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Ethosome: A Novel Vesicular Carrier

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Abstract: ***Delivery across skin is more popular due to its easy accessibility and advantages. However, drug delivery across skin is still a challenge and complicated. The use of lipid vesicles in delivery systems attracted increasing attention in recent years. However, it is found that classic liposomes are of little or no value as carriers for transdermal drug delivery because they do not deeply penetrate the skin, but rather remain confined to the upper layer of the stratum corneum. Ethosomes is gaining attention in the novel drug delivery system for topical use for their excellent abilities to reach deep skin layers and system circulation. Ethosomes are uniquely designed and tailored vesicles consisting high concentration of ethanol which makes them extra malleable resulting in successful delivery of therapeutic agents deeply across the skin. Enhanced delivery of bioactive molecules through the skin and cellular membranes by means of an ethosomal carrier opens numerous challenges and opportunities for the research and future development of novel improved therapies. This review attempts to describe all aspects of ethosomes including Merits, advanced applications, research findings, obstacles, challenges and future prospects.***

Keywords: Drug delivery, Ethosome, vesicular system, Liposomes, Transdermal system

I. INTRODUCTION

The skin which provides the largest boundary between the body and the external environment, acts as a major target as well as a principle barrier for topical and transdermal drug delivery (Glenn GM & Kenney RT 2006). One of the most important functions of skin is to regulate entry and exit of material.(Kogan A & Garti N 2006, Touitou E & Godin B. 2007).The skin is significant barrier properties are due to in large part to the stratum corneum, which embodies the thin outer layer of the epidermis. In contrast to other tissues in the body, the stratum corneum consists of coenocytes that are surrounded by an extracellular milieu of lipids organized as multiple lamellar bilayers. These structural lipids block the entry of most of the topically applied drugs, as well as those that are lipid-soluble and of low molecular weight.(Sloan KB et al 2006,Kiptoo PK et al 2006, Kalia YN et al 2004).This poses an important challenge to administering medications through the skin either for local cutaneous effects or as systemic therapy following their entry into superficial dermal capillaries. (Pikal MJ 2001, Subramony JA et al 2006).

The skin as a route of drug delivery can offer many significance over traditional drug delivery systems including lower fluctuations in plasma drug levels, avoidance of gastrointestinal disturbances and first-pass metabolism of the drugs, and high patient compliance (Scheuplein R & Blank H 1971).

Transdermal drug delivery (TDD) is designed to deliver a therapeutically effective dose of drug across a patient's skin. It offers several unique advantages including relatively large and readily accessible surface area for absorption, improved bioavailability, painless as compare to injectables, easy application, prompt termination of therapy and reduction in side effects (Ghulaxe C & Verma C 2015). It overcomes a

number of limitations of oral drug delivery such as degradation of drugs in GIT, gastrointestinal irritation and first pass metabolism. The disadvantages include, barrier properties of skin which make it difficult to penetrate and permeate drug through skin. There are various techniques to enhancing delivery of drug through skin such as, polymeric system, surfactant based and vesicular based drug delivery approaches (Guy RH & Hadgraft J 2003, Williams 2003, Prausnitz MR et al 2004, Bronaugh RL & Maibach HI 2005).

The use of lipid vesicles in delivery systems attracted increasing attention in recent years (Braun Falco O et al 1992, Touitou, E & Junginger N 1992) However, it is found that classic liposomes are of little or no value as carriers for transdermal drug delivery because they do not deeply penetrate the skin, but rather remain confined to the upper layer of the stratum corneum (Braun Falco O et al 1992).

Niosomes, microemulsion, nanoemulsions comes under surfactant based carrier systems while dendrimers, biodegradable and non biodegradable nanoparticles are examples of polymer based system. One of the novel approaches is vesicular drug delivery systems containing liposomes, deformable liposomes, and ethosomes (Elisa E & Evelyn M 2011)

A. VESICULAR SYSTEMS

First reported in 1965 by Bingham, and was given the name "Bingham bodies" -Vesicles, play a major role in modeling biological membranes, and in the transport and targeting of active agents. Among the different approaches for achieving an effective topical drug delivery, Liposomes have been widely used as safe and effective vehicles, due to their proved potential in improving skin penetration and clinical efficacy of several drugs (Gregoriadis G 2000, Verma D & Fahr A 2004, Mura P et al 2007). Liposomes are vesicles in which one or more lipid bilayers entrapped an aqueous volume. Their major components are usually phospholipids with or without cholesterol. The stratum corneum lipid liposomes (SCLL) are the vesicular systems made of lipids with a composition similar to the lipids found in the outer layer of human skin. (*Torchilin V 2006, Cevc G 1993).*

Their delivery mechanism is accumulation of the liposomes in the stratum corneum and upper skin layers, and as a local drug reservoir. Transfersomes are ultra deformable vesicles and structurally similar to liposomes but they differ in function. Phospholipids are the major components but an additional surfactant acts as an edge activator to modify elasticity and increase deformability. (*Cevc G & Richardsen H 1993, Barenholz Y & G Cevc 2000, Bertrand et al 2010,Barani H & Montazer, M 2008).*

But recent finding reveals that, that traditional liposomes do not deeply penetrate skin, but rather remain confined to upper layers of the stratum corneum Therefore, new strategies have been developed in the attempt of enhancing the skin penetration ability of liposomes (Marco, B et al 2012).

There are many limitations of Liposomes, Transfersomes, and Niosomes as depicted in table 1 (Madhulika P et al 2013)

Vesicular system	Limitations
Liposomes	✓ Degradation by oxidation, sedimentation, leaching of drug ✓ Lack of purity of the natural phospholipids ✓ Expensive to prepare ✓ Chemical instability because of their predisposition to oxidative degradation.
Transfersomes	✓ Lack of purity of the natural phospholipids. ✓ Expensive to prepare ✓ Aqueous suspension may exhibit aggregation, fusion, leaching or hydrolysis of entrapped drugs, thus limiting the shelf life
Niosomes	✓ Time consuming preparation ✓ Requires specialized equipment. ✓ Inefficient particularly if smaller quantities are required for a particular application or dose.

Table 1: Problems associated with liposome, transferosomes and noisome

Many research finding suggested, a novel vesicular sysrtem, "ethosomes,"as alternative to overcome the problems of poor skin permeability of classic liposomes by using lipid vesicles composed of phospholipids, water and ethanol in relatively high concentrations (Rahul G et al 2012)

B. ETHOSOME

One of the major advancement in vesicle research was the finding a vesicle derivative, defined as Ethosomes (Verma D & Fahr A 2004). Ethosomes are phospholipids vesicles as shown in figure 1, which include ethanol to increase elasticity, whereas niosomes comprise surfactants together with cholesterol and may include small proportions of phospholipids (Bhalaria M et al 2009).

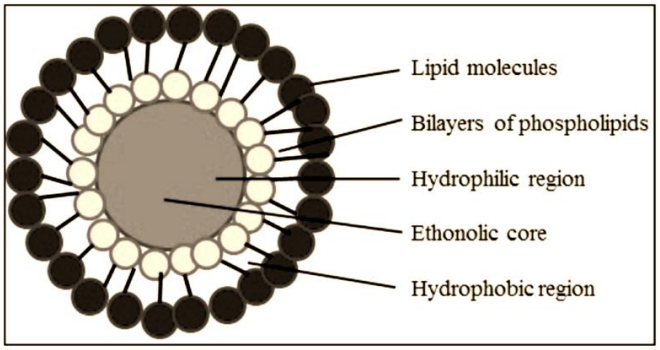

Figure 1: Structural feature of Ethosome

There are three types of flexible liposomes: Transferosomes, Ethosomes and Niosomes. Ethosomes are soft and flexible nanovesicles, which posses unique structure which makes them incompetent to overcome the natural skin barrier and delivering drugs through the skin layers. Ethosomes are lipid vesicles Size varies from tens of nano to micrometers containing phospholipids, alcohol in relatively high concentration, (Dubey V et al 2007, Sudhakar K et al 2012**).**

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 bilayers (Solanke P et al 2016, Kaisar R et al 2013). Due to non invasive properties, it is responsible for disturbing the organization of skin lipid bilayer (Christian C et al 2009). Release of drug could be result of combination of ethosomal system with skin lipids and drug release at various points along the penetration pathway (Carl S et al 2011).Delivery of drugs through ethosomes can be fabricated for enhanced skin permeation and localization of the drug at the site. They are found to entrap various hydrophilic, lipophilic or amphiphilic molecules (Kim S & Chien Y 1996, Touitou E et al 2001).

In ethosomes, on account of solubility of most of the drugs in ethanol, the high concentration of drug encorporation is possible .High concentration of ethanol makes them flexible as well as increases the penetrating power as, it increases the thermodynamic activity due to evaporation of ethanol .It also enhances penetration due to reduction in barrier property of stratum corneum (Spruance SL & Semin 1992).

The multi functional roles of vesicle is depicted in figure 2

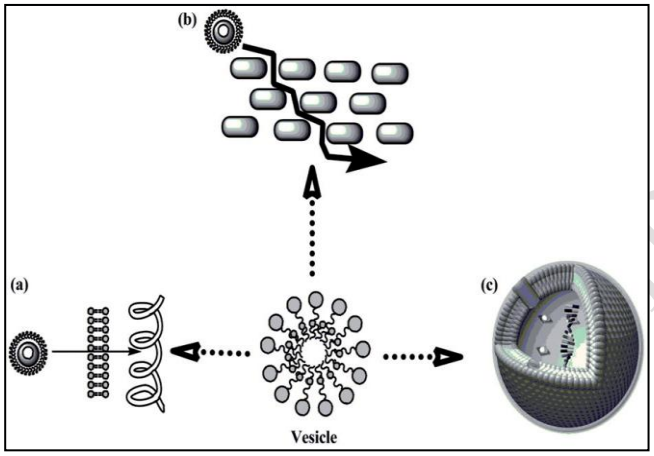

Figure 2: A schematic drawing showing multi functional roles of vesicle. (a) Delivering drug molecules into/across the skin, (b) penetration into stratum corneum and (c) acting as storage compartment for drug molecules

C. MERITS OF ETHOSOMES.(ESPOSITO E ET AL 2004)

- ✓ High flexibility
- ✓ High deformability
- ✓ Greater elasticity of ethosomal membrane.
- ✓ Retentive and adaptability in lipid bilayer.
- ✓ Non invasive m
- ✓ Highest transdermal flux.
- ✓ Suitable for the delivery of large and diverse groups of drugs like peptides, protein molecules
- ✓ More efficient at delivering a fluorescent explore (quantum dots) to the skin, in terms of quantity and depth.
- ✓ High patient compliance
- ✓ Biodegradable
- ✓ Increased permeation of drug.

II. RECENT STUDIES CITED IN LITERATURE ON ETHOSOMAL TECHNOLOGY

The field of vesicular delivery now expanding further into the chronic treatment of neurological disorders, Arthritis, Skin cancer, AIDS, etc. which has been show introduction of TDS-containing drugs such as stavudine, tetrandrine, celecoxib, Clopidogrel,etc. Many researcher worked on ethosomal formulations. Recent studies on Ethosomal technology are depicted in table 2.(Verma D & Fahr A 2004).

Author	Year	Research Studies
Maurya et al.	2010	Formulation Development and Evaluation of Ethosome of Stavudine.
Barupal et al.	2010	Preparation and Characterization of Ethosomes for Topical delivery of Aceclofenac
Bragagni M.et al.	2012	Comparative study of liposomes, transfersomes and ethosomes as carriers for improving topical delivery of celecoxib
Chao Fan et al.	2013	Enhanced Topical Delivery of Tetrandrine by Ethosomes
Bhosale and Avachat	2013	Designed and developed ethosomal transdermal drug delivery system of valsartan with preclinical assessment in Wistar albino rats.
Sarwa et al.	2014	conducted Penetration studies of tamoxifen citrate loaded ethosomes and liposomes across human skin: a comparative study with confocal laser scanning microscopy.
Zhai et al.	2015	prepared ethosomes for skin delivery of ropivacaine: preparation,characterization and ex-vivo penetration properties.
Shen et al	2015	Prepared ethosomes and evaluated Compound for antimalarial ethosomal cataplasm: preparation, evaluation, and mechanism of penetration enhancement
Khan and Wong	2016	prepared Microwave-aided skin drug penetration and retention of 5-fluorouracil-loaded ethosomes
Tripti Shukla	2016	Development and Characterization of Clopidogrel-loaded Ethosomal Transdermal Patch
Garg et al	2016	prepared nanosized ethosomes-based hydrogel formulations of methoxsalen for enhanced topical delivery against vitiligo: formulation optimization, in-vitro evaluation and preclinical assessment.
Limsuwan et al.,	2017	prepared and evaluated ethosomes of Phenylethyl Resorcinol as Vesicular Delivery System for Skin Lightening Applications
Yang et al	2017	investigated mechanism of transdermal permeation promotion of lipophilic drugs by ethosomes
Shubhra Rai	2017	Transfersomes as versatile and flexible nano-vesicular carriers in skin cancer therapy: the state of the art

Table 2: Recent studies on Ethosomal technology

III. CHALLENGES AND OPPORTUNITIES

Enhancement of stability is a major issue in the formulation and development aspect. Recently many researchers worked on to improve the stability of ethosomes and to reduce aggregation of ethosomes It consist of ethanol and PEG in place of single ethanol phase. Phospholipid, mixture of ethanol and propylene glycol were used to improve ethosomes stability and skin drug delivery. Fluid properties of lipid bilayers found to be affected by reversible sedimentation because of different pharmaceutical components present in colloidal suspension(Biju SS et al 2006).The balance between drug affinity to vesicles and drug solubility in lipids of stratum corneum is necessary to maintain rate and the amount of drug release. High temperature will cause degradation of phospholipids and that will affect the gel to liquid transition of lipid bilayer ultimately causes blemish in membrane packaging (Paolino D et al 2005).Sensitizing capacity of micro ethosomes is more than that of Nanoethosomes. Research finding suggests that, fraction of phospholipid is lost in the extruder membrane during extrusion process when producing nano form (Nirved V et al 2012) Determination of zeta potential is prognostic of storage stability of ethosomal suspension.

IV. APPLICATION OF ETHOSOMES

Ethosomes have wide applications in different categories of drugs like Antifungal, Antibiotics, Skin infections and Cosmetic field as shown in table 3.

Formulation	Rationale of ethosomal delivery	Application	Route of administration
5-aminolevulinic acid Ethosome	Significantly improved the delivery of ALA in the inflammatory skin.	Anti- psoriasis	Topical
Erythromycin ethosome	Ethosomal erythromycin was highly efficient in eradicating S.aureus-induced intradermal infections	Anti bacterial	Topical
Isoeugenol ethosome	Chemicals (allergen) in vesicular carrier system can enhance the sensitizing capacity.	allergen	Topical
Matrine ethosome	Improves the percutaneous permeation	Anti-inflammatory	Topical
Methotrexate ethosome	Ethosomes showed favorable skin permeation characteristics	Anti- pyretic	Topical
Minoxidil ethosome	Enhance the penetration and accumulation of minoxidil in the skin by Pilosebaceous targeting	Hair growth promoter	Topical
Testosterone ethosome	Testosterone ethosome for enhanced transdermal delivery	Steroid hormone	Topical
Trihexyphenidyl HCL ethosome	Increased drug entrapment efficiency, reduced side effect and constant systemic levels	Anti-parkinsonian	Topical
Acyclovir ethosome	Binary combination of the lipophilic drug ACV-C16 and the ethosomes synergistically enhanced ACV absorption into the skin	Anti-viral	Topical
Azelaic acid ethosome	Release rate was higher from ethosomes than from liposomes	Anti-keratinizing	Topical
Bacitracin ethosome	Ethosomal enhances intracellular delivery of and reduced drug toxicity in the skin	Polypeptide antibacterial	Topical
Colchicine ethosome	Enhance skin accumulation, prolong release and improve the specificity	Anti-gout	Topical
Finasteride ethosome	Enhanced percutaneous absorption of finasteride 5-a reductase inhibitor	Anti-Fungal	Topical
Fluconazole ethosome	Enhances the skin permeation	Anti-Fungal	Topical
Ibuprofen ethosome	Transdermal nanosystem, designed by	Antipyretic	Topical

	using an ethosomal carrier		
Ligustrazine	Ethosome patch enhances the permeation the skin	Pulmonary vasodilator	Topical
Salbutamol ethosome	Enhanced drug delivery through skin with ethosomes	Anti-asthmatic Anntiarrythmic	Topical
Sotalol ethosome	Enhances the systemic absorption		Topical
Vitamin A palmitate, Vitamin C, Vitamin E ethosome	Anti-oxidation of phospholipid was increase due to the synergistic interaction of all three together as compare to individual use	vitamins	Topical
Diclofenac	Selective delivery of drug to desired side for prolong period of time	NSAID	Topical

Table 3: Application of Ethosomes

Synthetic drugs have a disadvantage of adverse and toxic effects whereas herbal drugs are believed to be safe and biocompatible with no adverse effects. Herbal ethosomes is a novel concept n vesicular research for Transdermal Drug delivery System. The various applications of Herbal Ethosomes are shown in Table 4. (Paolino D et al 2005, Nirved V et al 2012, Zhou Y et al, Mathur M & Vyas,G 2013)

formulation	Rationale of ethosomal delivery	Application	Route of administration
Amonium Glycyrrhizinate Ethosomes	Increases of in vitro Percutaneous permeation and significantly enhanced anti inflammatory activity	Anti inflammatory	Topical
Triptolide	Good percutaneous Permeability	Anti inflammatory	Topical
Podophyllotoxin	enhance its therapeutic effect	Purgative, anti rheumatic, antiviral and antitumor	Topical
Sesbania Ethosome	Enhance Transdermal Permeation	Anti-microbial	Topical
Sophora ethosome	Enhance drug deliver and stability	Anti endotoxic, anticancer, And anti inflammatory	Topical
Matrine Ethosome	Improve precutaneous Permeation	Cardio protective, Anti inflammatory	Topical

Table 4: Applications of Herbal Ethosomes

V. MARKETED FORMULATIONS BASED ON ETHOSOMAL FORMULATION

There are abundant transdermal delivery systems currently available and used in the market. In the transdermal drug delivery market, worth $12.7 billion dollars in 2005, is expected to reach $32 billion in 2015.The field of transdermal delivery now seems to be growing further into the chronic treatment of neurological disorders, which has been show cased by the introduction of TDS-containing drugs such as methylphenidate for attention-deficit hyperactivity disorder (introduced in 2006), rotigotine for Parkinson's disease (2007) and rivastigmine for dementia (2007).

VI. TRANSDERMAL PRODUCTS CURRENTLY ON THE US MARKET

The exceptional structure with highest penetration ability and sound techniques of preparation make them ideal sformulations for commercialization of ethosomes in the market. They are suitable for incorporating different categories of drugs. The Novel Therapeutic Technology Inc, (Wilmington, Delaware, United states) is a Biopharmaceutical Company having a portfolio of pharmaceutical formulation based on ethosome technology, including formulation for the treatment of alopecia, deep skin infection, herpes, hormone deficiencies, inflammation, post operative nausea, atopic dermatitis and erectile dysfunction. The various marketed Ethosomal Formulation are shown in Table 4. (Shukla T 2016, Rai S 2017, Pawar P 2015, Li-Na et al 2014, Touitou E 1998).

Products	Description	Importance
BodyShape (MaccabiCARE)	Gel Executive solidification cellulite reduction, stretching the skin flexible and based on a technology	Deeper diffusion into the skin.
Cellulight EF (Hampden Health, USA)	Topical cellulite cream contains a powerful combination of ingredient to increase metabolism and breakdown fats	Deeper diffusion into the skin.
Nanominox Sinere,Germany	Composed of 4% minoxidil, adenosine, sophora flavescens extract, creatine ethyl ester, cephranthine absorb for 10 mins prior to washing your hair when other minoxidil solution	Pilosebaceous targeting and high penetration into deep layers of skin
Noinocellex	Topical anti- cellulite	Deeper diffusion

(NTT, Israel)	cream	into the skin
Osmotics Lipoduction cellulite cream (Osmotics, Israel)	Ethosomal cream is designed to help reduce cellulite and burn fat when applied to the skin	Deeper penetration into the skin into the skin.
Skin genuity (physonics,Nottingham,UK)	Drastically reduces those dimples. It also firms and softens your skin with natural antioxidants and moisturizing 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 with no stability problems, stable for at least 3 year at 2500C Skin permeation experiments showed that the creams retained its initial penetration enhancing properties even after 3 yrs	Lipid perturbation.

Table 5: Marketed Formulations of Ethosomes

VII. FUTURE PROSPECTS

There is a promising future of ethosomes in production of transdermal delivery of various agents in more effective manner. Advance 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 prospective for the non-invasive delivery of small, medium and large sized drug molecules Hence, it can be concluded that ethosomal formulations possess promising future in effective dermal/transdermal delivery of bioactive agents.

VIII. CONCLUSION

There are various techniques to enhance delivery of drug through skin such as, polymeric system, surfactant based and vesicular based drug delivery approaches. Traditional liposomes do not deeply penetrate skin, but rather remain confined to upper layers of the stratum corneum Therefore; new strategies have been developed in the attempt of enhancing the skin penetration ability of liposomes. Ethosomes are phospholipids vesicles which include ethanol to increase elasticity. Ethosomes are soft, malleable vesicles tailored for enhanced delivery of active agents, which makes them a promising candidate for future transdermal drug delivery product. Enhanced delivery of bioactive molecules through the skin and cellular membranes by means of an ethosomal carrier opens numerous challenges and opportunities. Enhanced delivery of synthetic and herbal drug molecules through the skin and cellular membranes by means of an ethosomal carrier opens tremendous opportunities for the research and future development of novel improved therapies.

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