IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Review Article
November 2022 Vol.:25, Issue:4

A Review on: Ethosomal Drug Delivery System

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
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Submitted: 30 October 2022
Accepted: 5 November 2022
Published: 30 November 2022

Keywords: Ethosomes, Transdermal drug delivery, vesicular drug delivery, Ethanol, Phospholipids.

ABSTRACT

The integument of humans i.e. skin particularly stratum corneum acts as a barrier to most drug absorption, which limits the ability of many molecules that have adequate physicochemical characteristics and pharmacokinetic/pharmacodynamics properties from diffusing through the skin. So, many novel vesicular drug delivery systems has been developed to overcome this limitations and to improve the transport of drugs through the skin. Ethosomes are novel lipid carriers, which are non-invasive, soft, malleable vesicular delivery carriers that enable drugs to reach the deep skin layers or the systemic circulation and enhanced the delivery of active agents. Ethosomal drug delivery systems are of different types such as Classical Ethosomes, Binary Ethosomes and Transethosomes. The high concentration of ethanol makes the Ethosomes unique and ethanol gives ability to the vesicle to penetrate the stratum corneum. Further incorporation of the Ethosomal system in a suitable vehicle for dermal or transdermal delivery has some advantages like preventing ethanol evaporation, prolonging contact time with the skin, enhancing the therapeutic efficacy of the entrapped drug, patient compliance, improving stability and shelf life of the final dosage form. Thus, Ethosomes possess promising future in effective transdermal delivery of drugs.

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INTRODUCTION:

Innovations in the area of drug delivery are taking place at a much quicker pace. Improved patient compliance and effectiveness are inseparable characteristics of new drug delivery systems. A more radical approach has been to explore newer interfaces on the body for introducing therapeutics one such approach is transdermal drug delivery.[1] Transdermal drug delivery is the non-invasive delivery of medications from the surface of skin which is the largest and most accessible organ of human body through its layers to the circulatory system.

TDDS offers many advantages over conventional injection and oral methods.[2] It consists of list of advantages over conventional routes such as:

- Easy to use and non-invasive.
- The first pass effect where active drug molecules can be converted to inactive molecules or even to molecules responsible for side effects can be avoided by transdermal delivery.
- Drug input can be stopped at any point after removal of the medicament from the site.
- Increases compliance and reduces medical costs.
- Suitable route for unconscious or vomiting patient and best route for paediatrics patients.
- Lesser chances of overdose and easy detection of drug.[3]

Drug molecules in contact with the skin surface can penetrate by three potential pathways: through the sweat ducts, by the hair follicles and sebaceous glands i.e. collectively called the shunt or appendageal route or directly across the stratum corneum.[4]

THE SKIN:

Human skin, the integument of humans has a valuable role. One of the most important functions is its ability to act as a protective barrier against the ingress of foreign material and the loss of excessive endogenous material such as water. The barrier function of the skin is thus reflected in its multi-layered structure. Each layer is known to represent different levels of cellular or epidermal differentiation.[5]

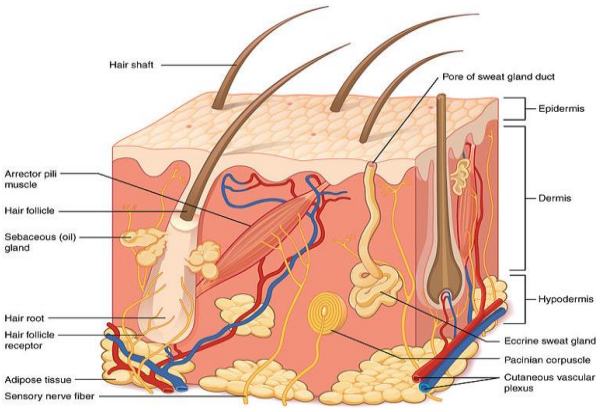

Figure no. 1: Structure of skin

Human skin comprises of three distinct but mutually dependent tissues, namely: The stratified, a vascular, cellular epidermis; underlying dermis of connective tissues and; Hypodermis.

EPIDERMIS:

The multilayered envelop of the epidermis varies in thickness, depending on cell size and number of cell layers, ranging from 0.8mm on palms and soles down to 0.06mm on the eyelids. Stratum corneum and the remainder of the epidermis, also called viable epidermis, cover a major area of skin.

STRATUM CORNEUM:

This is the outermost layer of skin, also known as horny layer. It is around 10mm thick when dry but swells to several times this thickness when fully hydrated. It accommodates 10 to 25 layers of parallel to the skin surface, lying dead, keratinized cells, called corneocytes. It is flexible but relatively impermeable. When it comes to the penetration, stratum corneum acts as the principal barrier.

VIABLE EPIDERMIS:

It is located beneath the stratum corneum and differs in thickness from 0.06mm on the eyelids to 0.8mm on the palms. While moving inwards, it consists of various layers as stratum lucidum, stratum granulosum, stratum spinosum and the stratum basale.

DERMIS:

Dermis is a 3 to 5mm thick layer and is composed of a matrix of connective tissue which contains blood vessels, lymph vessels and nerves. In the regulation of body temperature continuous blood supply has an essential function. Capillaries reach to within 0.2mm of skin surface and provide sink conditions for most molecules penetrating the skin barrier. The blood supply thus maintains the dermal concentration of permeate very low and the resulting concentration difference across the epidermis gives the required driving force for transdermal permeation.

HYPODERMIS:

The dermis and epidermis is supported by the hypodermis or subcutaneous fat tissue. It serves as a fat storage area. This layer help out to regulate temperature, provides nutritional support, mechanic protection and it carries principal blood vessels, nerves to skin and may contain sensory pressure organs. For transdermal drug delivery, the drug has to penetrate through all these three layers to reach into systemic circulation.[6]

Transdermal drug delivery has become an alternative to the traditional oral drug delivery route of administration because of numerous benefits in comparison to oral drug delivery. Technological advancements and novel drug delivery systems have led to the successful development of drugs with adequate molecular dimensions or delivery systems for efficient transdermal drug delivery.[7]

From the past years, novel drug delivery systems such as vesicular drug delivery system have been developed to improve physicochemical characteristics of drugs, pharmacokinetic/pharmacodynamics properties of drugs and transport of drugs through the skin.[8]

ETHOSOMES:

Ethosomes were developed by Touitou *et al.*, as additional novel lipid carriers, which are non-invasive, soft, malleable vesicular delivery carriers that enable drugs to reach the deep skin layers and or the systemic circulation and enhanced the delivery of active agents. They are mainly used for the delivery of drugs through the transdermal route and the drugs which have various physicochemical characteristics, i.e. hydrophilic, lipophilic or amphiphilic can be entrapped. The size range of ethosomes may vary from tens of nanometres to microns (μ).

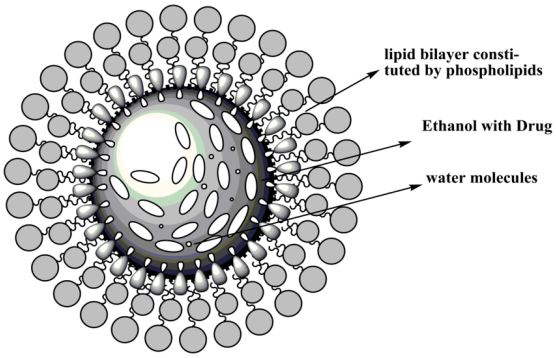

Figure no. 2: Structure of ethosomes

Ethosomes are composed of phospholipids, (phosphatidylcholine, phosphatidylserine, phosphatitidic acid), high concentration of ethyl alcohol (ethanol) and water. Ethanol is known for its disturbance of skin lipid bilayer organization, the high concentration of ethanol makes the ethosomes unique; therefore, when integrated into a vesicle membrane, ethanol gives ability to the vesicle to penetrate the stratum corneum, due to the high ethanol concentration; the lipid membrane is packed less tightly than typical vesicles. However it has equivalent stability, permitting an additional malleable structure and improves drug distribution ability in stratum lipids.[9, 10, 11]

ADVANTAGES OF ETHOSOMAL DRUG DELIVERY SYSTEM:

- Ethosomes are passive, non-invasive & available for immediate commercialization.
- Low risk profile, because the technology has no large scale drug development risk, since the toxicological profiles of the ethosomal components are well recorded in the scientific literature.
- Ethosomal drug is administered in semisolid form (Gel or Cream), producing high patient compliance.
- Ethosomes are simplest method for delivery of drug molecules instead of phonophoresis & iontophoresis.
- This is the type of formulation which is used for the delivery of peptide protein molecules.
- Transportation of active moieties by ethosomes in the skin layer has more importance than conventional liposomes on the basis of retention in the skin layer.

- The synergistic effect of combination of relatively high concentration of ethanol (20-50%) in vesicular form in Ethosomes was urged to be the main reason for their better skin permeation ability.

DISADVANTAGES OF ETHOSOMAL DRUG DELIVERY SYSTEM:

- The molecular size of the drug should be reasonable that it should be adsorbed percutaneously.
- Ethosomal formulations may not be economical.
- Skin irritation or dermatitis due to excipients & enhancers of drug delivery system.
- Loss of product during transfer from organic to water media.
- Adhesives may not be suitable for all types of skin.
- Yield will be very poor.[12]

TYPES OF ETHOSOMAL SYSTEM:

1. Classical ethosomes
2. Binary ethosomes
3. Transethosomes

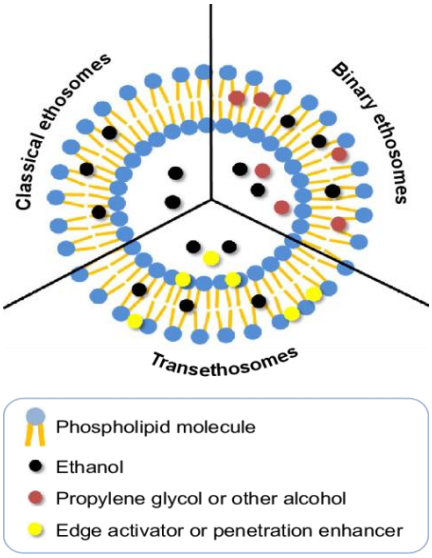

Figure no. 3: Different types of ethosomal System

CLASSICAL ETHOSOMES:

Classical ethosomes are a variation of classical liposomes, consisting of phospholipids, high ethanol concentrations of up to 45% w/w, and water. Classical ethosomes for transdermal drug delivery were stated to be superior to classical liposomes because they were smaller and had negative zeta potential for greater efficiency without clogging. Moreover, in contrast with classical liposomes, classical ethosomes displayed improved skin permeation and stability profiles. The molecular weights of drugs caught in traditional ethosomes ranged from 130.077Da to 24kda.

BINARY ETHOSOMES:

Binary ethosomes were introduced by Zhou *et al.,* which are basically classical ethosomes with a slight modification. Binary ethosomes are prepared by adding other types of alcohol to the classical ethosomes. Propylene glycol and isopropyl alcohol are the most commonly used alcohols in the preparation of binary ethosomes.

TRANSETHOSOMES:

Transethosomes are the latest generation of ethosomal systems and were first recorded in 2012 by Song *et al.*; these are lipid based vesicles which includes the basic components of classical ethosomes and an additional compound like penetration enhancer or an edge activator (surfactant) in its composition. In an attempt to combine the advantages of classical ethosomes with deformable liposomes (Transferosomes) in one formula, these novel vesicles were formed.[13]

Table no. 1: Comparison of classical ethosomes, binary ethosomes, and Transethosomes.[14]

Parameter	Classical Ethosomes	Binary Ethosomes	Transethosomes
Composition	1. Phospholipids 2. Ethanol 3. Stabilizer 4. Charge inducer 5. Water 6. Drug/agent	1. Phospholipids 2. Ethanol 3. Propylene glycol (PG) or other alcohol 4. Charge inducer 5. Water 6. Drug/agent	1. Phospholipids 2. Ethanol 3. Edge activator (surfactant) or penetration enhancer 4. Charge inducer 5. Water 6. Drug/agent
Morphology	Spherical	Spherical	Regular or irregular spherical shapes
Size	Smaller than the classical liposomes	Equal to or smaller than classical ethosomes	Size based on type and concentration of penetration enhancer or edge activator used
ζ-Potential	Negatively charged	Negatively charged	Positively or negatively charged
Entrapment efficiency	Higher than classical liposomes	Typically higher than classical ethosomes	Typically higher than classical ethosomes
Skin permeation	Typically higher than classical liposomes	Typically equal to or higher than classical ethosomes	Typically higher than classical ethosomes
Stability	Stable than classical liposomes	Stable than classical Ethosomes	No particular trend determined

MECHANISM OF DRUG PENETRATION:

The main benefit of ethosomes above liposomes is the increased permeation of the drug. The mechanism of the drug absorption from ethosomes is obscure. The drug absorption probably occurs in following two phases:

1. Ethanol effect

2. Ethosomes effect

1. ETHANOL EFFECT:

Ethanol acts as a penetration enhancer through the skin. The mechanism of its penetration enhancing effect is well established. Ethanol penetrates into intercellular lipids and increases the fluidity of cell membrane lipids and decrease the density of lipid multilayer of cell membrane.

2. ETHOSOME EFFECT:

Increased cell membrane lipid fluidity caused by the ethanol of ethosomes results increased skin permeability. So the ethosomes permeates efficiently inside the deep skin layers, where it got fused with skin lipids and releases the drugs into deep layer of skin.[15, 16]

METHODS OF PREPARATION OF ETHOSOMES:

Ethosomal formulation may be prepared by hot or cold method as described below. Both the methods are convenient, do not require any sophisticated equipment and are easy to scale up at industrial level.

COLD METHOD:

In this method phospholipids, drug and other lipid materials are dissolved in ethanol in a covered vessel at room temperature by vigorous stirring with the use of mixer. Propylene glycol or other polyol is added during stirring. This mixture is heated to 30˚C in a water bath. The water heated to 30˚C in a separate vessel is added to the mixture, which is then stirred for 5 min in a covered vessel. The vesicle size of ethosomal formulation can be decreased to the desire extent using probe sonication or extrusion method. Finally, the formulation is stored under refrigeration.

HOT METHOD:

In this method phospholipid is dispersed 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 mixtures reach 40˚C, the organic phase is added to the aqueous one. The drug is dissolved in water or ethanol depending on its hydrophilic/

hydrophobic properties. The vesicle size of ethosomal formulation can be decreased to the desire extent using probe sonication or extrusion method.[9, 17]

CHARACTERIZATION PARAMETERS OF ETHOSOMES:

I. MORPHOLOGY OF ETHOSOMES:[18]

Using transmission electron microscopy (TEM) and scanning electron microscopy (SEM), visual imaging of ethosomes can be done. Vesicles obtained are flexible because of their improper round shape.

II. VESICLE SIZE AND ZETA POTENTIAL:[19]

Particle size of the ethosomes can be determined by dynamic light scattering (DLS) and photon correlation spectroscopy (PCS). Zeta potential of the formulation can be measured by Zeta meter.

III. ENTRAPMENT EFFICIENCY:[18]

The efficiency of the ethosomes to entrap the drug can be measured using the ultracentrifugation method. Ethosomes will be centrifuged at high speeds and the free drug present in the supernatant layer will be measured using a suitable analytical technique. %EE can be expressed as:

$$\%EE = [Qt – Qs/Qt] \times 100$$

Where, Qt = total theoretical amount of drug added and

Qs = amount of drug found in supernatant

IV. TRANSITION TEMPERATURE:[20]

The transition temperature of ethosomes can be measured by using differential scanning calorimetry (DSC).

V. STABILITY STUDIES:[21]

The stability of vesicles can be determined by assessing the size and structure of the vesicles over time. It means size is measured by DLS and a structural change is observed by TEM.

VI. SKIN PERMEATION DETERMINATIONS:[15, 22]

The ability of the ethosomes to penetrate the layers of the skin can be determined by using confocal laser scanning microscopy (CLSM).

VII. *IN-VITRO* DRUG RELEASE STUDY AND DRUG DEPOSITION STUDY:[18]

In-vitro drug release study and drug deposition can be performed by Franz diffusion cell with artificial or biological membrane and Dialysis bag diffusion.

CONCLUSION:

Ethosomes are the novel lipid carriers, which are non-invasive, soft, malleable vesicular delivery carriers that enable drugs to reach the deep skin layers or the systemic circulation and enhanced the delivery of active agents. Drugs with various physicochemical characteristics like hydrophilic, lipophilic or amphiphilic can be entrapped in these vesicular carriers. Ethosomes are simple to prepare, safe to use and these vesicles can be used for transdermal delivery of various classes of drugs. Hence, ethosomes possess promising future in effective transdermal delivery of drugs.

CONFLICT OF INTEREST: None

ACKNOWLEDGEMENT:

First and foremost, I would like to thanks Allah, the Almighty for giving me the courage, knowledge and ability to undertake this review and complete it satisfactorily. I express my heartfelt gratitude and respectful thanks to my guide and Principal, SJM College of Pharmacy, Chitradurga, Nagaraja T S for his guidance and for providing the necessary facilities to carry out the work. I express my heartfelt thanks and gratitude to Yogananda R, Maruthi N, Uma M, Chethan Patel D N and Suban Sab for their support and Guidance.

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