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ETHOSOMES: UNIQUE ELASTIC VESICULAR CARRIER – AN OVERVIEW

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ABSTRACT: Ethosomes are phospholipid-based elastic vesicles which have a potential as novel topical and transdermal drug delivery systems. They are ethanolic phospholipids vesicles which can act as carriers for various medicaments. Ethosomes have gained importance in the area of research, because of their intensified skin permeation, better delivery of drug and increased drug entrapment efficiency. These systems are more efficient in delivering substances to the skin because of the presence of ethanol, which provides a net negative charge on the surface, which helps to avoid aggregation of vesicles due to electrostatic repulsion than either conventional liposomes or hydroalcoholic solutions in terms of quantity and depth. Ethosomes are simple to prepare and safe to use. This review attempts to compile the various aspects like mechanism of action, methods of preparation (Hot method, Cold Method, Dispersion method using rotary evaporator) ,advantages, limitations, characterization, applications in different conditions like Anti-inflammatory, Arthritis, Acne, Fungal infections, Bronchial asthma, chronic bronchitis, emphysema, Diabetic condition, Scleroderma, systemic lupus erythematosus and psoriasis, etc of reported ethosomal formulations for topical and transdermal use. Also, the patented literature has been tabulated.

INTRODUCTION: The main disadvantage of transdermal drug delivery is the poor penetration of most compounds into the human skin. The main barrier of the skin is the uppermost layer; the stratum corneum (SC). Several approaches have been reported to improve the penetration through the skin. One of the approaches is the use of vesicular systems like Ethosomes and Liposomes.

Ethosomes:

Ethosomes are phospholipid-based elastic vesicles containing 20–45% ethanol and water [1]. For the preparation of elastic vesicles; ethanol is a proven permeation enhancer that has been added in the vesicular systems.

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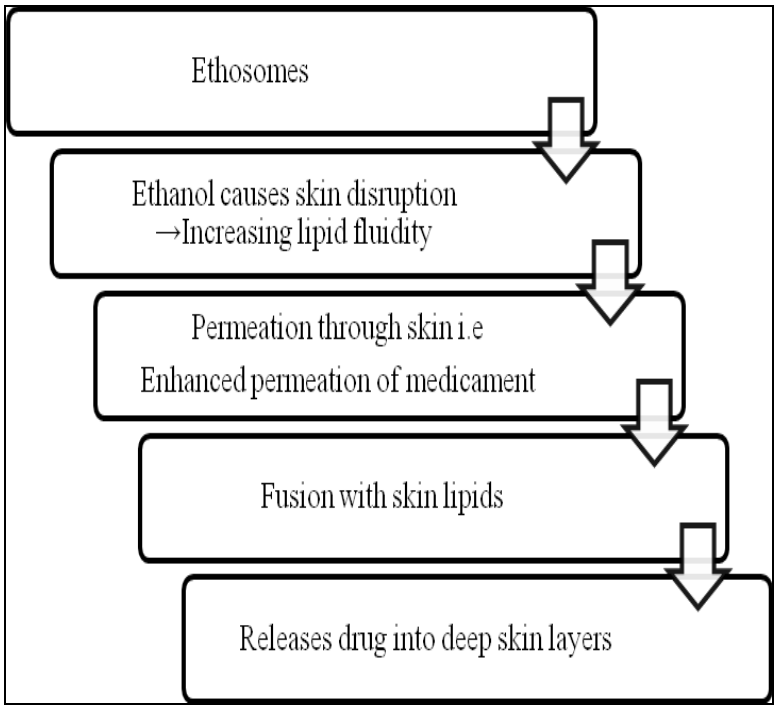
High flexibility imparted by ethanol of vesicular membranes permits the elastic vesicles to squeeze themselves through the pores. The proposed mechanism of penetration enhancement with the ethosomal system suggests the intercalation of ethanol into the polar head group environment resulting in increased membrane permeability. With respect to stability, Ethosomes have been reported to be more stable than liposomes because of the presence of ethanol, which provides a net negative charge on the surface [2], which helps to avoid aggregation of vesicles due to electrostatic repulsion. Topically applied ethosomes can increase the residence time of active ingredients in the stratum corneum, epidermis and reduce the systemic absorption of drugs. These properties allow Ethosomes to permeate easily into the deeper layers of the skin.

Advantages and Limitations of Ethosomes:

Advantages of ethosomes as a product include; ease of manufacture, high patient compliance,

enhancement of solubility and smaller size as compared to conventional vesicles. Ethosomes enhances the permeation of the drug through skin, disperse better, exhibit improved therapeutic efficacy and good storage stability, improved bioavailability and provide protection from toxicity. Ethosomes have applications in Veterinary, Pharmaceutical, Cosmetic, Biotechnology and Nutraceutical markets [3]. However, limitations include; Poor yield [2, 4,] unsuccessful vesicle formation can coalesce ethosomes [2] and product loss during transfer form organic to water media [2, 5].

Mechanism of Action of Ethosomes:



Methods of Preparation for Ethosomes: The following **Table 1** describes different preparation methods of ethosomes [2, 6, 7]

TABLE 1: METHODS OF PREPARATION

	Components		Order of Addition	Working temperature	Mixing time and speed	Size Reduction Technique
	Aqueous	Organic				
Cold Method	Water	Phospholipid, other lipid materials, drug, ethanol	Aqueous to organic	30°C	5minutes at 700-1000 rpm	Using high pressure homogeniz-ation, at 15,000 psi, in 3cycles
Hot method	Water, Ethanol, Propylene Glycol, drug	Phospholipid, drug	Aqueous to Organic	40°C	5minutes at 700- 1000 rpm	Using sonication or extrusion technique.
Dispersion method using rotary vaccum evaporator	Hydro-ethanolic Mixture, drug	Phospholipid, cholesterol, chloroform, methanol	Aqueous to Organic	Heating above lipid transition temperature for film formation	Suitable speed, temperature and time.	Not Reported

Characterization of Ethosomes: The following **Table 2** summarizes the tests and their techniques which enable characterization of Ethosomes [7, 8, 9]

TABLE 2: CHARACTERIZATION OF ETHOSOMES

Test	Technique/Instrument
Particle shape	Scanning Electron Microscopy, Transmission Electron Microscopy
Particle size analysis	Optical Microscopy
Drug Content	High Performance Liquid Chromatography/UV.
Drug Entrapment Efficiency	Ultra centrifugation technique.
In Vitro drug release study	Franz Diffusion cell.
In Vitro skin permeation study	Franz Diffusion cell.
Transition Temperature	Differential scanning calorimetry

Patents:

In 1995 and 1996 Touitou E filed first patent on ethosomes titled Composition for applying active substances to or through the skin US 5716638 and Compositions for applying active substances to or through the skin US5540934 A, respectively. It concluded the transdermal passage of an active ingredient, or in the introduction of such agent into the skin. [10, 11] The following **Table 3** summarizes patented literature on Ethosomes.

TABLE 3: PATENTS ON ETHOSOMES

Title	Patent Number	Inventors	Year	Reported Results
Chinese medicinal ethosome gel patch for treating herpes zoster and preparation method thereof [12]	CN103536700 (A)	Bu Ping; Hu Rong; Chen Lin; Wei Rong; Wu Huanhuan; Huang Xiaoli	2014	Easy in medication and convenient to use, has a good therapeutic effect, quick response, strong analgesic action but no adverse reaction.
Ethosome gel film-coating agent with multiple wound repair effects and preparation method of ethosome gel film-coating agent [13]	CN103893394 (A)	Chen Jie; Huang Changping; Zheng Maoxin; Nie Kaipin	2014	The Ethosome entrapped film-coating agent helps to promote healing and nutrition supplying of the wound tissue. The ethosome gel film-coating agent is suitable for wound clinical care and treatment.
Leflunomide ethosome composition and its preparation method[14]	CN103800277 (A)	Zhang Tao; Ding Yanji; Deng Jie; Luo Jing; Zhong Xiaodong	2014	Improves the transdermal rate of leflunomide, can significantly reduce side effects of oral administration of leflunomide and improves curative effects.
Daptomycin ethosome preparation [15]	CN103006562 (A)	Li Chong; Liu Xia; Yin Qikun; Wang Xiaoying; Chen Zhangbao	2013	The daptomycin ethosome preparation is a stable translucent dispersion system with light blue opalescence, small and uniform in particle size, high in entrapment efficiency and excellent in transdermal performance, drug release and has certain slow-release effect, and the preparation method is simple and convenient, low in cost and good in stability.
Bullatacin ethosome gel and preparation method thereof [16]	CN102552147 (A)	Jianping Tan; Lixin Jiang; Tanran Chang; Zhiwen Zhou	2012	The bullatacin ethosome gel provided by the invention can reduce irritation to the skin and has good percutaneous penetration effects.
Ethosome preparation of male hormone	CN102406605 (A)	Shu Meng; Jianxin Li; Yanmin Guan;	2012	To improve transdermal transport of male hormone

medicaments and its preparation method[17]		Dan Yang		medicaments and enhancing their curative effects.
Lidocaine ethosome and preparation method there of [18]	CN102813624 (A)	Zhao Xianying; Su Yongping; Gao Jining; Liu Yimin; Zhao Huawen; Xiao Xiang; Zhou Xiaoxia; Zhang Dinglin; Wu Liping	2012	The lidocaine ethosome of the present invention provides advantages of rapid onset, prolonged drug action time, further has advantages of small particle size, high penetration efficiency, high encapsulation efficiency and good stability.
Paclitaxel ethosome gel and preparation method there of [19]	CN102579323 (A)	Jianping Tan; Lixin Jiang; Tanran Chang; Zhiwen Zhou	2012	The action of stimulation to the skin can be reduced, and the percutaneous permeation effect is good.
Progesterone ethosome, and preparation method and application there of [20]	CN102397255 (A)	Shu Zhang; Hong Deng; Huaqing Lin; Xiaoling Zhang	2012	The progesterone ethosome is mainly applied to hormone replacement therapy, secondary amenorrhea, functional aplastic bleeding, premenstrual syndrome and the like clinically.
Acyclovir ethosome and preparation method there of [21]	CN102133183 (A)	Xuewen Wu; Yan Xiong	2011	Acyclovir ethosome has high stability and narrow particle size distribution.
Podophyllotoxin ethosomes and preparation methods there of [22]	CN102144972 (A)	Nianping Feng; Yanyan Yu; Jihui Zhao; Haiting Weng; Xiaoqin Shi	2011	The aims of increasing curative effect and reducing relapse and toxic and side effects are fulfilled. The invention also discloses two preparation methods for the podophyllotoxin ethosomes.

Applications of Ethosomal Formulations:

Reported literature indicates enhanced topical delivery of Azelaic acid, 5 aminolevulinic acid, Tretinoin, Isotretinoin, Naproxen, Ketotifen, Tetradrine, Apigenin, Bacitracin, Cyclosporin A, Mycophenolic Acid, Paclitaxel, Ammonium Glycyrrhizinate, Ketoconazole, Fluconazole and also enhanced transdermal delivery of Repaglinide, Tramadol, Aceclofenac, CiclopiroxOlamine, Alfuzosin Hydrochloride, Salbutamol, Valsartan, Curcumin, Diclofenac, Clotrimazole, Ketoprofen. Several phytochemicals and herbal extracts have also been successfully delivered via ethosomes which exhibit some distinct advantages over conventional drug delivery systems. [3] Following is a compilation of available literature on ethosomal formulations for specific conditions.

1. **Acne Treatment:**

✓ Sheba Rani Nakka David et al., compared ethosomal based Isotretinoin gel with marketed formulations of isotretinoin. Organoleptic properties, drug entrapment, drug content uniformity, in vitro drug release and skin permeation studies were compared. Ethosomal vesicles containing 2%w/w lecithin and 30%w/w ethanol were found to have shown the best entrapment percentage (99.21%). However, the in vitro skin permeation was increased with the addition of enhancers. It was concluded that the ethosomal vesicles and enhancers increased the skin permeation and depot formation of drug in the skin. [23]

2. **Anti-Inflammatory:**

✓ *In vitro* and *Ex vivo* skin deposition and transdermal flux of Apigenin loaded in deformable liposomes, ethosomes and liposomes were compared by Li-Na Shen et al. The efficiency of apigenin encapsulation increased with an increase in the amount of phospholipids in ethosomal formulations. Skin deposition and transdermal flux of apigenin improved with an increase in the levels of phospholipids (Lipoid S 75) and

short-chain alcohols like ethanol and propylene glycol, but decreased with an increase in the ratio of propylene glycol to ethanol. Optimized ethosomes showed superior skin targeting both in vitro and in vivo. They also reported the reduction of cyclooxygenase-2 levels in mouse skin inflammation induced by ultraviolet B (UVB) light and represent a promising therapeutic approach for the treatment of UVB-induced skin inflammation. [24]

3. Arthritis:

✓ Chao Fan, et al., worked to explore the feasibility of ethosomes prepared by pH gradient loading method for improving the antiarthritic efficacy of Tetrandrine by topical application. *Ex vivo* permeation and deposition behavior demonstrated that the drugs flux across rat skin and deposition of the drug in rat skin for ethosomes was 2.1 higher and for liposomes 1.7-fold higher. Confocal laser scanning microscopy confirmed that ethosomes could enhance the topical delivery of the drug in terms of depth and quantity compared with liposomes. [25]

4. Bronchial asthma, chronic bronchitis, and emphysema:

✓ Ehab R. Bendas, et al., compared the transdermal delivery of salbutamol sulfate (SS), from ethosomes and classic liposomes containing various cholesterol and dicetylphosphate concentrations. The vesicle size was significantly decreased by decreasing cholesterol concentration and increasing concentrations of dicetylphosphate and ethanol. The entrapment efficiency percentage was significantly increased by increasing concentrations of ethanol, cholesterol and dicetylphosphate.

✓ *In vitro* permeation studies of the prepared gels containing the selected vesicles showed that ethosomal systems were much more efficient at delivering SS into mice skin (in terms of quantity and depth)than were liposomes or aqueous or hydroalcoholic solutions. [26]

5. Diabetic condition:

✓ A.R. Rathore et al., evaluated the transdermal sustained release delivery systems potential of 'ethosomes'. Effect of different concentration of lipid studied, concluded that the size of the vesicles increased with increasing lipid concentration. Varying concentration of ethanol studied found that the size of the vesicles decreased with increasing ethanol concentration. The optimized formulation of ethosomes showed highest release (73.23 ± 2.32). Repaglinide encapsulated ethosomes in gel was found to have shown maximum in-vitro drug release (89.67 ± 2.35) as compared to other carbopol concentrations and free drug gel. It was concluded that ethosomes were a promising candidate for transdermal delivery of repaglinide. It possessed better skin permeation potential, leading to improvement in bioavailability of drug, reduction of dose and dosing frequency. [27]

6. Fungal Infections:

✓ Rahul G.S. Maheshwari et al, compared the transdermal potential of novel vesicular nanocarriers: ethosomes and ultradeformable liposomes, containing Clotrimazole. The ethosomal formulation and ultradeformable liposomal formulation showed entrapment in the range of 68 to 69% and 55-56% respectively and optimal nanometric size range 132 ± 9nm and 121± 9.7 nm respectively. The ethosomal formulation provided enhanced transdermal flux, smallest polydispersity index and decreased the lag time of 0.9 h in comparison to ultradeformable liposomal formulation. Skin interaction and FT-IR studies revealed greater penetration enhancing effect of ethosomal formulation.

✓ The ethosomal formulation also had the highest zone of inhibition, in contrast to liposomal formulation and marketed cream against candidal species. It was concluded that ethosomes are the most proficient carrier system for dermal and transdermal delivery of Clotrimazole. [28]

7. **Scleroderma, systemic lupus erythematosus and psoriasis:**

✓ T. Limsuwana et al., have developed ethosomes containing Mycophenolic Acid (MPA) for topical delivery. Ethosomal formulation composed of 4% w/v soya phosphotidylcholine with cholesterol, Tween80 and deoxycholic acid as additives in a molar ratio of 6:2:1:1 respectively. The dispersion medium was 30% v/v ethanol in phosphate buffer pH 7.4. The vesicle size, Zeta potential, entrapment efficiency of ethosomes are 371 ± 8nm (PI = 0.27 ± 0.02 nm), -46 ± 5 mV, 56 ± 1% respectively. [29]

The following **Table 4** summarizes formulation details of reported literature of Ethosomes for topical use.

TABLE 4: ETHOSOMES FOR TOPICAL USE

Active Pharmaceutical Ingredient	Medical Condition	Dosage form	In-vitro/Ex vivo release medium and time	Reported Results
Alfuzosin Hydrochloride [30]	Inflammation	Suspension	Phosphate Buffer Saline pH 7.4 for 24hrs	Ethosomes are better carriers for Alfuzosin hydrochloride transdermal delivery.
5-aminolevulinic acid (ALA) [31]	Inflammation	Suspension	pH 5 citrate–phosphate buffer for 12 hours.	ALA containing ethosomes improved penetration of ALA and the formation of protoporphyrin IX and reduced tumor necrosis factor -a compared to ALA aqueous solution
Ammonium Glycyrrhizinate [32]	Inflammation	Suspension	pH 7.4 isotonic phosphate-buffered solution for 24hours	Prolongation of its therapeutic activity, promising carrier for topical administration due to the enhanced delivery of drugs
Azelaic acid [33]	Acne	Ethosomal Gel	Isotonic Palitzsch Buffer/Ethanol 70:30 (v/v) for 6hours	Release rate was more rapid from ethosomal system than from liposomal system
Ciclopirox Olamine [34]	Fungal infections	Suspension	Not Reported	Enhanced accumulation of ciclopiroxolamine via ethosomal carrier within the skin might help to optimize targeting to the epidermal and dermal sites.
Curcumin [35]	Inflammation	Solution	0.25% sodium dodecyl sulfate and 10% ethanol solution for 24hours	Curcumin-Propylene glycol liposome had the best encapsulation efficiency and the highest and longest inhibition on paw edema, followed by Ethosomes and Traditional liposomes
Diclofenac [36]	Inflammation, Benign prostatic hyperplasia.	Suspension	Saline (NaCl 0.9%, w/v) for 24hours	Diclofenac loaded Penetration enhancer-containing vesicles, are capable of localizing the drug at the site of inflammation as compared to conventional.
Fluconazole [37]	Fungal infections	Ethosomal cream	Phosphate Buffer Saline, pH 7.4 and 10% methanol for 72hours	Better antifungal activity compared to marketed formulation.
Ketoconazole [38]	Fungal infections	Suspension	Phosphate buffer, pH 7.4 with 1% sodium lauryl for 72hours	Enhanced properties with increasing concentrations of ethanol and by subjecting vesicles for sonication.

Ketoprofen [39]	Inflammation	Suspension	Phosphate Buffer Saline, pH 7.4 for 24hours	Enhanced transdermal delivery.
Ketotifen [40]	As mast cell stabilizer	Suspension	pH 7.4 isotonic phosphate buffer with 0.11% (w/v) formaldehyde for 24hours	Ethosomes containing Ketotifen both inside and outside the vesicles exhibit superior skin deposition.
Paclitaxel [41]	Actinic keratoses	_	Water/ethanol solution for 24hours.	Paclitaxel-loaded ethosomes represent a promising topical drug delivery system for the clinical treatment of Actinic keratoses and Squamous cell carcinoma.
Tramadol Hydrochloride [6]		Ethosomal gel	Phosphate-buffered saline,pH 7.4 for 12hours	Optimum drug release and efficiency and non irritant on skin.
Tretinoin [42]	Acne	Suspension	Mixture of 0.01 M saline phosphate buffer,pH7.4 and 0.1% PEG-40 for 6hours	Tretinoin–ultradeformable vesicles formulation proved to be suitable for dermal delivery.
Valsartan [43]	Hypertension	Suspension	Ethanol: Phosphate-buffered saline, pH 7.4 for 24hours	Nanoethosomal formulation potentially useful carrier for transdermal delivery. Enhancement of skin permeation and bioavailability of valsartan.

CONCLUSION: A review of the published data suggests that topically used ethosomes prove to be superior when compared with conventional formulations and offer improved safety and efficacy. Drugs entrapped in ethosomes remain in intact vesicles and exhibit penetration enhancing effect. Drug vesicular based delivery systems are hence promising in the treatment of a variety of skin disorders.

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