

Ethosome: A nanocarrier for transdermal drug delivery

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ABSTRACT

Ethosomes are a novel and alternative drug delivery systems and currently the focus of many research activities. Ethosomes are soft, flexible vesicles that are composed mainly of phospholipids, ethanol and water. Ethosomes can provide better skin permeation than liposomes and deliver enhanced amounts of both small and large therapeutic agents through skin and targeting to deeper skin layers for various diseases. Finally deliver to the systemic circulation. It is clear that ethosomal carrier because of presences ethanol cause skin disruption and increases lipid fluidity. In this review, the mechanism of penetration, applications, preparation, advantages and disadvantages of ethosomes are illuminated.

Keywords: Nanosized ethosome; Drug delivery; Skin; Nanomedicine.

INTRODUCTION

The skin is a highly specialized structure that protects man from his environment. The primary function of the skin is to act as a barrier to passage of substances into the body. Delivery of drugs through the skin has been a most exciting as well as a challenging field of research [1]. Liposome-based drug delivery system has been considered as a promising carrier in which the drug is encapsulated securely in the liposome particle until it reaches its target cells. However, a number of studies have been conducted to liposome-based delivery of drugs, enhanced skin delivery of drugs can be obtained by novel lipid carriers known as ethosomes [2].

In recent years, ethosomes have attracted increasing attention as a new liposome carriers because of their high deformability, high enmeshment efficiency, and a great transdermal permeation rate in the drug-delivery system [3]. Ethosome carriers, developed by Touitou et al., are a modified form of liposomes that include a relatively high concentration of ethanol. They are very efficient at enhancing the skin permeation of a number of drugs to reach the deeper layer of skin or the systemic circulation [4]. It has been shown that the physicochemical characteristics of ethosomes permit this vesicular carrier to transport active substances more effectively through the stratum corneum (SC) into the

deeper layers of the skin than conventional liposomes [5].

Structure of ethosomes

The main difference between ethosomes and liposomes is in their composition. Ethosome comprises various types of phospholipid structures, water, and low molecular weight alcohol (ethanol or isopropyl alcohol) in high concentration that provide malleability to the vesicle membrane [6]. The ethosomal lipids are in a more-fluid state than liposomes containing the same ingredients without ethanol. Thus the ethanol can act as a "mixing" agent for lipid vesicles and provide vesicles with softness characteristics, which allow them to increase their distribution in different skin layers [7]. However, because of their high ethanol concentration, the lipid membrane is packed less firmly than conventional vesicles but has equivalent solidity, allowing a more malleable structure and enhance drug distribution ability in stratum corneum lipids. In the cases of drugs with high solubility, the presence of ethanol in ethosomes can exhibit high encapsulation efficiency and improved drug loading [8].

It has been reported that the decrease of ethanol concentration in the range of 20% to 45% can result in the increase in the size of ethosomes and makes the ethosomes unique [9]. The non-aqueous phase (alcohol and glycol combination)

may range between 22 to 70%. And polyglycols like propylene glycol, transcitol RTM are used as skin penetration enhancer. Various phospholipids which are used as vesicle forming component are phosphatidylcholine (for instance: soya phosphatidylcholine, egg phosphatidylcholine, dipalmitoyl phosphatidylcholine, distearoyl phosphatidylcholine) phosphatidic acid, phosphatidylethanolamine, phosphatidylserine, phosphatidylglycerol, and phosphatidylinositol (PI). In addition, non-ionic surfactants (PEG-alkyl ethers) can be combined with the phospholipids in these preparations. Cationic lipids like cocoamide, POE alkyl amines, dodecylamine, cetrimide etc can be added too [10]. Cholesterol used at a range of 0.1% - 1% provide stability to the vesicle membrane. Such a composition enables delivery of high concentration of active ingredients through skin. Drug delivery can be modulated by altering alcohol: water or alcohol-polyol: water ratio . In addition, soybean phosphatidylcholine (Phospholipon 90), ethanol, drug and distilled water can be served for production of Ethosomes. Table 1 shows various additives employed in preparation of ethosomes [11].

Skin

In order to understand the mechanism of ethosome-based drug delivery system, we must first understand the structure of skin and the layers that make it up. There are three structural layers to the skin: the epidermis, the dermis and subcutis. Epidermis is the outermost layer and is seen on the surface of the skin. The main cells of the epidermis are the keratinocytes, which synthesize the protein keratin. The keratinocytes develop at the bottom and rise to the top, where they are shed from the surface as dead cells [12].

The outer most portion of the epidermis known as the stratum corneum. It consists of 10 to 25 layers of dead, extended, fully keratinized corneocytes, which are inserted in a matrix of lipid bilayers. It has been shown that the stratum corneum is the main barrier to penetration through the skin. It is relatively waterproof and, when undamaged, obstructs most bacteria, viruses, and other foreign substances from entering the body. The keratinocytes in the stratum corneum are dead squamous cells that are no longer multiplying [12].

The dermis consists is mostly made of dense irregular connective tissue and is much thicker than the epidermis. The dermis is responsible for the tensile strength of skin. Its main roles are to regulate temperature and to supply the epidermis with nutrient-saturated blood. Much of the body's water supply is storage within the dermis [12, 13].

The subcutaneous layer (It is also called hypodermis) lies below the dermis. The subcutaneous layer is primarily composed of fat and connective tissue. It performs as a protective cushion and helps to insulate the body by monitoring heat gain and heat loss. Not all authors regard this layer a part of the skin, but it definitely has a strong impact on the way the skin looks [12, 13].

Mechanism of penetration

The basic advantage of ethosomes over liposomes is the increase permeation of drug. The mechanism of penetration of the ethosomes in and through the skin is not yet completely clear. But it is suggested that the drug absorption probably occurs in following two phases :

1. Ethanol effect; according the first mechanism, ethosomal formulations contain ethanol in their composition that interacts with intercellular lipid molecules in the polar head group region, thereby increasing their fluidity and decreasing the density of the lipid multilayer, which results in an increase in membrane permeability.
2. Ethosomes effect; the high alcohol content is expected to results in increased skin permeability. So the ethosomes permeates very easily inside the deep skin layers, where it got combined with skin lipids and releases the drugs into deep layer of skin [14].

Applications of ethosomes

In this part of paper, ten applications of ethosomes are illuminated:

1. Hormones delivery; oral administration of hormones is connected with issues like high first pass metabolism, low oral bioavailability and several dose dependent side effects. The risk of failure of treatment is known to growth with each pill missed [15].
2. Antibiotics delivery; topical delivery of antibiotics is a convenient option for increasing the therapeutic efficacy of these agents.

Table 1. Different Additive Employed In preparation of Ethosomes [29-32].

CLASS	EXAMPLE	USES
Phospholipid	Soya phosphatidyl choline, Dipalmityl phosphatidyl choline, Egg phosphatidyl choline	As vesicles forming component
Dye	Rhodamine red, Rhodamine-123, 6- Carboxy fluorescence, Fluorescene Isothiocyanate (FITC)	For characterization study
Cholesterol	Cholesterol	For providing the stability to vesicle membrane
Vehicle	Carbopol D-934	As a gel former
Polyglycol	Propylene glycol, Transcutol RTM	As a skin penetration enhancer
Alcohol	Isopropyl alcohol, Ethanol	For providing the softness for vesicle membrane As a penetration enhancer

Conventional oral therapy of antibiotics is often seen with several allergic reactions as well as side effects and low therapeutic efficacy. Regarding topical delivery of antibiotics, conventional external preparations have low permeability to deep layers of skin and subdermal tissues. Ethosomes can overcome this problem by delivering adequate quantity of antibiotic into deeper skin layers. Ethosomes penetrate quickly through the epidermis and bring considerable amount of drugs into the deeper layer of skin and suppress infection at their root. In view of this reason, Godin and Touitou prepared bacitracin and erythromycin loaded ethosomal formulation for dermal and intracellular delivery. They demonstrated that the ethosomal formulation of antibiotic could be highly efficient and would overcome the problems associated with conventional treatment [16].

3. Delivery of anti-parkinsonism agent; Dayan and Touitou prepared ethosomal formulation of psychoactive drug trihexyphenidyl hydrochloride (THP) and compared its delivery with that from classical liposomal formulation. THP is a M1 muscarinic receptors antagonist and used in the treatment of Parkinson disease. The results showed better skin permeation potential of ethosomal-THP formulation and its use for better management of Parkinson disease [17].

4 .Transcellular delivery; Touitou et al. demonstrated that better intracellular uptake of bacitracin, DNA and erythromycin can be achieved using CLSM and FACS techniques in different cell lines. In comparison with the marketed formulation ethosomes can be an attractive clinical alternative for anti-HIV therapy [18].

5. Topical delivery of DNA; ethosomes can be used as carrier for gene therapy application that

require transient expression of genes. It has been demonstrated that better intracellular uptake of DNA, better delivery and expression of genes in skin cells can be attained by ethosomal formulation. Gupta et al. recently have reported immunization potential using transfersomal formulation. Hence, better skin penetration ability of ethosomes enables the possibility of using these dosage forms for delivery of immunizing agents [19].

6. Anti-arthritis drug delivery; Cannabidol (CBD) is a recently developed drug candidate for treating rheumatoid arthritis. CBD-ethosomal formulation for transdermal delivery has been prepared by Lodzki et al. Results shows considerably increased its skin penetration, and hence it's activity [20].

7. Antiviral drug delivery; Zidovudine and Acyclovir are two potent antiviral agents. The first one acts on acquired immunodeficiency virus and another one is widely used topically for treatment of Herpes labialis. It has been reported that ethosomes can improve delivery of both of these antiviral drugs [21].

8. Delivery of problematic drug molecules; transdermal delivery is a convenient way for delivery of peptides and proteins, because oral delivery of these large biogenic molecules are pretty difficult and have poor permeation. To increase permeation and therapeutic efficacy of these above molecules, ethosomes is a good idea [22].

9. Delivery of antifungal drugs; as a vesicular carrier system, ethosomes was found to have incredible capability of improving transdermal permeation of Ketoconazole. Ethosomes offers advantages of rapid onset and maximum release of drug with reduction of side effects. Furthermore, ethosomes do not damage the architecture of skin and so, drug is transported into the systemic circulation across the

undamaged skin. Ethosomal fluconazole gel formulation offers better remission from the disease and reduces the duration of therapy in treatment of candidiasis patients [23].

10. Pilosebaceous targeting; Sebaceous glands and Hair follicles are being known as potentially key elements in the percutaneous drug delivery. Also, great consideration has been given to using the follicles as transport shunts for systemic drug delivery. Ethosomal formulation of minoxidil a lipid soluble drug used for baldness accumulate into nude mice skin two to seven fold higher and thus can be used for pilosebaceous targeting for better clinical efficacy [24].

Preparation

There are two methods that are frequently used for preparation of ethosomes, cold or hot method. These two methods are very simple and do not require any sophisticated equipment. Figure 1 illustrates both of two methods.

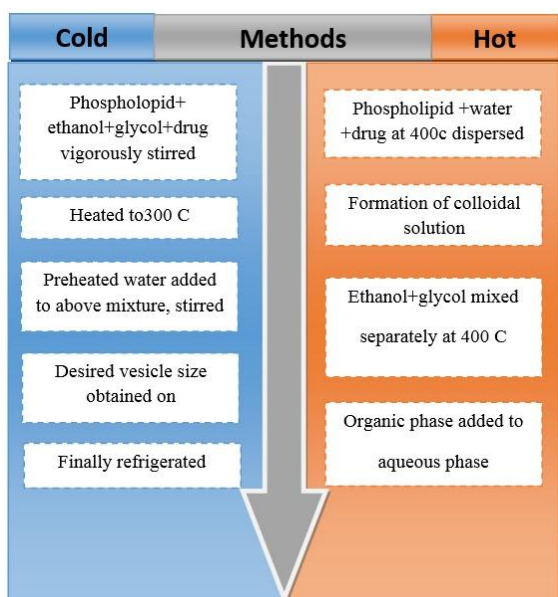


Figure 1. Cold and hot methods for preparation of ethosomes.

Advantages and disadvantages

In comparison to other transdermal and dermal delivery systems, ethosome shows essential advantages which make it an ideal candidate for drug delivery. The advantages of ethosome include:

1. Increasing efficacy and therapeutic index.
2. Reduction in toxicity of the encapsulated agent.
3. Improved permeation: Ethosomes are efficient method of drug delivery that improve permeation of drug through skin. In contrast

with deformation liposomes, ethosomes improve skin delivery of drugs both under occlusive and non-occlusive conditions.

4. Suitable for large and varied groups: Ethosomes are podium for the delivery of large and varied group of drugs. It can entrap all types of drug molecules such as hydrophilic, lipophilic or amphiphilic, peptides, and protein molecules .

5. Safety and Non-toxicity: It contains non-toxic raw material in formulation and reduce toxicity of the encapsulated agent.

6. Simplicity of manufacturing: It is relatively simple to manufacture with no complicated technical investments required for production and is available for immediate commercialization.

7. Being non-invasive: The ethosomal drug is administrated in semisolid form (gel or cream) therefore, presenting high patient compliance.

8. Acceptability: Ethosomes are approved greatly in Pharmaceutical, Veterinary, Cosmetic fields and herbal drug technology.

9. Better stability and solubility: Ethosomes can make many drugs more stable and soluble via encapsulation of them as compared to conventional vesicles.

10. Smaller size: Ethosomes are relatively smaller than other conventional vesicles.

11. Selective passive targeting: They provide selective passive targeting to tumor tissue.

12. Improvement of pharmacokinetic effect: Ethosomes increase pharmacokinetic effect (circulation time).

13. Flexibility to couple with site specific ligands: Ethosome is flexible to couple with site specific ligands to achieve active targeting [27-29].

Although ethosomes possess many advantages, there are certain disadvantages like:

1. Very low yield so may not be economical.
2. Percutaneous absorption depends on the molecular size of the drug which should be rational.
3. Ethosomal drug delivery system is limited to potent drugs and not for drugs that require high blood levels.
4. Skin irritation or dermatitis may occur in some patients due to permeation enhancer or the excipients used.
5. Ethosomal administration is not a means to achieve rapid bolus type drug input, rather it is usually designed to offer slow, sustained drug delivery.

6. Adequate solubility of the drug in both lipophilic and aqueous environments to reach dermal microcirculation and gain access to the systemic circulation.

7. Release of product during transfer from organic to water media [30-32].

CONCLUSION

In this paper, we have discussed the mechanism of penetration, applications, preparation, advantages and disadvantages of ethosomes. It can be concluded that Ethosomes

provides a number of important benefits including improving the drug's efficacy, enhancing patient compliance and comfort and reducing the total cost of treatment. Various hydrophilic drugs, cationic drugs, proteins and peptides can be easily administered through transdermal route by ethosomal encapsulation. So the main advantage is improved therapies. The ethosomal technology is safety and convenience of use. Important factors that need to be considered when developing alternate drug delivery systems.

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