WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 5.990
Volume 4, Issue 12, 750-762. Review Article ISSN 2277– 7105

VESICULAR CARRIER FOR TRANSDERMAL DRUG DELIVERY SYSTEM –ETHOSOMES

Suchita. G. Waghmare[*1], Dr. Satish. B. Kosalge[2], Rasika R. Nikhade[3], Shweta U. Kannao[4]

[1]Assistant Professor at Hi-Tech College of Pharmacy, Chandrapur, Maharashtra.

[2]Principal at Hi-Tech College of Pharmacy, Chandrapur, Maharashtra.

[3]Assistant Professor at Hi-Tech College of Pharmacy, Chandrapur, Maharashtra.

[4]Assistant Professor at Hi-Tech College of Pharmacy, Chandrapur, Maharashtra.

Article Received on
15 Oct 2015,

Revised on 05 Nov 2015,
Accepted on 25 Nov 2015

***Correspondence for Author**
Suchita. G. Waghmare
Assistant Professor at Hi-Tech College of Pharmacy, Chandrapur, Maharashtra.

ABSTRACT

Transdermal drug delivery system is one of the important drug delivery system. Skin is the main target of topical and transdermal preparations. The aim of transdermal drug delivery system is to cross the stratum corneum. Ethosomes are noninvasive delivery carriers that enable drugs to reach the deep skin layers and the systemic circulation. Now a days vesicles are used as cellular communication medium. Use of Ethosomes as vesicle widely spread. Ethosomes are the ethanolic phospholipids vesicles which are used mainly for transdermal delivery of drugs. Composed of hydroalcoholic or hydro/glycolic phospholipids in which the concentration of alcohols is relatively high. The high concentration of ethanol brings increase in fluidity of lipids hence increase in permeability of the skin and improves the drug penetration. Ethosomes formulation can contain many dugs. Ethosomes have higher penetration rate through the skin as compared to liposome so they can be used widely in place of liposome. Ethosomes have become an area of research interest, because of its enhanced skin Permeation, improved drug delivery, increased drug entrapment efficiency etc. The high concentration of ethanol makes the Ethosomes unique and Useful for transcellular delivery, delivery of hormones, anti-arthritis, anti-HIV etc.

KEYWORDS: Ethosomes, Ethanol, Transdermal delivery, Phospholipids, Vesicle.

INTRODUCTION

Transdermal drug delivery is importance drug delivery system due to its noninvasive procedure for administration. The transdermal drug delivery system is advantageous over the oral drug delivery system such as degradation of drugs by digestive enzymes, irritation of gastrointestinal mucosa and first pass effect. Also due the pain on administration associated with parenteral route, patients highly prefer transdermal route. Hence transdermal drug delivery system is patient compliance drug delivery system.[1,2]

Few problems are considered while designing Transdermal Dosage Forms The skin is a multi-layered structure made up of stratum corneum (SC), the outermost layer, under which lies the epidermis and dermis. Within these layers of skin are interspersed fibroblasts, hair follicles and sweat glands that originate in the dermis blood supply. The almost insurmountable nature of SC is a major challenge for systemic delivery of percutaneously applied drugs.[3] The Obrick and mortarO arrangement of corneocytes, flattened mononucleated keratinocytes, with interspersed lipids and proteins makes the SC approximately 1000 times less permeable than other biological membranes. Furthermore, it is even more difficult for anything to penetrate to the deeper strata of skin.[4,5] Ethosomes are mainly used for the delivery of drugs through transdermal route .The vesicles have been well known for their important in cellular communication and particle transportation for many years. The drug is incorporated within the cavities of vesicles. The soft, malleable vesicles adapt for superior delivery of active agents. Ethosomes are lipid vesicles containing phospholipids, alcohol (ethanol and isopropyl alcohol) in relatively high concentration and water.

ROUTES OF PENETRATION

Human skin comes into contact with sebum, cellular debris, microorganisms and other materials, which somewhat affect the permeation of vesicles. The penetrant permeates by three potential pathways to the viable tissue: (i) through hair follicles with associated sebaceous glands, (ii) via sweat ducts, or (iii) across continuous stratum corneum between these appendages. These pathways are important for ions and large polar molecules that struggle to cross intact stratum corneum.

ADVANTAGES OF ETHOSOMAL DRUG DELIVERY

1. Enhanced drug permeation through skin.
2. Delivery of large and different group of drugs (peptides, Protein molecules).

3. Safe composition and the components are approved for Pharmaceutical and cosmetic use.
4. Low risk profile.
5. High patient compliance.
6. Application in Pharmaceutical, Veterinary, Cosmetic Field.

ETHOSOMES

The Ethosomes are vesicular carrier consisting of Hydro alcoholic or hydro/alcoholic/glycolic phospholipids in which the concentration of alcohols or their combination is relatively high. The Ethosomes may contain phospholipids with various chemical structures like phosphatidylcholine (PC), hydrogenated PC, phosphatidic acid (PA), phosphatidylserine (PS), phosphatidylethanolamine (PE), phosphatidylglycerol (PPG), phosphatidylinositol (PI), hydrogenated PC, alcohol (ethanol or isopropyl alcohol), water and propylene glycol (or other glycols). Such a composition enables delivery of high concentration of active ingredients through skin. Change in alcohol: water or alcoholpolyol: water ratio, alters drug delivery. The phospholipids generally used are soya phospholipids such as Phospholipon 90 (PL-90) in concentration range of 0.5-10% w/w. Cholesterol at concentrations ranging between 0.1-1% can also be used in the preparation to increase stability of Ethosomes. Alcohols like ethanol and isopropyl alcohol and glycols like propylene glycol and Transcutol are generally used. In addition, non-ionic surfactants (PEG-alkyl ethers) in Combination with the phospholipids are sometimes used in these preparations. Cationic lipids like coco amide, POE alkyl Amines, dodecylamine, cetrimide etc. can also be included. The concentration of alcohol in the final product may range From 20 to 50%. The concentration of the non-aqueous phase (alcohol and glycol combination) may range between 22 to 70%.[6]

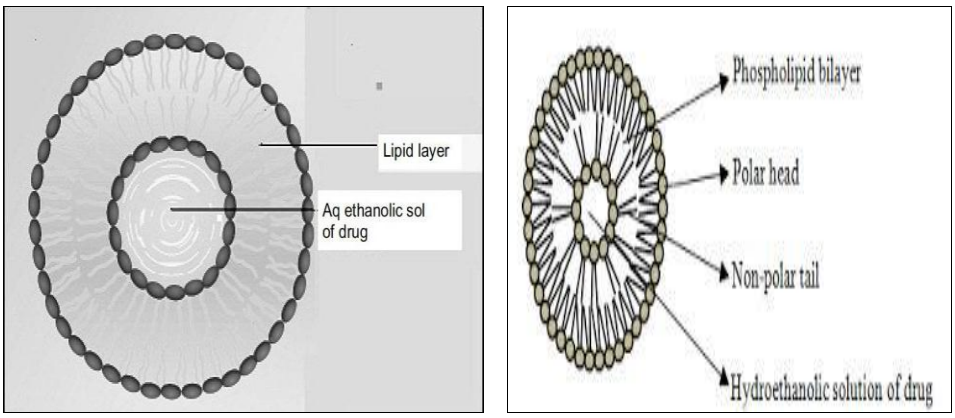

Fig 1: Diagram of Ethosome.

MECHANISM OF DRUG PENETRATION

The main advantage of Ethosomes over liposome is the increased permeation of the drug. The mechanism of the drug absorption from Ethosomes is not clear. The drug absorption probably occurs in following two phases:

1. Ethanol effect
2. Ethosomes effect

1. Ethanol effect

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

2. Ethosome effect

Increased cell membrane lipid fluidity caused by the ethanol of Ethosomes results increased skin permeability. So the Ethosomes permeates very easily inside the deep skin layers, where it got fused with skin lipids and releases the drugs into deep layer of skin.

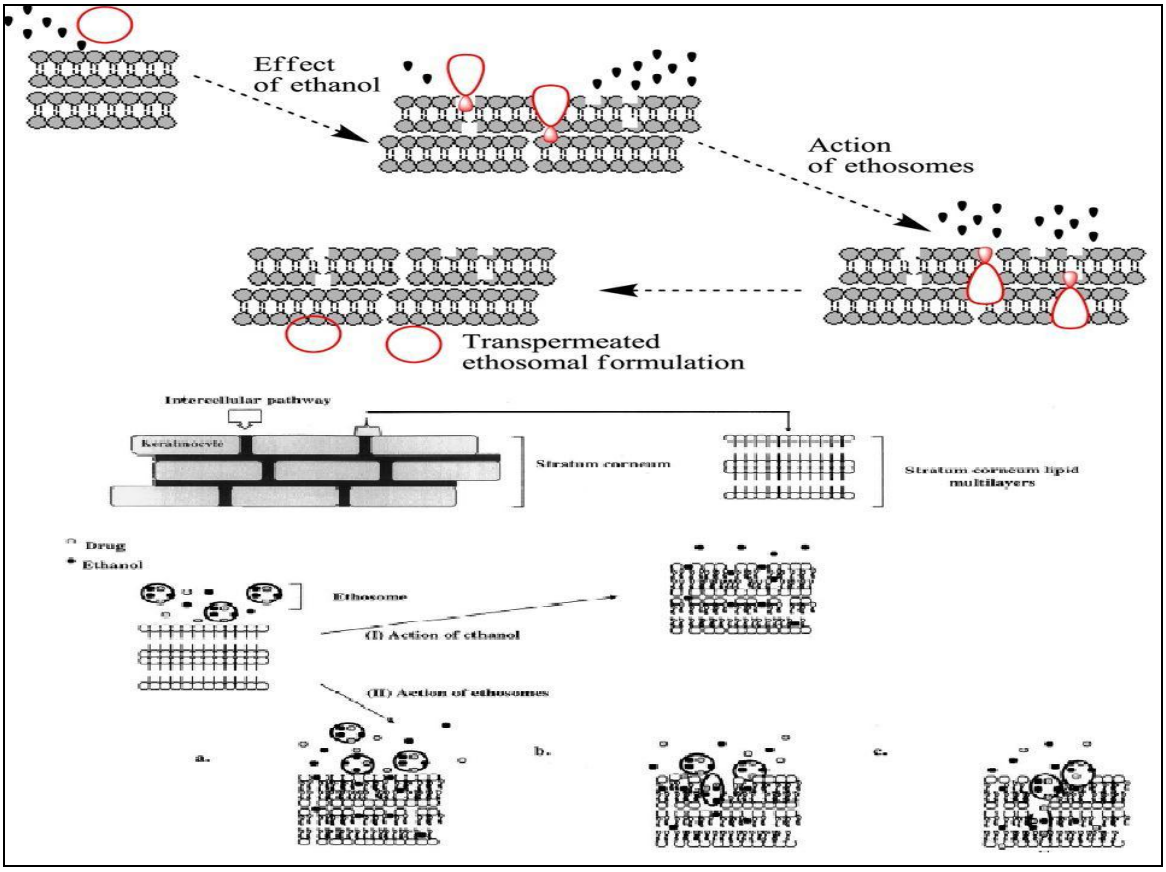

Fig. 2: Mechanism of Action of Ethosomes.

Methods of preparations of Ethosomes

Ethosomal formulation prepared by hot or cold method. Both the methods are Convenient, do not require any sophisticated equipment and are easy to scale up at industrial level.

1. Cold Method

In this method Phospholipids, drug and other lipid materials are dissolved in ethanol in a covered vessel at room temperature by vigorous stirring with the use of mixer. Propylene glycol or other polyol is added during stirring. This mixture is heated to 30^0C in a water bath. The water heated to 30^0C in a separate vessel is added to the mixture, which is then stirred for 5 min in a covered vessel. The vesicle size of ethosomal formulation can be decreased to the desire extent using probe sonication or extrusion method. Finally, the formulation is stored under refrigeration.[7]

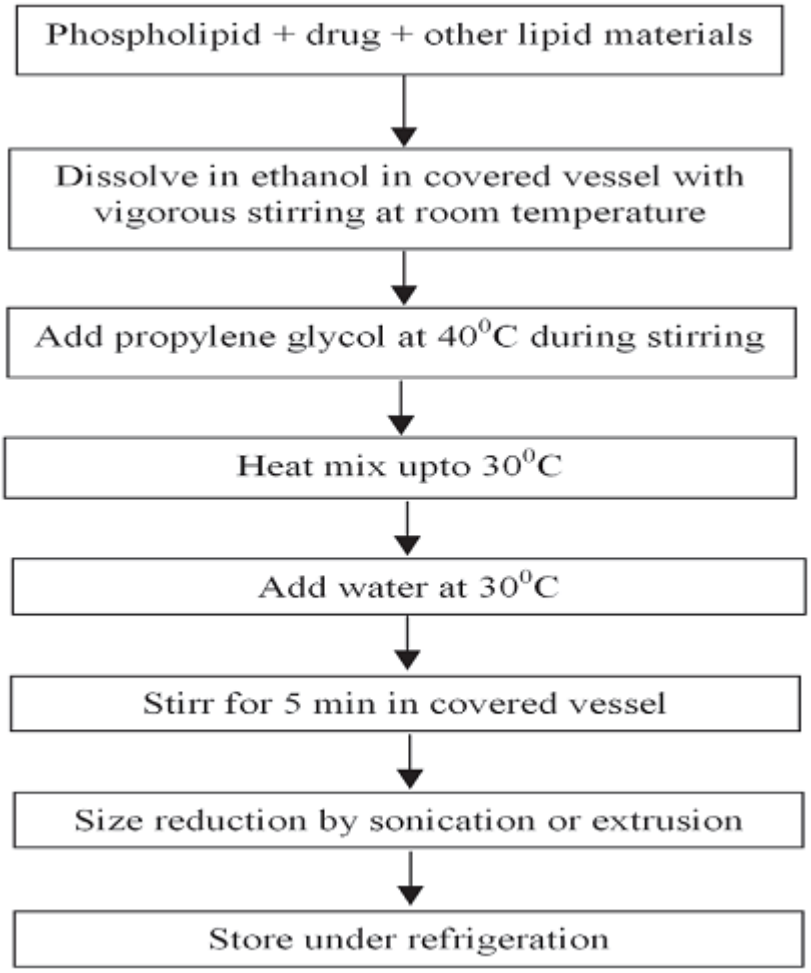

Fig. 3: Preparation of Ethosomes by Cold Method.

2. Hot Method

In this method Phospholipids is dispersed in water by heating in a water bath at 400C until a colloidal solution is obtained. In a separate vessel ethanol and propylene glycol are mixed and heated to 400C. Once both mixtures reach 400C, the organic phase is added to the aqueous one. The drug is dissolved in water or ethanol depending on its hydrophilic or hydrophobic properties. The vesicle size of ethosomal formulation can be decreased to the desire extent using probe sonication or extrusion method.[7,25]

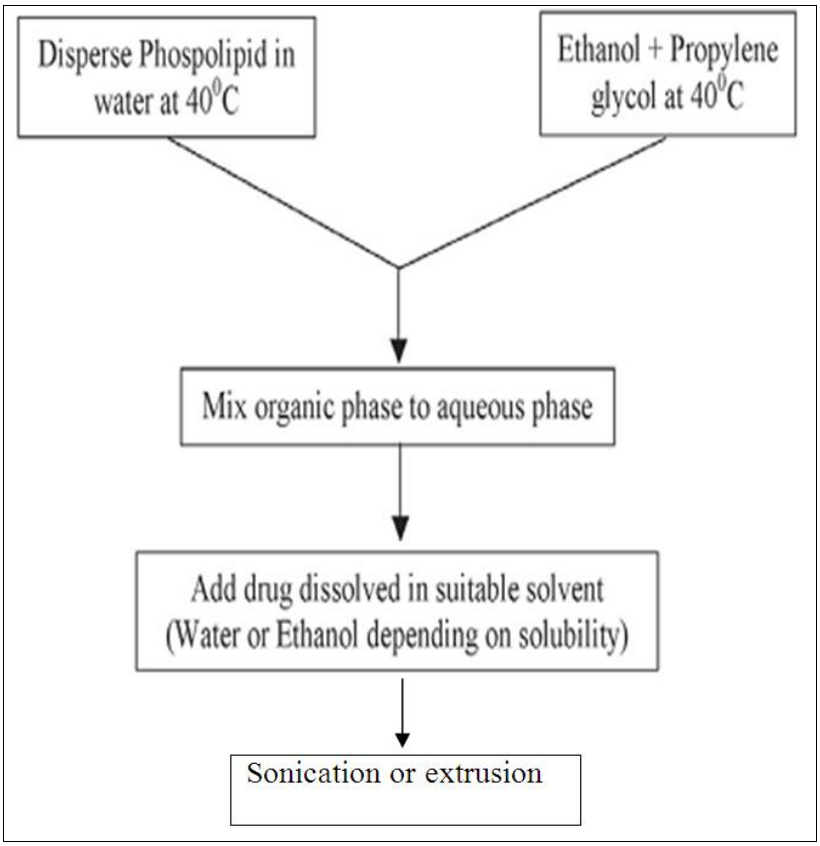

Fig. 4: Preparation of Ethosomes by Hot Method.

Characterization of Ethosomes[24]

1. Visualization

Visualization of Ethosomes can be done using transmission electron microscopy (TEM) and by scanning electron microscopy (SEM).

2. Vesicle size and Zeta potential[1,2]

Particle size and zeta potential can be determined by dynamic light scattering (DLS) using a computerized inspection system and photon correlation spectroscopy (PCS).[13]

3. Differential scanning calorimertry (DSC)[1]

Transition temperature (Tm) of the vesicular lipid systems was determined by using the Mettler DSC 60 computerized with Mettler Toledo star software system (Mettler, Switzerland). The transition temperature was measured by using the aluminium crucibles at a heating rate 10 degree/minute, within a temperature range from 20˚C–300˚C[9,10,11]

4. Surface Tension Activity Measurement

The surface tension activity of drug in aqueous solution can be measured by the ring method in a Du Nouy ring tensiometer.[10,11]

5. Entrapment Efficiency

The entrapment efficiency of drug by Ethosomes can be measured by the ultra centrifugation technique.[11]

6. Penetration and Permeation Studies

Depth of penetration from Ethosomes can be visualized by confocal laser scanning.[1,8]

7. Vesicle Stability

The stability of vesicles can be determined by assessing the size and structure of the vesicles over time. Mean size is measured by DLS and structure changes are observed by TEM.

EVALUATION TESTS[23, 24, 25]

1. Skin Permeation Studies

The hair of test animals (rats) were carefully trimmed short (<2 mm) with a pair of scissors, and the abdominal skin was separated from the underlying connective tissue with a scalpel. The excised skin was placed on aluminium foil, and the dermal side of the skin was gently teased off for any adhering fat and/or subcutaneous tissue. The effective permeation area of the diffusion cell and receptor cell volume was 1.0 cm2 and 10 mL, respectively. The temperature was maintained at 32°C ± 1°C. The receptor compartment contained PBS (10 mL of pH 6.5). Excised skin was mounted between the donor and the receptor compartment. 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 at 1-, 2-, 4-, 8-, 12-, 16-, 20- and 24-hour time intervals and analyzed by high performance liquid chromatography (HPLC) assay.[1,11]

2. Stability Study

Stability of the vesicles was determined by storing the vesicles at 4°C ± 0.5°C. Vesicle size, zeta potential and entrapment efficiency of the vesicles was measured after 180 days using the method described earlier.[1]

3. Vesicle-Skin Interaction Study by TEM and SEM

From animals ultra thin sections were cut (Ultracut, Vienna, Austria), collected on formvar-coated grids and examined under transmission electron microscope. For SEM analysis, the sections of skin after dehydration were mounted on stubs using an adhesive tape and were coated with gold palladium alloy using a fine coat ion sputter coater. The sections were examined under scanning electron microscope.[11,12]

4. Vesicle-Skin Interaction Study by Fluorescence Microscopy

Fluorescence microscopy was carried according to the protocol used for TEM and SEM study. Paraffin blocks are used, were made, 5-µm thick sections were cut using microtome (Erma optical works, Tokyo, Japan) and examined under a fluorescence micro Cytotoxicity Assay MT-2 cells (T-lymphoid cell lines) were propagated in Dulbecco's modified Eagle medium (HIMEDIA, Mumbai, India) 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.[1,2,11]

5. Filter Membrane-Vesicle Interaction Study by Scanning Electron Microscopy 40

Vesicle suspension (0.2 mL) was applied to filter membrane having a pore size of 50 nm and placed in diffusion cells. The upper side of the filter was exposed to the air, whereas the lower side was in contact with PBS (phosphate buffer saline solution), (pH 6.5). The filters were removed after 1 hour and prepared for SEM studies by fixation at 4°C in Karnovsky's fixative overnight followed by dehydration with graded ethanol solutions (30%, 50%, 70%, 90%, 95% and 100% vol/vol in water). Finally, filters were coated with gold and examined in SEM (Leica, Bensheim, Germany).[1,11]

6. Drug Uptake Studies

The uptake of drug into MT-2 cells (1×106 cells/mL) was performed in 24-well plates (Corning Inc) in which 100µL RPMI medium was added. Cells were incubated with 100µL

of the drug solution in PBS (pH 7.4), ethosomal formulation, or marketed formulation and then drug uptake was determined by analyzing the drug content by HPLC assay.[1,2,11,12]

7. HPLC Assay

The amount of drug permeated in the receptor compartment during in vitro skin permeation experiments and in MT-2 cell was determined by HPLC assay using methanol: distilled-water :acetonitrile (70:20:10 vol/vol) mixture as mobile phase delivered at 1 mL/min by LC 10-AT vp pump (Shimadzu, Kyoto, Japan). A twenty-microliter injection was eluted in C-18 column (4.6×150 mm, Luna, 54, Shimadzu) at room temperature. The column eluent was monitored at 271 nm using SPDM10A vp diode array UV detector. The coefficient of variance (CV) for standard curve ranged from 1.0% to 2.3%, and the squared correlation coefficient was 0.9968.[1,11,12]

8. Statistical Analysis

Statistical significance of all the data generated was tested by employing ANOVA followed by studentized range test. A confidence limit of $P < 0.05$ was fixed for interpretation of the results using the software PRISM (Graph Pad, Version 2.01, San Diego, CA).[1,2]

THERAPEUTIC APPLICATION OF ETHOSOMES

1. In the treatment herpetic infection

5% acyclovir Ethosomal preparation compared to the 5% acyclovir cream showed significant improvements in treatment of herpetic infections.

2. Transcellular Delivery- Ethosomes as

Compared to the marketed formulation suggested Ethosomes to be an attractive Clinical alternative for anti-HIV therapy.[28]

3. Ethosomes are used in pilosabeceous targeting

Ethosomes, the high ethanol containing vesicles are able to penetrate the deeper layers of the skin and hence appear to be vesicles of choice for transdermal drug delivery of hydrophilic and impermeable drugs through the skin.

4. Transdermal Delivery of Hormones

Oral administration of hormones is associated with problems like high first pass metabolism, low oral bioavailability and several dose dependent side effects. The risk of failure of treatment is known to increase with each pill missed.

5. Delivery of Anti-Arthritis Drug

Topical delivery of anti-arthritis drug is a better option for its site-specific delivery and overcomes the problem associated with conventional oral therapy.

6. Antihypertensive

E.g. Minoxidil.[13]

7. NSAIDs

E.g. Aceclofenac.[3] Diclofenac Potassium.[14] Ketoprofen.[15]

8. Antineoplastic agent

E.g. Methotrexate, Doxorubicin, Vincristine, bleomycin.[15,16]

9. Antibiotics

E.g. Cannabidol.[1] Erythromycin.[17] Bacitracin.[17]

10. Steroidal agents

E.g. Testosterone (Testosterone ®, Testoderm ®, Testosome ®).[20]

11. Beta blocker

E.g. Propranolol.[18]

12. Antidiabetics

E.g. Insulin.[19]

13. Antiasthmatics agents

E.g. Salbutamol.[20]

14. Cerebrovascular agent

E.g. Ligustrazine.[21]

15. Antiviral agents

E.g. Zidovudin, Lamivudine Stavudine, Acyclovir.[22,29]

16. Antifungal agents

E.g. Clotrimazole.[30]

17. Antiandrogen

E.g. Finasteride.[31]

18. Herbal drugs

E.g. *Sophora alopecurides* (Alkaloids). Fitoterapia. Tacrolimus. Paclitaxel.

CONCLUSION

Ethosomes are the soft vesicular carrier for transdermal drug delivery system. The main limiting factor of transdermal drug delivery system i.e. epidermal barrier can be overcome by Ethosomes to certain extent Ethosomes has initiated a new area in vesicular research for transdermal drug delivery. Ethosomes are characterized by simplicity in their preparation, safety and efficacy and can be tailored for enhanced skin permeation of active drugs. Ethosomes have been tested to encapsulate hydrophilic drugs, cationic drugs, proteins and peptides. It is administered in semisolid form. It shows high patient complienc.Thus, ethosomal formulations possess promising future in novel drug delivery system.

REFERENCES

1. Godin B, Tauitou Elka. Current Drug Delivery, 2005; 2: 269-275.
2. Akiladev D, Basak S, International Journal of Current pharmaceutical research, 2010; 2(4): 1-4.
3. Dave A, International Journal of Drug Delivery, 2010; 2: 81-92.
4. Hadgraft J, Guy R. Transdermal Drug Delivery, Developmental Issues and Research Initiatives. New York: Marcel Dekker, 1989.
5. Chourasia MK, Nanosized ethosomes bearing ketoprofen for improved transdermal delivery, Results in Pharma Sciences, 2011; (1): 60–67.
6. Michaels AS, Chandrasekaran SK, Shaw JW. Drug permeation through human skin: theory and in vitro ex-perimental measurement. AlChE, 1975; 21: 985-96.
7. Williams ML, Elias PM. The extracellular matrix of stratum corneum: role of lipids in normal and pathological function. Crit rev Therapy drug carrier Systems, 1987; 3: 95–122.
8. Schreier H, Bouwstra JA. J Control Rel., 1994; 30: 1–15.
9. Maghraby GM, Williams AC, Barry BW, “Oestradiol skin delivery from ultra deformable liposomes: refinement of surfactant concentration” Int. J. Pharma., 2000; 63-74.

10. 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.
11. Fry DW, White JC, Goldman ID, "Rapid secretion of low molecular weight solutes 1from liposomes without dilution", Analytical Biochemistry, 1978; 90: 809-815.
12. Anitha PS, Ramkanth K, Sankari UM, Alagusundaram K, Gnanapraksah P, Devaki DR, Indira P, "Ethosomes - A noninvasive vesicular carrier for transdermal drug delivery", Int. J. Rev. Life. Sci., 2011; 1(1): 17-241.
13. Touitou E, Dayan N, Bergelson L, Godin B, Eliaz M. J Control Release, 2000; 65: 403-18.
14. Sathalia et al., Int J Pharm Pharm Sci, 2(4): 8286.
15. Jha AK, Der Pharmacia Sinica, 2011; 2(4): 192-202.
16. Shingade G, International Journal of Universal Pharmacy and Life Sciences, 2012; 2(3).
17. Naimi TS, Le Dell KH, Como-Sabetti K JAMA, 2003; 290: 2976–84.
18. Kirjavainen M, Urtti A, Valjakka KR, Kiesvaara Jm, (1997) Eur. J. Pharm. Sci., 1999; 7(4): 279-286.
19. Subjeet J, Ashok KT, Bharti S, Narendra KJ. AAPS Pharm Sci Tech, 2007; 8(4): E1–E9.
20. Dayan N, Touitou E, Biomaterials, 2000; 21: 1879–1885.
21. Jun Shi, Yiming Wang and Guoan Luo, AAPS Pharm Sci Tech, 2012; 13(2): 485-492.
22. Fiddan AP, Yeo JM, Strubbings R, Dean D. Vesicular Approach for Drug Delivery into or Across the Skin Br. Med. J., 1983; 286, 701, 1699.
23. Tarun Parashar1*, Soniya1, Roopesh Sachan1, Vishal Singh1, Gaurav Singh1, Satyanand Tyagi 2, Chirag Patel 3, Ethosome a recent vesicle of transdermal drug delivery system, ijrdpl, 2013; 2: 28-292.
24. Pravin P. Aute*1, Meghana S. Kamble1, Dr. Pravin D. Chaudhari1, Dr. Ashok V. Bhosale 2, a comprehensive review on ethosomesijrdpl, 2012-2013; 2: 218-224.
25. Abhishek Chandel1*, Vishal Patil 1, Rohit Goyal 2, Hitesh Dhamija1 and Bharat Parashar 1 Ethosomes: A Novel Approach towards Transdermal Drug Delivery, Apr – Jun 2012; 1(2): 2277□5005.
26. Nida Akhtar and Kamla Pathak, AAPS Pharm Sci Tech, 2012; 13(1): 344-355.
27. Yuefeng Rao, Feiyue Zheng, Xingguo Zhang, Jianqing Gao and Wenquan Liang, AAPS Pharm Sci Tech, 2008; 9(3): 860-865.
28. Yan Zhou, Yuhui Wei, Huanxiang Liu, Guoqiang Zhang and Xin'an Wu, AAPS Pharm Sci Tech, 2010; 11(3): 1350-1358.

29. Ajazuddin, S. Saraf, Applications of novel drug delivery system for herbal formulations Fitoterapia, 2010; 81(7): 680-689.
30. Guiling Li, Yating Fan, Chao Fan, Xinru Li, Xiaoning Wang, Mei Li, Yan Liu, (2012), European Journal of Pharmaceutics and Biopharmaceutics, In Press, Corrected Proof, Available online 13 June.
31. Donatella Paolino, Christian Celia, Elena Trapasso, Felisa Cilurzo, Massimo Fresta, 2012.