



A Review on Ethosome as a Potential Drug Delivery System

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ABSTRACT

Transdermal route is a promising method to various drug delivery for its general impact and it is an easiest method to keep the drug intact to the skin for a few many treatment. Ethosomes are the ethanolic lipid vesicles that are used principally for transdermic delivery of medicine irrespective of the depth and quantity of the delivering substance to the skin. Ethosomes have higher penetration rate through the skin as compared to liposomes thus these may be used wide in situ of liposomes. Due to the use of ethanol in the formulation of ethosomes, the permittivity of drug enhances as the vesicular membranes become flexible and the elastic vesicles squeeze themselves on presence of ethanol through the pores, which are much smaller than their diameters. This paper reviews numerous facets of ethosomes together with their preparation, characterization, potential blessings and their applications in drug delivery. Ethosomes became a region of analysis interest, accrediting to its increased skin permeation, improved drug delivery, inflated drug defence potency, etc.

Keywords: Ethosomes, Transdermal delivery, Liposomes, Lipid vesicles, Permeation.

INTRODUCTION

The skin can be considered as the heaviest organ of the human body, on average accounting for 10% of the body mass and covering nearly 2m² of the body surface area.^{1,2} It can be defined as the boundary between the body and its surroundings, thus the vital bodily functions to occur within a controlled physiological environment which is allowed by the skin.

Human skin is a stratified epithelium, every tissue layer consisting of various cell types that perform distinct functions. It can be generally divided into the superimposed stratum, stratum and underlying hypodermis (or subcutis). The epidermis can further be divided, from the outside to the inside, into the stratum corneum (horny layer), stratum (granular layer), stratum spinosum (prickle cell layer) and stratum basale (basal layer also referred to as the stratum germinativum).³

Stratum corneum (SC) is the outermost layer of the skin that contains of corneocytes, flattened non nucleated terminally differentiated keratinocytes that is embedded in multilamellar, ordered lipid domain and has low tide contents (10-25%).⁴ This stratum is well considered as the main barrier for permeation of the drug into the deep strata of the skin and across the skin. Many active ingredients can function well only when they are transported at least across this outermost layer of the skin. However, because of the SC barrier properties, the drug efficacy is often far from that required. The efficiency of various anti-inflammatory agents, antibiotics, skin nutrients, lipolytic and other agents depends on their delivery into the deep skin strata. For this purpose, carriers

with adequate skin penetration enhancement properties are needed.⁵

In recent decades the researchers showed wide interest in exploring new techniques for increasing drug absorption through Stratum Corneum.

The multitude studies performed have shown the classic liposomes produce noteworthy reservoir of drugs ostensible strata of the skin where there was no delivery seen to its deepest layer.⁶ Not long ago, the vesicles that were able to contravene the SC barrier which ease the conveyance of active ingredients to the site of their action in the deep skin strata and systemic circulation have been designed.⁷

TRANSDERMAL DRUG DELIVERY SYSTEM

For decades, the oral route has been considered as the most customary for the delivery of the drug and was found that about 74% of drugs are taken orally but still are found not as effective as foreseen.⁸ Nevertheless oral administration has momentous advantage of easy administration, it also carries notable drawbacks which are poor bioavailability due to hepatic metabolism (first pass mechanism) and the proclivity to capitulate rapid blood level spikes (both high and low) are seen.

To get higher of the mentioned hindrances, the researchers thought of understanding /developing a brand new drug delivery route/ system; that may improve the therapeutic effectualness and safety of drugs by more precise which would conjointly show each spatial and temporal placement inside the body thereby reduction in each the dimensions and range of doses and conjointly showing inflated effectiveness with best dose

concentrations. To attain these goals and improve such characters transdermal drug delivery system was emerged.⁹

Transdermal drug delivery system is taken into account because the locally administered medications in self-contained, distinct indefinite quantity types of patches that once applied to the skin deliver the drug, through the skin portal to systemic circulation at a planned and controlled rate over a prolonged amount of your time so as to extend the therapeutic effectualness and reduced facet impact of drug. TDDS helps in maintaining the concentration of the drug inside the therapeutic window for extended amount of time, therefore making certain that drug levels neither fall below the minimum effective concentration nor exceed the most effective concentration. The researchers performed researches within the field that paved a way for the utilization of liposomes used for the topical delivery of triamcinolone.¹⁰ And after that a broad range of novel lipid-based vesicular systems have been expanded transfersomes (deformable or elastic liposomes) were instituted by Cevc and Blume in 1992.¹¹ Touitou et al, discovered a novel lipid vesicular system called ethosomes. Ethosomal systems contain relatively high concentrations of ethanol in addition to phospholipids and water which differ as that of liposome.¹²

New generations of ethosomal systems are introduced and from there forrader by the addition of latest generations of ethosomal systems are introduced since then by adding altogether completely different compounds to the basic ethosomal formula therefore to strengthen sac characteristics and skin permeation. However, to date, there has been no clear distinction among the classical ethosomes and their newer generations. The ethosomes helps meddling with the skin barrier leading to the penetration of the SC bilayers that allows for the improved delivery of the medication by transporting transdermally to the low skin strata.

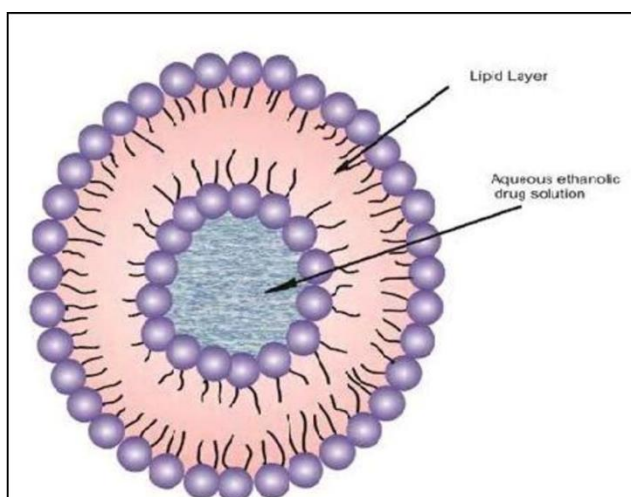


Figure 1: Structure of Ethosomes

Types of Ethosomes

1. Classical ethosomes

Classical ethosomes are the moderation of so called classical liposomes and contains phospholipids, a high concentration of upto 45% w/w, and water.¹³ Classical ethosomes are considered more condensing over that of classical liposomes for the purpose of transdermal delivery of the drug as they were smaller and had negative negative ζ -potential and higher entrapment efficiency. Classical liposomes showed higher skin permeation and stability profiles compared to that of classical liposomes. The molecular weights of drugs entrapped in classical ethosomes have ranged from 130.077 Da to 24 kDa.^{14,15}

2. Binary ethosomes

Binary ethosomes were prepared by adding another variety of alcohol to the classical ethosomes. The most normally used alcohols in binary ethosomes are propylene glycol (PG) and isopropyl alcohol (IPA).¹⁶

3. Transethosomes

This ethosomal system contains the fundamental parts of classical ethosomes and an extra compound, like a penetration enhancer or an edge activator (surfactant) in their formula.¹⁷ These novel vesicles were developed in an attempt to mix the benefits of classical ethosomes and deformable liposomes (transfersomes) in one formula to produce transethosomes. Transethosomes were reported to entrap drugs with molecular weights starting from 130.077 da to 200–325 kDa.¹⁸

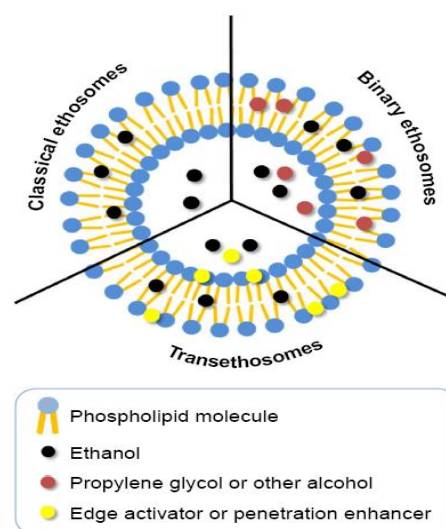


Figure 2: Different types of Ethosomes

Advantages of Ethosomes:¹⁹⁻²¹

1. Ethosomes enhance permeation of drugs across/through the skin in an efficient manner, thereby enabling the drug to reach the desired site in the skin or to the blood.
2. Ethosomes can deliver both hydrophilic and lipophilic molecules, peptides, and different macromolecules.

3. Higher entrapment efficiencies of drugs when compared to liposomes can be observed.
4. The components of the ethosomes are generally recognized as safe (GRAS) and approved for pharmaceutical and cosmetic use.
5. Excellent stability over long periods can be observed.
6. Alcohol in the ethosomes acts as natural preservative, and hence there is no necessity to add any other preservatives.
7. There is no necessity of using high-end instruments for producing ethosomes, and large-scale production is feasible.
8. The cost of manufacturing ethosomes is very cheap.
9. To improve patient compliance can be observed.
10. The transport of drugs across the skin is not concentration dependent.
11. It has varied applications in pharmaceutical, veterinary, and cosmetic segments.

Disadvantages of Ethosomes: ²²⁻²⁴

1. Drugs that require high blood levels cannot be administered. It is limited only to potent molecules, those requiring a daily dose of 10mg or less.
2. Ethosomal administration is not a means to achieve rapid bolus type drug input, rather it is usually designed to offer slow, sustained drug delivery.
3. Adequate solubility of the drug in both lipophilic and aqueous environments is necessary to reach dermal microcirculation and gain access to the systemic circulation.
4. The molecular size of the drug should be reasonable that it should be absorbed percutaneously.
5. Adhesive may not adhere well to all types of skin making it uncomfortable to wear.
6. May not be economical cause of poor yield.
7. Skin irritation or dermatitis may occur due to the presence of excipients and enhancers of drug delivery systems.
8. In case if shell locking is ineffective then the ethosomes may coalesce and fall apart or transfer into water.
9. Loss of product during transfer from organic to water media.

Physicochemical Characteristics and Skin Safety of Ethosomes

Ethosomal systems contains mainly phospholipids, ethanol or other volatile alcohols at comparatively lofty concentrations (up to 50%) and water. ²⁵

In disparity to liposomes, ethosomal systems are prepared by simple processes which do not normally require any

particular equipment. Before ethosomes were initially reported, high alcohol concentrations in high amount were generally considered to be harmful to lipid vesicles.²⁰ Moreover the presence of alcohol in the system together with soft vesicles imparts important and unique characteristics to the delivery carrier. The features of the ethosomal delivery systems were investigated in numerous studies. ³¹P-NMR study results showed that, phosphatidylcholine is organized in bilayers displayed a lineshape in ethanol concentrations up to 45%. Moreover, in paramagnetic-ion NMR experiments, fluorescent anisotropy measurements of AVPC (9-antrivinylyl labeled analogue of phosphatidylcholine) and DSC thermograms have conveyed that the phospholipid bilayers in ethosomes are packed less tightly, possess a high degree of fluidity and have a lower transition temperature compared to liposomes. Differences of up to 30°C in transition temperatures of ethosomal vs. liposomal lipids containing the same main ingredients were reported. ^{26,27}

Mode of Action of Ethosomal Systems

The ethosomal carrier allows for enhanced dermal and transdermal delivery by passive diffusion. Studies described earlier in this review reported that due to the presence of ethanol, ethosomes contain fluidized phospholipid bilayers generating vesicles with a soft structure. An additional essential role of ethanol present in the system is fluidization and disturbance of SC lipid organization. ²⁸

A model representing the mode of ethosomal system action was proposed based on system characteristics and numerous skin penetration and permeation studies which revealed that ethosomes perform significantly better than each of their individual system components or combinations.

The proposed model of penetration enhancement through the SC barrier is based on the dual fluidizing effect of ethanol on the lipid bilayers of SC and vesicle phospholipid bilayers. Soft vesicles penetrate into and across the disturbed SC lipid bilayers, promoting delivery of active agents beneath the SC barrier. Ethosomes penetrating the fluidized SC bilayers generate a passageway across the SC lipids and fuse with cell membranes in the deeper skin layers where they release their payload. ²⁹

Method of Preparation of Ethosome:

Ethosome formulations are prepared by using the following methods –

- Injection Method
- Optimized Method
- Hot Method
- Cold Method

1. Injection Method-

The drug and phospholipids are dissolved in ethanol and propylene glycol solution in a closed vessel. After that, the



mixture is heated up to 30°C in a water bath. Distilled water added slowly in a fine stream and mixing at 700 rpm for 5 min at 30°C temperature. Then the preparation is stored at 40°C, after that sonicated in 3 cycles of 5 min with 5 min rest between the cycle. The final preparation is stored at 4°C.^{30,31}

II. Optimized method (Thin film hydration method)-

In this method, the phospholipid is dissolved in a ratio of chloroform:methanol. The organic solvent is removed through the rotator flask evaporator above the lipid transition temperature 55°C at 600 rpm for 30 min. Then thin films are formed and the film hydrated with a hydroethanolic mixture (1% w/v) at 60 rpm for 1 hour. After that Sonicated the mixture in 3 cycles of 5 min with 5 min rest between the cycle. The final formulation is stored at 4°C in the container.³²

III. Hot method-

Phospholipids are dispersed in water by heating in a water bath at 40°C until a colloidal solution is obtained. Ethanol and propylene glycol are mixed in a separate vessel and heated to 40°C. Once both mixtures reach 40°C, the organic phase is added to the aqueous phase. The drug is dissolved in an organic or aqueous phase. The vesicle size of the formulation can be decreased to the desired extent using the extrusion or sonication method.³³

IV. Cold method-

In this method, drug, phospholipids, and other lipid materials are dissolved in ethanol in a closed vessel at room temperature by vigorous stirring with the use of a mixer. Propylene glycol is added during stirring and mixture is heated to 30°C in the water bath. Preheated water (30°C) is added to the mixture, which is then stirred in a closed vessel for 5 min. The vesicle size of the formulation can be decreased to the desired extent using the extrusion or sonication method. After that, the final ethosomal formulation is stored under refrigeration.³³

Characterizations of Ethosomes

1. Visualization or vehicle shape - Visualization of ethosomes can be done using transmission electron microscopy (TEM) and by scanning electron microscopy (SEM).³⁴

2. Vesicle size and size distribution - Particle size and size distribution can be determined by dynamic light scattering (DLS) using a computerized inspection system and photon correlation spectroscopy (PCS).³⁴

3. Differential scanning calorimetry (DSC) - Transition temperature (T_m) of the vesicular lipid systems was determined by using the differential scanning calorimetry instrument. The transition temperature was measured by using the aluminium crucibles at a heating rate 10 degree/minute, within a temperature range from 20°C–300°C.^{35,36}

4. Surface Tension Activity Measurement - The surface tension activity of drug in aqueous solution can be measured by the ring method with the help of tensiometer.³⁶

5. Entrapment efficiency - Entrapment efficiency is determined by using ultra centrifugation technique or mini column centrifugation method with the help of Fluorescence spectroscopy.³⁶

6. Vesicle skin interaction study - The vesicle skin interaction study can be found by using Confocal Laser scanning microscopy, Fluorescence microscopy, Transmission electron microscopy and Eosin-Hematoxylin staining. Confocal laser scanning microscopy also used for penetration and permeation studies of Ethosome.³⁷

7. Phospholipid-ethanol interaction - This factor can be determined by ³¹P NMR Differential Scanning Calorimeter.³⁸

8. Zeta potential - Zeta potential can be determined by using Zeta Meter.³⁸

9. Turbidity - To find out turbidity Nephelometer is used.³⁸

10. In vitro drug release study - To find out release study either Franz diffusion cell with artificial or biological membrane or Dialysis bag diffusion method can be used. By using Franz diffusion cell method also drug deposition study can be performed.³⁹

11. Stability study - To determine the stability of the product both Dynamic light scanning method and Transmission electron microscopy can be used.³⁹

Applications of Ethosome as a Delivery System

• As a transdermal delivery:

Ethosomal formulations enhance drug permeability through stratum corneum. This delivery system can be used for drugs which having less skin permeation, poor oral bioavailability, first pass metabolism.⁴⁰

• In Pilosebaceous targeting:

Sebaceous glands and hair follicles are highly identified as important elements in percutaneous drug delivery. For better clinical efficacy, in pilosebaceous targeting, ethosomal formulation can be used. The targeted treatment of follicle related disorders such as alopecia or acne, pilosebaceous targeting have been used.⁴¹

• Cosmeceutical application:

Applying ethosomes in cosmeceuticals increase the stability of the chemicals and decrease skin irritation. The compositions and the vesicle size are the main factors to be considered to obtain elastic vesicles for cosmeceutical applications.⁴²

• Delivery of large biogenic drug molecules:

Formulating the biogenic molecules such as peptides or protein and insulin into ethosomal preparation can

increase permeation and therapeutic efficacy. Because conventional transdermal formulation of large biogenic molecules has poor permeation.⁴³

• Anti-Psoriatic Drugs:

Psoriasis is a T-lymphocyte mediated autoimmune disease of the dermis and epidermis leading to development of scaling erythemaotus plaques. Methotrexate (MTX) a dihydrofolate reductase enzyme inhibitor is used at high doses in treatment of certain neoplasia. To reduce the side effects related with the oral route, Dubey and Jain et al. investigated the transdermal route for Ethosomal preparation of MTX and suggested that ethosomes have a promising carrier for the delivery of MTX.⁴⁴

• Delivery of Anti-Parkinsonism Agent:

Dayan and Touitou prepared ethosomal formulation of psychoactive drug trihexyphenidyl hydrochloride (THP) and compared its delivery with that of classical liposomal formulation. THP is a muscarinic antagonist used for the treatment of Parkinson's disease showed greater permeation and greater management through ethosomal formulation.⁴⁵

• Delivery of Anti hyperlipidemic agent:

Bile excretes 95% of simvastatin which was metabolized by liver. After oral administration active structures which are below 5% were found in blood circulation. Keyo An et al., had formulated simvastatin as Ethosome and In vitro evaluation was carried out. Lipid levels and coronary artery diseases are enhanced and thereby reduces Low Density Lipoprotein Cholesterol [LDL].⁴⁶

Current Research Areas of Ethosomes:

S NO.	DRUG	CLASS	APPLICATIONS	REFERENCE
1.	Diclofenac	NSAIDS	Selective delivery of drug to desired side for prolong period of time	47,48
2.	Acyclovir	Anti-viral	Increase skin permeation, Improved in biological activity two to three times	49
3.	Bacitracin	Antibiotics	Improved dermal deposition, Increased bioavailability.	50
4.	Azelaic acid	Dicarboxylic acids	Prolong drug release	51
5.	Trihexyphenidyl hydrochloride	Anti-cholinergic	Improved patient compliance, Provide controlled release, Improved transdermal flux	52
6.	Raloxifene HCl	Anticancer	used in the treatment of breast cancer	53
7.	Curcumin	Anti-neoplastic	antimicrobial, anti-tumoral, antioxidant properties	54
8.	Tacrolimus	Immunosuppressant	Treatment of atopic dermatitis, Improved pharmacological effect	55
9.	Phenylethyl Resorcinol	Anti-oxidant	Used in skin lightening products	56
10.	Cryptotanshinone	Anti-acne	effective dermal delivery system, slight skin irritation.	57
11.	Salbutamol	Anti-asthmatic	Enhanced drug delivery through skin with ethosomes	58, 59
12.	Colchicine	Anti-gout	Enhance skin accumulation, prolong release and improve the specificity	58, 59
13.	Felodipine	Anti-hypertensive	Sustained release of drug trans dermally	60

CONCLUSION

With emerging growth in research, Ethosomes have been proved to be interesting delivery systems for pharmaceutical and cosmetic products. With better skin permeation than liposomes Ethosomes are more effective for transdermal and dermal delivery that should possibly to be able to achieve bioavailabilities comparable to oral drug delivery by increasing the residence time of drugs in the stratum corneum and epidermis and reduce the systemic absorption of drugs allowing them to penetrate easily into

the deeper layers of the skin and circulation. Development of optimized elastic vesicular formulations of desired compositions and sizes, can be a promising means for the topical treatment of local and systemic disorders of many pharmaceuticals as well as cosmeceutical applications. With this possibility, developing safe and effective dermal and transdermal delivery systems should be far more successful and can open new challenges and opportunities for the development of novel improved therapies making it more effective.

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