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Ethosomes: An Advanced Approach to Transdermal Drug Delivery System

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ABSTRACT
A number of techniques can be employed to enhance bioavailability of medicament which shows gastrointestinal irritation and first pass metabolism. In order to improve bioavailability in such cases scientist approach towards transdermal drug delivery system. As transdermal drug delivery system also suffers from some drawbacks like poor permeability, skin irritation, etc; which can be improved by utilizing a combination of transdermal delivery and novel drug delivery system like ethososmes. Ethosomes are particularly modified with cellular vesicle system prepared to supply different drug molecule along with several physiochemical properties within deep skin layers and over the skin. An ethosomal carrier offers a lots of disputes and chances for the future build up of novel upgrade therapies by improving the delivery of bioactive molecules through the skin and cellular membrane.
Keywords: Transdermal, Ethosomes, Bioavailability, Gastrointestinal

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INTRODUCTION

The technique of delivering a drug had a remarkable effect on its therapeutic efficacy. The therapeutic range of a drug is that at which it shows best therapeutic effect and dose over or under this concentration may be toxic or give no therapeutic effect at all. Due to retarded treatment of severe diseases, there is a growing demand of associative approach for the delivery of drug to targets in tissues. To decrease drug degradation, to enhance drug bioavailability and to arrest harmful side-effects there is a need to reinforce advanced drug targeting systems and several drug delivery for the faith of human life. Novel and Controlled Drug Delivery system are now an approach to provide a new life to the existing drug molecule. The various approaches for targeting the drug are niosomes, nanoparticles, ethosomes, lipososmes, microparticles, microcapsules and lipoproteins etc [1.2].

TRANSDERMAL DRUG DELIVERY SYSTEM

As compared to oral drug delivery system, transdermal drug delivery system present favourable results as it abolish first pass metabolism and gastrointestinal disturbances of the therapeutic moiety. For transdermal delivery system stratum corneum is the primary obstruction which is required to be encountered as it allows passage to only lipophilic drugs possessing molecular weight 500 Da. For the purpose to raise the penetration across the skin of therapeutic moiety, diverse mechanisms have been scrutinized, which include use of chemical or physical enhancers, such as iontophoresis, sonophoresis, etc. The techniques like nanoparticles, niosomes, Liposomes, microparticles, ethosomes and transferosomes have been evolved for intensification of penetration of drug moiety beyond the stratum corneum. Advanced technique involving uses of penetration enhancers are now popularly utilized to enhance the drug permeability beyond the skin easily. Now a days in comparison to liposomes which is widely employed for the delivery of drug to the external surface of the skin ethosmes and transferosomes are famously employed to appreciate penetration beyond the stratum corneum barrier [3,4]. Ethosomes show greater transdermal flux across the stratum corneum in contrast to conventional delivery system that can easily permeate through the skin layers [5-7].

ADVANTAGES OF TRANSDERMAL DRUG DELIVERY SYSTEM

- Transdermal drug delivery system avoids peak and valley related with parenteral administration or oral dosing. TDDS also maintain concentration level of medicaments for a extended period of time and a constant release rate of medicament is also concluded by this system.
- By using transdermal drug delivery system technique i.e. transdermal patches the problems like first pass metabolism, decreased absorption rate, gastro intestinal disturbances and production of harmful substances can be avoided.
- For the purpose of decreasing the rate of drug administration or medicaments having short half life transdermal technique is very useful.
- By utilizing comprehensible medication regimen inter & intra patient – variability can be minimized.
- Patients like geriatric and paediatric which show difficulty by other routes of administration (oral and i.v) offer greater patient compliance by transdermal patch.
- Patients with dysphagia, constipation or unconscious present better compliance for transdermal drug delivery system.
- Dose of medicament can be minimized due to withdrawal of first pass metabolism which finally reduces the adverse effect associated with medicament.
- Transdermal delivery system can be discontinued at any point of treatment [8-12]**.**

SKIN AS A SITE FOR DRUG DELIVERY

The human skin is freely available surface for drug delivery. An average adult body skin coats a surface of nearly 2 m2 and contains around one third of the blood distribution throughout the body. The skin contain multilayered organ which consists of three histological tissues.

- Epidermis the ultimate layer of skin which offers a watertight barrier protection and produces our skin tone.
- Dermis and beneath epidermis which includes strong connective tissue, hair follicles and sweat glands.
- Hypodermis (Deeper subcutaneous tissue) is consisted of fat and connective tissue [13-17].

Human skin made up of a stratified, cellular epidermis and an undercoating dermis of connective tissue
Epidermis
Dermis

EPIDERMIS: It comprises of four layers such as
Stratum granulosum (granular cell layer)
Stratum corneum (horny layer)
Stratum basale (basal or germinativum cell layer)
Stratum spinosum (spinous or prickle cell layer)

The epidermis also consist stratifying squamous epithelium cells. In the epidermis keratin protein is synthesized by the cell called keratinocytes. Epidermis is also consists of a thin covering of translucent cells visible as thick epidermis known as stratum lucidum.

DERMIS

The region covered by dermis over the whole body is on the back, palm and sole which is about 3mm, and on the eyelids is about 0.6mm. Dermis layer possessed tough, supportive cell matrix and is present below the epidermis.

Dermis consists of two layers:
A thin papillary layer
A thicker reticular layer

FUNCTION OF SKIN

- It act as a physical barrier against any thermal or mechanical agents.
- It acts as a temperature regulator for maintain body temperature.
- It provide protection against dangerous effects of Ultravoilet radiation.
- It works as a sensory organ.
- It plays important role in immunological surveillance.
- It helps in the synthesizes of cholecalciferol

The release rate of a medicament from a formulation when it is applied to the skin surface follow mainly three ways by means of which medicament permeate in to the skin:

- Intracellular permeation through the stratum corneum/ Transcelluar
- Intercellular permeation by means of stratum corneum
- Transappendageal permeation through the hair follicles, sweat and sebaceous gland [18-20].

ETHOSOMES

Ethosomes are ethonolic liposomes. Ethosomes may be defined as noninvasive drug delivery that allows the drugs to contact with the skin layers or into the systemic circulation. Ethosomes are employed mainly for improved delivery of medicinal agent across the skin membrane. In return to the need of advanced drug delivery system Touitou invented a vesicular system called ethosoems for topical drug delivery across the skin. Ethosomes are flexible, smoothy, malleable vesicles utilized for novel delivery of medicaments. Ethosomes provide a controlled release of medicinal agent through a prolonged time period. In sustained and controlled release constant concentration of medicinal agent in the systemic circulation is required to maintain so ethosomes offer a efficienct delivery system. These are flexibile droplets which are composed of phospholipids and ethanol (in high concertration) and water [21, 22]. Ethosomal vesicular system size ranges from tens of nanometers (nm) to microns (μ). Ethosomal vesicular system offer enhanced permeation and have enhanced transdermal flux. Ethosomal drug delivery was investigated to be efficacious for delivering medicament into the skin.

BENEFITS OF ETHOSOMAL DRUG DELIVERY SYSTEM

Ethosomes includes a lots of benefits such as:

- Ethosomes are able to deliver enormous molecules like peptides, protein molecules, etc.
- Ethosomes are formulated by using biologically and eco-friendly chemicals rendring it non toxic to the human body.
- Ethosomal delivery is a good option for transdermal delivery of medicament as it enhances the permeation.
- It can be implement to various fields like Cosmetic, Pharmaceutical, Veterinary fields.
- Ethosomal delivery can be formulated into gel or cream so as to generate high patient compliance.
- In contrast to various alternative techniques ethosomes are better technique [23-25].

DRAWBACKS OF ETHOSOMAL DELIVERY SYSTEM

Ethosomal delivery system has following disadvantages:

- For rapid treatment ethosomal delivery is not effective as it delivers the medicament at sustained rate.
- For ethosomal delivery the medicament should have a good hydrophilic and lipophilic balance so as to reach deep into the skin.
- For ethosomal delivery the medicament should have a adequate molecular size.
- Ethosomes periodically may not be economical.
- Ethosomal delivery system occasionally results in poor yield.
- The loss of product occur during the transfer from organic to water media [26-29].

COMPOSITION OF ETHOSOMES

A number of phospholipids are utilized in the formulation of ethosomes like phosphatidylcholine, phosphatidylserine, phosphatidylinositol, phosphatidylglycerol, phosphatidic acid etc, and also contain various glycols including propylene glycol, increased concentration of ethanol and water. Ethosomal delivery system deliver medicament very efficiently across the skin membrane. Ethosomal vesicles can be prepared by varying the concentration of alcohol, propylene glycol and phospholipids. Mostly preferred phospholipid is soya lecithin (phosphatidylcholine). It is utilized in the concentration range of 0.5-10% w/w. Mostly preferred alcohols involves ethanol and isopropyl glycol. Cholesterol is also occasionally utilized in the preparation in the concentrations range of 0.1-1%. In expansion, the non ionic surfactants (PEG-alkyl ethers) are utilized along with the phospholipids. The alcohol concentration in final product is may be about 20 to 50%. The range of non- aqueous phase concentration (alcohol and glycol mixture) is may be about 22 to 70% [30].

FORMULATION METHOD

For formulating and designing of ethosomes two different methods can be utilized. These methods are easy and useful and does not require any sophisticated instrument or difficult process.

Methods are:

Hot method.

Cold method

Hot method

Ethosomes are prepared by using this method. In this method firstly the water and phospholipids are added in a vessel and heated up to 400 0C before a colloidal mixture is obtained. Secondly ethanol and propylene glycol are added in different container and heated at a temperature of 4000 C. At a point when

both the solution should be reached at a temperature of 400 °C then the organic phase is added in the aqueous phase. The dissolving properties of drug depends on its hydrophilic/ hydrophobic properties. The vesicular size range of ethosomes may be reduced by utilizing probe sonicator or extrusion method.

Cold method

In this method firstly phospholipids, drug and other lipid substances are blended with ethanol in a closed vessel at room temperature by forceful agitating with the help of a mixer. Secondly the propylene glycol and other polyols are taken in different vessel and heated at a temperature of 40oC and mixed to the above solution with stirring. Then the mixture was heated at a temperature of 300C in a water bath. Thirdly water was heated up to 300 C in a separated vessel and added to the initially formed organic phase with continuous stirring. The vesicular size range of ethosomes may be reduced by utilizing probe sonicator or extrusion method. After the preparation of ethosomes, the prepared ethosomes is kept under cold temperature [31-33].

MECHANISM OF PERMEATION

The primary benefit of ethosomes over the liposomes is the enhancement of the drug penetration. The mechanism of drug absorption from ethosomes is not understandable probably the procedure of drug absorption occurs within two phases that are:

Ethanol effect

Ethanol works as a permeation enhancer across the skin. Penetration enhancing mechanism of ethanol has already been proved in various studies. In the cell membrane lipid multilayer density was deceased and the fluidity of cell membrane was enhanced after the penetration of ethanol into the skin.

Ethosomes effect

Skin permeability increases as the ethanol in ethosomal formulation enhances the cell membrane fluidity. The ethosomes penetrates freely into the deep layer of skin. Due to the combination of skin lipid and ethosomes medicament is easily delivered to the deep skin [34, 35].

CHARACTERIZATION OF ETHOSOMES

Visualisation of vesicles by TEM and SEM: By employing the transmission electron microscopy the vesicle area of ethosomes are measured. In this technique the samples are dried on carbon wrapped grid and stained with an aqueous dispersion of phosphotungstic acid. Then the samples are allowed to dry and viewed under the microscope at 10-100k fold enlargement. Scanning Electron Microscopy technique (SEM) is utilized for the measurement of size and shape of ethsomes. In this technique the prepared ethosomes are mounted on clear glass slide, then gold coated with sodium aurothiomalate after drying and viewed under scanning electron microscope at 10,000 magnifications. Finally at last we can view the dried gold coated ethosomes with sodium aurothiomalate.

Size Distribution and Vesicular Size: In this method we can determine the size of ethosomal preparation by using Dynamic Light Scattering technique with the help of Malvern Autosizer 5002 inspection system.

Entrapment efficiency: The centrifugation technique is utilized for the quantification of ethosomal vesicles entrapment efficiency. In this process a high speed cooling centrifuge is used at speed 20000 rpm, at 40 C temperature for about 90 mins. The centrifuge is utilized for the separation of the sediment and supernatant liquids. The sediment so obtained is utilized for estimation of amount of drug by lysing the vesicles with methanol. By using this equation we can estimate the entrapment efficiency

$$\text{Entrapment efficiency} = DE/\ DT \times 100$$

In this equation

DE- the quantity of drug in ethosomal sediment

DT- Drug used in preparation of formulation (equivalent to the quantity of drug in supernatant liquid and in sediment)

Transition Temperature: Differential scanning calorimetry (DSC) is used for the estimation of transition temperature(T) of ethosomal vesicles. this technique envolves heating of sample on aluminium pan at a temperature of 10 °C per min, under a constant nitrogen stream.

Confocal Scanning Laser Microscopy (CSLM): The CSLM technique is utilized for the determination of penetration mechanism of skin. By scanning the skin optically, skin thickness can be estimated by employing this technique.

Drug Content: For the measurement of drug content of ethosomes UV spectrophotometer instrument is utilized. Another methods like high performance liquid chromatographic technique can also be utilized for the estimation of the drug content in ethosomal vesicles.

Surface Tension Measurement: The Du Nouy tensiometer is used for the estimation of surface tension of the medicament in a liquid in ethosomal vesicles.

Phospholipid-ethanol interaction: For the estimation of Phospholipid- ethanol interaction of the ethosomal vesicles the differential scanning calorimetry and Proton Decopuled 31P-NMR techniques are used.

Degree of deformability and Turbidity: In ethosomal preparation the nephalometer is used for measurement of the turbidity of the preparation. The extrusion technique is utilized for the determination of degree of deformability.

***In vitro* drug release study and Drug Deposition study:** This study involves the estimation drug release by utilizing franz diffusion cell with artificial or biological membrane [36.37]**.**

APPLICATION OF ETHOSOMES

Various studies had showed that ethosomal technology involving transdermal application was very efficient for the delivery of medicament having poor oral bioavailability. The various application of ethosomal technology in different fields of science involve following

Pilosebaceous targeting: In this drug delivery system the sebaceous glands and hair follicles have identified as potential element for the delivery of medicament across the hair follicles. This technique is mainly utilized for the medication of follicle-related problems like ance or alopecia. For the medication of alopecia Maiden a research scientist worked on the ethosomal preparation of minoxidil which is applied on the scalp and its result rely on its evaluation parameter. In comparison to other topical formulation like hydroethanolic solution or any other, ethosomal preparation of minoxidil has showed greater penetration efficiency upto 7 folds, also studies performed on mouse skin resulted about 140 folds of greater penetration than any other mode of delivery. So from the research it was stated that minoxidil ethosomes show better clinical efficiency[38]**.**

Transdermal delivery of hormones

Research scientist worked on the comparative study of transdermal patch of testosterone and ethosomal preparation of testosterone using rabbit pinna skin and they concluded that testosterone ethsosomes showed greater penetration of about 30 folds beyond the skin barrier in comparison to transdermal patch. Ethosomal preparation of different hormones are better delivery system in comparison to other delivery as ethosomes eliminate the chances of first pass metabolism, and also some dose related side effects with the drug. Ethosomal preparation resulted satisfactory patient compliance than any other route [36].

Topical delivery of DNA

Ethosomes can also be employed for the delivery of DNA molecules so as to express genes in skin cell. Research scientist Touitou et al studied the ethosomal preparation of green fluorescent protein GFP-CMVdriven transfecting construct in their study. Touitou then investigated the penetration power of the formulation on the mice skin for 48 hours. They finally concluded that above ethosomal preparation resulted more desirable delivery of genes beyond the skin. So from the above study it was stated that ethosomal delivery system is a superior technique for gene therapy and also can be utilized for transdermal immunization of different medicaments [38].

Anti-arthritis drug transdermal delivery

Ethosomes can also be utilized for delivery of several anti arthritic drugs as this delivery system provide site specificity for the medicament so better treatment with less side effects and no first pass metabolism with reduced dose. Cannabidol (CBD) is an anti arthritic drug whose ethosomal vesicles have been formulated by Lodzki et al. They studied the formulation for penetration study through the skin and resulted better penetration and greater residence time with in the skin for about 72 hours.

Delivery of antibiotics

Ethosomes permeate quickly through the epidermis and carry a considerable quantity of Drugs within the skin and remove the virus from their root. Ethosomal vesicular delivery system can be used for delivery of antibiotics as it provide site specificity for the medicament, so better treatment with less adverse effects and no first pass metabolism with reduced dose. Godin and Touitou worked on the ethosomal vesicles of bacitracin and erythromycin. They also investigated the penetration rate of the prepared formulation beyond the skin and it resulted remarkable penetration with greater residence time.

Delivery of Anti-Viral Drugs

Anti viral drugs can also be delivered by utilizing the advanced and transdermal delivery system. Ethosomal vesicle system show better patient compliance in comparison to other delivery system as ethosomal delivery system reduces the side effects associated with the dose and it also eliminates the first pass metabolism effect. A number of ethsomal vesicles of anti viral drugs have been formulated like zidovudine, acyclovir, stavudine and their penetration efficiency was compared with their other topical

formulation and also with oral formulation available in market. So the study revealed that ethosomal formulation of anti viral drug showed better efficiency and better clinical result.

Delivery of antifungal drugs

A number of antifungal drug like fluconazole, betamethasone, clobetasol etc were used to prepared ethsosomes. Ethosomal vesicles of these anti fungal drugs have been formulated and investigated for their penetration rate through the skin as compared with to their other formulation available in market which finally revealed better clinical efficacy and patient compliance [37, 38].

Table 1: Excipients utilized in formulation of ethosomes

S.no.	Class	Example	Uses
1	Phospholipids	Phosphatidylcholine, Phosphatidylserine, Phosphatidylinositol, Phosphatidylglycerol, Phosphatidic acid	Vesicles developing agents
2	Polyglycols	Propylene glycol, Transcutol RTM	As a skin permeation enhancer
3	Alcohol	Ethanol, Isopropyl alcohol	Provide softness to the vesicle membrane. As a penetration enhancer
4	Cholesterol	Cholesterol	Provide consistency to the vesicle membrane
5	Dye	Rhodamine-123 Rhodamine red Fluorescene Isothiocynate (FITC) 6- Carboxy fluorescence	For evaluation study
6	Vehicle	Carbopol D 934	As a gel forming agent

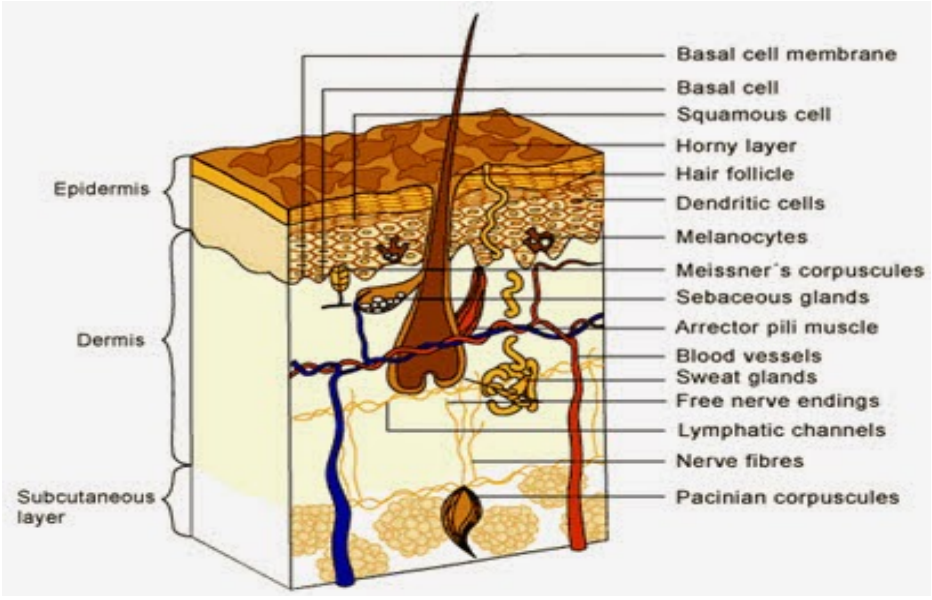

Fig. 1: Anatomy of skin represents different parts

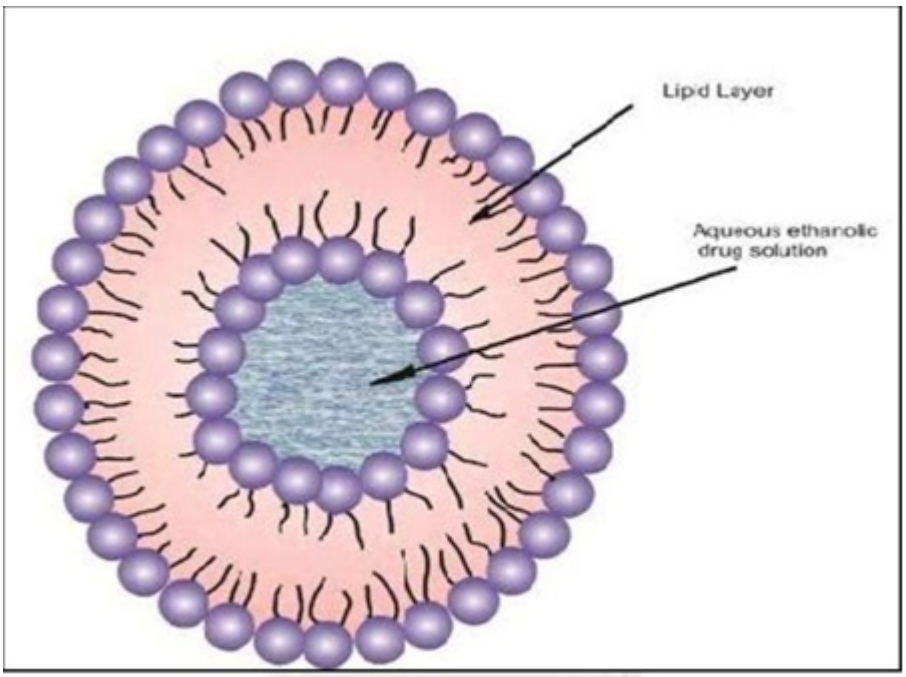

Fig. 2: Structure of ethosomes

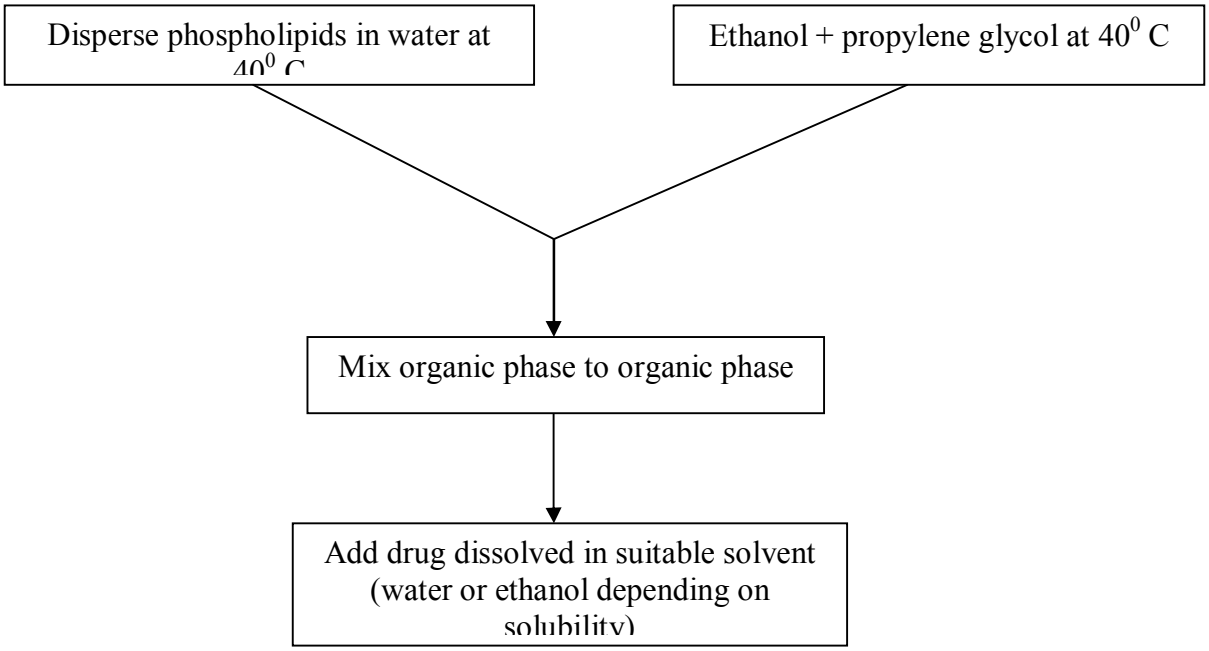

Fig. 3: Formulation method of ethosomes by hot method

CONCLUSION

From the above investigation it was concluded that ethsosomes seves as a advanced tool for the delivery of drugs through the skin. Ethosomes provide greater penetration rate across the skin than any other delivery system like liposomes. Ethosomes acts as a good carrier for the distribution of drugs which shows first pass metabolism for an oral route delivery system. For the advancement of novel drug delivery system the ethosomal carrier offers a new challenges and opportunities. Further, research in this area will allow better control over drug release in vivo and long term safety data, allowing the therapy more effective. Future aspect of the ethosomal formulation involves incorporating ethosomal vesicle into topical gel or any other topical formulation.

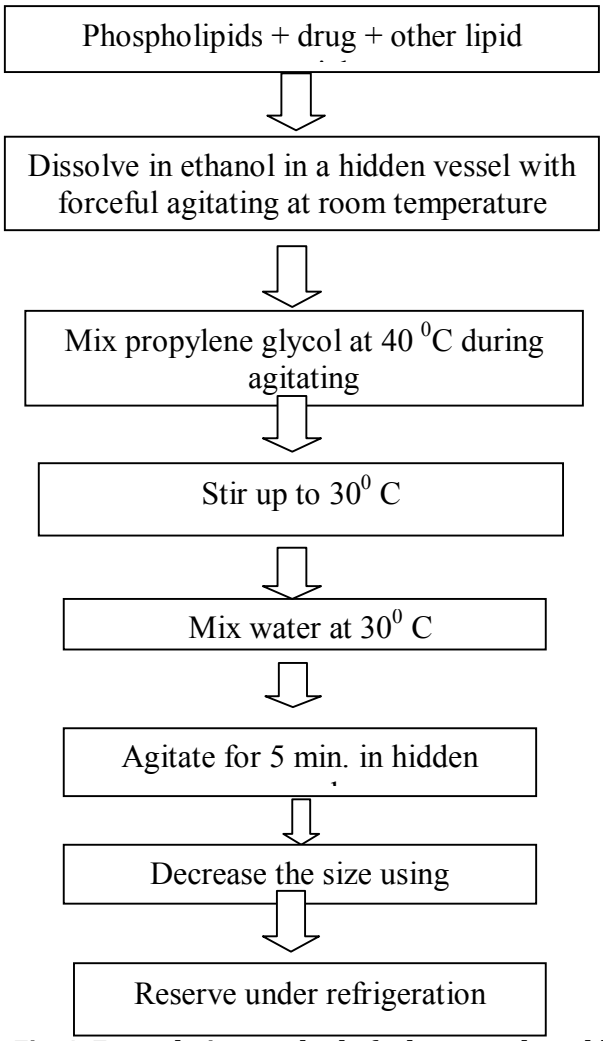

Fig. 4: Formulation method of ethosomes by cold method

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