Review Article

Ethiosomes - Novel Drug Delivery

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ABSTRACT

Transdermal drug delivery system was first introduced more than 30 years ago. The technology generated tremendous excitement and interest amongst major pharmaceutical companies in the 1980s and 90s. By the mid to late 1990s, the trend of transdermal drug delivery system merged into larger organizations. Skin acts as a major target as well as a principal barrier for topical/transdermal drug delivery. 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 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.

Keywords: Ethosome, Ethanol, Transdermal delivery, Phospholipid, Vesicle.

INTRODUCTION

The skin is one of the most extensive and readily accessible organs of the human body and the skin as a route of drug delivery can offer many advantages over traditional drug delivery systems including lower fluctuations in plasma drug levels, avoidance of gastrointestinal disturbances and first-pass metabolism of the drugs, and high patient compliance. One of the greatest disadvantages to transdermal drug delivery is the skin's low permeability that limits the number of drugs that can be delivered in this manner. The skin offers an excellent barrier to molecular transport, as stratum corneum is the most formidable barrier to the passage of most of the drugs, except for lipophilic and low molecular weight drugs. For transdermal and topical drug delivery system to be effective, the drug must obviously be able to penetrate the skin barrier andreach the target site . During the past several decades, researchers have developed numerous techniques to weaken or disrupt the skin barrier and deliver drugs into the body through the intact skin. Chemical skin permeation enhancers, iontophoresis, sonophoresis, electroporation, microneedles, and many other methods have been investigated to increase the efficacy of transdermal transport. Owing to their limited efficacy, resulting skin irritation,complexity of usage, and or high cost, none of these methods have been broadly applied to date. Lipid-based suspensions such as liposomes, niosomes, and microemulsions, have also been proposed as low- risk drug carriers, but they do not offer much value in transdermal drug delivery because they do not deeply penetrate the skin, but rather remain on the upper layers of skin strata.

Several researchers have developed novel elastic lipid vesicular systems in order to deeply and easily penetrate through the skin. Phospholipids, ethanol, bile salts and many surfactants have been used to prepare these elastic vesicles. The high flexibility of vesicular membranes allows these elastic vesicles to squeeze themselves through the pores in stratum corneum, which are much smaller than their vesicular sizes In 1992, Cevc et al introduced the first generation elastic lipid vesicular carrier, Transfersomes, mainly consisting of phospholipids and an edge

activator (non-ionic surfactant). They were reported to penetrate intactskin and able to deliver the drug into and across the skin, when applied under non-occlusive conditions[1].

STRUCTURE OF SKIN

Stratum corneum is the outermost layer of the epidermis. It consists of 10 to 25 layers of dead, elongated, fully keratinized corneocytes, which are embedded in a matrix of lipid bilayers. It has been shown that the stratum corneum is the main barrier to penetration through the skin. When a topical formulation is placed on the skin, the active drug is required to penetrate through the stratum corneum into the viable tissue. The limiting factor for these processes is the slow diffusion through the dead horny layer of skin. Stratum corneum behaves as a hydrophobic membrane. The rates of permeation of skin by low and high molecular weight organic nonelectrolytes are mostly determined within the stratum corneum[1].

3. Ethosomes

They are mainly used for the delivery of drugs through transdermal route. Drug can be entrapped in ethosomes which have various physicochemical characteristics *i.e.* hydrophilic, lipophilic, or amphiphilic (Verma and Fahr, 2004; Bhalaria *et al* 2009). Ethosomes are soft, malleable vesicles used for delivery of drugs to reach the deep skin layers and/or the systemic circulation. The size range of ethosomes may vary from tens of nano meters to microns (*μ*) (Patel, 2007). Ethosomes are the modified forms of liposomes that are high in ethanol content (Figure 1). The ethosomal system is composed of phospholipid (Phosphatidylcholine, phosphatidylserine, phosphatitidic acid), high concentration of alcohol (ethanol and isopropyl alcohol) and water. The high concentration of ethanol makes ethosomes unique because ethanol causes disturbance of skin lipid bilayer organization, hence when incorporated into a vesicle membrane, it enhances the vesicles' ability to penetrate the stratum corneum[2].

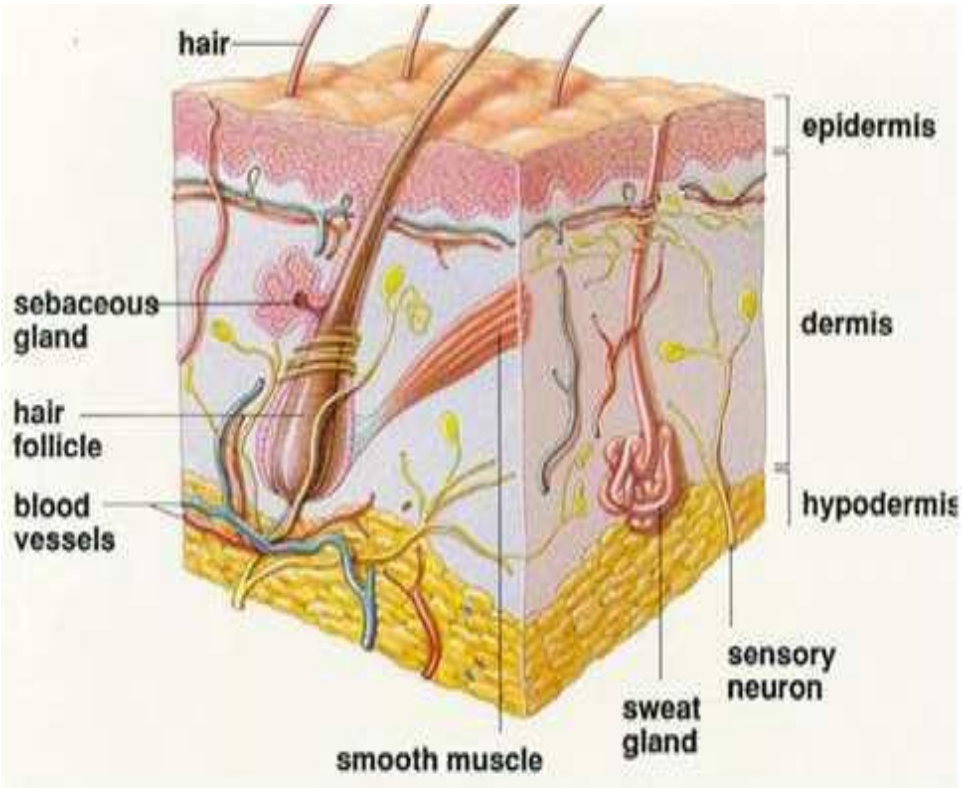

Fig. 1: Structure Of Skin

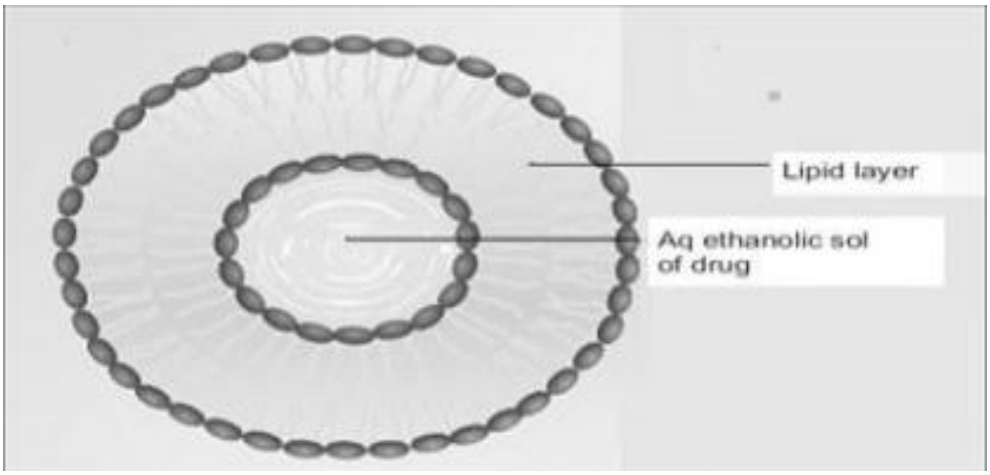

Fig. 2: Representation of ethosomes contents

4. MECHANISM OF DRUG PENETRATION

It is thought that the first part of the mechanism is due to the 'ethanol effect' whereby intercalation of the ethanol into intercellular lipids increasing lipid fluidity and decreases the density of the lipid multilayer. This is followed by the 'ethosome effect', which includes inter lipid penetration and permeation by the opening of new pathways due to the malleability and fusion of ethosomes with skin lipids. Absorption of ethosomes is still not clear.

The drug absorption probably occurs in following two phases

1. Ethanol effect
2. Ethosomes effect

1. ETHANOL EFFECT

Ethanol is major ingredient and acts as a penetration enhancer during the skin. The mechanism of its penetration enhancing effect is well known. Ethanol interacts with lipid molecules in the polar hard group region, resulting in a reducing the rigidity of the stratum corneum lipids, increasing their fluidity. The intercalation of ethanol into the polar head group environment can result in an increase in the membrane permeability. In addition to the effect of ethanol on stratum corneum structure, the ethosome itself may interact with the stratum corneum barrier[7].

2. ETHOSOMES EFFECT

Increased cell membrane lipid fluidity caused by the ethanol of ethosomes results increased skin permeability. In the case of ethosomes encapsulating drugs, the higher positive zeta potential imparted by the drug can improve skin attachment of the vesicles. While encapsulated drug in classic liposomes remained primarily at the surface of the skin the Ethosomal system was showed to be highly efficient carrier for enhanced drug delivery through the skin due to increased fluidity of the lipids[3].

5. Advantages of Ethosomes drug delivery

Ethosomal drug delivery system has much advantage as compared to other transdermal and dermal delivery systems. These advantages include enhanced permeation of drug through skin for transdermal drug delivery; Ethosomes provide platform for the delivery of large and diverse group of drugs across the skin (peptides, protein molecules); Ethosomes contain non-toxic materials in formulation, Ethosomal drug is administered in semisolid form (gel or cream) hence producing high patient compliance; Ethosomal drug delivery system can be used widely in pharmaceutical, veterinary, cosmetic fields; Ethosomal system is passive, non-invasive and is available for immediate commercialization; Ethosomal drug delivery is very simple in comparison to iontophoresis and phonophoresis and other complicated methods[4]

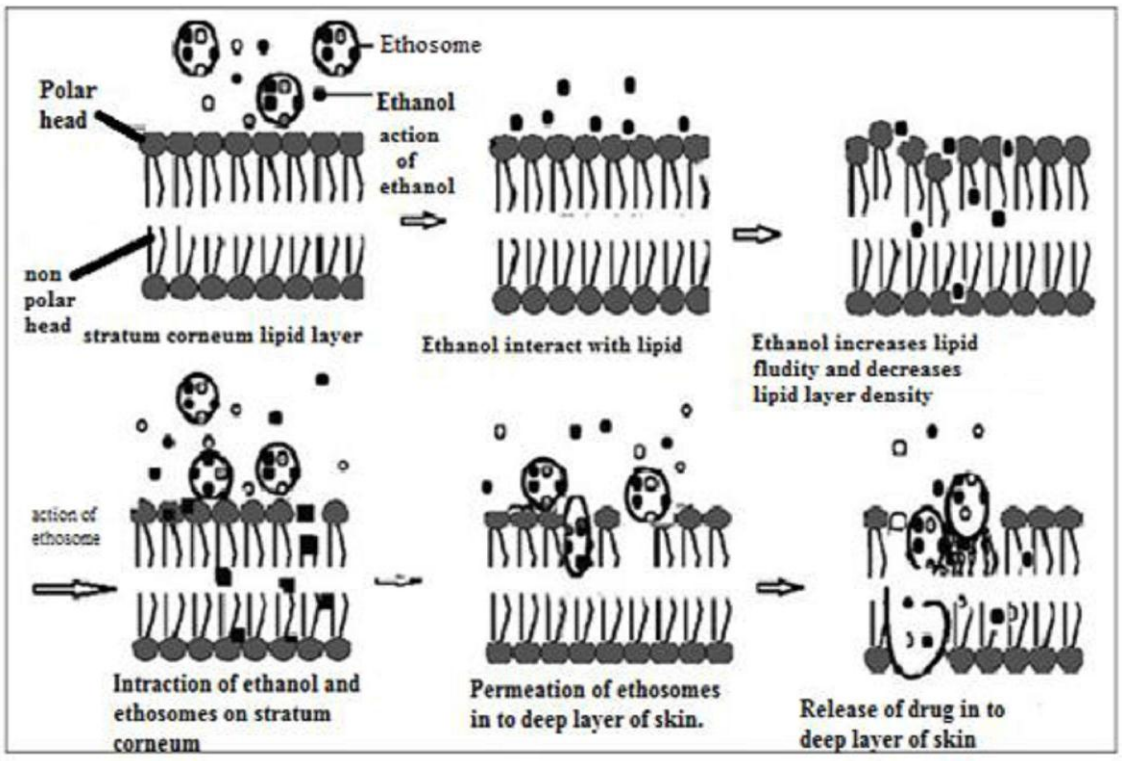

Fig. 3

6. Method of preparation

6.1. Cold method

This is the most common method utilized for the preparation of Ethosomal formulation. In this method, phospholipid, drug and other lipid materials is mixed.

Propylene glycol or other polyol is added during stirring. This mixture is heated to 300°C in a water bath. The water heated to 300°C in a separate vessel is added to the mixture, which is then stirred for 5 min in a covered vessel. The vesicles sizes can be decreased to desire extend using sonication or extrusion method. Finally, formulation is stored under refrigeration. [Fig. 3].

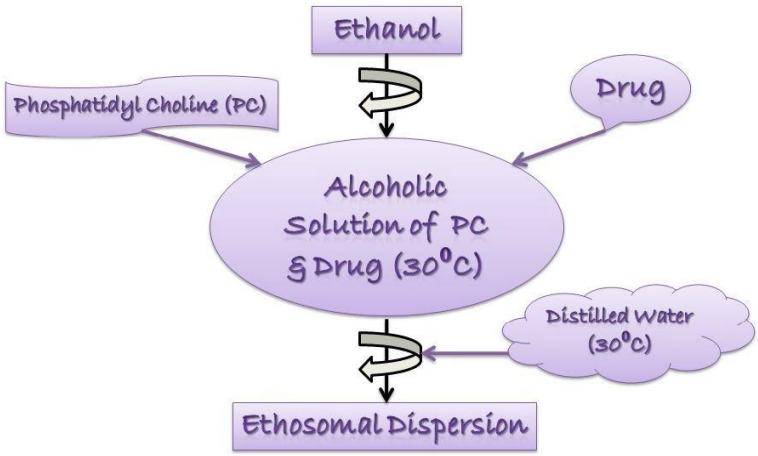

Fig. 4: Cold Method

6.2. Hot method

In this method, phospholipid is dispersed in water by heating in a water bath at 400°C until a colloidal solution is obtained. In a separate vessel ethanol and propylene glycol are mixed and heated to 400°C. Once both mixtures reach 400°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 desired extent using probe sonication or extrusion method[5].

CHARACTERIZATION OF ETHOSOMES

1. Visualization Visualization of Ethosomes can be done using transmission electron microscopy (TEM) and by scanning electron microscopy (SEM).

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. Phospholipid -ethanol interaction

Phospholipid-ethanol interaction determined by 31PNMR, Differential scanning calorimeter.

4. Surface tension activity measurement

Surface Tension Activity Measured by using Ring Method in a Du Nouy ring tensiometer.

5. Transition Temperature

Transition Temperature measured by Differential Scanning Calorimetry (DSC).

6. Drug deposition study

Drug deposition study carried out by using Franz diffusion cell.

7. Entrapment Efficiency

The entrapment efficiency of drug by ethosomes can be measured by the ultracentrifugation technique.

8. Transition Temperature

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

9. Tension Activity Measurement

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

10. Vesicle Stability

The stability of vesicles can be determined by assessing the size and structure of the vesicles over time. Mean size is measured by DLS and structure changes are observed by TEM.

11. Drug Content

Drug can be quantified by a modified high-performance liquid chromatographic method.

12. Penetration and Permeation Studies

Depth of penetration from ethosomes can be visualized by confocal laser scanning microscopy (CLSM).

13. Stability Study Stability of the vesicles was determined by storing the vesicles at 4°C ± 0.5°C. Vesicle size, zeta potential, and entrapment efficiency of the vesicles was measured after 180 days using the method described earlier[7].

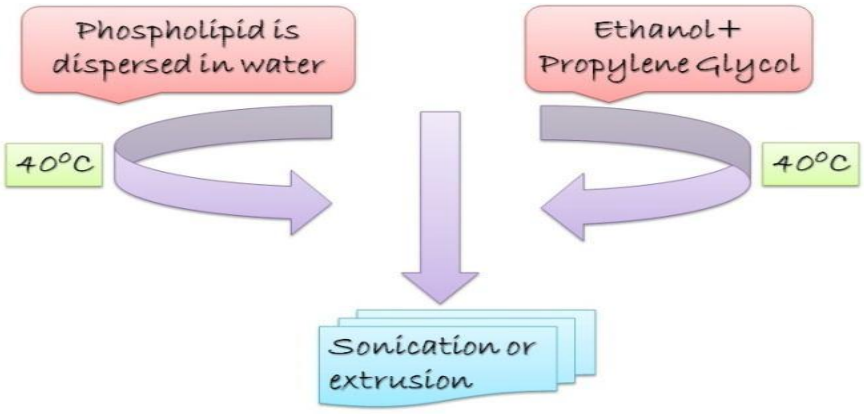

Fig. 5: Hot Method

Table 1: EVALUATION PARAMETERS[6]

Evaluation Parameters	Parameter	Importance	Method
1	Visicle size and shape	Determine skin penetration	SEM , TEM , DLS
2	Zeta potential	Stability of vesicles	Zeta meter
3	Entrapment efficiency	Stability of method	Ultracentrifugation
4	Drug content	Important in deciding the amount of vesicles preparation To be used.	UV , HPLC
5	Stability studies	To determine the shelf life of vesicle formulation	SEM , TEM , HPLC
6	*In vitro* dissolution	Determine the drug release rate from vesicle	Franz diffusion cell
7	Skin permeation	Determine rate of drug transport through skin	CLSM

Table 2: Example of ethosomes as a drug carrier[8]

S. No.	Drug	Purpose of ethosomal delivery	Application
1	Azelaic acid	Improves the sustained release	Treatment of acne
2	DNA	Expression into skin cells	Treatment of genetic disorders
3	Diclofenac	Selective targeting the cells	NSAIDS
4	Erythromycin	Better cellular uptake	Antimicrobial
5	Zidovudine	Better cellular uptake	Anti-HIV
6	Bacitracin	Better cellular uptake	Antibacterial
7	Insulin	GIT degradation	Treatment of diabetes
8	Trihexyphenidyl hydrochloride	4.5-times higher than that from liposome	Treatment of Parkinson's disease
9	Cannabidol	low bioavailability	Treatment of rheumatoid
10	Acyclovir	Poor skin permeation	Treatment of Herpes labialis
11	Enalapril maleate	Low oral bioavailability Major side effects in oral delivery	Treatment of Hypertension
12	Minoxidil	Pilocebaceous targeting Accumulation in skin increased	Treatment of baldness
13	Ammonium glycyrrhizinate	Poor skin permeation Poor oral bioavailability	Treatment of inflammatory based skin diseases
14	Fluconazole	Poor skin permeation	Treatment of candidiasis
15	Methotrexate	Poor skin permeation	Treatment of psoriasis
16	Salbutamol	Enhanced drug delivery through skin with ethosomes	Anti-asthmatic
17	Proteins and Peptides	Large molecules	overcoming the problems associated with oral delivery

CONCLUSION

The main disadvantage of transdermal drug delivery is the poor penetration of most compounds into the human skin. The main barrier of the skin is located within its uppermost layer, the stratum corneum. Ethosomal carrier gives opportunities and new challenges for the development of novel improved therapies .Ethosomes has initiated a new area in vesicular research for transdermal drug delivery which can provide better skin permeation than liposomes or hydro alcoholic solution. Ethosomes are soft, malleable vesicles and potential carrier for transportation of drugs. Ethosomes have been tested to encapsulate hydrophilic drugs, cationic drugs, proteins and peptides. Further, research in this area will allow better control over drug release *in vivo* and long term safety data, allowing the therapy more effective.

REFERENCES

1. Nandure HP, Puranik P, Giram P, Lone V ethosomes a novel drug carrier international journal of pharmaceutical research and allied science 2013 volume 2 issue 3 page no.18,19
2. Ghule AR, Shinkar DM, Saudagar RB ethosomes carrier for enhanced transdermal drug delivery system journal of advanced pharmacy and

research year 2014 vol 4 , issue 4 page no. 383
3. Chandel A, Patil V, Goyal R, Dhamija H , Parashar B Ethosomes– Radical Approach in Transdermal Drug Delivery. International journal of pharmaceutical and chemical sciences year 2012 vol 1(2) page no.565
4. Tyagi L, Kumar S, Maurya S , Kori M ethosomes novel vesicular carrier forenhanced transdermal drug delivery system bulletin of pharmaceuticalof research 2013 3(1) page no.6,7
5. Aute PP, Kamble MS, Chaudhari PD, Bhosale AV a comprehensive review on ethosome international journal of research and development in pharmacy in life sciences dec-jan 2012-13, vol 2 , no.1 page no. 220
6. Solanke P, Saboo S, Tidke P. Ehtosomes –radical approach in transdermal drug delivery jornal of current pharma research year 2016 vol 6 (2) page no .1788-1789
7. Patil R, Patil S, Patil S, Patil S ethosomes a versatile tool for novel drug delivery system journal of current pharma research year 2014 vol 4(2) 1176-1177
8. Parashar T, Soniya , Sachan R, Singh V, Singh G, Tyagi S, Patel C, et al Ethosomes: A recent vesicle of transdermal drug delivery system international jaournal of research and development in pharmacy and life sciences February –March 2013 vol 2, no.2, journal page no. 285
9. D. Akhiladevi , Sachinanandan Basak 2 ethosomes a noninvasive approach for transdermal drug delivery international journal of current pharmaceutical research 2010 vol 2 , issue 4 page no. 2.