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RESEARCH ARTICLE

ETHOSOMES - A NOVEL APPROACH FOR TRANSDERMAL DRUG DELIVERY

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ABSTRACT

Transdermal drug delivery system was first introduced more than 20 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. Transdermal drug delivery system is a type of convenient drug delivery system where drug goes to the systemic circulation through the protective barrier i.e. Skin. Over the year it has showed promising 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 Da can pass through it. Ethosomes have been found to be much more efficient in delivering drug to the skin; Ethosomes are the non invasive drug delivery carriers that enable drugs to reach the deep skin layers finally delivering to the systemic circulation. For optimal skin delivery, drug should be efficiently entrapped within ethosomal vesicles. Ethosomal drug delivery system is a new state of the art technique and easier to prepare in addition to safety and efficacy. Ethosomes have become a area of research interest, because of its enhanced skin permeation, improved drug delivery, increased drug entrapment efficiency etc.

INTRODUCTION

FDA approved the first transdermal patch products in 1981. These delivery systems provided the controlled systemic absorption of scopolamine for the prevention of motion sickness (*Transderm-Scop*, ALZA Corp.) and nitroglycerine for the prevention of angina pectoris associated with coronary artery disease (Transderm-Nitro). Over the last two decades, more than 35 transdermal products have been approved generating sales of $3.2 billion in 2002, which is predicted to rise to $4.5 billion in 2008. More recently, such dosage forms have been developed and/or modified in order to enhance the driving force of drug diffusion (thermodynamic activity) and/or increase the permeability of the skin. These approaches include the use of 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 procedure for drug delivery. Further, problem of drug degradation by digestive enzymes after oral administration and discomfort associated with arenteral drug administration can be avoided. It is the most preferred route for systemic delivery of drugs to pediatric, geriatric and patients having dysphasia.

Despite the promise, there were many problems that researchers had to face with while attempting successful transdermal drug delivery. The skin is a multi-layered structure 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. The almost insurmountable nature of SC is a major challenge for systemic delivery of percutaneously applied drugs Barry, 2001. The Òbrick and mortarÓ arrangement of corneocytes, flattened mononucleated keratinocytes, with interspersed lipids and proteins makes the SC approximately 1000 times less permeable than other biological membranes. Furthermore, it is even more difficult for anything to penetrate to the deeper strata of skin Hadgraft, 2001; Hadgraft, 2001. To overcome the stratum corneum barrier, various mechanisms have been investigated, including use of chemical or physical enhancers such as iontophoresis, sonophoresis, etc. Liposomes, niosomes, transferosomes and ethosomes also have the potential of overcoming the skin barrier and have been reported to enhance permeability of drug through the stratum corneum barrier.

The non-invasive approaches for providing transdermal drug delivery of various therapeutic substances are:

Drug and vehicle interactions

- Selection of correct drug or prodrug
- Chemical potential adjustment
- Ion pairs and complex coacervates
- Eutectic systems

Stratum corneum modification

- Hydration
- Chemical penetration enhancers

Stratum corneum bypassed or removed

- Microneedle array
- Stratum corneum ablated
- Follicular delivery

Electrically assisted methods

- Ultrasound (Phonophoresis, Sonophoresis)
- Iontophoresis
- Electroporation
- Magnetophoresis
- Photomechanical wave

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Vesicles and particles

- Liposomes and other vesicles
- Niosomes
- Transfersomes
- Ethosomes

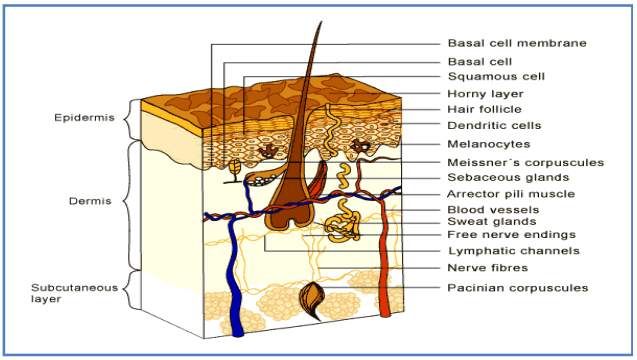

Fig. 1. Structure of skin

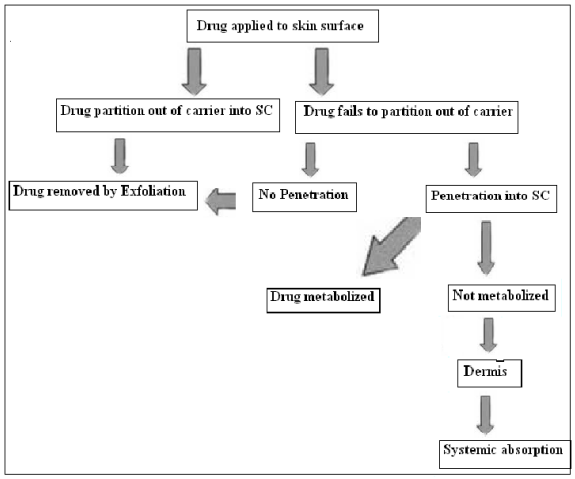

Fig. 2. Proposed mechanism of drug absorption through skin

Rational for Transdermal Drug Delivery

Given that the skin offers such an excellent barrier to molecular transport, the rationale for this delivery strategy needs to be carefully identified. There are several instances where the most convenient drug intake methods the oral route) were not feasible and alternative routes had to be sought. Although, intravenous introduction of the medicament avoids many of these shortfalls (such as gastrointestinal and hepatic metabolism), its invasive and apprehensive nature (particularly for chronic administration) has encouraged the search for alternative strategies. Transdermal drug delivery (TDD) offers several distinct advantages including relatively large and readily accessible surface area (1Ð2 m2) for absorption, ease of application and termination of therapy. Further, evolution of better technologies for delivering drug molecules, safe penetration enhancers and the use of vesicular carriers have rejuvenated the interest for designing TDD system for drugs that were thought to be unfit for transdermal delivery Guy, 1985; Panchagnula *et al*., 2000.

Vesicular approaches for topical drug delivery

Drug encapsulated in lipid vesicles prepared from phospholipids and nonionic surfactants is known to be transported into and across the skin. Lipids present in the skin contribute to the barrier properties of skin and prevent systemic absorption of drugs. Due to the amphiphilic nature, lipid vesicles may serve as non-toxic penetration enhancer for drugs. In addition, vesicles can be used for encapsulating hydrophilic and lipophilic as well as low and high molecular weight drugs. Therefore, these lipid rich vesicles are hypothesized to carry significant quantity of drugs across the skin thus, enhancing the systemic absorption of drugs. Drug delivery from liposomes in transdermal formulation has been studied for many purposes but unstable nature and poor skin permeation limits their use for topical delivery Mezei and Gulusekharam 1980. In order to increase the stability of liposomes, the concept of proliposomes was proposed Deo *et al*., 1997. This approach was extended to niosomes, which exhibited superior stability as compared to liposomes Vora, Khopade and Jain 1998. However, due to poor skin permeability, liposomes and niosomes could not be successfully used for systemic drug delivery and their use was limited for topical use Lasch, Laub and Wohlrab 1991. To overcome problems of poor skin permeability Cevc *et al.*, 1996 and Touitou *et al.*, 2000 recently introduced two new vesicular carrier systems transfersomes and ethosomes, respectively for non-invasive delivery of drugs into or across the skin. Transfersomes¨ and ethosomes incorporated edge activators (surfactants) and penetration enhancers (alcohols and polyols), respectively, to influence the properties of vesicles and stratum corneum Cevc, Blume and Schatzlein 1997. The vesicles have been well known for their importance in cellular communication and particle transportation for many years. Researchers have understood the properties of vesicles structure for use in better drug delivery within their cavities, which would to tag the vesicle for cell specificity. One of the major advances in vesicle research was the finding a vesicle derivatives, known as an Ethosomes Jain, 2001.

Ethosomes

Ethosomes are the slight modification of well established drug carrier liposome. Ethosomes are lipid vesicles containing phospholipids, alcohol (ethanol and isopropyl alcohol) in relatively high concentration and water. Ethosomes are soft vesicles made of phospholipids and ethanol (in higher quantity) and water. The size range of ethosomes may vary from tens of nanometers (nm) to microns (µ) ethosomes permeate through the skin layers more rapidly and possess significantly higher transdermal flux Touitou, 1996.

Structure of Ethosomes

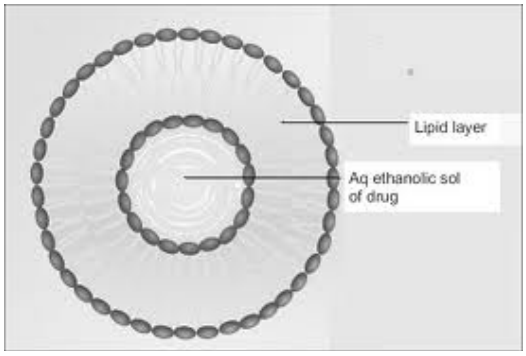

Figure 3. Structure of Ethosomes

Ethosomes Composition

The ethosomal system consists of phospholipids, ethanol and water. The phospholipids with various chemical structure includes phosphatidylcoholine (PC), hydrogenated PC, phosphatidyl ethanolamine (PE), phosphatidyl glycerol (PPG), phosphatidy linositol (PI), hydrogenated PC etc. The nonaqueous phase range between 22 % to 70 %. The alcohol may be ethanol or isopropyl alcohol. Dyes or amphiphilic fluorescent probe such as D – 289, Rhodamine – 123 , fluorescence isothiocynate (FITC), 6 – carboxy fluorescence are often added to ethosomes for characterization study.

Effect of high alcohol concentration

Ethanol is an established permeation enhancer and is proposed that it fluidizes the ethosomal lipids and stratum corneum bilayer thus

Table 1. Different Additives Employed In Formulation of Ethosomes

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 Ð934	As a gel former

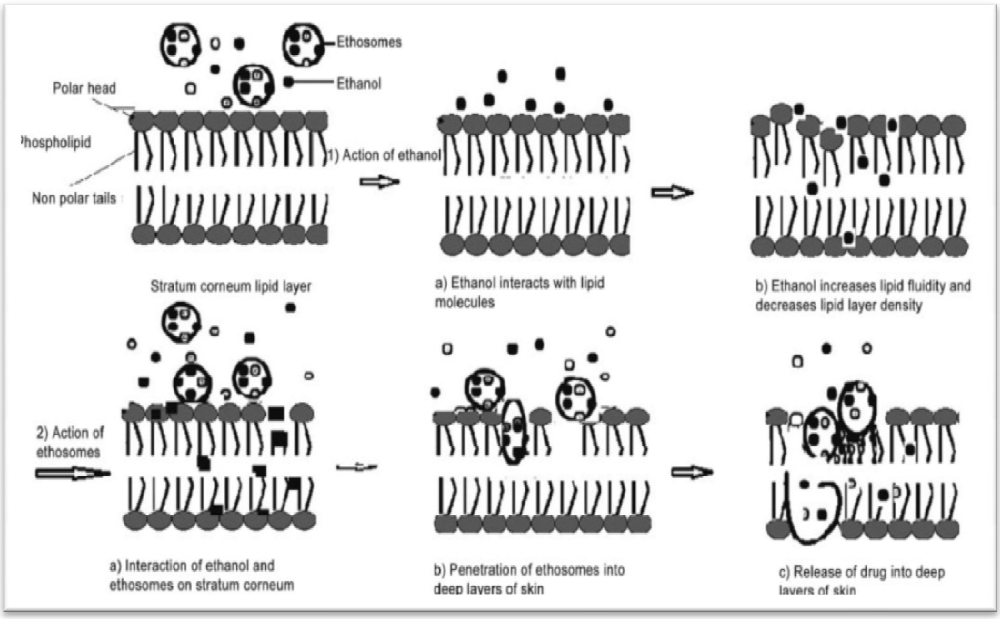

Fig 4. Proposed mechanism for penetration of molecule from ethosomal system across the lipid domain of stratum corneum

allowing the soft, malleable vesicles to penetrate the disorganized lipid bilayer. The relatively high concentration of ethanol (20 – 50 %) is the main reason for better skin permeation ability and is packed less tightly than conventional vesicles but has equivalent stability and better solubility of many drugs. Moreover the vesicular nature of ethosomal formulation could be modified by varying the components ratio and phospholipids. Ethanol consfers a surface negative net charge to the ethosome which causes the size of vesicles to decrease. The size of ethosomal vesicles increase with decreasing ethanol concentration. The enhanced delivery of actives using ethosomes over liposomes can be ascribed to an interaction between ethosomes and skin lipids. A possible mechanism for this interaction has been proposed. 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, resulting in the release of the drug in deep layers of the skin as shown in Fig 4. The drug absorption probably occurs in following two phases:

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.

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.

Advantages of ethosomes

- Enhanced permeation of drug molecules to and through the skin to the systemic circulation.
- Contrary to deformation liposomes, ethosomes improve skin delivery of drugs both under occlusive and non-occlusive conditions.
- Since composition and components of ethosomes are safe, they have various applications in pharmaceutical, veterinary and cosmetic field.
- Better patient compliance.
- Better stability and solubility of many drugs as compared to conventional vesicles.
- Relatively smaller size as compared to conventional vesicles.

Limitations of ethosomes

- Poor yield.
- In case if shell locking is ineffective then the ethosomes may coalescence and fall apart on transfer into water.

- Loss of product during transfer form organic to water media.

Methods of preparation ethosomes

Ethosomes can be prepared by two very simple and convenient methods that is hot method (Fig 7) and cold method (Fig.6).

Cold Method

This is the most common method utilized for the preparation of ethosomal formulation. 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 300C in a water bath. The water heated to 300C 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 sonication or extrusion method. Finally, the formulation is stored under refrigeration.

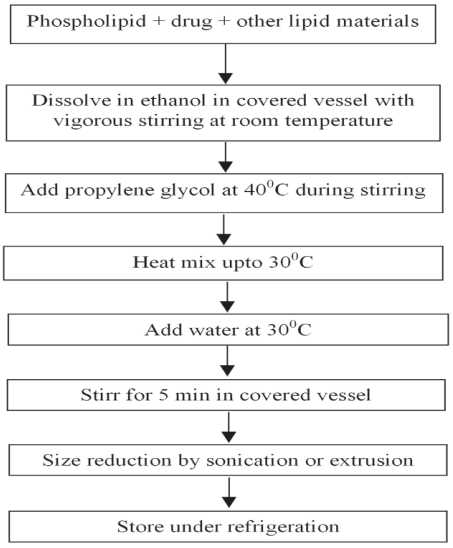

Fig 6. Cold method for the preparation of ethosomes.

Hot method

In this method phospholipid is dispersed in water by heating in a water bath at 400C until a colloidal solution is obtained. In a separate vessel ethanol and propylene glycol are mixed and heated to 400C. Once both mixtures reach 400C, 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.

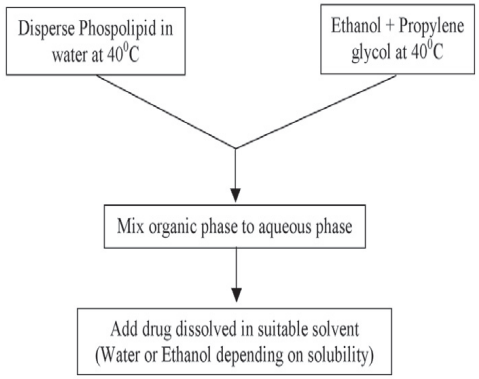

Fig 7. Hot method for the preparation of ethosomes

Characterizations of Ethosomes

Visualization

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

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).

Entrapment Efficiency

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

Transition Temperature

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

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.

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.

Penetration and Permeation Studies

Depth of penetration from ethosomes can be visualized by confocal laser scanning.

Different Studies Related to the Application of Ethosomes as a Carrier System

Various studies employing ethosomal formulation have shown better skin permeability of drugs. The uses of ethosomes as carrier system for transdermal/topical drug delivery are summarized below.

Pilosebaceous targeting

Pilosebaceous units have been use for localized therapy, particularly for the treatment of follicle related disorders such as acne or alopecia. Ethosomal formulation of minoxidil a lipid soluble drug used for baldness accumulate into nude mice skin two to seven fold higher and thus can be use for pilosebaceous targeting for better clinical efficacy.

Transdermal delivery

Since ethosomes enhance permeability of drug through stratum corneum barrier, it can be use for administration of drugs having poor skin permeation, low oral bioavability, first pass metabolism and dose skin and suppress infection at their root.

Delivery of HIV drugs

An effective antiretroviral therapy is required on a long term basis and is associated with strong side effects. Adequate zero order delivery of zidovudine, Lamivudine a potent antiviral agent is required to maintain expected anti – AIDS effect. Subheet Jain et al reported that ethosomal formulation of the above drugs prolong the release with increased transdermal flux. Conventional topical preparation acyclovir an topically used antiviral drug for treatment of herpes labials show low therapeutic efficiency due to poor permeation through skin as replication of virus take places at the basal dermis. Ethosomal formulation of acyclovir show high therapeutic efficiency with shorter healing time and higher percentage of abortive lesions.

Table 2. Application of Ethosomes as a Drug Carrier

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 ofdrug
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

Delivery of problematic drug molecules

Oral delivery of large biogenic molecules such as peptides or proteins and insulin is difficult because they are completely degraded in the GIT tract hence transdermal delivery is a better alternative. But conventional transdermal formulation of biogenic molecules such as peptides or protein and insulin has poor permeation. Formulating these above molecules into ethosomes significantly increase permeation and therapeutic efficacy.

Patented and marketed formulation of ethosome

Ethosome was invented and patented by Prof. Elka Touitou along with her students of department of Pharmaceutics at the Hebrew University School of Pharmacy 44, 45. Novel Therapeutic Technologies Inc (NTT) of Hebrew University have been succeeded in bringing a number of products to the market based on ethosome delivery system. Noicellex TM an anti – cellulite formulation of ethosome is currently marketed in Japan. Lipoduction TM another formulation is currently used in treatment of cellulite containing pure grape seed extracts (antioxidant) is marketed in USA. Similarly Physonics is marketing anti – cellulite gel Skin Genuity in London. Nanominox© containing monoxidil is used as hair tonic to promote hair growth is marketed by Sinere.

Future Prospects

Introduction of ethosomes has initiated a new area in vesicular research for transdermal drug delivery. Different reports show a promising future of ethosomes in making transdermal delivery of various agents more effective. Further, research in this area will allow better control over drug release in vivo, allowing physician to make the therapy more effective. Ethosomes offers a good opportunity for the non-invasive delivery of small, medium and large sized drug molecules. The results of the first clinical study of acyclovir-ethosomal formulation support this conclusion. Multiliter quantities of ethosomal formulation can be prepared very easily. It, therefore, should be not before long that the corresponding drug formulation would have found their way into clinics to be tested for widespread usage. Thus, it can be a logical conclusion that ethosomal formulations possess promising future in effective dermal/ transdermal delivery of bioactive agents.

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