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ETHOSOMES: A NEW PATHWAY FOR NOVEL DRUG DELIVERY

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Abstract:

Transdermal is the route for delivery of drug to the viable epidermis at controlled rate to systemic circulation. All ethosomal system are simple in their preparation , safe for use in a combination that can highly expands their application .Ethosomes are the drug carriers that enable drug to reach into systemic circulation made up of phospholipids ,high concentration of ethanol and water.

Key words: *Transdermal, Ethosomes, Ethanol effect etc ….*

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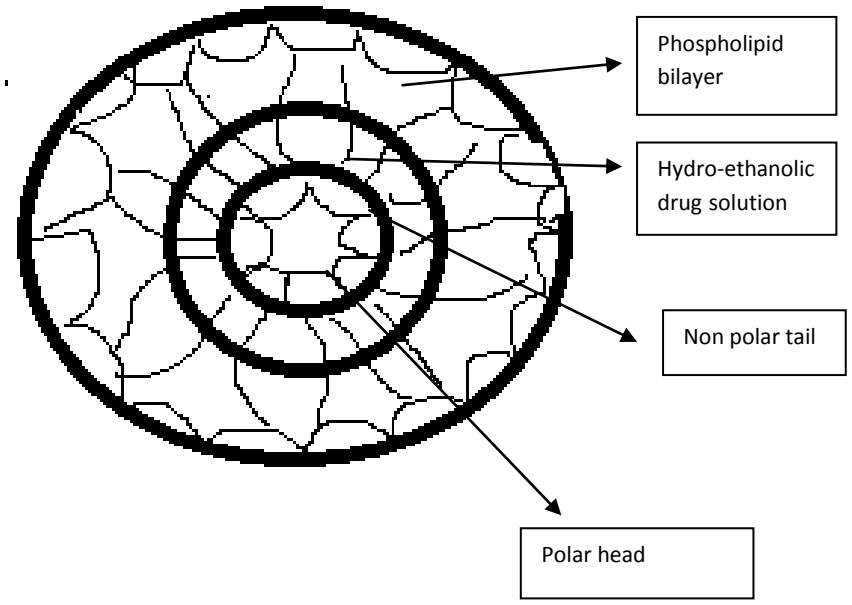
INTRODUCTION:

Transdermal drug delivery system has given best result in comparison to conventional oral drug delivery system and it eliminates gastrointestinal involvement and hepatic first pass metabolism of the drug but the main consequences of TDDS is it encounters the barrier properties of the horny layer (Stratum Coneum) and hence only the lipophilic drugs that have molecular weight <500 Da can pass through it(1,2). In order to improve the permeation of drugs through the skin surfaces various mechanisms have been studied, including use of chemical or physical methods of penetration enhancers such as iontophoresis, sonophoresis, etc. Liposomes, niosomes, transferosomes and ethosomes also have been investigated to enhance permeation of drug through the stratum corneum barrier layer. Permeation enhancers increase the permeability of the skin, so that the drugs can easily pass through the skin. Unlike liposomes[3],that are known mainly to deliver drugs to the outer layers of skin, ethosomes can enhance permeation through the stratum corneum barrier layer (4,5) Ethosomes can permeate through the skin layers more rapidly and possess significantly higher transdermal flux while comparing to liposomes(6,7,8).

Ethosomes

"Ethosomes are ethanolic vesicles". Ethosomes can be defined as novel delivery carriers that enable drugs to reach deep into the skin layers or the systemic circulation. These are soft, malleable vesicles used for enhanced delivery of active agents. The vesicles have been well known for their importance in cellular communication and particle transportation. These vesicles allow in controlling the release rate of drug over an extended period of time, keeping the drug protected from immune response or other body removal systems and thus be able to release just the right amount of drug and maintains that constant concentration for longer periods of time.(9).

Ethosomes are lipid vesicles that contain the phospholipids, alcohol (ethanol and isopropyl alcohol) in relatively high amount and water. Ethosomes are soft vesicles made of phospholipids and ethanol (in higher quantity) and water. The size range of ethosomes may vary from few nanometers (nm) to microns (μ) ethosomes can penetrate through the skin layers at faster rates and possess significantly higher transdermal flux.



STRUCTURE OF ETHOSOMES

ADVANTAGES

1. Delivery of proteins and peptides molecules is possible.
2. Transdermal drug delivery through skin is enhanced.
3. More patient compliance.
4. Due to gel formulation bitter taste of drug is masked.
5. Simple method for drug delivery then iontophorosis, sonophorosis and other methods.
6. Ethosomal drug delivery is passive, non invasive and is available for immediate commercialization. (10, 11)

DISADVANTAGES

1 The molecular size of the drug should be reasonable that it should be absorbed percutaneously.
2 Adhesive may not adhere well to all types of skin.
3. May not be economical.
4. Poor yield.

5. Skin irritation or dermatitis due to excipients and enhancers of drug delivery systems.
6. In case if shell locking is ineffective then the ethosomes may fall apart on transfer into water.

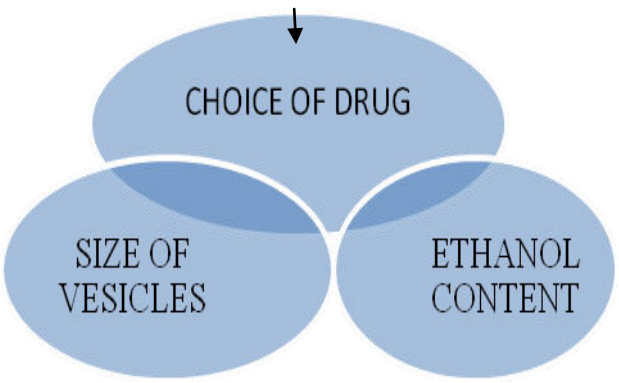
7. Loss of product during transfer from organic to water media. (12,13,14,15)

CHALLENGES DURING TRASDERMAL DRUG DELIVERY

The skin has a multi-layered structure made up of stratum corneum (horny layer), the outermost layer which contains the epidermis and dermis layer. These layers of skin contain fibroblasts, hair follicles and sweat glands that originate in the area of dermis and having blood supply. The nature of SC is a major challenge for systemic delivery of percutaneously absorption of drugs. The arrangement of corneocytes, flattened mononucleotide keratinocytes, with lipids and proteins makes the SC approximately least permeable than other body biological membranes. Hence it is then more difficult for other drugs to penetrate to the deeper layers of skin. (16,17,18)

FACTORS AFFECTING ETHOSOMAL PREAPARATION

1. CHOICE OF DRUG: During formulation the most important factor to be considered in ethosomes is the nature and physicochemical properties of the drug that is going to be selected. This is because the drug ultimately may affect the properties of the ethosomal systems, especially particle size and zeta-potential. Therefore lipophilic type of drug candidate is selected, because hydrophilic drug may have chances of leakage. (19)
2. SIZE OF VESICLES: Ethosomes are specially designed for topical and transdermal drug delivery system, and hence the size of these carriers are very important. The size of these vesicles should be <200 nm or 300 nm and is suitable for this type of administration.(20,21)
3. CONCENTRATION OF ETHANOL: Ethanol is used as an penetration enhancer. (22). It plays an important role in ethosomal systems by giving the vesicles unique characteristics in terms of size, zeta-potential, stability, entrapment efficacy, and enhanced skin permeability. Concentrations of ethanol in ethosomal systems must be in approximately 10%–50%. Over this concentration inc size of ethosomal vesicles. (23, 24)



COMPOSITION OF ETHOSOMES

CLASS	EXAMPLE	USES
PHOSPHOLIPIDS	Soya phosphatidyl choline,	Vesicles forming component
	Egg phosphatidyl choline	
ALCOHAL	Ethanol, Isopropyl alcohol	For providing the softness for vesicle and as penetration enhancer.
POLYGLYCOL	Propylene glycol, Transcutol RTM	As a skin penetration enhancer
CHOLESTEROL	Cholesterol	For providing the stability to vesicle membrane
Dye	Rhodamine-123, Rhodamine red, Fluorescene Isothiocynate,	For characterization study

MECHANISM OF DRUG PENITRATION

1. ETHANOL EFFECT: Ethanol plays its role as penetration enhancer through the skin different layers. The mechanism of its penetration enhancing effect is well known. Ethanol get enters into intercellular lipids layers and increases the fluidity of cell membrane lipids and then decrease the density of the lipid multicellular layer of cell membrane.

2. ETHOSOMES EFFECT: This effect increased cell membrane lipid fluidity by the ethanol of ethosomes results increased skin permeability. Thus, the ethosomes permeates easily inside the skin layers, where it got fused with lipids of the skin and releases the drugs into deep inside layer of skin (25).

METHODS OF PREPRATION

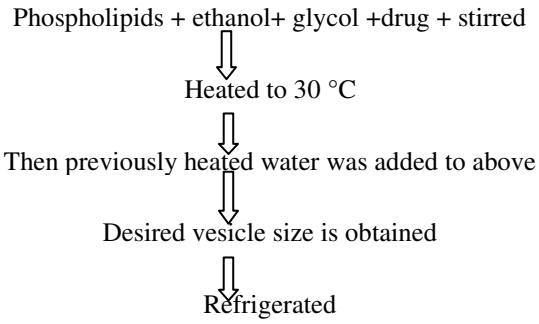
1 THE ETHANOL INJECTION AND SONICATION METHOD

This method contains, the organic phase which contains the dissolved phospholipids in ethanol and then it is injected to the aqueous phase, using a syringe system and the flow rate must be 200 µL/min, then homogenized with an ultrasonic probe for 5 minutes.(26,27)

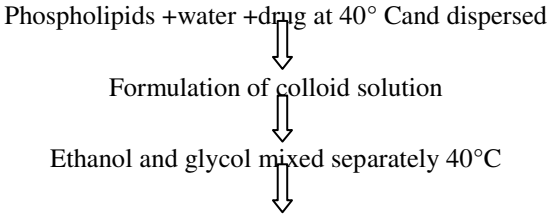
2 THIN FILM HYDRATION METHOD

This method contains the lipid film which is hydrated by a hydro-ethanol solution and then phospholipids dissolved in chloroform only or in a chloroform–methanol mixture at certain ratios in a clean and dry Rbf. Then the organic solvents are removed by using a rotary vacuum evaporator at a temperature above the lipid-phase transition temperature. At last, the traces of the solvents are removed from the deposited film under vacuum. The lipid film is then hydrated with a water–ethanol solution or phosphate buffered saline–ethanol solution. (28,29,30)

3 COLD METHOD



4 HOT METHOD



CHARACTERIZATION OF ETHOSOMES (32,33)

1. Vesicle shape: Visual imaging of ethosomes can be done by using transmission electron microscopy (TEM) and by scanning electron microscopy (SEM). Visual inspection by electron microscopy shows that an ethosomal formulation has vesicular size of 300-400 nm in diameter. Vesicles obtain on are malleable because of their not proper or imperfect round shape.
2. Vesicle size and zeta-potential: Both can be seen by dynamic light scattering and photon correlation spectroscopy.
3. Drug entrapment efficiency: This can be measured by ultracentrifugation method.
4. Temperature of transition: This can be measured by deferential scanning calorimetry.
5. Drug content: Ethosomes drug content can be measured by using UV spectrophotometer. This can also be measured by modified liquid chromatography method.
6. Stability studies: Stability of ethosomes can be determined by mean size using DLS and changes in structure can be seen by TEM.
7. Skin permeation: This can be determined by using confocal laser scanning microscopy

. CHARACTERIZATION OF ETHOSOMES

S.no	Parameter	Importance	Method
1	**size and shape**	**skin penetration**	SEM , TEM , DLS
2	**zeta potential**	**vesicle stability**	Zeta meter
3	**entrapment efficency**	**suitability**	Ultracentrifugation
4	**Drug content**	**amount of drug**	UV , HPLC
5	**Invitro dissolution**	**release rate**	Franz diffusion cell
6	**skin permeation**	**rate drug movement**	CL ,SM

ETHOSOMES MARKETED FORMULATION

NAME OF PRODUCT	USES	MANUFACTU-RER
Nanominox	Hair growth promoter that must be metabolized by sulfation to active compound	Sinere , Germany
Supravir cream	For treatment of herpes virus formulation of acyclovir	Trima, Isarel
Cellutight	Topical cream to breakdown of fat metabolism	USA
Niocellex	Topical anti-cellulite cream	Isarel

Applications of ethosomes (34,35,36,37)

Active ingredients	Formulation	Application	Observation
Ketoprofen	Suspension	Treatment of arthritis related inflammatory pain and musculoskeletal pain	Enhanced transdermal delivery
Linoleic acid	Suspension	Treatment of melasma	Improved skin per meation and accumulation
Ligustrazine	Patch	Treatment of angina pectoris	Better drug ab sorption and Increased bioavailability.

FUTURE ASPECTS OF ETHOSOMES

With the tremendous work of ethosomes has created a new area of interest in vesicular research for TDDS. On obtaining different reports ethosomes shows a promising future perspective in making TDD of various agents more effectively. Further on purifying research in this area will allow better hold on drug release pattern in vivo, allowing researchers to make therapy more effective. In ethosomal formulation special focus is on the skin delivery of proteins and other macromolecules. The near future also impact on the growing success of new commercial ethosomes based topical products. Novel Therapeutics Technology (NTT) increase in demand for biopharmaceutical products for treating alopecia, deep skin infection, herpes, hormone deficiency, inflammatory disorders, atopic dermatitis and erectile dysfunctioning .

CONCLUSION:

Ethosomes offered the safety, efficacy, long term stability and can be simplified manufactured at industrial as well as better patient compliance. Thus, it can be a logical conclusion, that ethosomes can become a promising drug carrier in future for not only topical treatment of local and systemic disorders, but also for the cosmetic and pharmaceutical field. (38)

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