International Journal of ChemTech Research
CODEN (USA): IJCRGG, ISSN: 0974-4290, ISSN(Online):2455-9555
Vol.11 No.08, pp 219-226, 2018

Ethosomes: A Novel Approach For Transdermal Drug Delivery

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Abstract : Transdermal drug delivery technology generated tremendous excitement and interest amongst major pharmaceutical companies in the 1980s and 90s. Ethosomes are the ethanolic phospholipid vesicles which are used mainly for transdermal delivery of drugs. Ethosomes have higher penetration rate through the skin as compared to liposomes hence these can be used widely in place of liposomes. Ethosomes have become an area of research interest, because of its enhanced skin permeation, improved drug delivery, increased drug entrapment efficiency etc. The purpose of writing this review on ethosomes drug delivery was to compile the focus on the various aspects of ethosomes including their mechanism of penetration, preparation, advantages, composition, characterization, application and marketed product of ethosomes. Characterizations of ethosomes include Particle size, Zeta potential, Differential Scanning Calorimertry, Entrapment efficiency, Surface tension activity measurement, Vesicle stability and Penetration Studies etc.

Introduction:

Transdermal drug delivery system (TDDS) showed promising [1] result in comparison to oral drug delivery system as it eliminates gastrointestinal interferences and first pass metabolism of the drug but the main drawback of TDDS is it encounters the barrier properties of the stratum corneum i.e. only the lipophilic drugs having molecular weight < 500 Dacan pass through it.TDDS have been developed in order to enhance the driving force of drug diffusion or increase the permeability of the skin. These approaches [2] include the use of

DOI= http://dx.doi.org/10.20902/IJCTR.2018.110826

penetration enhancers, supersaturated systems, prodrugs, liposomes and other vesicles. One of the major advances in vesicle research was the finding that some modified vesicles possessed properties that allowed them to successfully deliver drugs in deeper layers of skin. Transdermal delivery is important because it is a noninvasive [3] procedure for drug delivery. Further, problem of drug degradation by digestive enzymes after oral administration and discomfort associated with parenteral drug administration can be avoided. It is the most preferred route for systemic delivery of drugs to pediatric, geriatric and patients having dysphasia.

The skin is a multi-layered structure [4] made up of stratum corneum (SC), the outermost layer, under which lies the epidermis and dermis. Within these layers of skin are interspersed fibroblasts, hair follicles and sweat glands that originate in the dermis blood supply. To overcome the stratum corneum barrier, various mechanisms have been investigated, including use of chemical or physical enhancers such as iontophoresis, sonophoresis, etc. Liposomes [5], niosomes, transferosomes and ethosomes [6] also have the potential of overcoming the skin barrier and have been reported to enhance permeability of drug through the stratum corneum barrier.Ethosomes are ethanolic liposomes.Ethosomes are defined as noninvasive delivery carriers that enable drugs to reach deep into the skin layers or systemic circulation. These are soft, malleable vesicles tailored for enhanced delivery of active agents. The vesicles have been well known for their importance in cellular communication and for many years. Vesicles would also allow controlling the release rate of drug over an extended time, keeping the drug shielded from immune response or other removal systems and thus be able to release just the right amount of drug and keep that concentration constant for longer [7] period of time.

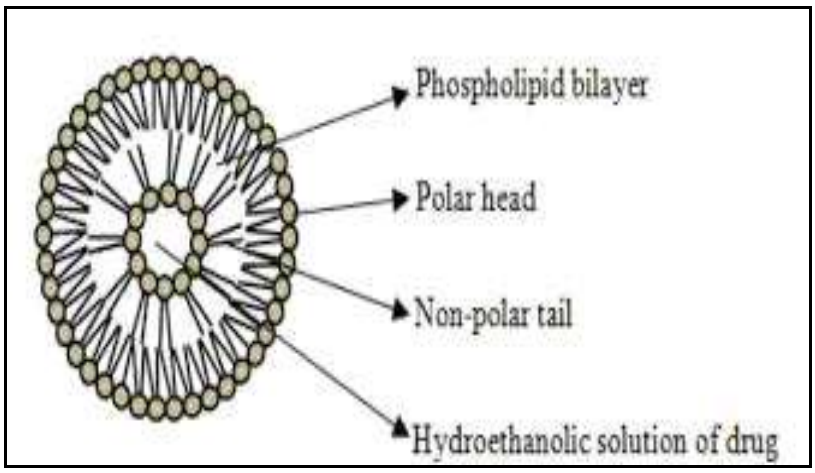

Figure 1:Structure of ethosome

Types of ethosomal systems

Classical ethosomes

Classical ethosomes are a modification of classical liposomes and are composed of phospholipids, a high concentration of ethanol up to 45% w/w, and water. Classical ethosomes were reported to be superior over classical liposomes for transdermal drug delivery because they were smaller and had negative ζ-potential and higher entrapment efficiency. Moreover, classical ethosomes showed better skin permeation and stability profiles compared to classical liposomes. **Binary ethosomes**

Binary ethosomes were developed by adding another type of alcohol to the classical ethosomes. The most commonly used alcohols in binary ethosomes are propylene glycol (PG) and isopropyl alcohol (IPA).

Transethosomes

This ethosomal system contains the basic components of classical ethosomes and an additional compound, such as a penetration enhancer or an edge activator (surfactant) in their formula. These novel vesicles were developed in an attempt to combine the advantages of classical ethosomes and deformable liposomes (transfersomes) in one formula to produce transethosomes.

Advantages of ethosomal drug delivery[8-10]

1. Delivery of large molecules (peptides, protein molecules) is possible.
2. It contains non-toxic raw material in formulation.
3. Enhanced permeation of drug through skin for transdermal drug delivery.
4. Ethosomal drug delivery system can be applied widely in Pharmaceutical, Veterinary, Cosmetic fields.
5. High patient compliance: The ethosomal drug is administrated in semisolid form (gel or cream) hence producing high patient compliance.
6. Simple method for drug delivery for comparison of Iontophoresis and Phonophoresis and other complicated methods
7. The Ethosomal system is passive, non-invasive and is available for immediate commercialization

Disadvantages of ethosomal drug delivery [11, 12]

1. They require high blood levels. It is limited only to potent molecules, those requiring a daily dose of 10mg or less.
2. It is not a means to achieve rapid bolus type drug input, rather it usually designed to offer slow, sustained drug delivery.
3. Adequate solubility of the drug in both lipophilic and aqueous environments 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.
5. It may not be economical.
6. Poor yield.
7. Skin irritation or dermatitis due to excipients and enhancers of drug delivery systems.

Composition of ethosomes [13, 14]

They are composed mainly of phospholipids, high concentration of ethanol and water. The high concentration of ethanol makes the ethosomesunique.Theethosomes are vesicular carrier comprise of hydroalcoholic or hydro/alcoholic/glycolic phospholipid in which the concentration of alcohols or their combination is relatively high. Typically, ethosomes may contain phospholipids with various chemical structures like phosphatidylcholine (PC), hydrogenated PC, phosphatidic acid (PA), phosphatidylserine (PS), phosphatidylethanolamine (PE), phosphatidylglycerol (PPG), phosphatidylinositol (PI), hydrogenated PC, alcohol (ethanol or isopropyl alcohol), water and propylene glycol (or other glycols). 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. Some preferred phospholipids are soya phospholipids such as Phospholipon 90 (PL90). It is usually employed in a range of 0.5-10% w/w. Cholesterol at concentrations ranging between 0.1-1% can also be added to the preparation. Examples of alcohols, which can be used, include ethanol and isopropyl alcohol. Among glycols, propylene glycol and Transcutol are generally used. 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 to concentration of the nonaqueous phase (alcohol and glycol combination) may range between 22 to 70%.

Table 1: Composition of ethosomes

S.No	Materials	Examples	Uses
1	Phospholipid	Soya Phosphatidyl Choline Egg Phosphatidyl Choline Dipalmitylphosphatidyl Choline Distearylphosphatidyl Choline	Vesicles Forming Component
2	Polyglycol	Propylene Glycol TranscutolRtm	As A Skin Penetration Enhancer
3	Alcohol	Ethanol Isopropyl Alcohol	For Providing The Softness For Vesicle Membrane As A Penetration Enhancer
4	Cholesterol	Cholesterol	For Providing The Stability To Vesicle Membrane

5	Dye	Rhodamine-123 Rhodamine Red Fluorescenisothiocynate (Fitc) 6-Carboxy Fluorescence	Rhodamine-123 Rhodamine Red Fluorescenisothiocynate (Fitc) 6- Carboxy Fluorescence
6	Vehicle	Carbopol 934	As A Gel Former

Methods of preparation of ethosomes [15, 16]

Ethosomes can be prepared by two very simple and convenient methods such as cold method and hot method.

- **Cold Method** :

In this method phospholipid, 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 30^0C in a water bath. The water heated to 30^0C 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 desire extend using sonicationor extrusion method. Finally, the formulation is stored under refrigera

- **Hot method**

In this method phospholipid is dispersed in water by heating in a water bath at 40^0C until a colloidal solution is obtained. In a separate vessel ethanol and propylene glycol are mixed and heated to 40^0C. Once both mixtures reach 40^0C, 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.

Characterisation of ethosomes [17-19]

1.Vesicle shape:

Transmission Electron Microscopy (TEM) And Scanningelectronic Microscopy (SEM) are used to characterize the surface morphology of the ethosomal vesicles.

2.Vesicle size and Zeta potential:

Particle size and zeta potential can be determined by dynamic light scattering (DLS) using a computerized inspection system and photon correlation spectroscopy (PCS).

3. Entrapment Efficiency:

Ultracentrifugation technique is used to measure the entrapment efficiency of ethosomes. The vesicles are separated in a high speed cooling centrifuge at 20,000 rpm for 90 minutes maintaining the temperature at 4°C.Separate the sediment and Supernatant liquids. Determine the amount of drug in the sediment by lysing the vesicles usingmethanol. The entrapment efficiency by the following equation

Entrapment efficiency= $\frac{De}{Dt} \times 100$…… (1)

De - Amount of drug in the ethosomal sediment Dt - Theoretical amount of drug used to prepare the formulation (Equal to amount of drug in supernatant liquid and in the sediment)

4.Transition Temperature:

The transition temperature of the vesicular lipid systems can be determined by using differential scanning calorimetry.

5.Drug content:

Drug content of the ethosomes can be determined using UV spectrophotometer. This can also be quantified by a modified high performance liquid chromatographic method.

6. Surface tension measurement:

The surface tension activity of drug in aqueous solution can be measured by the ring method in a Du Nouy ring tensiometer.

7.Stability studies:

The ability of ethosomal formulations to retain the drug was checked by keeping the preparations at different temperatures, *i.e.*25±2°C, 37±2°C and 45±2°C for different periods of time. The stability of ethosomes can also be determined quantitatively by monitoring size and morphology of the vesicles using DLS and TEM.

8.Skin permeation studies:

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

Application of ethosomes[20, 21]

1.Treatment of microbial and viral skin infections

Ethosomal systems containing antibiotic drugs have beeninvestigated in the treatment of various skin infections. Bacitracin and erythromycin ethosomal systems were formulated and tested for their efficiency in animal modelsof deep skin infections.

2.Anti-inflammatory ethosomal systems

Ammonium glycyrrhizinate (AG) ethosome was tested by Paolino and colleagues for the treatment ofinflammatory-based skin diseases on human volunteers with methyl-nicotinate chemically induced erythema.The anti-inflammatory effect of ethosomal AG system following either pre-treatment or treatment of skin erythemawas compared to aqueous or hydroethanolic drug solutions and evaluated by a reflectance visible spectrophotometerused for the quantification of the erythema index. Results showed that AG ethosomes induced a significant reduction in the intensity and the duration of erythemawith respect to the other formulations.

3.Ethosomal Systems for Menopausal Syndromes

Ethosomal compositions have been tested for their efficiencyin the treatment of androgen deficiency associatedwith menopause in men and menopausal syndromesin women. A testosterone ethosomal patch system, Testosome, was designed for the treatment of androgen deficiency in men. An *in vivo* study, comparing testosteroneserum levels in rabbits, following single or multiple(once a day for five days) application from either Testosome or Testoderm® patch (Alza) was carried out. Results of single patch application showed no significantdifferences between the tested groups.

4. Management of Erectile Dysfunction

In an "in-office" pilot clinical study, carried out on 16 menwith 17 episodes of erectile dysfunction, patients were treated with ethosomal prostaglandin E1 (PGE1_ systemsapplied on the glans penis.23 The patients were asked toevaluate their ability to have sexual intercourse by scoringthe erectile response, in addition to erection assessment by a physician. The effect was furthertested by Duplex examination of the cavernous arteries15 minutes following the application, in order to assessPeak-Systolic Velocity (PSV) and Pulsative index (PI) ofboth left and right cavernous arteries. The durationof the erection was recorded. Results of this study showed that following a single topical application of PGE1ethosomal system, enhanced penile rigidity and improvedpeak systolic velocity were observed in 12 patients out of15 men tested.

5. Analgesic and Antipyretic Ethosomal Systems

A recent study investigated the *in vivo* analgesic andantipyretic therapeutic effects of transdermal ethosomal ibuprofen in two animal models, the Brewer's yeastinduced fever rat and tail flick nociception mice.24 Applicationof ibuprofen gel on the animal skin resulted in agradual decrease in the body temperature of fevered rats, The analgesic effect of ethosomal ibuprofen gel wascompared to oral treatment by tail flick test in mice. A statisticallysignificant higher effect was obtained for theethosomal ibuprofen system 120 and 360 min after administration.The duration of effect was at least 6 h.

6. Topical Delivery of DNA

Many environmental pathogens attempt to enter the body through the skin. Skin therefore, has evolved into an excellent protective barrier, which is also Immunologically active and able to express the gene. On the basis of above facts another important application of ethosomes is to use them for topical delivery of DNA molecules to express genes in skin cells. Touitou et al. in their study encapsulated the GFP-CMV-driven transfecting construct into ethosomal formulation. They applied this formulation to the dorsal skin of 5-week male CD-1 nude mice for 48 hr. After 48 hr, treated skin was removed and penetration of green fluorescent protein (GFP) formulation was observed by CLSM. It was observed that topically applied ethosomes-GFP-CMV-driven transfecting construct enabled efficient delivery and expression of genes in skin cells. It was suggested that ethosomes could be used as carriers for gene therapy applications that require transient expression of genes.

Marketed formulations of ethosomes [22]

A variety of products to the market founded on ethosomes delivery system were listed below.

Table 1: List of marketed products of Ethosomes

S. No	Products	Applications	Manufacturer
1.	**Cellutight EF**	Topical cellulite cream, contains a powerful combination of ingredients to enhance metabolism and breakdown of the fat	Hampden Health, USA
2.	**Decorin Cream**	Anti aging cream, treating, repairing, and delaying the visible aging signs of the skin including wrinkle lines, sagging age spots, loss of elasticity, and hyperpigmentation	Genome Cosmetics, Pennsylvania, US
3.	**Nanominox**	First minoxidil containing product, which uses ethosomes. Contain 4% Minoxidil, well known hair growth promoter that must be metabolized by sulfation to the active compound	Sinere, Germany
4.	**Noicellex**	Topical anti – cellulite cream	Novel Therapeutic Technologies, Israel
5.	**Skin genuity**	Powerful cellulite buster, reduces orange peel	Physonics, Nottingham, UK
6.	**Supravir Cream**	For the treatment of herpes virus, formulation of acyclovir drug has a long shelf life with no stability problems, stable for at least three years, at 25^0C. Skin permeation experiments showed that the cream maintained its initial permeation enhancing properties even after three years	Trima, Israel

Conclusion:

Ethosomal carriers opens new challanges and opprtunities for the development of novel improved therapies. Ethosomes are soft, malleable vesicle and potenial carrier for transportation of drugs. Ethosomes are characterised by simplicity in their preparation, saftey and efficacy and can be tailored for enchanced skin permeation of active drugs. Ethosomes have been found to be much more efficient at delivering drug to the skin ,than either liposomes or hydroalcholic solution. It can be easily concluded that ethosomes can provide better skin permeation than liposomes. The main limiting factor of transdermal drug delivery system i.e. epidermal barrier can be overcome by ethosomes to significant extent.

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