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An innovative method for transdermal medication delivery: Ethosomes

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ABSTRACT

Skin is a major target and a principal barrier for topical or transdermal drug delivery. Despite many advantages of this system, the major obstacle is the low diffusion rate of drugs across the stratum corneum. Ethosomes, as novel vesicles in transdermal drug delivery, significantly affect drug penetration through the biological membrane. Ethosomes are phospholipid-based elastic nanovesicles containing a high content of ethanol (20-45%). Ethosomal systems are much more efficient in delivering substances to the skin in terms of quantity and depth than either conventional hydroalcoholic or hydroalcoholic solutions. Enhanced delivery of bioactive molecules through the skin and cellular membranes using an ethosomal carrier opens numerous challenges and opportunities for the research and future development of novel improved therapies.

Keywords: Transdermal drug delivery, Ethosomes, Phospholipid, Hydroalcoholic, Bioactive.

I. INTRODUCTION

The skin is the largest and most easily accessible organ of the body; it serves as a potential route of drug administration for systemic effects. However, the outer layer of the skin, the stratum corneum, represents the most resistant 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 non-invasive and can be self-administered.[19,20]

A new era of research in this field was opened with the use of liposomes for the topical delivery of triamcinolone,[21,] and since then, a wide range of novel lipid-based vesicular systems have been developed. Deformable or elastic liposomes, which arecurrently known as transfersomes, were introduced by Cevc and Blume in 1992[16]and followed by the innovative work of Touitou et al, which led to the discovery of a novel lipid vesicular system called ethosomes. Ethosomal systems differ from liposomes because they contain relatively high concentrations of ethanol, in addition to phospholipids and water.[17,18]New generations of ethosomal systems have been introduced since then by adding other compounds to the basic ethosomal formula in an attempt to enhance vesicular characteristics and skin permeation.[1]

ETHOSOMES

The “Somes” are the cell-like formulations of a novel drug delivery system.Ethosomes are non-invasive delivery vehicles that enable drugs to reach the deep skin layers and/or the systemic circulation. Ethosomes contain phospholipids, alcohol (ethanol and isopropyl alcohol) in comparatively high concentration, and water. [22] Ethosomes are soft, malleable vesicles composed mainly of phospholipids, ethanol (relatively high concentration) and water. These “soft vesicles” signifya novel vesicular carrier for boosted delivery through the skin. The size of ethosome vesicles can be controlled from tens of nanometres to microns.

Ethosomes contain phospholipids like conventional liposomes; however, they also contain high levels of alcohol. It has also been demonstrated that its components can reach deeper layers of the skin or enter systemic circulation. [7]The structure of ethosomes is illustrated in Figure 1.

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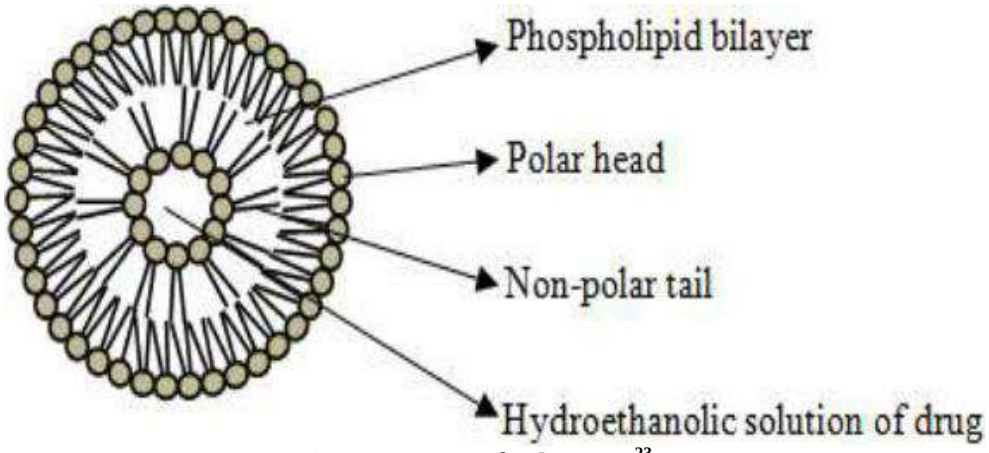

Fig.1. Structure of Ethosomes[23]

ETHOSOMES COMPOSITION:

The ethosomal system consists of phospholipids, ethanol and water. The phospholipids with various chemical structures include phosphatidyl choline (PC), hydrogenated PC, phosphatidyl ethanolamine (PE), phosphatidyl glycerol (PGG), phosphatidyl inositol (PI), hydrogenated PC etc. The non-aqueous phase ranges between 22 % to 70 %. The alcohol may be ethanol or isopropyl alcohol. Dyes or amphiphilic fluorescent probes such as D–289, Rhodamine–123, fluorescence isothiocyanate (FITC), 6 – carboxy 6-carboxyfluorescein are often added to ethosomes for characterisation studies.[6]

Table 1. Various additives are incorporated in the ethosomal formulation.

S. No.	Class	Examples	Uses
1.	Phospholipid	Soya phosphatidyl choline Egg phosphatidyl choline Dipalmitoyl phosphatidyl choline Distearyl phosphatidyl choline	Vesicles forming component.
2.	Polyglycol	Propylene glycol Transcutol RTM	As a skin penetration enhancer.
3.	Alcohol	Ethanol Isopropyl alcohol	For providing softness to the vesicle's membrane, as a penetration enhancer
4.	Cholesterol	Cholesterol	For providing stability to the vesicle membrane.
5.	Dyes	Rhodamine red Fluorescence isothiocyanate	For a characterisation study

TYPES OF ETHOSOMES:

1. Classical Ethosomes: Phospholipids, ethanol at a high concentration of up to 45% w/w, and water make up traditional ethosomes. From 130.077 Da to 24 kDa, the molecular weights of medicines contained in conventional ethosomes have been reported.[24,25]

2. Binary Ethosomes: Zhou et al. introduced binary ethosomes.[26] In general, they were created by mixing a different form of alcohol with the traditional ethosomes. Propylene glycol (PG) and isopropyl alcohol (IPA)are the two alcohols that are most frequently utilised in binary ethosomes.

3. Transethosomes: The new generation of ethosomal systems, known as transethosomes, was initially described by Song et al. in 2012.[27] This ethosomal system includes a substance, such as a surfactant or a penetration enhancer, in addition to the fundamental elements of classicalethosomes. According to reports, transethosomes can entrap

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pharmaceuticals with molecular weights ranging from 200-325 kDa to 130.077 Da.[28,29]

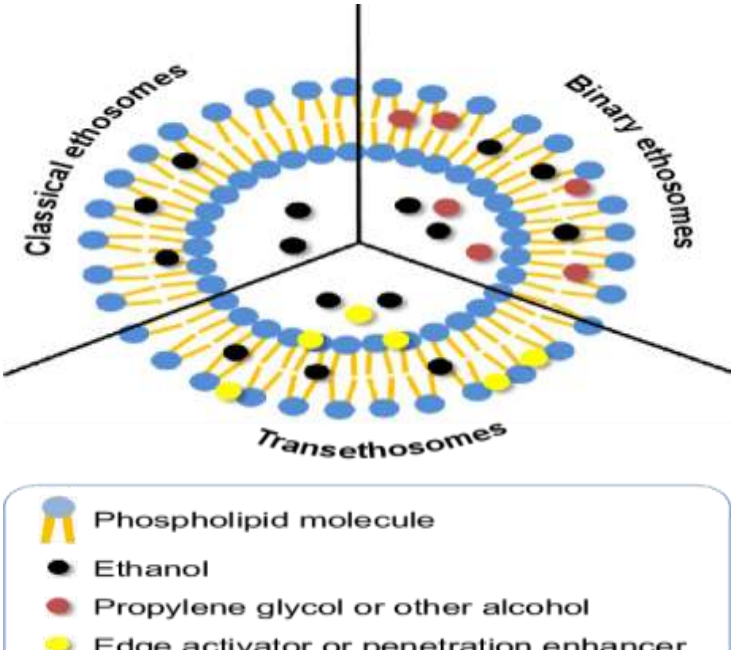

Figure 2:Schematic representation of the different types of endosomal systems. [1]

ADVANTAGES OF ETHOSOMES:

1. Delivery of large molecules (peptides, protein molecules) is possible.
2. It contains non-toxic raw materials in the formulation.
3.Ethosomal drug permeation of the drug through skin for a transdermal drug delivery system can be applied widely in pharmaceutical, veterinary, and cosmetic fields.
4. High patient compliance: The ethosomal drug is administered in semisolid form (gel or cream), hence producing high patient compliance.
5. Simple method for drug delivery in comparison to iontophoresis and phonophoresis, and other complicated methods.
6. The ethosomal system is passive, non-invasive and is available for immediate commercialisation.[30,31]

LIMITATION OF ETHOSOMES

1.There is a Poor yield.
2. Where shell locking is not effective, then the ethosomes may coalesce and fall apart on transfer into the water.
3. During the transfer from organic to water media, lossof product may occur**.**

MECHANISM OF PENETRATION OF ETHOSOMES

- **Effect of ethanol**

Ethanol interacts with polar head groups of lipid molecules, thereby decreasing the stratum corneum's melting point and increasing the membrane permeability and fluidity. It also acts by pull and push mechanisms. Due to an increase in thermodynamic activity with the stratum corneum, ethanol evaporates from the vesicular system, resulting in a push effect, which enhances the penetration and permeability of the vesicles, resulting in a pull effect. So, the soft and flexible vesicles penetrate deeper skin layers, thus ethanol works as an effective enhancer in penetration.[32,33,34]

- **Ethosomes effect**

The presence of ethanol in the ethosomes results in increased fluidity of lipids and permeability of the cell membrane, so ethosomes fuse with the skin lipids and penetrate to the deeper layer of the skin and release the drug.[35] These mechanisms of action, along with the structure described in Figure 3.

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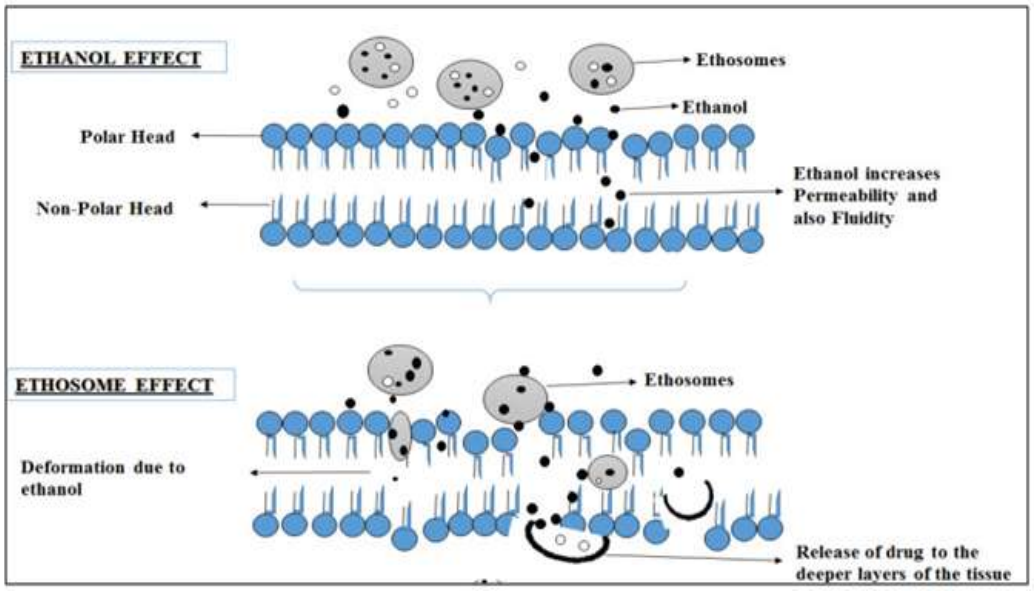

Fig 3:Mechanism of Penetration of Ethosomal Drug Delivery System[4]

METHODS OF PREPARATION OF ETHOSOMES

The preparation of ethosomes is done using a variety of techniques. The three most popular methods are as follows:

1. Cold method
2. Hot method
3. Thin film hydration method
4.Ethanol injection–sonication method
5. Transmembrane pH-gradient Method

1. Cold Method: One of the procedures frequently used to manufacture ethosomes. First, in this method, ethanol is continuously stirred while phospholipid, cholesterol, and drug are solubilised. This procedure is being done at room temperature and in a covered vessel at the same time. Propylene glycol is then added at 40℃while being continuously stirred. The temperature of this mixture is raised to 30℃. For an additional five minutes, the mixture is stirred in a covered vessel.The sonication or extrusion processes can be used to conduct or carry out size reduction of the particles or a combination. It is then placed in a refrigerator for storage. [37,38]

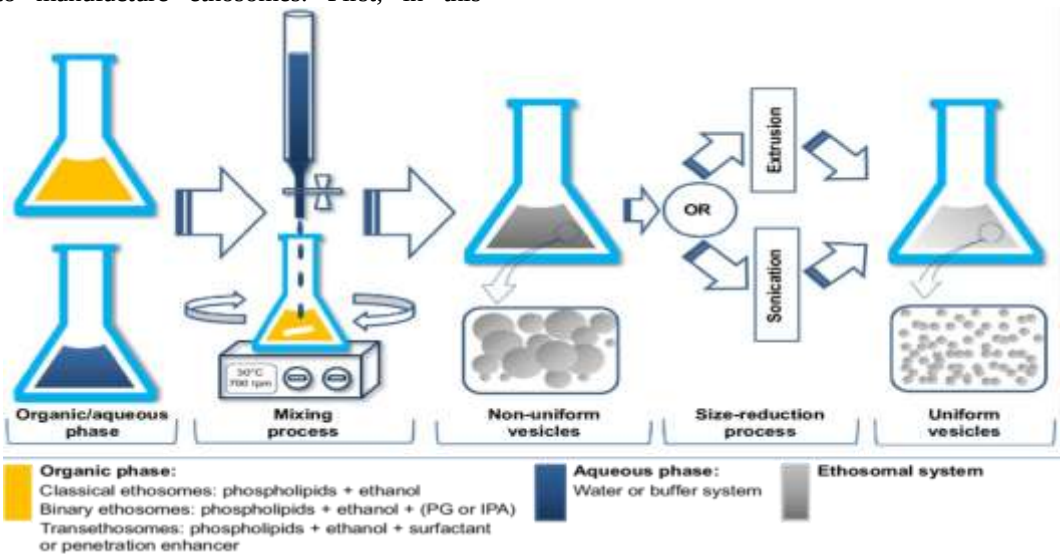

Figure 4: Cold method for the preparation of ethosomal systems. Abbreviations: PG, propylene glycol; IPA, isopropyl alcohol.[1]

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2. Hot Method: When ethosomes are made using the Hot technique, first, the phospholipid is dissolved in water and heated in a water bath at 40℃ to create a colloidal solution. The organic phase is also combined with propylene glycol and ethanol at 40℃. This is then added and combined with the aqueous phase at a temperature of 40℃. The medicine is then simultaneously added to the aforementioned mixes after being solubilised by dissolving in asuitable solvent, such as water or ethanol (depending on solubility). Extrusion or sonication techniques can be used for further size reduction. [36,5]

3. Ethanol injection–sonication method: Using a syringe system and a flow rate of 200 L/min, the organic phase containing the phospholipid dissolved in ethanol is introduced to the aqueous phase in this method. The mixture is then homogenised for 5 minutes with an ultrasonic probe.[39]

4. Transmembrane pH-gradient Method: All of the aforementioned techniques add the drug to the organic or aqueous phase, where it is then "passively" or spontaneously loaded into the ethosomal system. Based on the pH gradient difference between the basic exterior of the external phase of the ethosomal system and the acidic interior of the internal phase, the medication is loaded "actively" in the transmembrane pH-gradient approach. The idea behind this technique was first used to create liposomes, after which Zhou et al. and Fan et al. [40] used it to create ethosomal systems of tetrandrine and S. alopecuroides total alkaloid extracts, respectively.

Any of the aforementioned methods are used to prepare the empty ethosomal suspension in the first stage, but an acidic buffer is used during the aqueous phase or the hydration process. The active loading of the drug into the unfilled ethosomal suspension occurs in the second stage, which is followed by continuous stirring. To make the external phase more alkaline and to establish the pH gradient between the acidic internal (pH 3) and basic external phases of the ethosomal system, an alkali, usually a sodium hydroxide solution of 0.5 M, is added to make the external pH 7.4.[26]

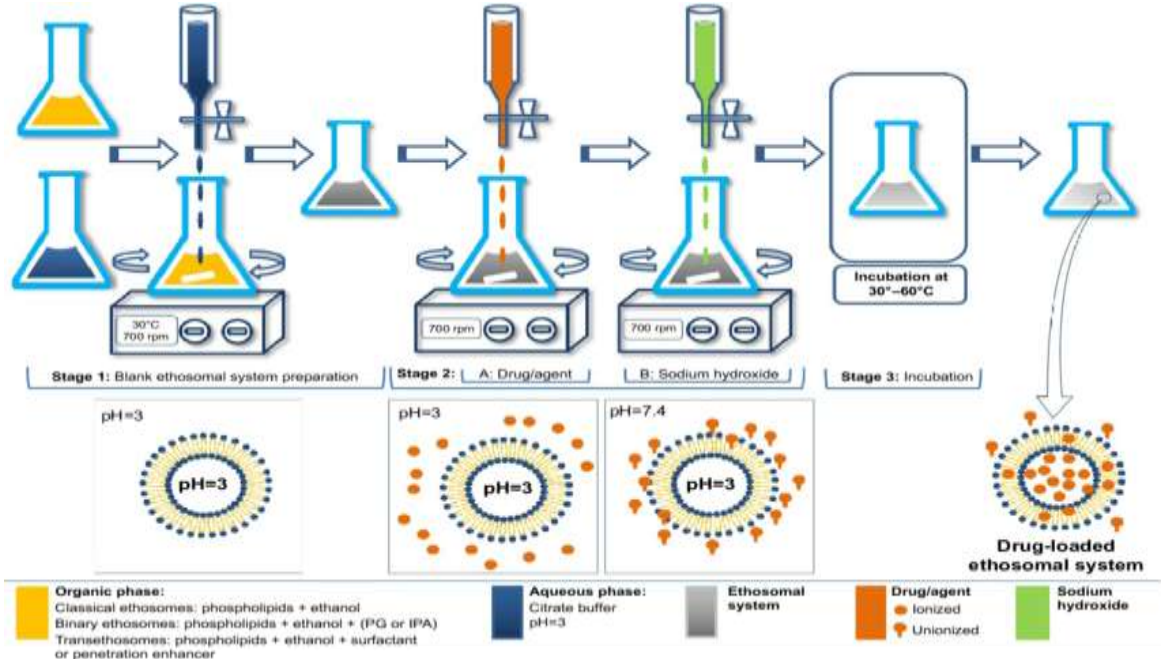

Figure 5: The transmembrane pH-gradient method for the preparation of ethosomal systems. Abbreviations: PG, propylene glycol; IPA, isopropyl alcohol.[1]

5. Thin film hydration Method: This is an advancement over the standard liposome synthesis technique, but in this technique, a hydroethanolic solution hydrates the lipid film. In a clean, dry, round-bottom flask, the phospholipid is first dissolved in chloroform only[43] or a chloroform-methanol mixture at ratios of 3:1[25] or 2:1[33]. Rotating vacuum evaporators are used to extract organic solvents at temperatures higher than the lipid-phase transition temperature. The solvent remnants are then overnight vacuum-extracted from the deposited lipid film. A water-ethanol

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solution[42] or phosphate-buffered saline-ethanol solution[25] is then used to hydrate the lipid film. The lipid film is rotated and heated for 30 minutes, 1 hour, or 6 hours, depending on the phospholipid property, during the hydration process [7]

CHARACTERISATION OF ETHOSOMES:

There are various methods for the characterisation of ethosomes. They are as follows-

- **Physical Characterisation:** Ethosomes can be physically characterised using Motic Image Plus software. It is an economic way to find out whether the ethosomes have been prepared or not. Also, a primary particle size evaluation can be done for the formulation. Further evaluation and appropriate sizing should be done using Malvern Zetasizer.
- **Visualisation:** Ethosomes can be visualised using transmission electron microscopy (TEM) and scanning electron microscopy (SEM). .[44]
- **Vesicle size and Zeta potential:** Particle size and zeta potential for ethosomes can be determined by dynamic light scattering (DLS) using a computerised inspection system and photon correlation spectroscopy (PCS).[9]
- **Entrapment Efficiency:** The entrapment efficiency of the drug entrapped inethosomes can be measured by the ultracentrifugation technique. [10]
- **Transition Temperature:** The transition temperature of the vesicular lipid systems can be determined by using differential scanning calorimetry (DSC). .[11]
- **Surface Tension Activity Measurement:** The surface tension activity of the drug in aqueous solution can be measured by the ring method in a Du Nouy ring tensiometer.[12]
- **Vesicle Stability:** The stability of ethosomal 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.[13]
- **Drug Content:**The Drug can be quantified by a modified high-performance liquid chromatographic (HPLC) method.[14]
- **Penetration and Permeation Studies:** Depth of penetration from ethosomes can be visualised by confocal laser scanning microscopy (CLSM). .[15]

STABILITY OF ETHOSOMES:

Ethosomes extend better stability as compared to conventional pharmaceutical liposomes [45,46 Liposomes], on storage, tend to fuse and grow into larger vesicles, and this fusion and breakage of liposome vesicles on storage describes an important problem of drug leakage from the vesicles.[47]The absence of electrostatic repulsion is likely to be the reason for the tendency of neutral liposomes to aggregate, whereas in ethosomes, ethanol grounds a modification of the net charge of the system (imparts negative charge to the system) and confers it some degree of steric stabilization, resulting into increased stability of vesicles against agglomeration and drug leakage from vesicles. Increasing the concentration of ethanol from 20 to 45% increases the entrapment efficiency owing to an upsurge in the fluidity of the membranes. However, anextra increase in the ethanol concentration (>45%) destabilises the vesicles and possibly makes the vesicle membrane further leaky, thus leading to a decline in entrapment efficiency.[48]

APPLICATION OF ETHOSOMES THERAPEUTICALLY:

Ethosomes may be used for a variety of drug delivery applications. Ethosomes are primarily used to replace liposomes. The transdermal route of drug delivery is generally preferred. Ethosomes can be used to deliver hydrophilic and impermeable drugs through the skin. Various drugs have been used in conjunction with an ethosome carrier.

1. Ethosomes in transdermal drug delivery

By virtue of their ability to pass through the intact human skin lucratively, the use of ethosomes can result in drug delivery efficiency of more than 65%.[2]Ethosomes have been successfully investigated for the transport of various therapeutic agents across the skin for their effectiveness in the treatment of various skin diseases.

2. DNA delivery

Several environmental pathogens try to cross the verge of body through the skin, which serves as an excellent defensive barrier, which is also immunologically active and able to express genes.[49] These facts support another essential application of ethosomes, as their utility in the delivery of DNA molecules to express genes in skin cells. [50]Touitou et al. encapsulated green fluorescent protein (GFP)–cytomegalovirus (CMV)- driven transfecting construct into an ethosomal formulation. They applied this formulation to the dorsal skin of 5-week-old male CD-1 nude mice for 48 h. After 48 h, the treated skin was removed, and penetration of the GFP formulation was observed by CLSM studies. It was observed that topically applied ethosomes–GFP–CMV-driven transfecting construct enabled efficient delivery and expression of genes in skin cells.[2]

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3. Hormone delivery

Oral delivery of hormones is allied with various problems like high first-pass metabolism, low oral bioavailability and several dose-dependent side effects. In addition, along with these side effects, oral hormonal preparations relyheavily on patient compliance. The risk of failure of treatment is known to increase with each pill missed.[51] Touitou et al. revealed the potential of ethosomes in hormonal delivery by performing a comparative study of transdermal delivery of testosterone-loaded ethosomes (Testosome) in contrast to a transdermal patch of testosterone (Testoderm patch, Alza) across rabbit pinna skin, which showed about 30 timeshigher skin permeation of testosterone from the ethosomal formulation. The amount of drug deposited was significantly (p 50.05) higher in the case of ethosomal formulation (130.76 ± 18.14 and 18.32 ± 4.05 mg at the end of 7 h for Testosome and Testoderm, respectively). The area under the curve (AUC) and C_{max} of testosterone significantly improved after the application of Testosome as compared to Testoderm. Hence, both in vitro and in vivo studies demonstrated improved skin permeation and bioavailability of testosterone from the ethosomal formulation. This group, in their further study, designs the testosterone non-patch formulation to reduce the area of application. It has been found that with ethosomal testosterone formulation area of application required to produce the effective plasma concentration was 10 times less than required by the commercially available gel (Androgen) formulation.[2]

4. Delivery of Anti-Viral Drugs

Zidovudine is a potent antiviral agent acting on the acquiredimmunodeficiency virus. Oral administration of zidovudine is associated with strong side effects. Therefore, anadequate zero-order delivery of zidovudine is desired tomaintain the expected anti-AIDS effect. Jain et al. (2004) concluded that ethosomes could increase the transdermalflux, prolong the release and present an attractive routefor sustained delivery of zidovudine.Acyclovir is another antiviral drug that is widely usedtopically for the treatment of Herpes labialis.Theconventionally marketed acyclovir external formulation isassociated with poor skin penetration of hydrophilicacyclovir to the dermal layer, resulting in weak therapeuticefficiency. It is reported that the replication of the virus takesplace at the basal dermis. To overcome the problemassociated with the conventional topical preparation of Acyclovir. Horwitz et al. formulated the acyclovirethosomal formulation for dermal delivery. The resultsshowed that shorter healing time and higher percentageof abortive lesions were observed when acyclovir wasloaded into ethosomes.[3]

5. Delivery of anti-Parkinsonism agent

Dayan and Touitou prepared an ethosomes mal formulation ofpsychoactive drug trihexyphenidyl hydrochloride (THP)and compared its delivery with that from a classicalliposomal formulation. THP is an M1 muscarinic receptorantagonist and is used in the treatment of Parkinsondisease. The results indicated better skin permeationpotential of ethosomal-THP formulation and its use forbetter management of Parkinson disease.[52]

6. Transcellular Delivery

Touitou et al., in their study demonstrated betterintracellular uptake of bacitracin, DNA and erythromycin using CLSM and FACS techniques in different cell lines.Better cellular uptake of anti-HIV drug zidovudine andlamivudine in MT-2 cell line from ethosomes as comparedto the marketed formulation suggested ethosomes to bean attractive clinical alternative for anti-HIV therapy.[5,8]

7. Delivery of Anti-Arthritis Drug

Topical delivery of anti-arthritis drug is a better optionfor its site-specific delivery and overcomes the problemassociated with conventional oral therapy. Cannabidol(CBD) is a recently developed drug candidate fortreating rheumatoid arthritis. Lodzki et al., prepared CBDethosomalformulation for transdermal delivery. Resultsshow significantly increased in biological anti-inflammatoryactivity of CBD-ethosomal formulation wasobserved when tested by carrageenan induced rat pawed Ema model. It was concluded encapsulation of CBD inethosomes significantly increased its skin permeation,accumulation and hence it's biological activity.[52]

8. Delivery of Antibiotics

Topical delivery of antibiotics is a better choice forincreasing the therapeutic efficacy of these agents.Conventional oral therapy causes several allergicreactions along with several side effects. Conventionalexternal preparations possess low permeability to deepskin layers and subdermal tissues.[41] Ethosomes can circumvent this problem by delivering sufficient quantityof antibiotic into

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deeper layers of skin. Ethosomespenetrate rapidly through the epidermis and bringappreciable amount of drugs into the deeper layer ofskin and suppress infection at their root. With this purposein mind Godin and Touitou prepared bacitracin anderythromycin loaded ethosomal formulation for dermaland intracellular delivery. The results of this study showedthat the ethosomal formulation of antibiotic could behighly efficient and would overcome the problemsassociated with conventional therapy.[52]

MARKETED PRODUCT OF ETHOSOMES

The ethosomes technology started to be commercialised in the year 2000.Only two companies have produced ethosomes-related goods (Table 2).

Table 2. Products marketed based on ethosomal drug delivery system

S.No.	Product Name	Uses	Manufacturer
1.	Decorin cream	Wrinkles, sagging, age wrinkles, loss of elasticity, and hyperpigmentation are some of the noticeable ageing symptoms of the skin that can be treated, healed, and delayed with an anti-aging cream.	Genome Cosmetics, Pennsylvania, US
2.	Noicellex	Anti-cellulite cream for the skin.	Novel Therapeutic Technologies, Israel
3.	Cellutight EF	Aeffective combination of ingredients in a topical cellulite cream helps to boost metabolism and breakdown fat.	Hampden Health, USA
4.	Nanominox	The ethosomes are used for the first time in a minoxidil containing product. Contains 4% Minoxidil, a well-known hair growth promoter that must be metabolised to the active compound through sulfation.	Sinere, Germany
5.	Supravir cream	In order to cure the herpes virus	Trima, Israel
6.	Skin genuity	Cellulite-busting agent that also decreases the appearance of orange peel.	Physonics, Nottingham, UK

II. CONCLUSION AND FUTURE POSSIBILITIES:

The stratum corneum barrier of skin does not permit transport of most of the therapeutic agents and drugs. Ethosomes are uniquely designed and tailored vesicles consisting high concentration of ethanol which makes them extra malleable and proficient enough of retorting to peripheral hassling by fluidizing and disturbing the rigid lipid system of stratum corneum finally resulting in successful delivery of therapeutic agents deeply across the skin. These systems not only offer a superior prospect for the non-invasive delivery of small, medium and large-sized drug molecules but also provides simplified patient compliance and low-cost treatment. Results of the first clinical study of acyclovir-ethosomal formulation support this conclusion, however ethosomes needs more exploration in terms of safety in some clinical conditions like the irritant effect of ethanol applied to open areas of eczema cannot be ignored as a possible potential inadequacy of ethosomes.

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Therefore, further research in this area will allow better control over drug release in vivo, permitting physician to make the therapy more efficient. Given the interest of researchers in these ethanol-based vesicles, it is evident that these systems clasps immense prospective in future on various grounds like their easy manufacturing, vastness in drug delivery and therapeutic effectiveness. All these perspective makes ethosomes a promising carrier in delivery of bioactive agents.

REFERENCES:

[1]. Abdulbaqi IM, Darwis Y, Khan NA, Abou Assi R, Khan AA. Ethosomal nanocarriers: the impact of constituents and formulation techniques on ethosomal properties, in vivo studies, and clinical trials. International journal of nanomedicine. 2016; 11:2279.

[2]. Touitou E, Godin B. Ethosomes for skin delivery. Journal of drug delivery science and technology. 2007 Jan 1;17(5):303-8.

[3]. Verma NK, Singh AK, Mall PC, Yadav V, Jaiswal R. Ethosomal Drug Delivery System: A Novel Approach to Transdermal Drug Delivery-A Review.

[4]. Nayak D, Tippavajhala VK. A comprehensive review on preparation, evaluation and applications of deformable liposomes. Iranian Journal of Pharmaceutical Research: IJPR. 2021;20(1):186.

[5]. Verma P, Pathak K. Therapeutic and cosmeceutical potential of ethosomes: An overview. Journal of advanced pharmaceutical technology & research. 2010 Jul;1(3):274.

[6]. Nandure HP, Puranik P, Giram P, Lone V. Ethosome: A Novel Drug Carrier. International Journal of Pharmaceutical Research & Allied Sciences. 2013 Jul 1;2(3).

[7]. Pingale P. Ethosomes—Newer Trend in Transdermal Drug Delivery: A Review. Int. J. Pharma Res. Health Sci. 2018; 6:2586-90.

[8]. Touitou E.; Preparation of liposomes and size determination, In: Liposomes A Practical Approach, New RRC (Ed.),Oxford University Press, Oxford, 1990:36-39.

[9]. Guo J, Ping Q, Sun G, and Jiao C, Lecithin vesicular carriers for transdermal delivery of cyclosporine A, Int. J.Pharm., 2000, 194(2), 201-207.

[10]. Maghraby GMM, Williams AC, and Barry BW, Oestradiol skin delivery from ultradeformable liposomes: refinement of surfactant concentration, Int. J. Pharm., 2000, 196(1), 63-74.

[11]. Fry DW, White JC, and Goldman ID, Rapid secretion of low molecular weight solutes from liposomes withoutdilution, Anal. Biochem.,1978, 90, 809-815.

[12]. Cevc G, Schatzlein A, and Blume G, Transdermal drug carriers: Basic properties, optimization and transfer efficiency in case of epicutaneously applied peptides, J. Control. Release, 1995, 36, 3-16.

[13]. Vanden Berge BAI, Swartzendruber VAB, and Geest J, Development of an optimal protocol for the ultrastructural examination of skin by transmission electron microscopy, J. Microsc.,1997, 187(2), 125-133.

[14]. Dayan N, and Touitou E, Carrier for skin delivery of trihexyphenidyl HCl: Ethosomes vs liposomes. Biomaterials,2002, 21, 1879-1885.

[15]. Toll R, Jacobi U, Richter H, Lademann J, Schaefer H, and Blume U, Penetration profile of microspheres in follicular targeting of terminal hair follicles, J. Invest. Dermatol., 2004, 123, 168-176.

[16]. Cevc G, Blume G. Lipid vesicles penetrate into intact skin owing to the transdermal osmotic gradients and hydration force. Biochim Biophys Acta. 1992;1104(1):226–232.

[17]. Touitou E. inventor and assignee. Compositions for applying active substances to or through the skin. United States patent US 5540934 A. 1996 Jul 30.

[18]. Touitou E, Dayan N, Bergelson L, Godin B, Eliaz M. Ethosomes — novel vesicular carriers for enhanced delivery: characterization and skin penetration properties. J Control Release. 2000;65(3):403-418.

[19]. Prausnitz MR, Langer R. Transdermal drug delivery. Nat Biotechnol. 2008;26(11):1261–1268.

[20]. Schoellhammer CM, Blankschtein D, Langer R. Skin permeabilization for transdermal drug delivery: recent

advances and future prospects. Expert Opin Drug Deliv. 2014;11(3):393–407.

[21]. Mezei M, Gulasekharam V. Liposomes – a selective drug delivery system for the topical route of administration: I. Lotion dosage form. Life Sci. 1980;26(18):1473–1477.

[22]. Vinod KR et al., A Review on Genesis and Characterization of Phytosomes, International Journal of Pharmaceutical Sciences Review and Research, September – October 2010; Volume 4, Issue 3, Article 013,69-72.

[23]. R Rakesh et al., Ethosomes for Transdermal and Topical Drug Delivery, International Journal of Pharmacy and Pharmaceutical Sciences, Volume 4, Supplement 3, 17-24.

[24]. Zhang Z, Wo Y, Zhang Y, et al. In vitro study of ethosome penetration in human skin and hypertrophic scar tissue. Nanomedicine. 2012;8(6): 1026–1033.

[25]. Mishra D, Mishra PK, Dabadghao S, Dubey V, Nahar M, Jain NK. Comparative evaluation of hepatitis B surface antigen-loaded elastic liposomes and ethosomes for human dendritic cell uptake and immune response. Nanomedicine. 2010;6(1):110–118.

[26]. Zhou Y, Wei Y, Liu H, Zhang G, Wu X. Preparation and in vitro evaluation of ethosomal total alkaloids of Sophora alopecuroides loaded by a transmembrane pH-gradient method. AAPS PharmSciTech. 2010;11(3):1350–1358.

[27]. Song CK, Balakrishnan P, Shim CK, Chung SJ, Chong S, Kim DD. A novel vesicular carrier, transethosome, for enhanced skin delivery of voriconazole: characterization and in vitro/in vivo evaluation. Colloids Surf B Bio interfaces. 2012;92:299–304.

[28]. Ainbinder D, Touitou E. A new approach for skin tumor treatment: from delivery system characterization to in vivo evaluation. Drug Deliv Transl Res. 2011;1(1):53–65.

[29]. Chen M, Gupta V, Anselmo AC, Muraski JA, Mitragotri S. Topical delivery of hyaluronic acid into skin using SPACE-peptide carriers. J Control Release. 2014; 173:67–74.

[30]. Dhamecha, D. L., Rathi, A. A., Saifee, M., Lahoti, S. R., & Dehghan, M. H. G. (2009). Drug vehicle-based approaches of penetration enhancement. Int J Pharm Pharm Sci, 1(1), 24-46.

[31]. Verma NK, Singh AK, Mall PC, Yadav V, Jaiswal R. Ethosomal drug delivery system: A novel approach to transdermal drug delivery: A review.

[32]. Verma P and Pathak K. Nanosized ethanolic vesicles loaded with econazole nitrate for the treatment of deep fungal infections through topical gel formulation. Nanomedicine (2012) 8: 489–96.

[33]. Maheshwari RGS, Tekade RK, Sharma PA, Darwhekar G, Tyagi A and Patel RP. Ethosomes and ultradeformable liposomes for transdermal delivery of clotrimazole: A comparative assessment. Saudi Pharm. J. (2012) 20: 161–70.

[34]. Limsuwan T and Amnuaikit T. Development of ethosomes containing mycophenolic acid. Procedia Chem. (2012) 4: 328–35.

[35]. Tyagi LK, Kumar S, Maurya SS and Kori ML. An official publication of association of pharmacy professionals ethosomes: novel vesicular carrier for therapeutic application. IOSR J. Pharm. (2013) 3: 6–13.

[36]. Bhalaria MK, Naik S, Mishra AN. Ethosomes: A novel system for antifungal drugs in the treatment of topical fungal disease. Ind J Exp Biol 2009; 47:368-75.

[37]. Dubey V, Mishra D, Jain NK. Melatonin loaded ethanolic liposomes: Physicochemical characterization and enhanced transdermal delivery. Eur J Pharm Biopharm 2007; 67:398-405.

[38]. Dubey V, Mishra D, Dutta T, Nahar M, Saraf DK, Jain NK. Dermal and transdermal delivery of an anti-psoriatic agent via ethanolic liposomes. J Control Release 2007; 123:148-154.

[39]. Liu X, Liu H, Liu J, et al. Preparation of a ligustrazine ethosome patch and its evaluation in vitro and in vivo. Int J Nanomedicine. 2011;6: 241–247.

[40]. Fan C, Li X, Zhou Y, et al. Enhanced topical delivery of tetrandrine by ethosomes for treatment of arthritis. Biomed Res Int. 2013;2013:161943.

[41]. Fang YP, Tsai YH, Wu PC, Huang YB. Comparison of 5-aminolevulinic acid-encapsulated liposome versus ethosome for skin delivery for photodynamic

therapy. Int J Pharm. 2008;356(1–2):144–152.
[42]. López-Pinto JM, González-Rodríguez ML, Rabasco AM. Effect of cholesterol and ethanol on dermal delivery from DPPC liposomes. Int J Pharm. 2005;298(1):1–12.
[43]. Park S, Lee H, Gu H. Enhanced skin delivery and characterization of rutin-loaded ethosomes. Korean J Chem Eng. 2014;31(3):485–489.
[44]. Touitou E.; Preparation of liposomes and size determination, In: Liposomes A Practical Approach, New RRC (Ed.), Oxford University Press, Oxford, 1990:36-39.
[45]. Goti A, Patel V. Ethosomally entrapped clotrimazole: a view to improve therapeutic response of antifungal drug (AAPS Pharmaceutical Sciences World Congress Abstract). AAPS J 2007; 15.
[46]. Xiao-yu L, Yue-feng R, Wen-quan L. Study on transdermal penetration of ethinyl estradiol ethosome gel. Chinese Pharm J 2006; 41:284-286.
[47]. Riaz M. Stability and uses of liposomes. Pakistan J Pharm Sci 1995; 8:69-79.
[48]. Verma P, Pathak K. Therapeutic and cosmeceutical potential of ethosomes: an overview. J AdvPharm Tech Res 2010; 1:274-282.
[49]. Tu ¨ting T, Storkus WJ, Falo LD. (1998). DNA immunization targeting the skin: molecular control of adaptive immunity. J Invest Dermatol 2: 183–8.
[50]. Pre ´at V, Dujardin N. (2001). Topical delivery of nucleic acids in the skin. STP Pharma Sci 11:57–68.
[51]. Johnsen SG, Bennett EP, Jensen VG. (1974). Therapeutic effectiveness of oral testosterone. Lancet 2:1473–5.
[52]. Verma NK, Singh AK, Mall PC, Yadav V, Jaiswal R. Ethosomal drug delivery system: A novel approach to transdermal drug delivery: A review.