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A REVIEW ON NOVEL APPROACH OF DRUG DELIVERY-ETHOSOMES

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ABSTRACT

Skin is the largest and most easily accessible organ of the body, it serves as a potential route of drug administration for systemic effects, but the outer layer of the skin i.e the stratum corneum, represents the most resistible barrier to drug penetration across the skin, which limits the transdermal bioavailability of drugs. Therefore, special carriers are required to combat the natural skin barrier to deliver drug molecules with different physicochemical properties to the systemic circulation. Transdermal drug-delivery systems offer many advantages, such as avoidance of first-pass metabolism by the liver, controlled delivery of drugs, reduced dosing frequency, and improved patient compliance, as they are noninvasive and can be self-administered. A classical approach is ethosomal drug delivery. Ethosomes are noninvasive delivery carriers that enable drugs to reach the deep skin layers and/or the systemic circulation. These are soft, malleable vesicles tailored for enhanced delivery of active agents. They are composed mainly of phospholipids, high concentration of ethanol and water. The methods that are used extensively to prepare ethosomes are hot method, cold method and classic mechanical dispersion method. The characterization techniques used to determine ethosomes are Scanning electron microscopy, zeta potential, Entrapment efficiency, Transmission electron microscopy, etc. The marketed products of ethosomes are Nanominox, Noicellex, Supavir cream, Cellutight EF etc. The advantage of applying ethosomes in cosmeceuticals is not only to increase the stability of the cosmetic chemicals and decrease skin irritation from the irritating cosmetic chemicals, but also for transdermal permeation enhancement, especially in the elastic forms. The scope of

this review is to introduce the novel concept of ethosomes and to describe some approaches and mechanisms of stimulating topical and transdermal products with ethosomes.

KEYWORDS: Ethosomes, Novel drug delivery, penetration enhancer, Percutaneous absorption.

INTRODUCTION

The skin is the largest and most simply accessible organ of the body; it is a possible route of drug administration for systematic effects. However, the outer layer of the skin, the corneum, represents the foremost resistible barrier to drug penetration across the skin that limits the stratum bioavailability of drugs. Therefore, special carriers are needed to combat the natural skin barrier to deliver drug molecules with totally different chemical properties to the circulation.

Transdermal drug-delivery systems provide several benefits, like avoidance of first-pass metabolism by the liver, controlled delivery of drugs, reduced dosing frequency, and improved patient compliance, as they're noninvasive and can be self-administered.[1,2]

Ethosomes are noninvasive delivery carriers that allow medication to enter the deep skin layers and/or the circulation. These are soft, malleable vesicles tailored for increased delivery of active agents. They are principally composed of phospholipids (phosphatidylcholine, phosphatidylserine, and phosphatitidic acid), high concentration of ethanol and water.[3] The high concentration of ethanol makes the ethosomes distinctive, as ethanol is understood for its disturbance of skin macromolecule bilayer organization; so, once integrated into a cyst membrane, it offers that cyst the flexibility to penetrate the corneum. Also, due to their high ethanol concentration, the macromolecular lipid membrane is packed less tightly than typical vesicles however it possess equivalent stability, permitting an additional malleable structure and improves drug distribution ability in corneum lipids.

Merits of Ethosomal Drug Delivery

- In comparison to different transcutaneous and dermal delivery systems,
- Ethosomes enhance permeation of the drug through skin transcutaneous and dermal delivery.
- Ethosomes are platforms for the delivery of enormous and numerous group of drugs. (peptides, macromolecular protein molecules).

- Ethosomal systems are much more economical and efficient at delivering a fluorescent probe (quantum dots) to the skin in terms of quantity (amount) and depth.
- Low risk profile – The technology has no large-scale drug development risk, because the toxicological profiles of the ethosomal components are well-documented within the scientific literature.
- High patient compliance–The ethosome medication are administrated in a semisolid form (gel or cream), providing high patient compliance. In distinction, ionophores and phonophoresis are comparatively complicated to use, which can have an effect on patient compliance.
- High market attractiveness for product with proprietary technology. Comparatively straightforward to manufacture with no sophisticated technical investments needed for the assembly of ethosomes.
- The ethosomes system is passive, non-passive, and on the market for immediate commercialization.

Demerits of Ethosomal Drug Delivery

They needed High blood levels can't be administered – restricted solely to potent molecules, those requiring a daily dose of 10mg or less.

1. Ethosomal administration isn't a method to achieve fast bolus type drug input, rather it always designed to supply slow, sustained drug delivery.
2. The molecular size of the drug ought to be cheap that it should be absorbed percutaneously.
3. Adhesive might not adhere well to all types of skin.
4. Might not be economical.
5. Poor yield.
6. Skin irritation or eczema because of excipients and enhancers of drug delivery systems.
7. Just in case if shell locking is ineffective then the ethosomes could coalescence and collapse when transferred into water.
8. Loss of product throughout transfer from organic to water media.
9. The major advantage of ethosomes over liposomes is enhances permeation of the drug.[4-9]

Mechanism of Action

A synergistic mechanism was steered between ethanol, vesicles, and skin lipids[10] the improved delivery of actives of ethosomes over liposomes is ascribed to associate degree of

interaction between ethosomes and skin lipids. A doable mechanism for this interaction has been proposed.

From Figure, it's thought that the primary a part of the mechanism is because of the ETHANOL EFFECT, where ethanol interacts with the macromolecular lipid molecules within the polar head cluster region leading to a decrease in the transition temperature of the lipids within the stratum corneum, increasing their fluidity and decreasing the density of the macromolecular lipid multilayer.

This is followed by the 'ETHOSOME EFFECT,' which has lipid penetration and permeation by the opening of new pathways, because of the physical property(malleability) and fusion of ethosomes with skin lipids, leading to the discharge of the drug into the deep layers of the skin.

Ethanol may additionally offer vesicles with soft versatile characteristics, which permit them to penetrate into the deeper layers of the skin. The discharge of the drug within the deep layers of the skin and its transdermal (transcutaneous) absorption may then be the results of a fusion of ethosomes, with skin lipids and drug release at varied points along the penetration pathway.[11]

Fig. 1: Effect of Ethosome on skin after application.

Methods of Preparation of Ethosomes

The literature reports numerous strategies for the preparation of ethosomes and a few usually used strategies are as follows:

1. Hot method

The drug is dissolved in mixture of ethyl alcohol and propylene glycol and then the mixture is added to the phospholipid dispersion in water at 40°C. When mixture is mixed for 5 minutes then the preparation is sonicated at 4°C for 3 cycles of 5 minutes, with a remainder of 5 minutes between every cycle, using the Probe Sonicator. The formulation is then homogenized at 15,000 psi pressure, in 3 cycles, employing an air mass homogenizer to obtain Nano -sized ethosomes.[12]

2. Cold Method

This is the foremost common and widely used technique for ethosomal preparation. The phospholipids, drug, and other macromolecular lipid materials are dissolved in ethyl alcohol, in a covered vessel, at 25°C, with vigorous stirring. The mixture is then heated to 30°C in a water bath. The water is heated to 30°C in separate vessel, and added to the above mixture then stirred for 5 minutes in a closed vessel. The vesicle size of the ethosomal formulation can be reduced if desired, to extend using the sonication or extrusion. Finally the formulation should be properly stored under refrigeration.

3. Classic Mechanical Dispersion technique

Soya phosphotidylcholine is dissolved in mixture of chloroform: methanol (3:1) in round bottom flask. The organic solvents are removed by using rotary vacuum evaporator above lipid transition temperature to make a thin lipid film on wall of the flask. Then the traces of solvent mixture are removed from the lipid film by leaving the contents under vacuum overnight. Hydration is achieved with different concentration of hydroethanolic mixture containing drug by rotating the flask at appropriate temperature.[13,14]

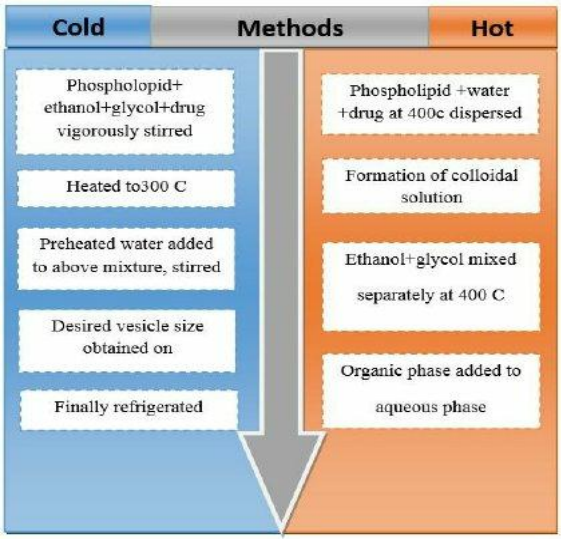

Fig. 2: Methods of Preparation of Ethosomes.

Characterization Techniques

1. Vesicle size and surface morphology

The vesicle shape is simply visualized by employing a photomicrograph, or transmission microscopy (TEM) and scanning microscopy (SEM) micrographs.[15,16] The vesicle size(sac size) and zeta potential of the formulation is measured with the zeta meter.[17] The size of the ethosomes vary between tens of nanometers to microns and it's influenced by the composition of the formulation. Varied factors have an effect on the size and zeta potential of the ethosomes. Reduction in mean diameter of vesicle is due to the presence of ethanol, as it causes a modification of net charge of the system and confers it some degree of stearic stabilization that will finally cause a decrease in the mean vesicle size,[18] whereas the size of the vesicles increase with increasing the phospholipid concentration. This could be explained in terms of the tendency of lipid coalesces at high concentration of lipids.[19,20] The transition temperature of the vesicular lipid systems is determined by use of differential scanning colorimetry, that conjointly detects ethanol-skin phospholipid interaction, a characteristic attributed to the fluidizing impact/effect of ethanol on the phospholipid bilayers.[21]

2. Entrapment efficiency

Ultracentrifugation technique is used for measuring the entrapment efficiency of ethosomes. The power of ethosomes to expeditiously entrap lipophilic and hydrophilic drug is explained by the high degree of lamellarity and also the presence of ethanol within the vesicles, additionally, ethosomal formulations possess larger entrapment capability than liposomes.[22]

3. In vitro drug permeation study

Laser scanning microscopy is used to determine the ability of the ethosomal preparation to penetrate into the skin layers. In vitro and in vivo skin permeation studies have demonstrated the power (ability) of the ethosomal formulation to enhance the permeation of each hydrophobic and hydrophilic molecule as compared to standard liposomes. Different workers have reported a 5-10 fold higher skin permeation of drugs developed in ethosomes, as compared to the traditional liposomal formulation.[23,24]

Therapeutics Application of Ethosomes

Ethosomes can be used for several purposes in drug delivery. Ethosomes are principally used as replacement of liposomes. Mainly the transdermal (percutaneous) route of drug delivery is mostly preferred. Transdermal hydrophilic and impermeable drugs can be administered through the skin by using ethosomes. Numerous drugs are been used with ethosomal carrier.[25,26]

1. Pilosebacious targeting: Hair follicles and sebaceous glands are more and more being recognized as probably vital elements in percutaneous drug delivery. Minoxidil is a lipid-soluble drug used topically (locally) on the scalp for the treatment of baldness by pilosebacious delivery. Interest in pilosebacious units has been directed towards their use as depots for localized medical aid, notably for the treatment of follicle-related disorders like skin disorder or alopecia.[27]

2. Trans cellular Delivery: Touitou et al.[28] in their study showed better intracellular uptake of bacitracin (antibiotic), deoxyribonucleic acid and erythromycin using CLSM and FACS techniques in numerous cell lines. Ethosomes increases the cellular uptake of anti-HIV drug in MT-2 cell line when compared to the marketed formulation, thereby making ethosomes to be an attractive clinical alternate for anti-HIV therapy.

3. Delivery of problematic drug molecules

Oral delivery of huge biogenic molecules like peptides or proteins and hormone is troublesome as a result of they are fully degraded within gastro intestinal tract therefore transdermal delivery could be a better alternative. However conventional transdermal formulation of biogenic molecules like peptides or proteins and insulin has poor permeation. Formulating these molecules into ethosomes considerably increase permeation and therapeutic efficacy.[29]

4. Delivery of Anti-Arthritis Drug

Topical delivery of anti-arthritis drug could be a much better choice for its site-specific delivery and it overcomes the problems related to standard oral therapy.

5. Delivery of Antibiotics

Topical delivery of antibiotics could be a more sensible choice for increasing the therapeutic effectiveness of these agents. Conventional oral therapy causes many allergic reactions along with many side effects. The standard external preparations possess very less permeability to deeper skin layers. Ethosomes penetrate quickly through the stratum and convey considerable quantity of drug into the deeper layer of skin and suppress infection at their root.[30]

List of Various Drugs Used In Market

PRODUCTS	NARRATIVE	MECHANISM
Body Shape (Maccabi-CARE)	Gel executive solidification Cellulose reduction, stretching the skin flexible and based on a technology called Ethosome	Deeper diffusion into the skin
Cellutight EF (Hampden Health, USA)	Topical cellulite cream contains a powerful combination of ingredient to increase metabolism and breakdown fats.	Deeper penetration into the skin.
Nanominox (Sinere, Germany)	Nanominox composed of 4% Minoxidil, Adenosine, Sophora Flavescens extract, Creatinine Ethyl Ester, Cepharanthine, B12, ethanol, distilled water, and uses ethosomes as vehicle to deliver the active ingredients. Nanominox absorbs for 10 minutes prior to washing your hair when other Minoxidil solutions, including those with nanosomes and/or liposomes, suggest 2-4 hr for adequate absorption.	Pilosebaceous Targeting and High penetration into deep layers of the skin.
Noicellex(NTT, Israel)	Topically anticellulite creams	Deeper diffusion into the skin.
Osmotics Lipoduction Cellulite cream (Osmotics, Israel)	Ethanol cream is designed to help reduce cellulite and burn fat when applied to the skin.	Deeper penetration into the skin.
SkinGenuity (Physonics, Nottingham, UK)	Using a unique blend of active anticellulite ingredients with the ingenious Ethosomes Delivery system to ensure good penetration, Skin Genuity drastically reduces those dimples. It also firms and softens your skin with natural antioxidants and moisturising agents to give you the peachy thighs and dimple free derriere	High penetration into deep layers of the skin.
Supravir cream (Trima, Israel)	For the treatment of herpes virus, formulation of acyclovir drug has a long shelf life	Lipid Perturbation

Cosmeceutical Applications of Ethosomes

The advantage of using ethosomes in cosmeceuticals isn't only to extend the stability of the cosmetics and reduce skin irritation, but also for enhancement for transdermal permeation, particularly within the elastic forms.[32] However, the vesicle size and composition are the most crucial factors to be thought of to get these advantages of the elastic vesicles for cosmeceutical applications.

 Oxidative injury can be prevented by topical administration of antioxidants within the skin for cosmetic and cosmeceutical applications.

 However, antioxidants are typically not stable and may be degraded by exposing to light. Vitamin E is one of the most important exogenous lipophilic antioxidants that are mostly found in tissues. Its topical application will enhance the skin protection from exogenous oxidants.

 Once vitamin E is added to cosmetics and many dermatological products, it's found to decrease the production of lipid peroxides within the stratum further it also shields against ultraviolet radiation exposure and a few harmful chemicals and physical agents, so as to deliver antioxidant into the deeper layer of skin.[31]

CONCLUSION

Ethosomes are soft, malleable vesicles and potential carrier for transportation of drugs. Ethosomes are characterized by simplicity in their preparation, safety and efficacy and can be tailored for enhanced skin permeation of active drugs. Ethosomes have been found to be much more efficient at delivering drug to the skin, than either liposomes or hydroalcoholic solution. Ethosomes have been tested to encapsulate hydrophilic drugs, cationic drugs, proteins and peptides. Ethosomal carrier opens new challenges and opportunities for the development of novel improved therapies.

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