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ETHOSOME: A NEW TECHNOLOGY USED AS TOPICAL & TRANSDERMAL DELIVERY SYSTEM

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ABSTRACT

Transdermal drug delivery system was first introduced more than 20 years ago. Transdermal drug delivery system is a type of convenient drug delivery system where drug goes to the systemic circulation through the protective barrier i.e. Skin is the main target of topical and transdermal preparations. Major aim of transdermal drug delivery system is to cross the stratum corneum. Various methods have been tried to increase the permeation rate of drugs temporarily. Vesicular system is one of the most controversial methods for transdermal delivery of active substances in that ethosome are the ethanolic phospholipids vesicles which are used mainly for transdermal delivery of drugs. Ethosomes are soft, malleable vesicles tailored for enhanced delivery of active agents. Ethosomes have higher penetration rate through the skin. The increased permeation of ethosomes is probably due to its ethanolic content. Ethanol increases the cell membrane lipid fluidity which results in increased skin penetrability of the ethosomes. These ethosomes permeates inside the skin and fuse with cell membrane lipids and release the drug. Hot and cold methods are used for formulation of ethosomes. Evaluation parameters include size, shape, drug content, zeta potential etc. Ethosomes have been successfully evaluated for the delivery of many drugs for e.g. Cyclosporine A, insulin, salbutamol, trihexyphenidil, etc. Ethosomes provides a number of important benefits including improving the drug's efficacy, enhancing patient compliance and comfort and reducing the total cost of treatment. Ethosomes can be important drug delivery tool in the future.

Keywords: Ethosomes, Transdermal, Vesicular carriers, Ethanol, Phospholipid.

INTERODUCTION

The oral drug delivery system has overcome a no. of limitation such as degradation of drug by enzyme, irritation of gastro intestinal mucosa and first pass metabolism effect. Also due to the pain on administration associated with parental route.[1,2] Due to the above resion the transdermal route is highly prefer by the patient hence research the ethosome carrier moiety for the transdermal drug delivery system. The ethosome are used for delivery of drug by transdermal route, this route is most important route of drug administration. Ethosome are interesting and innovative drug delivery system that have large field in pharmaceutical technology and drug delivery in resent year. The ethosome are used for those drugs that have lower penetration to the membrane of skin. These are ethonlic liposomes. Ethosome are lipid vesicle containing phospholipids alcohol (ethonal and isopropyl alcohol) in high concentration and water. [3] It is a soft vesicle. The size range of ethosome may vary from tens nanometers to microns ethosomes permeate through the skin layers more rapidly and possess significantly higher transdermal flux. [3, 4, 5, 6] The ethosome is used for delivery of drug by transdermal route. This route is most important route of drug administration. The ethosome is transport the active drug through the stratum corneum layer of skin in comparison to the conventional liposome. [3, 7] For the trance dermal drug delivery the stratum corneum layer is main barrier for permeation , for this aspect design a carrier to be applied topically both for topically and systemic drug administration. The combination of phospholipids and higher concentration of ethanol in vesicular formulation is responsible for the systemic effect and for the deeper distribution and penetration in the skin lipid bilayers. Ethosome can entrap drug molecule with various physiochemical characteristics i.e. of hydro phallic and lipophilic or amphiphilic. [(3, 8, 9)] Liposome, noisome, transferosome and ethosome also have been reported to enhance permeability of drug through the stratum corneum barrier. Permeation enhancer increases the permeability of the skin, so that the drug can be cross through the skin. [3, 10, 11]

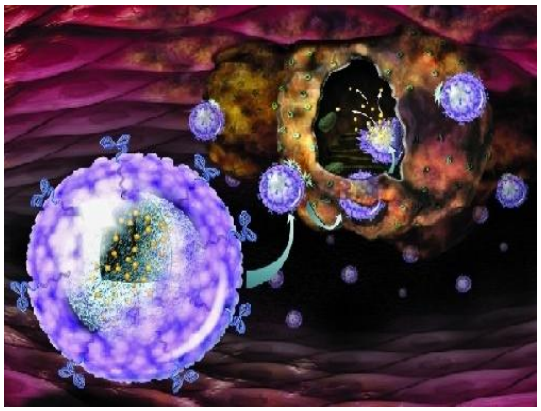


Figure 1: Microscopic view of Ethosome vesicle [12]

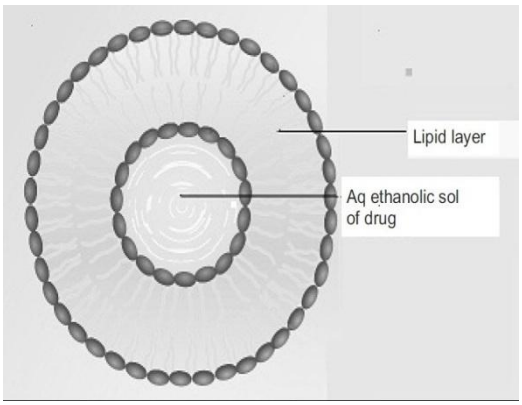


Figure 2: Structure of ethosome vesicle [13]

NEED FOR TRANSDERMAL DRUG DELIVERY-

Despite the challenges, Transdermal delivery (TDD) offers several unique advantages including relatively large and readily accessible surface area for absorption, ease of application and termination of therapy. Further, evolution of better technologies for delivering drug molecules, safe penetration enhancers and the use of vesicular carriers have rejuvenated the interest for designing TDD system for drugs that were thought to be unfit for trans dermal delivery.

ADVANTAGE OF ETHOSOMAL DRUG DELIVERY- [14, 15, 16, 17]

- Enhanced permeation of drug through skin for transdermal drug delivery.
- It contains non-toxic row material in formulation.
- Ethosome composition is safe and the components are approved for pharmaceutical and cosmetic use.
- Delivery of lunge molecules (peptides protein molecules) is possible.
- Simple method for drug delivery in comparison to iontophoresis and phonophorresis and other complication method.
- The ethosome system is passive non-invasive and is available for immediate commercialization.
- High patient compliance the ethosomal drug is administrated in semisolid form (gel or cream) hence producing high patient compliance.
- Ethosomal drug delivery system can be applied widely in pharmaceutical vet nary cosmetic field.

DISADVANTAGE OF ETHOSOME DRUG DELIVEY- [15, 18, 19]

- Drugs that require high blood levels cannot be administered – limited only to potent molecules, those requiring a daily dose of 10mg or less.
- Ethosomal administration is not a means to achieve rapid bolus type drug input, rather it is usually designed to offer slow, sustained drug delivery.
- Adequate solubility of the drug in both lipophilic and aqueous environments to reach dermal microcirculation and gain access to the systemic circulation.
- The molecular size of the drug should be reasonable that it should be absorbed percutaneously.
- Adhesive may not adhere well to all types of skin. Uncomfortable to wear.
- May not be economical. Poor yield.
- Skin irritation or dermatitis due to excipients and enhancers of drug delivery systems.
- In case if shell locking is ineffective then the ethosomes may coalescence and fall apart on transfer into water.
- Loss of product during transfer from organic to water media.
- The main advantage of ethosomes over liposomes is the increased permeation of the drug.

COMPOSITION OF ETHOSOME [17, 20]

Ethosome are vesicular carrier composed of hydroalcohalic orhydrolglycolic phospholipids, in which the concentration of water and alcohol is high. The high concentration of ethanol makes the ethosome unique. The rang of alcohol in final product is -20-30%. The ethosome is contain phaspholipid with various chemical structure like phasphotidyl choline, hydrogenated phasphotidyl choline phasphatic acid and phasphotidyl glycerol, phasphatidyl inositol, alcohol, water and propylenrglycol. The drug delivery can be change by chainging the ratio of alcohol:water or alcohol-polyol:water.Some preferred phaspholipid are soyaphaspholipids such as phaspholipon90 (PL-90), it is usually employed in range of 0.5-10% w/w cholesterol at connected rangimg b/w 0.1/1% can also be added to the preparation.

EXAMPLE- Alcohol like ethanol and isopropyl alcohol and glycols like propylene glycol transcutol are generally used. Some time non-ionic surfactant is used with phospholipids preparation and cationic lipid like coca-amide POE alkyl amine, dodecylamine, cetrimide etc are generally used. The concentration of the non-aqueous phase (alcohol and glycol) may long b/w 22-70%.

Table 1: Defferent Additive Employed in Formulation of Ethosome

CLASS	EXAMPLE	USE
Phospholipids	Soya phosphatidyl choline Egg phosphatidyl choline Dipalmityl phosphatidyl choline Distearyl phosphatidyl choline	Vesicles forming component
Polyglycol	Propylene glycol Transcutol RTM	As a skin penetration enhancer
Alcohol	Ethanol Isopropyl alcohol	For providing the softness for vesicle membrane As a penetration enhancer
Cholesterol	Cholesterol	For providing the stability to vesicle membrane
Dye	Rhodamine-123 Rhodamine red Fluorescene Isothiocynate (FITC) 6- Carboxy fluorescence	For characterization study
Vehicle	Carbopol Đ934	As a gel former

SKIN-[21]

The skin is the largest organ of the body and has surface area about 1.5-2cm^2 in adult. There are 2 important layer- a. Epidermis b. Dermis

The epidermis is most superficial layer of the skin and is composed of stratified keratinized squamous epithelium.

The epidermis is composed of 4-5 layers depending on the region of skin being considered. The layers are-

a) - cornified layer (stratum corneum)

b) - translucent layer (stratum granulosm)

c) - spinous layer (stratum spinosm)

d) - germinal layer (stratum basale)

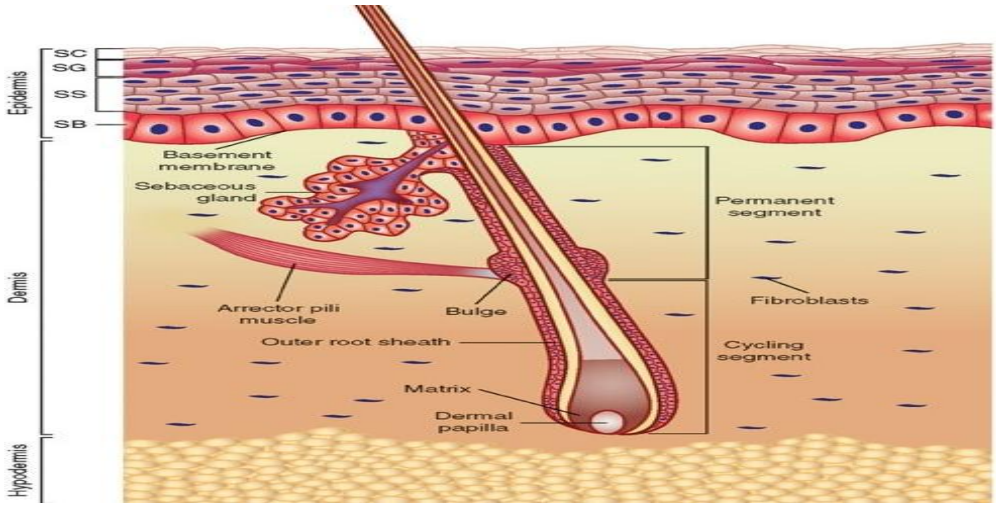


Figure 3: Structure of Skin [22]

a) **Stratum corneum** –it is composed of 10-30 layers of polyhedral anucleated corneocytes, with the palms and soles having the most layers. Corneocytes are surrounded by a protein envelope, filled with water-retaining keratin proteins, attached through corneodesmosomes and surrounded in the extracellular space by stacked layer of lipid. The stratum corneum layer plays an important role in the barrier function of topical/ transdermal drug delivery. Human skin has selective permeability for drug, lipophilic drug can pass through the skin but the drug which are hydrophilic in nature cannot pass through skin.Water soluble drug show either very less or no permeation. To improve the permeation of drug through the skin various mechanisms have been investigated, including use of chemical or physical enhancer such as iontophoresis or sonophoresis. Liposomes, niosomes, transferosomes and ethosome are also enhancing the permeability of drug through stratum corneum. Permeability enhancer increase the permeability of the skin so that the drug can cross the through the skin easily. Ethosomes can enhance permeation through the stratum corneum barrier. [3, 23, 24] The thickness of stratum corneum layer is 10 micro grams and it consists of 10-25 rows of dead carneocytes embedded in a lipid matrix. The heterogeneous structure of the stratum corneum is composed of approximately 75-80% protein, 5-15% lipid, 5-10% unidened on a drug ewight basis. [25]

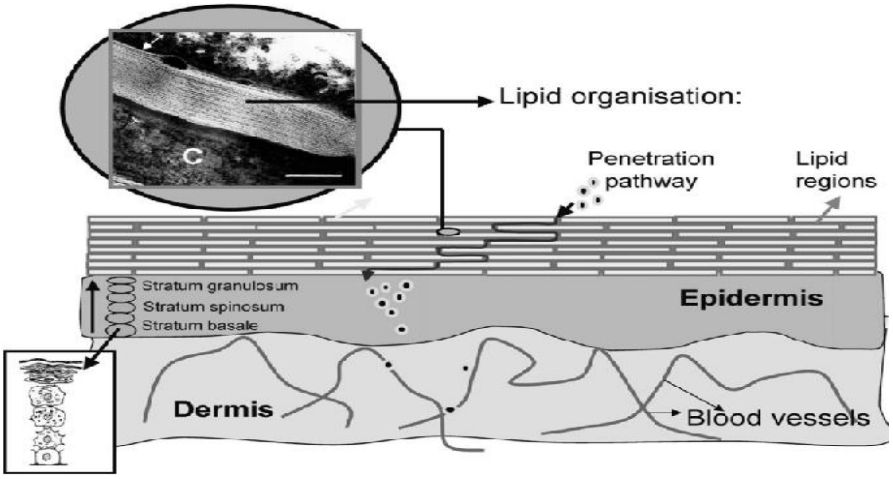
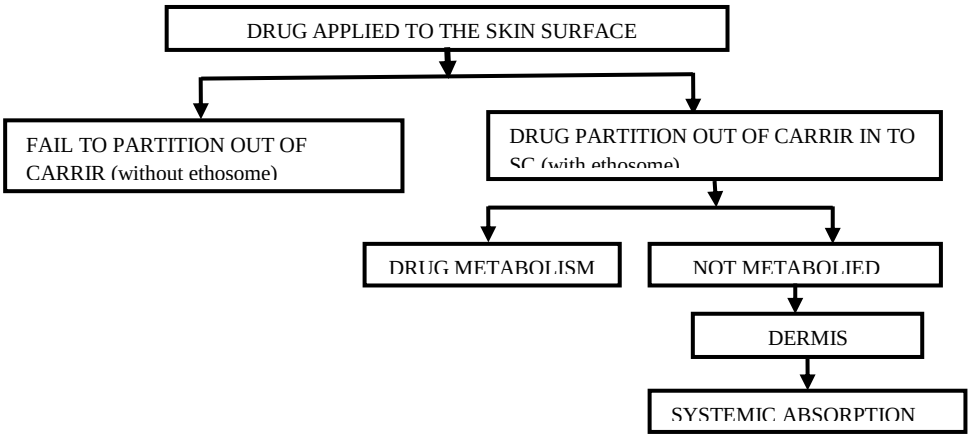


Figure 4: Cross section of Skin [26]

MECHANISM OF DRUG PENETRATION-

It is the pass through that the first pass part of the mechanism is due to the ethanol effect where by interaction of the ethanol into intracellular lipid increasing lipid fluidity and decreasing the density of lipid multilayer.

This is followed by the ethosome effect, that includes inter lipid penetration and permeation by the opening of new pathways due to the fusion of ethosome with skin lipid.



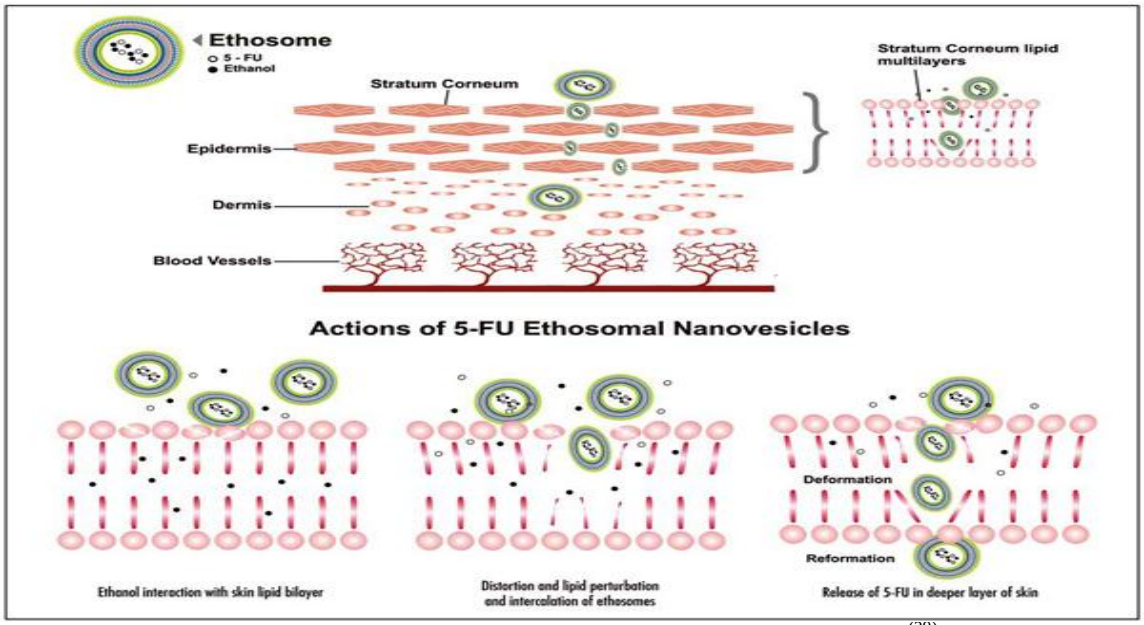


Figure 5: Release of drug from ethosome in deep layer of the skin [(29)]

THE DRUG ABSOPTION OCCURS IN FOLLOWING TWO PHASE- [27, 28]

a) - Ethanol effect
b) - Ethosome effect

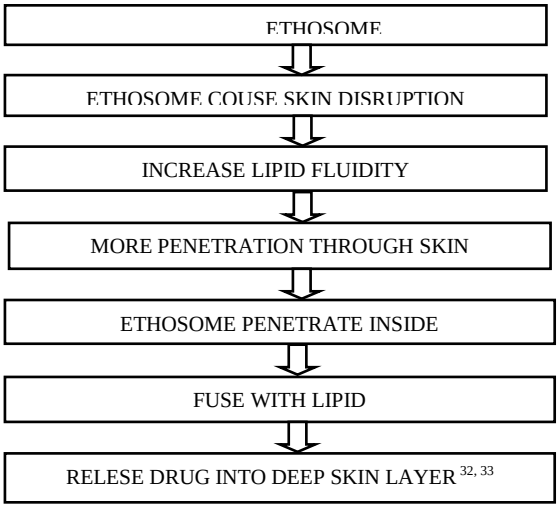
a) - ETHANOL EFFECT-

Ethanol acts as a penetration enhancer through the skin. The mechanism of penetration enhancing effect is well known. Ethanol penetrates into intracellular lipid sand increase the fluidity of cell membrane lipid and decrease the density of lipid multilayer of cell membrane.

ETHANOL: AS PENETRATION ENHANCER-

Substances that reversibly reduce the barrier resistance of the stratum corneum are known as chemical penetration enhancers. 20 Ethanol is one of the most commonly used permeation enhancers. A number of mechanisms have been proposed for permeation enhancing action of ethanol. As a solvent, ethanol can be included in the formulation to enhance the solubility of the drug. This is particularly important for poorly soluble permeants, as they are prone to depletion in the donor vehicle. Ethanol is a relatively volatile solvent and will rapidly evaporate at skin tem-perature. Ethanol loss from a formulation may lead to the drug becoming supersaturated, which influ-ence drug will flux across the membrane.[27, 30, 31]

b) – ETHOSOMES EFFECT-

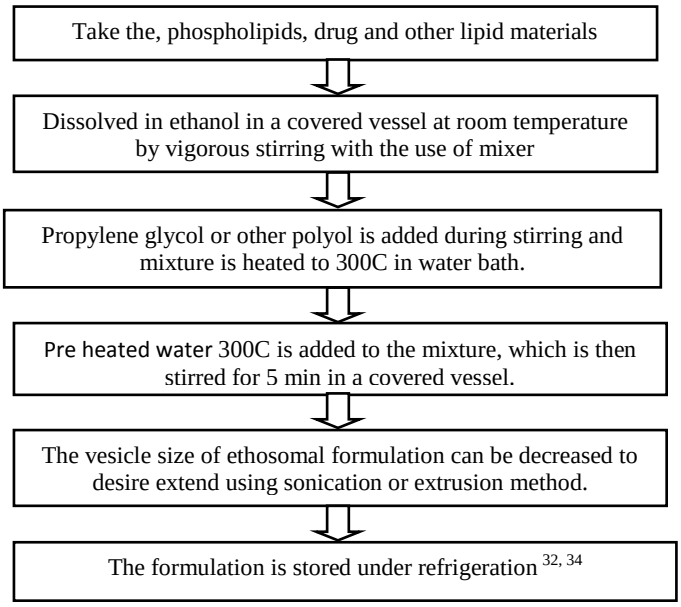


METHOD OF PREPRATION OF ETHOSOME

Ethosomal formulation may be prepared by hot or cold or injection method or optimized method.

These methods are very simple and convenient and do not involve any sophisticated instrument or complicated process and easy to scale up at industrial level.

A) - COLD METHOD-



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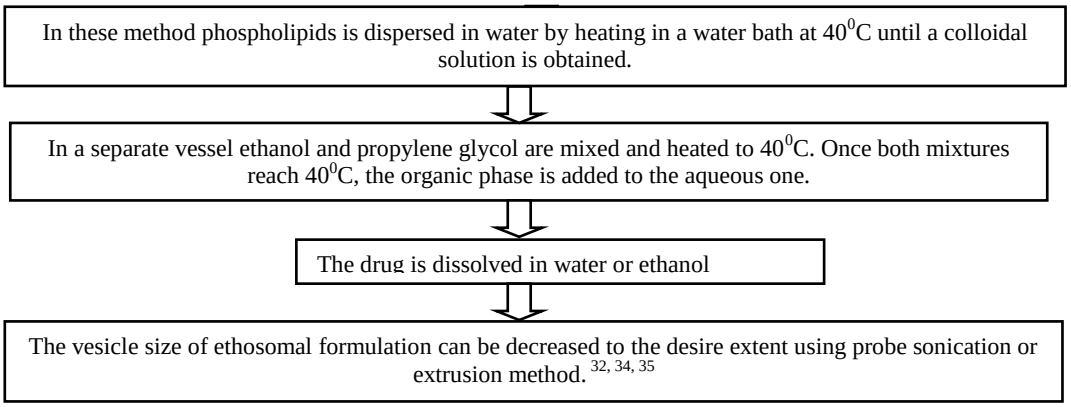
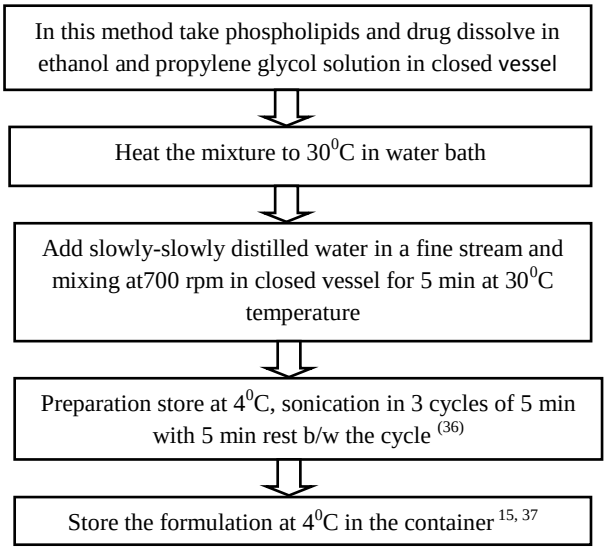
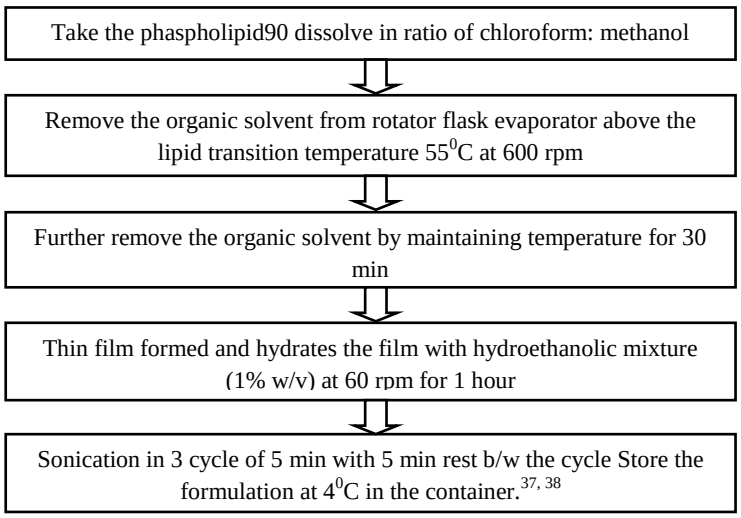
B) - HOT METHOD



C) - INJECTION METHOD



D) - OPTIMIZATION METHOD-



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VARIOUS METHOD OF CHARECTERIZATION OF ETHOSOME-

1. Optical Microscope Observation-

The ethosomal dispersion is spread on the glass slide with the help of glass rod. Prepare the multilamella vesicles were detected by examining the ethosomal suspension using an optical microscope with the magnification power of 100 X. [27, 39, 40]

2. Vesicle size and zeta potential-

Particle size of the ethosomes can be detected by dynamic light scattering (DLS) and photon correlation spectroscopy (PCS). Zeta potential of the ethosome suspension can be measured by Zeta meter. [27, 41]

3. Transition temperature-

The transition temperature of the vesicular lipid systems can be measured by using differential scanning calorimetric. [27, 42]

4. Visualization-

Visualization of ethosomes can be done by using instrument transmission electron microscopy (TEM) and by scanning electron microscopy (SEM). Visualization of an ethosomal formulation by the electron microscopy reveals exhibited vesicular structure 300-400 nm in diameter. [5, 43]

5. Scanning electron microscopy (SEM)-

The different type of lipid affects the surface morphology or shape of the particles. Solid lipid microparticles are deposits on metallic surface then it placed in liquid nitrogen and dried under vacuum. The microparticles are coated uniformly with gold by freeze-dried. The morphology and surface properties of ethosome formulation can be measured by a scanning electron microscope.

6. Drug content-

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

7. Stability studies-

The stability of vesicles can be determined by assessing the size and structure of the vesicles over time. It means size is measured by DLS and a structural change is observed by TEM. [27, 44]

8. Entrapment Efficiency-

The entrapment efficiency of drug by ethosomes can be measured by the ultra centrifugation

Technique. [5, 45]

8. 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. [5, 46]

9. Skin permeation studies-

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

EVALUATION OF ETHOSOME-

1. Filter Membrane: Vesicle Interaction Study by Scanning Electron Microscopy- Take vesicle suspension (0.2 mL) and take a filter membrane having a pore size of 50 nm. The formulation is applied on the filter membrane and placing it in diffusion cells. The upper side of the filter membrane was exposed to the air, and the lower side of filter membrane is contact with phosphate buffer solution, (having pH 6.5). The filter membranes removed after 1 hour and were prepared for SEM studies by fixation at the 4°C in Karnovsky's fixative overnight followed by dehydration with graded ethanol solutions (30%, 50%, 70%, 90%, 95%, and 100% v/v in water). Finally, filter membranes was coated with gold and examined in SEM. [47, 48]

2. Skin Permeation Studies-

The hair of test animals (rats) is remove or carefully trimmed short (<2 mm) with the help of scissors, and the abdominal skin is removed from the connective tissue with the help of scalpel. The skin is placed on aluminum foil, and the dermal side of the skin was gently teased off for any adhering fat. The standard permeation area of the diffusion cell and receptor cell volume is 1.0 cm^2 and 10 ml, respectively. The temperature is maintained at 32°C+- 1°C. The receptor compartment contained phosphate buffer solution (10 ml of pH 6.5). Ethosomal formulation (1.0 ml) was applied to the epidermal surface of skin. Samples (0.5 ml) were withdrawn through the sampling port of the diffusion cell by the pippet at 1, 2, 4, 8, 12, 16, 20 & 24 hour time intervals and analyzed by high performance liquid chromatography assay. [47]

3. Vesicle-Skin Interaction Study by TEM and SEM-

Take the animal and cut the ultra thin sections like (Ultra cut, Vienna, and Austria), collect the section to coated grids and analyzed by transmission electron microscope. For SEM analysis, take the sections of skin and dehydrated and mounted on stubs using an adhesive tape and coated with gold palladium with the help of fine coat ion sputter coater. The sections were analyzed under scanning electron microscope. [47, 48]

4. Vesicle-Skin Interaction Study by Fluorescence Microscopy-

Fluorescence microscopy was carried according to the protocol used for TEM and SEM study. 5-µm thick skin sections were cut using microtome and examined under a fluorescence micro Cytotoxicity Assay MT-2 cells (T-lymphoid cell lines) were propagated in Dulbecco's modified Eagle medium containing 10% fetal calf serum, 100 U/ml penicillin, 100 mg/Ml streptomycin, and 2 mmol/L L glutamine at 37°C under a 5% CO2 atmosphere. Cytotoxicity was expressed as the cytotoxic dose 50 (CD50) that induced a 50% reduction of absorbance at 540 nm. [47, 49]

5. Drug Uptake Studies-

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The uptake of drug into MT-2(T-lymphoid cell lines) cells was incubated with 100 µl of the drug solution in phosphate buffer saline solution (pH 7.4), Ethosomal formulation, or marketed formulation, and then drug uptake was determined by analyzing the drug content by HPLC assay.[47, 50, 51]

6. HPLC Assay-

The drug bind with our receptor, and the amount of drug permeated in the receptor compartment in the vitro skin permeation experiments and in MT-2 cell was determined by HPLC. In the HPLC assay using methanol: distilled-water : acetonitrile (70:20:10 vol/vol). This mixture is a mobile phase delivered at 1 ml/min by LC 10-AT pump. A twenty-micro liter injection was eluted in column at room temperature. The column Eluent (solution) was examined at 271 nm using SPDM10A VP diode array UV detector. The coefficient of variance for standard curve ranged from 1.0% to 2.3%, and the squared correlation coefficient was 0.9968. [47, 52, 53]

7. Statistical Analysis-

Statistical significance of all the data generated was tested by employing ANOVA followed by studentized range test. A confidence limit of $P < .05$ was fixed for interpretation of the results using the software PRISM. [47, 54]

APPLICATION OF ETHOSOME AS A CARRIER SYSTEM-

Various methods employing ethosomal formulation have shown better skin permeability of drugs. The uses of ethosomes as carrier system for transdermal/topical drug delivery are given below.

1. Pilosebaceous targeting-

Pilosebaceous units have been use for targeted drug therapy, and the targeted treatment of follicle related disorders such as acne or alopecia. Ethosomal formulation of minoxidil is a lipid soluble drug used for the baldness accumulates into nude mice skin two to seven folds higher and thus can be use for pilosebaceous targeting for better clinical efficacy.[5, 55, 56]

2. Transdermal delivery-

Ethosomes enhance permeability of drug through stratum corneum skin barrier, it can be use for administration of those drugs having poor skin permeation, low oral bioavability, first pass metabolism and suppress infection of transdermal root. [5, 56, 57, 58]

Table 2: Application of Ethosomes as a Drug Carrier- [5]

Drugs	Results
Anti- viral agents (Zidovudine) [59] (Lamivudine)[60] (Stavudine) [61]	Prolonged drug action, reduced drug toxicity. Control release for prolonged period of time. Improved biological anti-inflammatory activity, sustained effect
NSAIDS[62,63] (Diclofenac) (Aceclofenac)	Selective and prolong delivery of drug to desired site. Superior to the marketed gel for the topical administration.
Acyclovir[64]	Increased skin permeation and biological activity two to three times.
Topical[65] Photodynamic Therapy (PDT) (5- aminolevulinic acid)	Greater penetration ability than that of liposomes, More entrapment efficiency
Insulin[66,67]	Significant decrease in blood glucose level.
Trihexyphenidyl Hydrochloride[67]	Higher entrapment capacity, improved tansdermal flux, improved patient compliance.
Antibiotic[68] (Erythromycin) (Cannabidol)	Complete inhibition of infection, prolonged drug action. Improved skin deposition and biological activity.
Pilosebaceous[69] (Minoxidil)	High penetration into deep layers of the skin. Targeting
Ammonium[70] Glycrrhizinate	Improved biological anti-inflammatory activity, sustained effect.
Salbutamol sulfate[71]	Controlled release rate, enhanced skin permeation.
Testosterone[72]	Significantly higher permeation into the skin increased systemically delivery
Propranolol[73]	Better skin permeation.
Finasteride [74]	Enhanced percutaneous absorption.
Bacitracin[75]	Reduced drug toxicity.
Methotrexate[76] (MTX)	Enhanced trans dermal flux, lower lag time, higher entrapment efficiency and better stability profile
Gold Nanopartical[77]	Gold nanopartical in ethosomes shows enhancement of pharmacological efficacy in trans dermal and dermal delivery systems.

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3. Delivery of HIV drugs-

The antiretroviral therapy is a prolong therapy and has strong side effects.[5, 78] The zero order delivery of zidovudine, Lamivudine is a potent antiviral agent and it required to maintain anti – AIDS effect. Ethosomal formulations of the above drugs prolong the release with increased transdermal influx.[5, 70] The topical preparation of acyclovir is used as antiviral drug for treatment of herpes labials. It shows low therapeutic efficiency due to poor permeation through skin as replication of virus take places at the basal dermis. Ethosomal formulation of acyclovir show high therapeutic efficiency with shorter healing time and higher percentage of abortive lesions.

4. Delivery of problematic drug molecules-

Oral delivery of large biogenic molecules such as peptides or proteins and insulin is difficult because they are completely degraded in the GIT tract hence transdermal delivery is a better dosage form. But conventional transdermal formulation of biogenic molecules such as peptides or protein and insulin has poor permeation. Formulating these biogenic molecules into ethosomal preparation increase permeation and therapeutic efficacy. [5, 79]

5. Future Prospects-

Introduction of ethosomes has started a new area in vesicular research for transdermal drug delivery. Different reports show a promising future of ethosomes in making transdermal delivery of various agents more effective. Further, 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 opportunity for the non-invasive delivery of small, medium and large sized drug molecules. The results of the first clinical study of acyclovir-ethosomal formulation support this conclusion. Multiliter quantities of ethosomal formulation can be prepared very easily. it can be a logical conclusion that ethosomal formulations possess promising future in effective dermal/transdermal delivery of bioactive agents.

PATENTED AND MARKETED FORMULATION OF ETHOSOME-

Ethosomes was invented and patented by Prof. Elka Touitou along with her students of department of Pharmaceutics at the Hebrew University School of Pharmacy. Novel Therapeutic Technologies Inc (NTT) of Hebrew University has been succeeded in bringing a number of products to the market based on Ethosomal delivery system. Noicellex TM an anti cellulite formulation of Ethosome is currently marketed in Japan. Lipoduction TM another formulation is currently used in treatment of cellulite containing pure grape seed extracts (antioxidant) is marketed in USA. Similarly Physonics is marketing anti cellulite gel Skin Genuity in London. Nanominoxc containing monoxidil is used as hair tonic to promote hair growth is marketed by Sinere. [5, 62, 63]

Table 3: Marketed products based on Ethosomal drug delivery system-

Name of product	Uses	Uses Manufacturer
Celltight EF	Topical cellulite cream, contains a powerful combination of ingredients to increase metabolism and break down fat	Hampden Health,USA
Decorin cream	Anti-aging cream, treating, repairing, and delaying the visible aging signs of the skin including wrinkle lines, sagging, age spots, loss of elasticity, and hyper pigmentation	Genome Cosmetics, Pennsylvania, US
Nanominox	First monoxidil containing product, which uses Ethosomes. Contains 4% Monoxidil, well-known hair growth promoter that must be metabolized by sulfation to the active compound	Sinere, Germany
Noicellex	Topical anti-cellulite cream	Novel Therapeutic Technologies, Israel
Skin genuity	Powerful cellulite buster, reduces orange peel	Powerful cellulite buster, reduces orange peel

CONCLUSION

Ethosomes have been found to be much more efficient at delivering drug to the skin, it can be easily concluded that ethosomes can provide better skin permeation than liposomes. Ethosomes have been tested to encapsulate hydrophilic drugs, cationic drugs, proteins and peptides. Ethosomal carrier opens new challenges and opportunities for the development of novel improved therapies. Ethosomes are interesting and innovative vesicular systems that have appeared in the field of pharmaceutical technology and drug delivery in recent years. This carrier presents interesting features correlated with its ability to permeate intact through the human skin due to its high deformability.

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REFERENCES

1) Aute P. Pravin, Kamble S. Meghana, Dr. Chaudhari D. Pravin, Dr. Bhosale VA, "A comprehensive review on ethosomes". *Int. J. Res. Dev. Pharm. L. Sci.* 2012-13, 2(1): 218-224.
2) Basak S, Akiladev D, *International Journal of Current pharmaceutical research* 2010, 2(4): 1-4.
3) Akhiladevi D, Basak Sachinandan, "ETHOSOMES- A noninvasive approach for transdermal drug delivery". *Int J Curr Pharm Res.* 2013, 2(4): 1-4
4) Patel S, "Ethosomes: A promising tool for transdermal delivery of drug". *Pharma Info.Net* 2007, 5(3).
5) Nikalje Anna Pratima, Tiwari S, "Ethosomes: A Novel Tool for Transdermal Drug Delivery". *IJRPS* 2012, 2(1): 1-20.
6) Toutitou E, Dayan N, Bergelson L, Godin B, Eliaz M, "Ethosomes novel vesicular carriers for enhanced delivery: characterization and skin penetration properties". *Journal of Controlled Release* 2000, 65: 403 – 418.
7) Jain S, Umamaheshwari RB, Bhadra D, Jain NK, "Ethosomes: a novel vesicular carrier for enhanced transdermal delivery of an anti-HIV agent". *Ind J Pharma Sci* 2004, 66: 72-81
8) Verma DD, Fahr A, "Synergistic penetration effect of ethanol and phospholipids on the topical delivery of Cyclosporin". *A. J. Control Release* 2004, 97: 55-66.
9) Bhalaria MK, Naik S, and Misra AN, "Ethosomes: A novel delivery system for antifungal drugs in the treatment of topical fungal diseases". *Indian Journal of Experimental Biology* 2009, 47: 368- 375
10) "Size determination of liposomes, Liposomes A practical approach". *RRC New (Oxford University Press, NewYork)* 1990, 154.
11) Heeremans JLM, Gerristen HR, Meusen SP, Mijnheer FW, Gangaram RS, Panday G, Prevost R, Kluft C, Crommelin DJA, "The preparation of tissue type plasminogen activator (t-PA) containing liposomes: entrapment efficacy and ultracentrifugation damage". *J Drug Target* 1995, 3: 301.
12) www.hd, "photo of microscopic view of ethosome vesicle".
13) www.hd, "photo of ethosome vesicle*". JAdvPharmTechRes*_2010,_1_3_274_72415_f4.
14) Kesharwani Roohi, Patel K Dillip, Sachan Anupam, Kumar Vikas, Mazumdar Bhaskar, "Ethosomes: A novel Approach For Transdermal and Topical Drug Delivery". WJPPS 2015, 4(6): 348-359.
15) Vijay kumar SK, Parthiban S, Kumarsenthil P G, Mani Tamiz T, "ETHOSOMES- A New Trends In Vesicular Approaches For Topical Drug Delivery". *Asian Journal of Research in Pharmaceutical Sciences and Biotechnology* 2014, 2(1): 23-30.
16) Kumar R, Aslam M D, Tripathi A, Prasad D, Chaudhary V, Jain V, Mishra S K and Singh R, "Ethosomes: novel vesicular carriers in transdermal drug delivery". *J Global Pharma Tech* 2010, 2(6): 1-7.
17) Prajapati SK, Maurya SD, Das MK, Tilak VK, Verma KK, Dhakar RC, Dendrimers in drug delivery, diagnosis and therapy: basics and potential applications,Journal of Drug Delivery and Therapeutics 6 (1), 67-92.
18) Jain H, Patel j, Joshi k, Patel p, and Upadhyay U M, "Ethosomes: A novel drug carrier". *IJCP* 2011, 7(01): 1-4.
19) Shahwal V, Samnani A, Dubey B, Bhowmick M, "Ethosomes: an overview". *Int.J. Bio Adv Res* 2011, 2: 161-168.
20) Kumar KP, Radhika PR, Sivakumar T, "Ethosomes-A Priority in Transdermal Drug Delivery", *International Journal of Advances in Pharmaceutical Sciences* 2010, 1: 111-121.
21) Wough A, Grent A, "Ross &Wilson anatomy and physiology in health and illness". 11th edition *Churchill living stone elsevir publication* 2010,
22) www.hd, "photo of strature of skin". collageneire_skin1
23) "Preparation of liposomes and size determination Liposomes-A practical approach". *RRC New (Oxford University Press, New York)* 1990, 36.
24) Asbill CS, El-Kattan AF, Michniak B, "Enhancement of transdermal drug delivery: chemical and physical approaches". *Crit Rev Therapeut Drug Carrier Sys* 2000, 17: 621.
25) Anitha P, Ramkanth S, Sankari U K, Alagusundaram M, Gnanaprakash K, Devi Devaki P, Prasanna Indira R, "ETHOSOMES- A noninvasive vesicular carrier for Transdermal Drug Delivery". *Int. J. Rev. Life. Sci.* 2011, 1(1): 17-24.
26) www.hd, "photo of cross section of skin". collageneire_skin1
27) Jyothi A, Sowjanya Sai K, Sreekanth N, Karuna B, Rao B C, "ETHOSOMES: A novel drug carrier for transdermal drug delivery". *IJIDD* 2013, 3(1): 39-44.
28) Riaz M, Weiner N, Martin F. In: Lieberman HA, New (Ed.), Liposome - A Rieger, G.S. Banker (Eds.), "Pharmaceutical Dosage Forms. Practical Approach". *Oxford University Press* 1990, 154.
29) www.hd, "photo of Release of drug from ethosome in deep layer of the skin". 0007PNT
30) Lauer AC, Ramachandran C, Leib LM, Niemiec S, Simon ND, "Effect of ethanol on membrane order: fluorescence Weiner, Targeted delivery to the pilosebaceous units via studies". *Ann. NY Acad. Sci* 1987, 492, 125–133.
31) Bergelson LD, Molotkovsky JM, Manevich YM, Lipid-Touitou, "A clinical evaluation of a novel liposomal carrier specific fluorescent probes in studies of biological mem-for acyclovir in the topical treatment of recurrent herpesbranes". *Chem. Phys. Lipids* 1985, 37: 165–195
32) Patel D, Bhargava P, "ETHOSOMES -A Phyto Drug Delivery System", *ARPB* 2012, 2(1) .
33) Godin B, and Touitou E, *Crit. Rev. Therp. Drug Carrier Sys* 2003, 20(1): 63-102.
34) Touitou E, "Composition of applying active substance to or through the skin". *US patent* 1996, 5,716,638.
35) Touitou E, "Composition of applying active substance to or through the skin". *US patent* 1998, 5, 540,934.
36) Dwivedi, R Sahu, SP Tiwari, T Satapathy, A Roy, Role of liposome in novel drug delivery system, Journal of Drug Delivery and Therapeutics 4 (2), 116-129.
37) Guo J, Ping Q, Sun G, Jiao C, "Lecithin vesicular carriers form transdermal delivery of cyclosporine A*". Int. J. Pharm* 2000, 194(2): 201- 207.
38) Rakesh R, Anoop K R, "Ethosomes for transdermal and topical drug delivery". *Int J Pharm Sci.* 2012, 4(3): 17-24.
39) Blume A, Jansen M, Ghyczy M, Gareis J, "Interaction of depth of the spin label probe". *Mol. Pharmacol* 1997, 13.
40) Lauer AC, Ramachandran C, Leib LM, Niemiec S, Simon ND, "Effect of ethanol on membrane order fluorescence Weiner, Targeted delivery to the pilosebaceous units via studies". *Ann. NY Acad. Sci* 1987, 492: 125–133.
41) Touitou E, "Drug delivery across the skin". *Exp Opinion Biol Their* 2002, 2: 723-733.
42) Touitou E, God in B, Dayan N, Piliponsky A, Levi-Schaffer F, Weiss C, "Intracellular delivery mediated by an ethosomal carrier". *Biomaterials* 2001, 22: 3053-3059.
43) Asadujjaman MD, Mishuk AU, Novel approaches in lipid based drug delivery systems, Journal of Drug Delivery and Therapeutics 3 (4), 124-130
44) Touitou E, Godin B, Weiss C, "Enhanced delivery of drugs into and across the skin by ethosomal carriers". *Drug Dev Res*, 50, 200, 406-15.
45) Fry D W, White J.C, Goldman I.D, "Rapid secretion of low molecular weight solutes 1from liposomes without dilution". *Analytical Biochemistry* 1978, 90: 809- 815.
46) Cevc G, Schatzlein A, Blume G. "Transdermal drug carriers: Basic properties, optimization and transfer efficiency in case of epicutaneously applied peptides". *J. Cont. Release* 1995, 36: 3-16.
47) Ghule Arpan Ramakrishna, Shinkar Dattatraya Manohar, Saudagar Ravindra Bhanudas, "Ethosomes: Carrier for Enhanced Transdermal Drug Delivery System". *Journal of Advanced Pharmacy Education & Research* 2014, 4(4): 380-387.
48) Katz M, Poulsen B J, "In Handbook of Experimental Pharmacology". Broie B, *Gillette J R. Eds. Springer- Verlag, Berlin* **1971**, 27: 103-174.

49) Verma DD, Fahr A, "Synergistic penetrations effect of ethanol and phospholipids on the topical delivery of Cyclosporine". *AJ Control Release* 2004, 97: 55-66.
50) Touitou E, "Drug delivery across skin". *Expert Opinion on Biological Therapy* 2002, 2: 723–733.
51) Dayan N, Touitou E, "Carriers for skin delivery of triexphenidyl HCl Ethosome Vs Lipsomes". *Biomaterials* 2000, 21: 1879 – 1885.
52) New RRC, "Preparation and size determination In: Liposomes a practical approach". *NewRRC (Ed.), Oxford University Press, Oxford* 1990, 36-39.
53) "Preparation of Liposomes and size determation Liposomes-a practical approach". *RRC new (oxford university press, New York)* 1990, 46-48.
54) Maghraby E l, Williams A C, Barry B W, "Ostradiol skin delivery from ultra deformable Liposomes: refinement of surfactant concentration". *Int j Pharm 2*000, 196(1): 63-74.
55) Toutitou E, Dayan N, Bergelson L, Godin B and Eliaz M, "Ethosomes novel vesicular carriers for enhanced delivery: characterization and skin penetration properties". *J. Cont. Release* 2000, 65: 403 – 418.
56) Biju SS, Sushama T, Mishra P R, Khar R K, "Vesicular systems: An overview". *Ind. J. Pharma. Sci.* 2006, 68 (2): 141-153.
57) Banga A.K, Chein Y.W, "Hydrogel – based iontotheraputic delivery devices for transdermal delivery of peptide protein drugs". *Pharmaceutical Research* 1993, 10: 697–702.
58) Jia-You F, Chi-Tzong H, Wen-Ta C, Ying-Yue W, "Effect of liposomes and niosomes on skin permeation of enoxacin". *Int. J. Pharma* 2001, 219 (1): 61–72
59) Jain S, Umamaheshwari R.B, Bhadra D, Jain N.K, "Ethosomes – A novel vesicular carrier for enhanced Transdermal delivery of an anti –HIV agent". *Ind.J.Pharm. Sci*. 2004, 66(1): 72– 81.
60) Subjeet J, Ashok K.T, Bharti S, Narendra K.J, "Formulation and evaluation of ethosomes for transdermal delivery of lamivudine". *AAPS Pharm SciTech* 2007, 8(4): E1–E9.
61) D.M, Sunil K.P, Anish K.G, Gyanendra K.S, Ram C.D, "Formulation development and evaluation of ethosome of stavudine". *Ind. J. Pharm. Edu. Res*. 2010, 44(1): 102–108.
62) Touitou E, "Composition of applying active substance to or through the skin". *US Patent*: 5716638, 1996.
63) Touitou E, "Composition of applying active substance to or through the skin". *US Patent*: 5540934, 1998.
64) Barry B.W, "Novel mechanism and devices to enable successful Transdermal drug delivery". *Eur. J. Pharma. Sci*. 2001, 14(2): 101–114.
65) Yi-Ping F, Yi-Hung T, Pao-chu W,Yaw – Bin H, "Comparison of 5 aminolevulinic acid – encapsulated liposome versus ethosome for skin delivery for photodynamic therapy". *Int. J. Pharma* 2008, 356: 144–152.
66) Banga A.K, Chein Y.W, "Hydrogel – based iontotheraputic delivery devices for transdermal delivery of peptide protein drugs". *Pharmaceutical Research* 1993, 10: 697–702.
67) Dayan N, Touitou E, "Carriers for skin delivery of triexphenidyl HCl Ethosome Vs Lipsomes". *Biomaterials* 2000, 21: 1879–1885.
68) Godin B, Touitou E, Rubinstein F, Athamna A, Athamna M, "A new approach for treatment of deep skin infections by an ethosomal antibiotic preparation: an in vivo study". *Journal of Antimicrobial Chemotherapy* 2005, 55(6): 989–994.
69) Toutitou E, Dayan N, Bergelson L, Godin B and Eliaz M, "Ethosomes novel vesicular carriers for enhanced delivery: characterization and skin penetration properties". *J. Cont. Release* 2000, 65: 403–418.
70) Donatella P, Giuseppe L, Domenico M, Franco A, and Massimo F, "Ethosomes for skin delivery of ammonium glycyrrhizinate permeation through human skin and in vivo anti inflammatory activity on human volunteers". *J.Cont. Release* 2005, 106: 99–110.
71) Ehab R.B, Mina I.T, "Enhanced transdermal delivery of salbutamol sulfate via ethosomes". *AAPS Pharm SciTech* 2007, 8(4): E1–E8.
72) Kirjavainen M, Urtti A, Valjakka – Koskela R, Kiesvaara J. Monkkoonen J, "Liposome – skin interactions and their effects on the skin permeation of drugs". *Eur. J. Pharm. Sci*. 1999, 7(4): 279-286.
73) Kaplun – Friscкhoff Y, Touitou E, "Testosterone skin permeation enhancement by menthol through formation of eutectic with drug and interaction with skin lipids". *J. Pharma. Sci*. 1997, 86: 1394–1399.
74) Yuefeng R, Feiyue Z, Xingguo Z, Jianqing G, Wenquan L, "*In vitro* percutaneous permeation and skin accumulation of finasteride using vesicular ethosomal carriers". *AAPS Pharm. Sci. Tech* 2008, 9(3): 860–865.
75) Godin B, Touitou E, "Mechanism of bacitracin permeation enhancement through the skin and Cellular membrane from an ethosomal carrier". *J. Cont.Release* 2004, 94: 365–379.
76) Vaibhav D, Dinesh M, Tathagata D *et al.* "Dermal and transdermal delivery of an anti – psoriatic agent via ethanolic liposomes". *J. Cont. Release* 2007, 123: 148–154.
77) Patricia de la, P, *et al.* "Gold nanoparticals generated in ethosomes bilayers, as revealed by cryo electron – tomography". *J. Phy. Chem*. 2009, 113(10): 3051–3053
78) Jarivis B, Faulds D, "Lamivudine: a review of its therapeutic potential in chronic hepatits B Drugs" 1999, 58(1): 101–141.
79) Jain S, Jain P, Jain N.K, "Transfersomes: a novel vesicular carrier for enhanced transdermal delivery: development, characterization and performance evaluation, Drug Development and Industrial Pharmacy" 2003, 29: 1013–1026.

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