International Journal of CURRENT PHARMACEUTICAL RESEARCH
ISSN- 0975-1491 Vol 2, Issue 4, 2010

Review Article

ETHOSOMES - A NONINVASIVE APPROACH FOR TRANSDERMAL DRUG DELIVERY

D. AKILADEVI[1], SACHINANDAN BASAK[2]

[1]Department of Pharmaceutics, MSAJ College of Pharmacy, Sholinganallur, Chennai-600119. Email: akisaravana@yahoo.co.in,

[2]Dr.Reddy's Laboratories Ltd, Bachupalli, Qutubullapur, RR district 500090, Andhra Pradesh.Email:sachinandanb@drreddys.com

Received: 10 Jun 2010, Revised and Accepted: 16 July 2010

ABSTRACT

Ethosomes are noninvasive delivery carriers that enable drugs to reach the deep skin layers and/or the systemic circulation. Although ethosomal systems are conceptually sophisticated, they are characterized by simplicity in their preparation, safety, and efficacy a combination that can highly expand their application. Ethosomes are soft, malleable vesicles tailored for enhanced delivery of active agents. This article reviews various aspect of ethosomes including their preparation, characterization, potential advantages and their applications in drug delivery. Because of their unique structure, ethosomes are able to encapsulate and deliver through the skin highly lipophilic molecules such as cannabinoids, testosterone, and minoxidil, as well as cationic drugs such as propranolol, trihexyphenidil, Cyclosporine A, insulin, salbutamol 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. Enhanced delivery of bioactive molecules through the skin and cellular membranes by means of an ethosomal carrier opens numerous challenges and opportunities for the research and future development of novel improved therapies.

Keywords: Ethosomes, Noninvasive, Transdermal, Skin permeation, Vesicles

INTRODUCTION

Ethosome are novel carrier system used for delivery of drugs having low penetration through the biological membrane mainly skin. Ethosomes are the slight modification of well established drug carrier liposome. Ethosomes are lipid vesicles containing phospholipids, alcohol (ethanol and isopropyl alcohol) in relatively high concentration and water.[1] Ethosomes are soft vesicles made of phospholipids and ethanol (in higher quantity) and water. The size range of ethosomes may vary from tens of nanometers to microns (μ).[2] ethosomes permeate through the skin layers more rapidly and possess significantly higher transdermal flux in comparison to conventional liposomes.[1, 3-6] Although, the exact mechanism for better permeation into deeper skin layers from ethosomes is still not clear. The synergistic effects of combination of phospholipids and high concentration of ethanol in vesicular formulations have been suggested to be responsible for deeper distribution and penetration in the skin lipid bilyers. Ethosomes are mainly used for the delivery of drugs through transdermal route. The transdermal delivery is one of the most important routes of drug administration. The main factor which limits the application of transdermal route for drug delivery is the permeation ofdrugs through the skin. Human skin has selective permeability for drugs. Lipophilic drugs can pass through the skin but the drugs which are hydrophilic in nature can't pass through. Water soluble drugs either show very less or no permeation. To improve the permeation of drugs through the skin various mechanisms have been investigated, including use of chemical or physical enhancers, such as iontophoresis, sonophoresis, etc. Liposomes, niosomes, transferosomes and ethosomes also have been reported to enhance permeability of drug through the stratum corneum barrier. Permeation enhancers increase the permeability of the skin, so that the drugs can cross through the skin easily. Unlike classic liposomes,[7, 8] that are known mainly to deliver drugs to the outer layers of skin, ethosomes can enhance permeation through the stratum corneum barrier.[9-11] Ethosomes can entrap drug molecule with various physicochemical characteristics i.e. of hydrophilic, lipophilic, or amphiphilic.[12, 13] Ethosomal drug delivery is noninvasive and delivers the drug to the deep skin layers or the systemic circulation. These are soft, malleable vesicles tailored for enhanced delivery of active agents. They are composed mainly of phospholipids, (phosphatidylcholine, phosphatidylserine, phosphatitidic acid), high concentration of ethanol and water. The high concentration of ethanol makes the ethosomes unique. The ethanol in ethosomes causes disturbance of skin lipid bilayer organization, hence when incorporated into a vesicle membrane, it enhances the vesicle's ability to penetrate the stratum corneum. Also, because of their high ethanol concentration, the lipid membrane is packed less tightly than conventional vesicles but has equivalent stability, allowing a more malleable structure and improves drug distribution ability in stratum corneum lipids.

ADVANTAGES OF ETHOSOMAL DRUG DELIVERY [2]

In comparison to other transdermal & dermal delivery systems

- Enhanced permeation of drug through skin for transdermal drug delivery.
- Delivery of large molecules (peptides, protein molecules] is possible.
- It contains non-toxic raw material in formulation.
- High patient compliance- The ethosomal drug is administrated in semisolid form (gel or cream) hence producing high patient compliance.
- The Ethosomal system is passive, non-invasive and is available for immediate commercialization.
- Ethosomal drug delivery system can be applied widely in Pharmaceutical, Veterinary, Cosmetic fields.
- Simple method for drug delivery in comparison to Iontophoresis and Phonophoresis and other complicated methods.

MECHANISM OF DRUG PENETRATION

The main advantage of ethosomes over liposomes 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. Ethosomes 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.

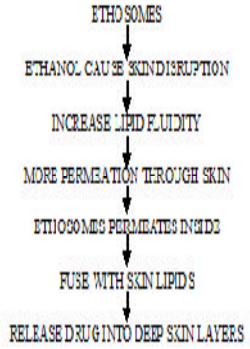

Fig. 1: Mechanism of action of ethosomes

METHOD OF PREPARTION

There are two methods which can be used for the formulation and preparation of ethosomes. Both of the methods are very simple and convenient and do not involve any sophisticated instrument or complicated process.

Ethosomes can be formulated by following two methods

Hot method

In this method disperse phospholipid in water by heating in a water bath at 400 ^{0}C until a colloidal solution is obtained. In a separate vessel properly mix ethanol and propylene glycol and heat upto 400c. Add the organic phase into the aqueous phase. Dissolve the drug in water or ethanol depending on its solubility.[1, 4] The vesicle size of ethosomal formulation can be decreased to the desire extent using probe sonication or extrusion method.

Table 1: Characterisation of ethosomes

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

Cold method

This is the most common and widely used method for the ethosomal preparation. Dissolve phospholipid, drug and other lipid materials in ethanol in a covered vessel at room temperature with vigorous stirring. Add propylene glycol or other polyol during stirring. Heat the mixture upto 300 ^{0}C in a water bath. Heat the water upto 300c in a separate vessel and add to the mixture and then stir it for 5 min in a covered vessel. The vesicle size of ethosomal formulation can be decreased to desire extend using sonication [6] or extrusion [13] method. Finally, the formulation should be properly stored under refrigeration.[1]

Table 2: Ethosomes as a carrier for drugs

S. no	Drug	Purpose of ethosomal delivery	Uses ·
1	Minoxidil	· Pilocebaceous targeting · Accumulation in skin increased significantly	Treatment of baldness
2	Testosterone	· High first pass metabolism · low oral bioavailability · several dose dependent side effects	Steroidal hormone
3	Trihexyphenidyl hydrochloride	· 4.5-times higher than that from liposome · short biological half-life (3hr) oral administration is difficult due to motor disorders and neurogical manifestations associated with parkinsonian syndrome	Treatment of Parkinson's disease
4	Zidovudine and lamivudine	· Better cellular uptake	Anti-HIV
5	Bacitracin	· Better cellular uptake	Antibacterial
6	Erythromycin	· Better cellular uptake	Antimicrobial
7	DNA	· Expression into skin cells	Treatment of genetic disorders
8	Cannabidol	· low bioavailability · first pass metabolism · GIT degradation · Encapsulation of CBD in ethosomes significantly increased its skin permeation, accumulation and hence its biological activity.	Treatment of rheumatoid arthiritis
9	Acyclovir	· Poor skin permeation	Treatment of Herpes labialis
10	Insulin	· GIT degradation	Treatment of diabetes
11	Cyclosporin	· GIT degradation · Poor oral absorption and bioavailability	Treatment of Inflammatory skin disease
12	Ammonium glycyrrhizinate	· Poor skin permeation · Poor oral bioavailability	Treatment of various inflammatory based skin diseases
13	Fluconazole	· Poor skin permeation	Treatment of candidiasis
14	Methotrexate	· Poor skin permeation	Treatment of psoriasis
15	Salbutamol	· Enhanced drug delivery through skin with ethosomes	Anti-asthmatic

VARIOUS METHODS OF CHARACTERIZATION OF ETHOSOMES [9,14-20]

1. Vesicle shape

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

2. Vesicle size and zeta potential

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

3. Transition temperature

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

4. Drug entrapment

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

5. Drug content

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

6. 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.

7. Stability studies

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

8. Skin permeation studies

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

THERAPEUTICS APPLICATION OF ETHOSOMES [3, 5, 13, 14, 25-31]

Ethosomes can be used for many purposes in drug delivery.Ethosomes are mainly used as replacement of liposomes. Mainly the transdermal route of drug delivery is preferred. Ethosomes can be used for the transdermal delivery of hydrophilic and impermeable drugs through the skin. Various drugs have been used with ethosomal carrier (Table 2).

CONCLUSION

It can be easily concluded that ethosomes can provide better skin permeation than liposomes. The main limiting factor of transdermal drug delivery system i.e. epidermal barrier can be overcome by ethosomes to significant extent. Application of ethosomes provides the advantages such as improved permeation through skin and targeting to deeper skin layers for various skin diseases. 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.

REFERENCES

1. Touitou E, inventor. Composition of applying active substance to or through the skin. US patent 5 540 934. July 30, 1996.
2. Patel S, Ethosomes: A promising tool for transdermal delivery of drug, Pharma Info.Net, 5(3), 2007.
3. 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, 65, 2000, 403-418.
4. Touitou E, inventor. Composition of applying active substance to or through the skin. US patent 5 716 638. October 2, 1998.
5. Touitou E, Godin B, Dayan N, Weiss C, Piliponsky A, Levi-Schaffer F, Intracellular delivery mediated by an ethosomal carrier. Biomaterials, 22, 2001, 3053-3059.
6. 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, 66, 2004, 72-81.
7. Size determination of liposomes, Liposomes-A practical approach, edited by RRC New (Oxford University Press, NewYork) 1990, 154.
8. 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, 3, 1995, 301.
9. Preparation of liposomes and size determination, Liposomes-A practical approach, edited by RRC New (Oxford University Press, New York) 1990, 36.
10. Touitou E, Dayan N, Levi-Schaffer F, Piliponsky A, Novel lipid vesicular system for enhanced delivery, J Lip Res, 8, 1998, 113.
11. Asbill CS, El-Kattan AF, Michniak B, Enhancement of transdermal drug delivery: chemical and physical approaches, Crit Rev Therapeut Drug Carrier Sys, 17, 2000, 621.
12. Verma, DD, Fahr A, Synergistic penetration effect of ethanol and phospholipids on the topical delivery of Cyclosporin A, J. Control Release, 97, 2004, 55-66.
13. Bhalaria MK, Naik S, Misra AN, Ethosomes: A novel delivery system for antifungal drugs in the treatment of topical fungal diseases, Indian Journal of Experimental Biology 47, 2009, 368-375.
14. Guo J, Ping Q, Sun G, Jiao C, Lecithin vesicular carriers for transdermal delivery of cyclosporine A, Int. J. Pharm, 194(2), 2000, 201-207.
15. Maghraby GMM, Williams AC, Barry BW, Oestradiol skin delivery from ultra deformable liposomes: refinement of surfactant concentration, Int. J. Pharm, 196(1), 2000, 63-74.
16. Fry DW, White JC, and Goldman ID, Rapid secretion of low molecular weight solutes from liposomes without dilution. Anal. Biochem, 90, 1978, 809-815.
17. Cevc G, Schatzlein A, Blume G, Transdermal drug carriers: Basic properties, optimization and transfer efficiency in case of epicutaneously applied peptides, J. Control. Release, 36, 1995, 3-16.
18. Vanden Berge BAI, Swartzendruber VAB, Geest J, Development of an optimal protocol for the ultrastructural examination of skin by transmission electron microscopy, J. Microsc, 187(2), 1997, 125-133.
19. Dayan N, Touitou E, Carrier for skin delivery of trihexyphenidyl HCl: Ethosomes vs liposomes, Biomaterials, 21, 2002, 1879-1885.
20. Toll R, Jacobi U, Richter H, Lademann J, Schaefer H, Blume U,Penetration profile of microspheres in follicular targeting of terminal hair follicles, J. Invest. Dermatol, 123, 2004, 168-176.
21. Meidan, VM, Alhaique F, Touitou E, Acta Technologiae et Legis Medicament, 9(1), 1998, 1-6.
22. Jain S. Vesicular approaches for transdermal delivery of bioactive agent. Ph.D thesis, Dr. H.S. Gour University, Sagar, India, 2005.
23. Godin B, Touitou E, Mechanism of bacitracin permeation enhancement through the skin and cellular membranes from an ethosomal carrier, J. Control Release. 2004, 94(2-3), 365-379.
24. Godin B, Touitou E, Erythromycin Ethosomal Systems: Physicochemical Characterization and Enhanced Antibacterial Activity, Current Drug Delivery 2(3), 2005, 265-275.
25. Touitou E, Godin B, Dayan N, Vaisman B, Intracellular delivery by cationic ethosomes not containing positively charged phospholipids: Characterization and intracellular delivery properties. Proceedings of the 6th PAT & 4th ICRS International Symposium, Eilat, Israel.2001.
26. Lodzki M, Godin B, Rakou L, Mechoulam R, Gallily R, Touitou E, cannabidiol- transdermal delivery and anti-inflammatory effects in a murine model, J. Control. Release, 93, 2003, 377-387. 27.
27. Horwitz E, Pisanty S, Czerninsky R, Helser M, Eliav E, Touitou E, a clinical evaluation of a novel liposomal carrier for acyclovir in the topical treatments of recurrent herpes labialis, Oral Surg Oral Pathol Oral Radiol Endod, 88, 1999, 700-05.

28. Dkeidek I, Touitou E, AAPS Pharm. Sci, 1, 1999, S202.
29. Paolino D, Lucania G, Mardente D, Alhaique F, Fresta M, J. Control. Release. 106, 2005, 99-110.
30. Dubey V, Mishra D, Dutta T, Nahar M, Saraf DK, Jain NK, Dermal and transdermal delivery of an anti-psoriatic agent via ethanolic liposomes, Journal of Controlled Release 123 (2007) 148–154.
31. Ehab R, Bendas L, Mina I, Tadros, Enhanced Transdermal Delivery of Salbutamol Sulfate via Ethosomes, AAPS PharmSciTech, 8 (4), 2007, Article 107.