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ETHOSOMES: A NOVEL VESICULAR DRUG DELIVERY SYSTEM

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ABSTRACT

Optimization of drug delivery through human skin is important in modern therapy. Recently, the transdermal route vied with oral treatment as the most successful innovative research area in drug delivery. Improved method of drug delivery for biopharmaceuticals is important for two reasons; these drugs represent rapidly growing portion of new therapeutics, and are most often given by injection. Discovery of new medicinal agents and related innovation in drug delivery system have not been only enabled the successful implementation of novel pharmaceutical, but also permitted the development of new medical treatment with existing drugs. Ethosomes are modified lipid carriers that enable drugs to reach into deeper skin layers and/or the systemic circulation. These are soft, malleable vesicles tailored for enhanced systemic delivery of drugs. Ethosomes represent a lipid vesicular carrier system embodying ethanol in relatively high concentration and are very efficient in delivering drugs into and across the skin. Unlike classic liposomes, that are known to mainly deliver drugs to outer layers of skin, ethosomes penetrate through the stratum corneum and deliver drugs to the deeper layers of skin.

Key words: Ethosomes, Lipid carriers, Drug delivery, Vesicular Drug Delivery System.

INTRODUCTION

TDDS are defined as self-contained, discrete dosage forms which when applied to the intact skin, deliver the drug through the skin, at a controlled rate to the systemic circulation.For transdermal delivery of drugs, stratum corneum is the main barrier for permeation of drug. Now-a-days liposomes, niosomes, transferosomes and ethosomes (vesicular and non- invasive drug delivery) are used to increase the permeation of drug through the stratum corneum.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 non-invasive 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. Hence, transdermal dosage forms enjoy being the most patient compliant mode of drug delivery.

Ethosomes are the slight modification of well established drug carrier liposome. They are soft, malleable lipid vesicles made of phospholipids and ethanol and water for enhanced delivery of active agents.

CHARACERISTIC FEATURES

⇒ They are developed by TOUITOU et al in 1997.
⇒ Size range: tens of nanometers to microns.
⇒ Compared to conventional liposomes they permeate more rapidly and possessed higher transdermal flux.
⇒ The synergistic effects of combination of phospholipids and high concentration of ethanol in vesicular formulations have been suggested to be responsible for deeper distribution and penetration in the skin lipid layers.

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⇒ Permeation enhancers are used to improve the permeability of the skin, so that the drugs can cross through the skin easily.
⇒ Ethosomes can entrap drug molecules with various physicochemical characteristics i.e., of hydrophilic, lipophilic or amphipilic.
⇒ The high concentration of ethanol in ethosomes causes disturbance of skin lipid bilayer organization hence it enhances the vesicles ability to penetrate the stratum corneum.
⇒ Also, because of their high ethanol concentration the lipid membrane is packed less tightly than the conventional vesicles, although it has equivalent stability, allowing a more malleable structure and includes the drug distribution ability in the stratum corneum lipids.
⇒ Ethosomal system is much more efficient at delivery a fluorescent probe to the skin in terms of quantity and capacity for molecule of various lyophilicities [17].

CROSS SECTION OF HUMAN SKIN

Skin is a multilayered organ complex in both structure and function. Macroscopically, the outer epidermis and the inner dermis are two distinct layers of the skin.

The layers of epidermis are:

- Stratum Corneum (Horny Layer)
- Stratum Lucidum(Clear Layer)
- Stratum Granulosum (Granular Layer)
- Stratum Spinosum (Prickly cell Layer)
- Malpighian Layer (pigment Layer)
- Stratum Germinativum (regenerative Layer)

Epidermis is the outermost layer of the skin, which is approximately 150 micrometers thick. Cells from lowers layers of the skin travel upward during their life cycle and become flat dead cells of the corneum. The epidermis is a multilayered structure consisting of viable cells and dead keratinized cells. The layer that interacts with the environment is the stratum corneum, or horny layer. The stratum corneum consists of many layers of compact, flat, dehydrated and keratinized cells. These cells are physiologically inactive and are continuously shed with constant replacement from the underlying viable epidermal tissue. The stratum corneum has a water content of only 20% as compared to the normal physiological level of 70%, such as in the physiologically active stratum germinativum (which is the regenerative layer of the epidermis).

Stratum Corneum

The stratum corneum (10-15µm thick) is the skin's primary defense layer against invasion .The major lipid classes within the stratum corneum are ceramides, cholesterol, and fatty acids. Their major structural components are aggregates of keratin filaments. All these contribute to tightness and impermeability characteristics of the skin.

Stratum Lucidum

In the palm of the hand and sole of the foot, a zone forms a thin, translucent layer immediately above the granule layer. The cells are non-nuclear.

Stratum Granulosum

This layer is above the keratinocytes. They manufacture the basic staining particle, the keratinohylline granules. This keratogenous or transitional zone is a region of intense biochemical activity and morphological change.

Stratum Spinosum

The cells of this layer are produced by morphological and histochemical alteration of the cells basal layers as they moved upward. The cells flatten and their nuclei shrink. They are interconnected by fine prickles and forms intercellular bridges- the desmosomes. These links maintain the integrity of the epidermis.

Malpighian Layer

The basal cells also include melanocytes which produce and distribute the melanin granules to the keratinocytes required for pigmentation - a protective measure against radiation.

Stratum Germinativum

Basal cells are nucleated, columnar. Cells of this layer have high mitotic index and constantly renew the epidermis and this proliferation in healthy skin balances the loss of dead horny cells from the skin surface.

- The human skin contains the dermis, approximately 2-3 mm thick, forms the bulk of the skin. The dermis contains a network of blood vessels, lymph vessels, hair follicles, sweat glands & sebaceous glands – skin appendages.
- Beneath the dermis is the hypodermis, which is primarily composed of fibroblasts and adipocytes - sub cutaneous fatty tissues. Bulbs of hair project into these fatty tissues.
- The hypodermis binds skin to the underlying structures, in addition to serving as a thermo regulator and a cushion to internal organs against trauma.
- The skin is interspersed with hair follicles and associated sebaceous glands and sweat glands. Collectively these are referred to as skin appendages.
- On an average of 10-70 hair follicles and 200-500 sweat ducts per square centimeter are present on the skin surface. These skin appendages occupy only 0.1% of the total human skin surface.

Advantages of Ethosomal Drug delivery

In comparison to other transdermal & dermal delivery systems,

a. Ethosomes are enhanced permeation of drug through skin for transdermal and dermal delivery.
b. Ethosomes are platform for the delivery of large and diverse group of drugs (peptides, protein molecules).

c. Ethosome composition is safe and the components are approved for pharmaceutical and cosmetic use.
d. **Low risk profile**-The technology has no large-scale drug development risk since the toxicological profiles of the ethosomal components are well documented in the scientific literature.
e. **High patient compliance**-The Ethosomal drug is administrated in semisolid form (gel or cream), producing high patient compliance by is high. In contrast, Iontophoresis and Phonophoresis are relatively complicated to use which will affect patient compliance.
f. High market attractiveness for products with proprietary technology. Relatively simple to manufacture with no complicated technical investments required for production of Ethosomes.
g. The Ethosomal system is passive, non-invasive and is available for immediate commercialization.
h. Various application in Pharmaceutical, Veterinary, Cosmetic field.

DISADVANTAGES OF ETHOSOMES

a. Drugs that require high blood levels cannot be administered – limited only to potent molecules, those requiring a daily dose of 10mg or less.
b. Ethosomal administration is not a means to achieve rapid bolus type drug input, rather it is usually designed to offer slow, sustained drug delivery.
c. Adequate solubility of the drug in both lipophilic and aqueous environments to reach dermal microcirculation and gain access to the systemic circulation.
d. The molecular size of the drug should be reasonable that it should be absorbed percutaneously.
e. Adhesive may not adhere well to all types of skin. Uncomfortable to wear.
f. May not be economical. Poor yield
g. Skin irritation or dermatitis due to excipients and enhancers of drug delivery systems.
h. In case if shell locking is ineffective then the ethosomes may coalescence and fall apart on transfer into water.
i. Loss of product during transfer from organic to water media.

MECHANISM OF DRUG PENETRATION [1]

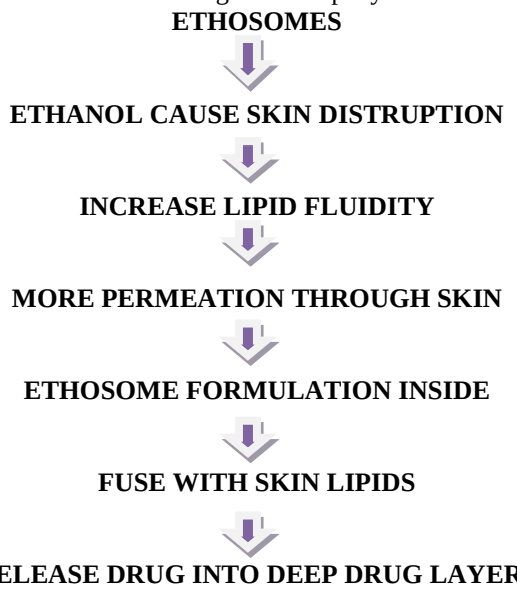
The main advantage of ethosomes over liposomes is the increase permeation of the drug. The mechanism of the drug absorption from ethosomes is not clear. The drug absorption probably occurs in following two phases:
1. Ethanol effect
2. Ethosomes effect

1. Ethanol effect

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

2. Ethosomes effect

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



APPLICATIONS OF ETHOSOMES

a. **Pilosebaceous Targeting**

Hair follicles and sebaceous glands are increasingly being recognized as potentially significant elements in the percutaneous drug delivery [3]. Furthermore, considerable attention has also been focused on exploiting the follicles as transport shunts for systemic drug delivery. With the purpose of pilosebaceous targeting, Maiden et al. prepared and evaluated minoxidil ethosomal formulation.

b. **Transdermal Delivery of Hormones**

Oral administration of hormones is associated with problems like high first pass metabolism, low oral bioavailability and several dose dependent side effects. The risk of failure of treatment is known to increase with each pill missed [4]. Touitou *et al.* compared the skin permeation potential of testosterone Ethosomes (Testosome) across rabbit pinna skin with marketed transdermal patch of testosterone (Testoderm¨ patch, Alza). They observed nearly 30-times higher skin permeation of testosterone from ethosomal formulation as compared to that marketed formulation.

c. **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 indicated better skin permeation potential of ethosomal-THP formulation and its use for better management of Parkinson disease.

d. **Transcellular Delivery**

Touitou *et al.* in their study demonstrated better intracellular uptake of bacitracin, DNA and erythromycin using CLSM and FACS techniques in different cell lines. Better cellular uptake of anti-HIV drug zidovudine and lamivudine in MT-2 cell line from ethosomes as compared to the marketed formulation suggested ethosomes to be an attractive clinical alternative for anti-HIV therapy [5].

e. **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. These results also showed the possibility of using ethosomes for effective transdermal immunization. Gupta et al. recently reported immunization potential using transfersomal formulation. Hence, better skin permeation ability of ethosomes opens the possibility of using these dosage forms for delivery of immunizing agents.

f. **Delivery of Anti-Arthritis Drug**

Topical delivery of anti-arthritis drug is a better option for its site-specific delivery and overcomes the problem associated with conventional oral therapy. Cannabidol (CBD) is a recently developed drug candidate for treating rheumatoid arthritis. Lodzki *et al.* prepared CBD-ethosomal formulation for transdermal delivery. Results shows significantly increased in biological anti-inflammatory activity of CBD-ethosomal formulation was observed when tested by carrageenan induced rat paw edema model. It was concluded encapsulation of CBD in ethosomes significantly increased its skin permeation, accumulation and hence it's biological activity.

g. **Delivery Antibiotics**

Topical delivery of antibiotics is a better choice for increasing the therapeutic efficacy of these agents. Conventional oral therapy causes several allergic reactions along with several side effects. Conventional external preparations possess low permeability to deep skin layers and subdermal tissues [6]. Ethosomes can circumvent this problem by delivering sufficient quantity of antibiotic into deeper layers of skin. Ethosomes penetrate rapidly through the epidermis and bring appreciable amount of drugs into the deeper layer of skin and suppress infection at their root. With this purpose in mind Godin and Touitou prepared bacitracin and erythromycin loaded ethosomal formulation for dermal and intracellular delivery. The results of this study showed that the ethosomal formulation of antibiotic could be highly efficient and would overcome the problems associated with conventional therapy.

h. **Delivery of Anti-Viral Drugs**

Zidovudine is a potent antiviral agent acting on acquired immunodeficiency virus. Oral administration of zidovudine is associated with strong side effects. Therefore, an adequate zero order delivery of zidovudine is desired to maintain expected anti-AIDS effect [7]. Jain *et al* [8] concluded that ethosomes could increase the transdermal flux, prolong the release and present an attractive route for sustained delivery of zidovudine.

Acyclovir is another anti-viral drug that widely used topically for treatment of Herpes labialis [9]. The conventional marketed acyclovir external formulation is associated with poor skin penetration of hydrophilic acyclovir to dermal layer resulting in weak therapeutic efficiency. It is reported that the replication of virus takes place at the basal dermis. To overcome the problem associated with conventional topical preparation of acyclovir [10], Horwitz *et al.* [11] formulated the acyclovir ethosomal formulation for dermal delivery. The results showed that shorter healing time and higher percentage of abortive lesions were observed when acyclovir was loaded into ethosomes.

Delivery of Problematic drug molecules

The oral delivery [12] of large biogenic molecules such as peptides or proteins is difficult because they are completely degraded in the GI tract. Non-invasive delivery of proteins is a better option for overcoming the problems associated with oral delivery. Dkeidek and Touitou investigated the effect of ethosomal insulin delivery in lowering blood glucose levels (BGL) *in vivo* in normal and diabetic SDI rats. In this study a Hill Top patch containing insulin ethosomes was applied on the abdominal area of an overnight fated rat. The result showed that insulin delivered from this patch produced a significant decrease (up to 60%) in BGL in both normal and diabetic rats. On the other hand, insulin application from a control formulation was not able to reduce the BGL.

Verma and Fahr [13] reported the cyclosporin. An ethosomal formulation for the treatment of inflammatory skin disease like psoriasis, atopic dermatitis and disease of hair follicle like alopecia areata etc. Paolino *et al* [14],

investigated the potential application of ethosomes for glycyrrhizinate is naturally occurring triterpenes obtained from Glycyrrhizinate Glabra and useful for the treatment of various inflammatory based skin diseases [15].

COMPOSITION OF ETHOSOMES

- The ethosomes 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) [16].
- 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 (PL-90). 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 too. The concentration of alcohol in the final product may range from 20 to 50%.
- The concentration of the non-aqueous phase (alcohol and glycol combination) may range between 22 to 70%.

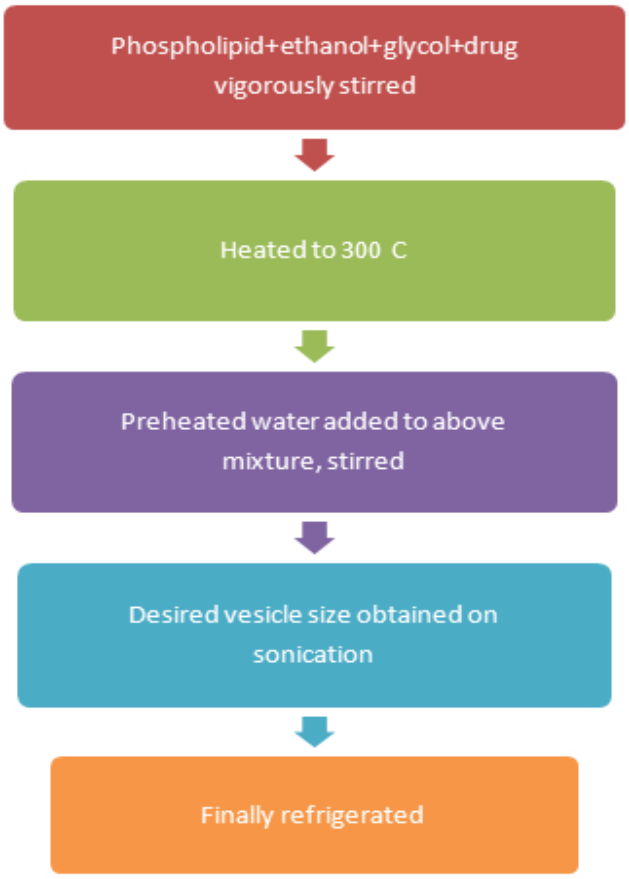
Influence of high alcohol content

- Ethanol is an established efficient permeation enhancer [18] and is present in quite high concentration (20-50%) in ethosomes. However, due to the interdigitation effect of ethanol on lipid bilayers, it was commonly believed that vesicles could not coexist with high concentration of ethanol [19].
- Touitou [20] discovered and investigated lipid vesicular systems embodying ethanol in relatively high concentration and named them ethosomes.
- The basic difference between liposomes and ethosomes lies in their composition. The synergistic effect of combination of relatively high concentration of ethanol (20-50%) in vesicular form in ethosomes was suggested to be the main reason for their better skin permeation ability.
- The high concentration of ethanol (20-50%) in ethosomal formulation could disturb the skin lipid bilayer dermal delivery of ammonium glycyrrhizinate. Ammonium organization. Therefore, when integrated into a vesicle membrane, it could give an ability to the vesicles to penetrate the SC.
- Furthermore, due to high ethanol concentration the ethosomal lipid membrane was packed less tightly than conventional vesicles but possessed equivalent stability. This allowed a softer and malleable structure giving more freedom and stability to its membrane, which could squeeze through small openings created in the disturbed SC lipids [21].
- In addition, the vesicular nature of ethosomal formulations could be modified by varying the ratio of components and chemical structure of the phospholipids. The versatility of ethosomes for systemic delivery is evident from the reports of enhanced delivery of quite a few drugs like acyclovir [22], minoxidil [23], triphexyphenidyl [24], testosterone [25], cannabidol [26] and zidovudine [27].

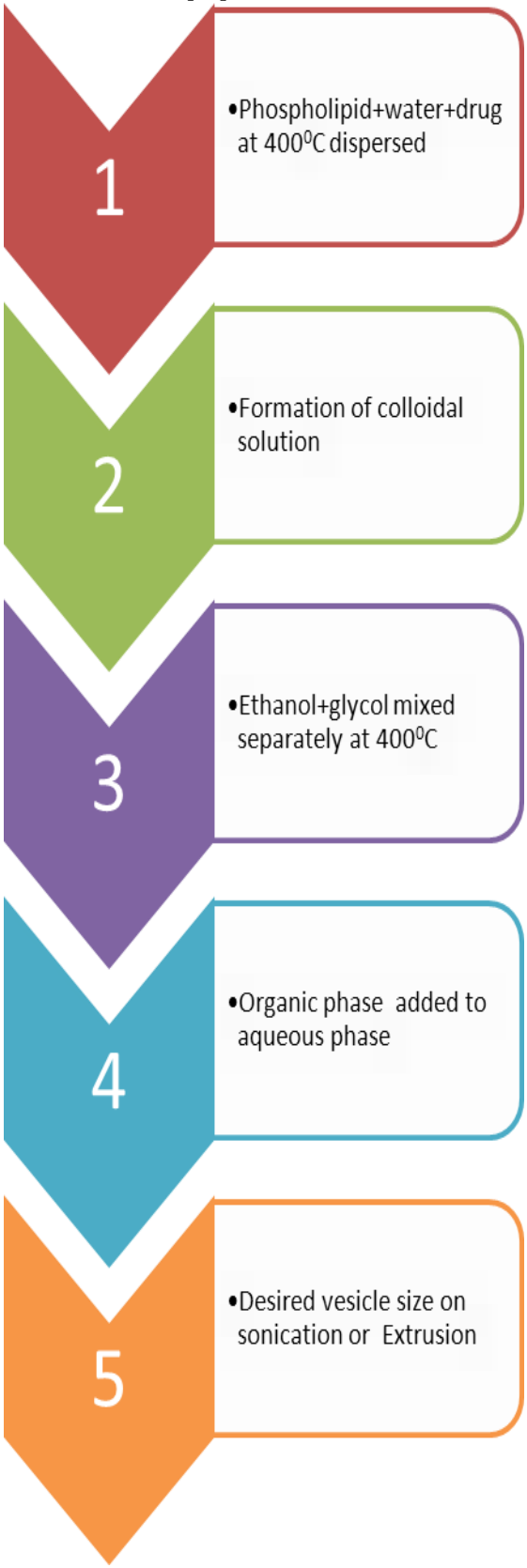
METHODS OF PREPARATION

1. Cold method
2. Hot method
3. Classic mechanical dispersion method
4. Classic method

COLD METHOD

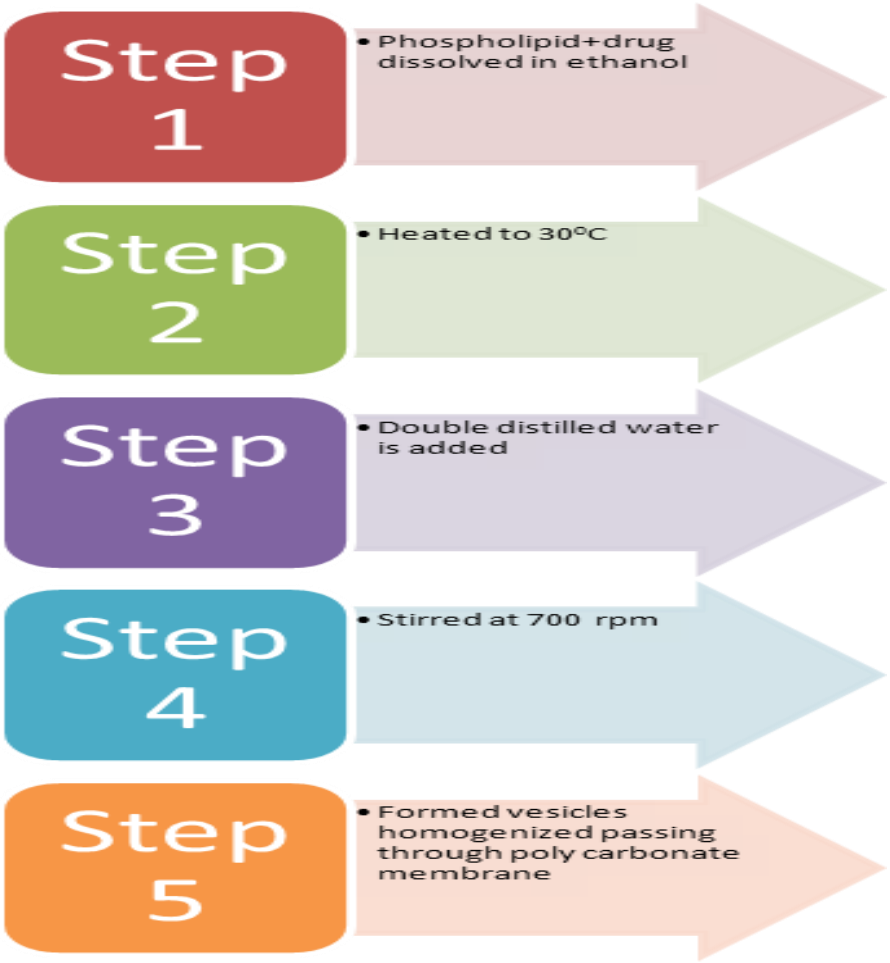


HOT METHOD [28]



CLASSIC MECHANICAL DISPERSION METHOD [29]

CLASSIC METHOD [30]



METHODS OF CHARACTERIZATION

a. Visualization

Visualization of ethosomes can be done using transmission electron microscopy (TEM) and by scanning electron microscopy (SEM) [31]. Visualization by electron microscopy reveals an ethosomal formulation exhibited vesicular structure 300-400 nm in diameter.

b. Scanning electron microscopy (SEM)

Different lipid types might influence the surface morphology or shape of the particles. Solid lipid microparticle suspensions were deposited on metallic stubs then placed in liquid nitrogen and dried under vacuum. The freeze-dried microparticles were coated uniformly with gold. It is characterized for morphology and surface properties using a scanning electron microscope.

c. Entrapment Efficiency

The entrapment efficiency of drug by ethosomes can be measured by the ultracentrifugation technique [32].The chemical nature of the lipid is an important factor in determining the EE of drug in the SLM because lipid which forms highly crystalline particles with a perfect lattice lead to drug expulsion. On the other hand, the imperfection (lattice defects) of the lipid structure could offer space to accommodate the drug. The percentage EE ranged from 80.7–95.7%.The lost or unentrapped drug could be due to the solubility of the drug in the water–poloxamer phase. Also reported a reduction in drugentrapment in the presence of poloxamer. Dayan and Touitou [33] have shown that entrapment efficiency of trihexyphenidyl hydrochloride increased from 36% for liposomes to 75% for ethosomes.

d. Differential scanning calorimertry (DSC)

Transition temperature (Tm) of the vesicular lipid systems was determined by using the Mettler DSC 60 computerized with Mettler Toledo star software system (Mettler, Switzerland).The transition temperature was measured by using the aluminium crucibles at a heating rate 10 degree/minute within a temperature range from 20º-300ºC.

e. 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) [34]. The size of ethosomes ranges between tens of nanometers to microns and is influenced by the

composition of the formulation. Zeta potential is an important and useful indicator of particle surface charge, which can be used to predict and control the stability. In general, particles could be dispersed stably when the absolute value of zeta potential was above30mV due to the electric repulsion between particles.

f. Drug Content

Drug can be quantified by a modified high performance liquid chromatographic method [35].

g. Surface 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 [36].

h. **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 [37].

i. **Transition Temperature**

The transition temperature of the vesicular lipid systems can be determined by using differential scanning calorimetry [38].

j. **Penetration and Permeation Studies**

Depth of penetration from ethosomes can be visualized by confocal laser scanning microscopy (CLSM) [39].

STABILITY PARAMETERS

- Stability was evaluated in terms of the entrapment capacity and the particle size for a specified period.
- Basically, the proper choice of the lipid composition appeared to be an important factor in obtaining stable ethosomes dispersions with optimum pharmaceutical and therapeutic characteristics.
- In case of liposomes, upon storage, many different changes could occur. Liposomes tend to fuse and grow into bigger vesicles and this fusion and breakage of liposomes on storage pose an important problem of drug leakage from the vesicles. The absence of electrostatic repulsion is likely to a account for the tendency of neutral liposomes to aggregate, but in case of ethosomes, ethanol causes a modification of the net charge of the system and confers it some degree of steric stabilization leading to increased stability of dispersion against agglomeration that may also lead to a decrease in the mean vesicle size.
- Increasing the concentration of ethanol from 15 to 45% increases the entrapment efficiency owing to an increase in fluidity of the membranes. However, a further increase in the ethanol concentration (>45%) probably makes the vesicle membrane more leaky, thus leading to a decrease in entrapment efficiency. Therefore it causes destabilization of the ethosomes.
- The lipid portion of the ethosomes is derived from natural and / or synthetic phospholipid sources. Phospholipids containing unsaturated fatty acids are known to undergo oxidative reactions. The reaction products can cause permeability changes in the ethosomes bilayers.
- Oxidative degradation of the lipids in general can be minimized by protecting the lipid preparation from light, by adding anti-oxidants such as alpha tocopherol.
- Furthermore, hydrolysis of lipids leads to the formation of lyso-PC. The presence of lyso-PC enhances the permeability of ethosomes and thus, it is essential to keep its level to a minimum in a given preparation.

Fig 1. Structure of Ethosomes

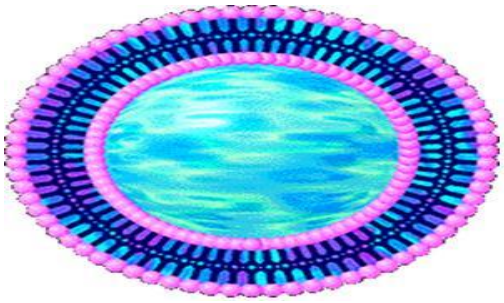


Fig 2 . Ethosomes

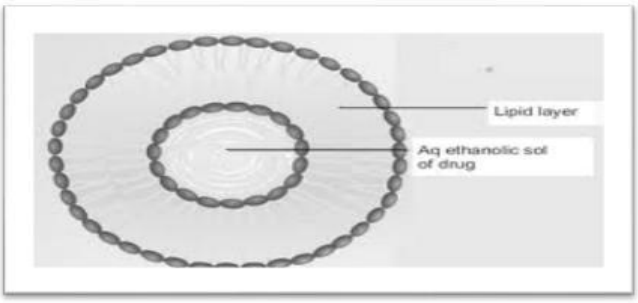


Fig 3. Layer of Skin

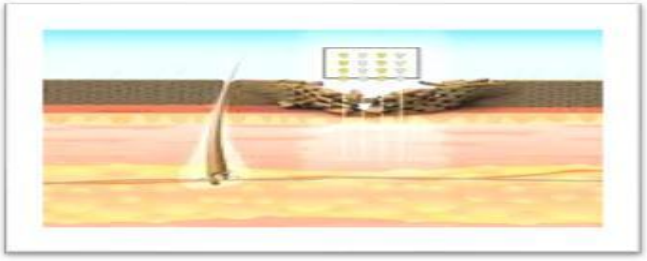


Fig4. T.S of Skin layer

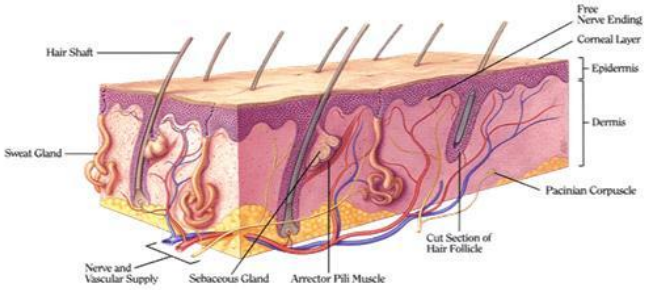


Fig 5. Proposed mechanism for penetration of molecule from ethosomal system across the lipid domain of stratum corneum [2]

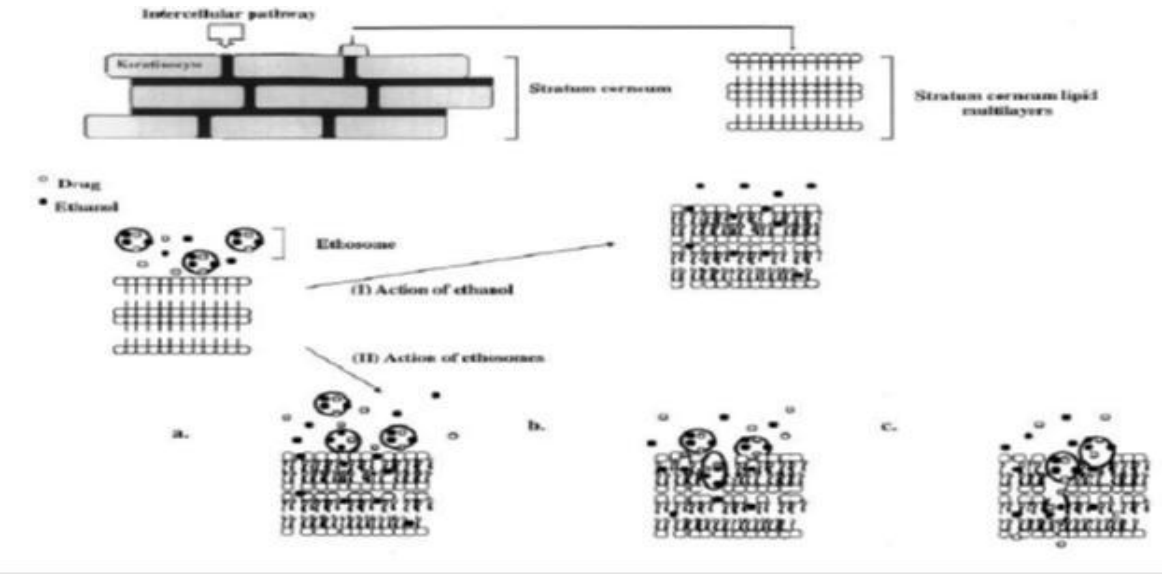


Table 1. Ethosomes as a carrier of various drug molecules has been listed below

DRUG	APPLICATIONS	COMMENTS
Acyclovir	Treatment of Herpetic infection	Improved drug delivery
Zidovudine	Treatment of AIDS	Improved transdermal flux
Trihexypenidyl HCl	Treatment of Parkinsonian syndrome	Increased drug entrapment efficiency, reduced side effect & constant systemic levels
Erythromycin	Efficient healing of *S. aureus* -induced deep dermal infections	Improved drug penetration and systemic effect.
Insulin	Treatment of Diabetes	Improved therapeutic efficacy of drug
Testosterone	Treatment of male hypogonodism	Enhance skin permeation
Cannabidol	Prevents inflammation and edema	Significant accumulation of the drug in the skin
Minodixil	Hair growth promotion effect	Higher skin retention
Bacitracin	Treatment of dermal infections	Reduced drug toxicity

Table 2. Different Additives Employed In Formulation of Ethosomes [17]

Class	Example	Uses
Phospholipid	Soya phosphatidyl choline Egg phosphatidyl choline Dipalmityl phosphatidyl choline Distearyl phosphatidyl choline	Vesicles forming component
Polyglycol	Propylene glycol Transcutol RTM	As a skin penetration enhancer
Alcohol	Ethanol Isopropyl alcohol	For providing the softness for vesicle membrane As a penetration enhancer
Cholesterol	Cholesterol	For providing the stability to vesicle membrane
Dye	Rhodamine-123 Rhodamine red Fluorescene Isothiocynate (FITC) 6- Carboxy fluorescence	For characterization study
Vehicle	Carbopol Đ934	As a gel former

Table 3. Table of characterization of ethosomal formulation

Parameters	Methods
Vesicle shape (morphology)	*Transmission electron microscopy[40]* Scanning electron microscopy
Entrapment efficiency	Mini column centrifugation method Fluorescence spectrophotometry[41]
Vesicle size and size distribution	Dynamic light scattering method [42]
Vesicle Skin interaction study	Confocal laser scanning microscopy [Fluorescence microscopy Transmission electron microscopy Eosin-Hematoxylin staining [43,44]
Phospholipid-ethanol interaction	31P NMR Differential scanning calorimeter[45]
Degree of deformability	Extrusion method [46]
Zeta potential	Zeta meter [47]
Turbidity	Nephalometer [48]
In vitro drug release study	Franz diffusion cell with artificial or biological membrane, Dialysis bag diffusion [49]
Drug deposition study	Franz diffusion cell [50]

CONCLUSION

New and alternative drug delivery systems are currently the focus of many research activities. Efficacy, safety and convenience of use are important factors that need to be considered when developing alternate drug delivery systems. In recent years, the transdermal route of drug delivery has evolved considerably and it now competes with oral treatment. Most of the device-induced transdermal drug delivery techniques are still in the early stages of commercialization. All device-induced transdermal delivery techniques have a common concern regarding the safety of use, and skin reactions arising due to perturbing the stratum corneum – even though it is only temporary. Ethosomal carrier opens new challenges and opportunities for the development of novel improved therapies.

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