is then hydrated using an aqueous medium, resulting in the formation of lipid bilayer vesicles encapsulating the drug. The desired size of the ethosomes is obtained using sonication and/or extrusion.[21]

5. **Classic method/ Transmembrane pH-gradient method**: This method is used for formulating binary ethosomes, by active loading of the drug. The phospholipid is dissolved in an ethanol and propylene glycol mixture. A citrate buffer solution is gradually added to the solution with continuous stirring at 700 rpm and 30 ± 1°C. The system is later cooled to room temperature and the binary ethosomes are ready. The drug is then actively loaded into the ethosomes, through continuous agitation at 700 rpm. The system is then incubated at an appropriate temperature and time, that allows the unionized drugs to actively pass through the lipid bilayer.[22]

3.4 Reagents used:

SR. NO	CLASS	EXAMPLE	USE
1	Phospholipids	Soya phosphatidyl choline, Egg phosphatidylcholine, Distearoylphosphatidylcholine	Vesicles forming agent
2	Polyglycol	Propylene glycol, Transcutol	Skin penetration enhancer.
3	Alcohol	Ethanol, Isopropyl alcohol	Penetration enhancer, provides softness for vesicle membrane.
4	Cholesterol	Cholesterol	Provide stability to vesicle membrane.
5	Surfactant	Stearylamine	Improve solubility of poorly soluble drugs.

Table 1. Different reagent employed in formulation of Ethosomes

3.5 Currently available ethosomal formulations

Currently, Nanominox is the only marketed ethosomal formulation available for the treatment of hair loss. It contains minoxidil 4% solution.[49] It functions through pilosebaceous Targeting and High penetration into deep layers of the skin. It is available in 3 different variations:

1) Nanominox 5%:

It contains the following active components:

- Minoxidil 4%: Operates by activating ATP sensitive potassium channels in vascular smooth muscle cells, thereby enhancing hair cell viability.[44]
- Adenosine: Stimulates the expression of hair growth factors FGF2 and FGF7, regulating the hair follicle cycle.[45]
- Sophora flavescens extract: Upregulates Keratinocyte Growth Factor (KGF) expression, inhibits Prostaglandin D2 (PGD2) synthesis, and possesses antibacterial properties.[46]
- Creatine ethyl ester: Supports cellular energy production, protects mitochondria from Reactive Oxygen Species (ROS), reducing apoptosis.[47]
- Cepharanthine: Acts as an antioxidant, scavenging free radicals, and protects against inflammatory cytokine-mediated responses like TNF-α and IL-1β.[48]
- Cyanocobalamin (Vitamin B12): Provides nourishment as a vitamin.

The formulation vehicle consists of high-quality phosphatidylcholine, ethanol (less than 30%), and distilled water, for maintaining a liquid consistency.

Application involves gently massaging the product directly on to the scalp 1 to 2 times daily. It absorbs rapidly with minimal visible residue. Leave the product on the scalp for at least 10 minutes after application to ensure adequate absorption.

2) Nanominox-MS:

The active ingredients list for this formulation remains unchanged, with only the addition of ketoconazole and specific antioxidants such as ascorbic acid (vitamin C) and gamma tocopherol (vitamin E).

3) Nanominox-FMS:
This formulation includes the similar ingredients as others, with only the addition of finasteride 1%.

3.6 Ethosomes in treatment of Alopecia Areata:

Alopecia areata, simply put, is a condition characterized by patchy hair loss, that is contributed due to various potential causes. These includes genetic factors, hormonal changes, certain medical conditions, and diseases like thyroid disorders, autoimmune conditions reasons. Additionally, some medications like chemotherapy drugs, antidepressants, and blood thinners may cause hair loss or treatments like radiation therapy can also cause temporary or permanent hair loss in the treated areas. Moreover, factors like physical, emotional, nutritional deficiencies or aging can lead to hair loss especially in women.

Ethosomes have been studied as a potential treatment for hair loss by delivering drugs such as minoxidil, finasteride, glucocorticoids and topical immunosuppressants directly to the hair follicles. Enhanced penetration in the skin by ethosomes can improve the efficacy of these drugs and promote hair growth.[23] The drug molecules penetrate the hair shaft and reach the target site more efficiently, promoting hair growth. Saleem[45] et al. has shown that the use of minoxidil and finasteride in ethosomal formulation significantly improves the efficacy of these drugs compared to traditional creams and solutions. However, further research may confirm the safety and efficacy of ethosomes as a hair loss treatment.

Minoxidil is currently the only FDA approved topical medication for treating alopecia. It works by increasing the blood flow to the hair follicles, which in turn stimulates hair growth. However, minoxidil is known to have poor skin penetration, which limits its effectiveness. Thus, by incorporating minoxidil into ethosomes, the drug can be directly delivered to the pilo sebaceous follicle layer of skin, leading to improved efficacy and hastened hair growth.[24] Dubey et al.[25] and similar studies are suggestive beneficial effects of the minoxidil in alopecia areata.

Finasteride is a drug, commonly used to treat male pattern type alopecia. It is an FDA approved oral medication for the treatment of hair loss. It works by inhibiting the action of an enzyme called 5-alpha reductase, responsible for converting testosterone into dihydrotestosterone which is the hormone that causes hair loss.[26] By incorporating finasteride into ethosomes, the drug can be directly delivered to the hair follicles, leading to improved drug efficacy and decreased hair loss. There have been some studies that have investigated the potential of finasteride ethosomes as a treatment for hair loss, but these studies have been done in laboratory and preclinical level, and it is not yet FDA approved.[27] Topical corticosteroids are yet another effective therapy options available for treatment of alopecia.

Multidrug ethosomes are a promising area of research in drug delivery systems for hair loss treatments. Wang et al. (2022)[28] demonstrated the potential benefits of combining two or more drugs in a single vesicular formulation. Drugs combined with herbal formulation can also prove efficacious. By targeting multiple mechanisms of hair loss, multidrug ethosomes could improve the efficacy of hair loss treatments. However, the development of drug formulations and their effectiveness in treating hair loss is an ongoing and complex area of research. Therefore, further studies are needed to understand the safety and efficacy of multidrug ethosomes in hair loss treatment.

3.7 Limitations:

While ethosomes offer advantages as a drug delivery system, there are several limitations that must be considered. Some of the key limitations are:

1. Complex and time-consuming method which can make the production process lengthy and less efficient.[29]
2. Instability is observed due to sensitivity towards temperature, pH and humidity[30], that can make it difficult to store and transport the formulation.[31]
3. Limited in vivo studies make it difficult to understand the potential benefits and risks of using ethosomes as a drug delivery system.[32]
4. Ethosomes can cause skin irritation, erythema or similar adverse events if they are not optimized correctly.[33]
5. Loss of product while transferring from organic to water media is reported.[34] If shell locking process is not proper; then there are chances of coalescence while transferring into water media resulting into poor yield of the product.[35]
6. Furthermore, they may have potential interactions with drugs and other excipients in the formulation.[36,37]

7. However, many of these limitations can be overcome by optimizing the composition and preparation of the ethosomes and using appropriate formulations.[38] Additionally, further research is needed to fully understand the potential benefits and limitations of ethosomes as a drug delivery system.

3.8 Future scope:

The introduction of ethosomes has opened up a new area in the research for transdermal drug delivery. Various reports are suggestive of a promising future for ethosomes by enhancing the transdermal delivery of various agents. Continued research in this domain will improve the control over drug release, thereby leading to enhanced therapeutic efficacy.

Ethosomes could potentially revolutionize cancer therapy by delivering anti-cancer drugs transdermally, offering a less invasive alternative to traditional chemotherapy. Similarly, in gene therapy, ethosomes may facilitate the delivery of genetic material through skin or mucous membranes, promising advancements in treating genetic disorders and other targeted therapies.[39] The initial clinical study of acyclovir-loaded ethosomal formulations has shown the ease with which large quantities of ethosomal formulations can be prepared. Moreover, it indicates that these formulations will soon find their way into clinical settings for extensive evaluation.[40] Ethosomes have also shown potential in delivering various cosmetic actives such as hyaluronic acid, collagen, and peptides, which can improve skin hydration, firmness, and elasticity.[41]

Future research is likely to be concentrated on overcoming challenges such as stability, scalability, and precise targeting of tissues or cells, as well as ensuring safety and compliance with regulatory standards. Ethosomes represent a versatile drug delivery system with vast potential applications, driven by ongoing advancements in nanotechnology and pharmaceutical sciences.[42]

In conclusion, ethosomal formulations have shown promising effect in dermal and transdermal delivery of bioactive agents.

IV. CONCLUSION:

In conclusion, Ethosomes presents both opportunities and new challenges for the development of novel therapies. They are soft malleable vesicles composed mainly of phospholipids, water and ethanol serving as potential carrier for transportation of drugs. Their ability to enhance the penetration of drugs through the skin makes them a versatile and effective alternative to traditional transdermal drug delivery systems. Moreover, ethosomes have brought new understanding towards vesicular research for topical delivery.

Ethosomes can be potential carriers for transportation of drugs across the scalp for treating alopecia areata and male pattern hair loss. Drugs like finasteride, and minoxidil can be benefited for their topical applications using ethosomes to overcome the conventional dosage form side effects, despite their mechanism of action remaining largely unidentified. However, further research is needed to fully understand the potential benefits and limitations of using ethosomes in this indications, and to optimize the formulations and methods of administration.

V. CONFLICT OF INTEREST:

The authors have no conflicts of interest regarding this investigation**.**

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