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Review Article

Ethosomes– Radical Approach in Transdermal Drug Delivery.

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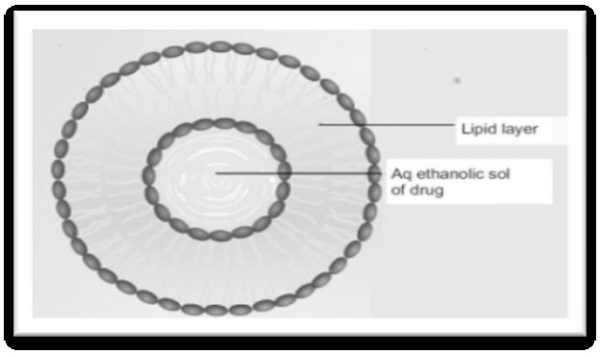
ABSTRACT
There are numerous transdermal delivery systems currently available in the market. The transdermal drug delivery market, worth $12.7 billion dollars in 2005, is expected to reach $32 billion in 2020.Ethosomes are gaining attention in the fabrication of novel drug delivery systems for topical and transdermal use for their excellent capability to reach deep skin layers and systemic circulation and being non-invasive carriers. It shares numerous advantages like Simple method of preparation as well as their safety profile. Although with their great efficiency they show strong potential of expansion of their application. The aim of the review is to focus the Formulation aspects of ethosomes, challenges and opportunities they share, And Marketed Formulations Available in the market.

KEYWORDS
Delivery System, Ethosome, Liposome, Pilosebaceous targeting.

1. INTRODUCTION

Delivery of drug through topical route represents more convenient and innovative approach. Major task is to deliver the drug through skin. Barrier properties of skin make it difficult to penetrate and permeate through skin. It is selectively permeable for drugs. Lipophilic drugs can pass through skin but hydrophilic drug has either very low or no permeation. There are many means of enhancing delivery of drug through skin. Carrier based drug delivery system has gained attention of many researchers. It involves surfactant based, polymer based and vesicle based drug delivery approaches. Niosomes, microemulsion, nanoemulsions comes under surfactant based carrier systems while dendrimers, biodegradable and nonbiodegradable nanoparticles are examples of polymer based system. One of the novel approaches is vesicular drug delivery systems containing liposomes, deformable liposomes, and ethosomes. Vesicles are nano or microparticulate colloidal carriers usually 0.05- 5 um in diameter which form spontaneously when certain lipids are hydrated in aqueous media[1]They have been known for their cellular communication and particle transportation many years. One of the major advances in vesicle research was the finding a vesicle derivative, known as Ethosomes [2]. Flexible liposomes are common vectors in transdermal delivery systems, with good liquidity and deformability. There are three types of flexible liposomes: Transferosomes, Ethosomes and Niosomes. Ethosomes are soft and flexible nanovesicles. They posses unique structure which makes them capable of overcoming the natural skin barrier and delivering drugs through the skin layers. Ethosomes are lipid vesicles containing phospholipids, alcohol (ethanol and isopropyl alcohol) in relatively high concentration and water [3]. Size of vesicles varies from tens of nano to micrometers [4].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 [5].Being non invasive it is responsible for disturbing the organization of skin lipid bilayer [6]. Release of drug could be result of fusion of ethosomal system with skin lipids and drug release at various points along the penetration pathway [7].Delivery of drugs through ethosomes can be modulated not only for enhanced skin permeation but localizes the drug at the site of action which enables drugs to reach the deep skin layers. They can efficiently entrap various kinds of molecules such as hydrophilic, lipophilic or amphiphilic [8, 9]. In ethosomes high drug loading is possible because of reasons like solubility of many drugs in ethanol, and high degree of lamellarity in vesicles [7].High concentration of ethanol makes them flexible as well increases the penetrating power because it increases the thermodynamic activity of due to evaporation of ethanol and enhances penetration due to reduction in barrier property of stratum corneum [10].



1.1. Advantages of Ethosomes:

- Extremely high flexibility high deformability and elasticity of ethosomal membrane.[11]
- Retentive and adaptability in lipid bilayer.
- Non invasive in comparison with iontophoresis and phonophoresis.
- Highest transdermal flux.
- Platforms for the delivery of large and diverse groups of drugs (peptides, protein molecules etc.)
- More efficient at delivering a fluorescent probe (quantum dots) to the skin, in terms of quantity and depth.
- High patient compliance because available in the semisolid dosage forms.
- It contains non toxic raw materials in the formulation.

1.2. Mechanism of drug penetration:

Ethosomes are modified liposomes which incorporate ethanol to enhance the ability of ultra deformability. It is claimed that this allows ethosomes to transport the active species into deeper skin layers via a variety of mechanisms. Mechanism of skin permeation of ethosomes is still not known completely but it has been anticipated that it may be due to: a) fluidizing effect of ethanol on Phospholipid bilayer creating a soft deformable vesicle. b) The stratum corneum lipid disruption by ethanol there by permitting entry of ethosomes with associated drug molecules into the deeper skin layers[2]. Ethanol retards the lipid transition temperature of skin lipid leads to the increase in solubility of drug in skin lipids. Dense arrangements of lipid molecules get altered because ethanol causes crystal phase transition of solid and liquid lipids in lipid bilayer hence phase separation. Owing to this ethosomes get facilitated through gaps smaller than the ethosomes themselves to successfully reach the deep layers of skin. Ethanol combined with moderate propylene glycol in ethosomes can significantly enhance the skin deposition of drugs [12].Mechanism proposed by Cevc.et al (1992) is that when elastic liposomes are applied onto the skin and allowed to dry the vesicles are attracted by the moisture in the epidermis and due to their flexibility they penetrate the skin. The osmotic gradient caused by the differences in water concentration between the skin surfaces and interiors, has been proposed as the major driving forces for the penetration of vesicles. Osmotic gradient is sufficiently strong to push at least 0.5 mg of lipids per hr and cm2 through the skin permeability barrier in the region of stratum corneum. [11]

1.3. Formulation aspects of ethosomes:

Things to be considered for ethosomal formulation are composition of lipid, Optimized ratio of additive mixture, Charge of the vesicle, Entrapment efficiency of drug and type of skin barrier. The crucial factors giving an optimized formulation are entrapment efficiency, vesicle size and transdermal flux and less influencing factors are phospholipid, ethanol, and sonication time. Entrapment efficiency is fraction of total drug entrapped in ethosomal system. It is deciding parameter for determining Polydispersibility index. Vesicle size precisely depends upon concentration of ethanol as it increases with decrease in ethanol concentration and increases with

Phospholipid concentration. Concentration ratio between phospholipid and ethanol and water is needed to be optimized.

1.3.1. Method of preparation

Ethosomes can be prepared and formulated by two methods i.e. Hot method and Cold method. Both methods are sound simple and convenient because no need of complex processes or sophisticated instruments.

1.3.1.1. Hot method

In this method disperse phospholipid in water by heating in a water bath at 400^0 C until a colloidal solution is obtained. In a separate vessel properly mix ethanol and propylene glycol and heat up to 400^oC. Add the organic phase into the aqueous phase.

Dissolve the drug in water or ethanol depending on its solubility [3, 13]. Once both mixtures reach 40^oC, add the aqueous phase into organic one.

1.3.1.2. Cold method

This method is the most widely used for the ethosomal preparation. Drug and Phospholipid is dissolved in ethanol at room temperature by vigorous stirring with the use of mixer. Propylene glycol is added during the stirring. The mixture is heated to 30^oC in a water bath. The water heated to 30^oC in a separate vessel is added to the mixture which is then stirred for 5 minutes in a covered vessel. The vesicle size of ethosomal formulation can be decreased to desire extend using sonication method [14, 9].

1.4. Evaluation Parameters:

Sr. no	Parameter	Importance	Method
1	Vesicle Size and shape	Determine skin penetration	SEM, TEM, DLS
2	Zeta potential	Stability of vesicles	Zeta Meter
3	Entrapment efficiency	Suitability of method	Ultracentrifugation
4	Drug content	Important in deciding the amount of vesicle preparation To be used.	UV, HPLC
5	Stability studies	To determine the shelf life of vesicle formulation	SEM, TEM, HPLC
6	*In vitro* dissolution	Determine the drug release rate from vesicle	Franz diffusion cell
7	Skin permeation	Determines rate of drug transport through skin	CLSM

A. Vesicle shape

Ethosomes can be easily visualized by using transmission electron microscopy (TEM) and by scanning electron microscopy (SEM).

B. Vesicle size and zeta potential

Particle size of the ethosomes can be determined by dynamic light scattering (DLS) and photon correlation spectroscopy (PCS). Zeta potential of the formulation can be measured by Zeta meter.

C. Transition temperature

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

D. Drug entrapment

The entrapment efficiency of ethosomes can be measured by the ultracentrifugation technique.

E. Drug content

Drug content of the ethosomes can be determined using UV spectrophotometer. This can also be quantified by a modified high performance liquid chromatographic method.

F. Surface tension measurement

The surface tension activity of drug in aqueous solution can be measured by the ring method in a Du Nouy ring tensiometer.

G. Stability studies

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.

H. Skin permeation studies

The ability of the ethosomal preparation to penetrate into the skin layers can be determined by using confocal laser scanning microscopy (CLSM).

1.5. Challenges and Opportunities:

Enhancement of stability is major issue. According to photostability study the degradation pattern of various formulation is ethanolic solution>ethosomes>gel~liposomes>solid liquid nanoparticles [15].Recently to improve the stability of ethosomes and to reduce aggregation concept of binary ethosomes has developed. It consist of ethanol and PEG instead of single ethanol phase. Lipoid 575 and mixture of ethanol and propylene glycol were used to improve ethosomes stability and skin drug delivery [12]. Finding the appropriate combination of variables that will form ethosomal formulation with optimal properties.

Fluid properties of lipid bilayers can be affected by reversible sedimentation due to different pharmaceutical components are present in colloidal suspension [16]. Optimum Polydispersibility index of ethosomal formulation could justify the homogenous nature of drug inside vesicle. To maintain rate and amount of drug release, it is the balance between drug affinity to vesicles and drug solubility in lipids of stratum corneum. High temperature will cause degradation of phospholipids and that will affect the gel to liquid transition of lipid bilayer ultimately defect in membrane packaging [17].Sensitizing capacity of micro scale ethosomes is more than that of Nanoethosomes. One possible mechanism for that fraction of phospholipid is lost in the extruder

membrane during extrusion process when producing nano form. [18] Determination of zeta potential is predictive of storage stability of ethosomal suspension.

1.6. Application of Ethosomes [11]:

Formulation	Principle ingredients	Rationale of ethosomal delivery	Application	Route of administration	Reference
5-aminolevulinic acid ethosomes	5-aminolevulinic acid(ALA)	Significantly improved the delivery of ALA in the inflammatory skin.	Anti-psoriasis	Topical	Yi-ping et al., 2009
Ammonium glycyrhizinate ethosomes	Ammonium glycyrhizinate	Ethosomes reduced the erytherma more rapidly with respect to drug solutions.	Anti-inflammatory	Topical	Paolino et al., 2005
Epigallocatechin gallete ethosome	Epigallocatechin gallete	Entrapment (-)-Epigallocatechin gallete (EGCG) into ethosomes was carried out for improving its stability against decomposition.	Anti-inflammatory	skin	Hyo et al., 2007
Erythromycin ethosome	Erythromycin	Ethosomal erythromycin was highly efficient in eradicating S.aureus-induced intradermal infections	Anti bacterial	skin	Godin &touitou 2005

Isoeugenol ethosome	Isoeugenol	Chemicals (allergen) in vesicular carrier system can enhance the sensitizing capacity.	allergen	skin	Jacob et.al.,2010
Matrine ethosome	Matrine	Improves the percutaneous permeation	Anti-inflammatory	topical	Zhaowvet et.al.2009
Methotrexate ethosome	Methotrexate	Ethosomes showed favourable skin permeation characteristics	Anti- pyretic	Topical	Dubey et al., 2007
Minoxidil ethosome	Minoxidil	Enhance the penetration and accumulation of minoxidil in the skin by Pilosebaceous targeting.	Hair growth promoter	Topical	Lopez-Pinto et al., 2005
Testosterone ethosome	Testosterone	Testosterone ethosome for enhanced transdermal delivery	Steroid hormone	Skin	Touitou et al., 2000
Trihexyphenidyl HCL ethosome	Trihexyphenidyl HCL	Increased drug entrapment efficiency, reduced side effect and constant systemic levels.	Anti-parkinsonian	Skin	Dayan and Touitou 2000
Acyclovir ethosome	Acyclovir	Binary combination of the lipophilic drug ACV-C16 and	Anti-viral	skin	Zhou et al.,2010

		the ethosomes synergistically enhanced ACV absorption into the skin			
Azelaic acid ethosome	Azelaic acid	Release rate was higher from ethosomes than from liposomes	Anti-keratinizing	Topical	Esposito et al.,2004
Bacitracin ethosome	Bacitracin	Ethosomal enhances intracellular delivery of and reduced drug toxicity in the skin	Polypeptide antibacterial	Topical	Godin &touitou 2004
Colchicine ethosome	Colchicine	Enhance skin accumulation, prolong release and improve the specificity	Anti-gout	Skin	Sing et al., 2008
Finasteride ethosome	Finasteride	Enhanced percutaneous absorption of finasteride 5-a reductase inhibitor		Skin	Roa et al., 2008
Fluconazole ethosome	Fluconazole	Enhances the skin permeation	Anti-Fungal	Topical	Bhalaria et al.,2009
Ibuprofen ethosome	Ibuprofen	Transdermal nanosystem, designed by using an ethosomal carrier	Antipyretic	Topical	Shumilov et al., 2010
Ligustrazine ethosome	Ligustrazine	Ethosome patch	Pulmonary vasodilator	Skin	Liu et al ., 2010

		enhances the permeation the skin			
Salbutamol ethosome	Salbutamol	Enhanced drug delivery through skin with ethosomes	Anti-asthmatic	Skin	Bendas& Tadros., 2007
Sotalol ethosome	Sotalol	Enhances the systemic absorption	anntiarrythmic	Skin	Kirjavanine m et al ., 1999
Vitamin A palmitate, Vitamin C, Vitamin E ethosome	Vitamin A Vitamin C Vitamin E	Anti-oxidation of phospholipid was increase due to the synergistic interaction of all three together as compare to individual use	vitamins	topical	Koli et al ., 2008

1.7. Transdermal Products Currently On the Us Market

The unique structure with highest penetration power and sound techniques of preparation make them popular formulations for commercialization of ethosomes. And they are suitable for incorporating different types of drug molecules.

Products	Narrative	Importance
BodyShape (MaccabiCARE)	Gel Executive solidification cellulite reduction, stretching the skin flexible and based on a technology called ethosomes.	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	Pilosebaceous targeting and high penetration into deep layers of skin.

	your hair when other minoxidil solution.	
Noinocellex (NTT, Israel)	Topical anti- cellulite cream	Deeper diffusion 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 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 with no stability problems, stable for at least 3 year at 250c Skin permeation experiments showed that the creams retained its initial penetration enhancing properties even after 3 yrs	Lipid perturbation.

The NTT, Novel Therapeutic Technology Inc, is 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.

1.8. Marketed Formulations based on Ethosomal Formulation:

There are numerous transdermal delivery systems currently available in the market. The transdermal drug delivery market, worth $12.7 billion dollars in 2005, is expected to reach $32 billion in 2015 [19]. The field of transdermal delivery now seems to be expanding further into the chronic treatment of neurological disorders, which has been showcased 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) [2,9,201,202][20].

2. CONCLUSION

This efficient transport system has been demonstrated to be effective with macromolecules such as peptides and proteins. This makes ethosome 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.

These are sophisticated conceptually but characterized by simplicity in their preparation, safety and efficiency.

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