IJISET - International Journal of Innovative Science, Engineering & Technology, Vol. 7 Issue 7, July 2020
ISSN (Online) 2348 – 7968 | Impact Factor (2020) – 6.72
www.ijiset.com

A review on Ethosomes

[1]Sandeep Kumar, [2]Rashmi Kumari, [3]Dr. Satish manchanda
[1,2]Department of hospital pharmacy
[3]Department of pharmaceutics
Delhi Institute of pharmaceutical sciences and research(DIPSAR)

Abstract

Skin play a main role in the protection of body from foreign particles and prevent body from many attacks. skin is the primary defence of body, but at the same time it won't allow many topical formulations to cross stadium corneum and halt the action of many topical preparation. Ethosomes are the novel formulation which contains high concentration of ethanol that's why they are called ethosomes. High concentration of ethanol helps to cross the drug to striatum corneum and reach the drug to the affected area. Phospholipid also helps to cross the lipid layer of skin. Ethanol is act as permeation enhancer in the ethosomes.

1.Introduction

Ethosomes

Touitou et al.,1997 developed an innovative lipid carrier, referred as ethosomes which comprised of ethanol, phospholipids, and water. Enhancement of the skin delivery of several drugs is reported [1]. They are soft malleable vesicles. Because the new vesicular system comprised ethanol in it, it is referred as ethosomes. Ethanol is an effective permeation enhancer, which supposed to perform its action by altering the stratum corneum's intracellular region. [2] as the system have the ability to interfere the barriers present in skin and are able to penetrate the SC lipid bilayer which allow improvement in the drug delivery through passive transport to the beneath skin strata and trans dermally. The systems include soft phospholipid vesicles in a hydroethanolic environment. [3,4] Skin is the outer multi-layered organ which act as a protective tissue and as a penetrability barrier, inhibit permeation of the foreign molecules from the external environment [5,6]

They are non-invasive delivery carriers, which allow the drug to move deep in the skin layer and / or in the systemic circulation. Lipophilic drugs which have molecular weight < 500 Da can undergo the stratum corneum [7,8].

The ethosomes are available in varying sizes thirty nanometre's to microns. It had been reported that Ethosomes have uniform size distribution and they are small in comparison to

liposomes. [9,10] As for the example, by raising the concentration of ethanol from 20 to 45% in a system which contain 2% soya lecithin result in gradual size reduction from 193 to 103 nm. Ethosomes have great encapsulation ability for lipophilic drugs for example minoxidil and testosterone (83 and 90%, respectively). (4)

The ethosomal system permit improved dermal and transdermal delivery through passive diffusion. Other function of ethanol available in the system is fluidization and cause disturbance of SC lipid organization. [11]

Soft vesicles diffuse into and pass through the disturbed SC lipid bilayers, and advancing the delivery of active agent below the SC barrier

Soft vesicles penetrate into and across the disturbed SC lipid bilayers, promoting delivery of active agents beneath the SC barrier. Ethosomes penetrating the fluidized SC bilayers generate a passageway across the SC lipids and fuse with cell membranes in the deeper skin layers where they release their payload. (12)

Lipophilic drug minoxidil is the most widely used topical agent, which is used for alopecia androgenata prevention and treatment. The concentration of minoxidil aggregation into hair skin after administering from an ethosomal system modified for hair follicles were found to be two, seven and five times higher relative to ethanolic phospholipid dispersion, hydroethanolic solution and pure ethanol, respectively. Because of the properties of ethosomes, they can be effectively used in dermal therapies also in transdermal delivery.

2.Mechanism of ethosomal action

In ethosomes, ethanol engages with the lipid molecules which are present in the polar head group region which cause decline in the transition temperature of lipids in stratum corneum, which lead to increase in the fluidity and reduction in the density of the lipid multilayer. This is trailed by ethosomal effect which comprise lipid penetration and permeation through the opening of new pathways, because of pliability and blending of ethosomes along with skin lipids, which results in the drug liberation deep in the layers of skin. Soft flexible property of vesicle may be due to the ethanol, by which they can penetrate readily in the deeper skin layer. Drug liberation in the deeper skin layer and the transdermal absorption may be due to the outcome of fusion of ethosomes and skin lipids, and drug release at several parts along the penetration pathway [13].

3. Advantages of Ethosomal Drug Delivery

According to the comparison with other delivery systems like transdermal and dermal -

i. Improvement of the drug permeation via skin dermal and transdermal delivery.

ii. Provide, opportunities for the delivery of macro and varied groups of drugs (protein, peptides).
iii. Much more effective for the delivery of a fluorescent probe (quantum dots) into the skin particularly in terms of quality and depth.
iv. Ethosomes have low risk profile – this technique does not have large-scale drug development risk, in the scientific literature the toxicology profile of ethosomal constituents are well stated.
v. Great patient compliance- as the drugs in ethosomes are delivered in semisolid form (gel or cream), which contribute better patient compliance. Corresponding to the iontophoresis and phonophoresis which are difficult to use, which influence patient compliance.
vi. Have great market interest for the products with proprietary technology. Manufacturing is simple, for ethosomal production there is no need for complicated technical investment.
vii. This system is passive, non-passive and available for instant commercialization.
viii. several applications in the pharmaceutical, such as in veterinary and cosmetic fields.

4. Disadvantages of Ethosomal Drug Delivery

They required High blood levels cannot be administered – limited only to potent molecules, those requiring a daily dose of 10mg or less.

i. Ethosomal administration is not a means to achieve rapid bolus type drug input, rather it usually designed to offer slow, sustained drug delivery.
ii. Adequate solubility of the drug in both lipophilic and aqueous environments to reach dermal microcirculation and gain access to the systemic circulation.
iii. Drug molecular size should be rational, as it will be absorbed percutaneously.
iv. There are chance of adhesives not does remain still with all kinds of skin
v. Not so economical.
vi. low yield.
vii. May cause skin irritation or dermatitis because of excipients and enhancers used in the drug delivery systems.
viii. In case if shell locking is ineffective then the ethosomes may coalescence and fall apart on transfer into water.
ix. Product loss, when it is conveyed to water media from organic media. [14-19]

5. Methods of Preparation of Ethosomes

According to the literature there are several methods for the preparation of ethosomes, some widely employed methods have been assembled in the proceeding text-

Hot method

In hot method, the drug is dissolved in a mixture, containing ethanol and propylene glycol and then in phospholipid dispersion in water (40°C) this mixture is added. The mixture is mixed for five minutes after that it is sonicated at 4°C Probe Sonicator using for three cycles of five minutes, also between each cycle five minutes rest is included. The preparation is homogenized (at 15,000 psi pressure), in three cycles, by using a high-pressure homogenizer to obtain nano-sized ethosomes**. [20]**

Cold method

For the preparation of ethosomes this is the most widely used method. At room temperature in a covered vessel phospholipids, drug and other lipid materials are dissolved in ethanol with constant stirring. In a water bath, the mixture is allowed to heat up to 30°C. In a separate container, water is heated up to 30°C and mixed with the above mixture, then allowed to stir for five minutes in a covered container. By using sonication or extrusion, the vesicle size of the ethosomal preparation can be reduced if preferred. The preparation should be properly stored in refrigeration.

Mechanical Dispersion Method

In this method, in a round bottom flask containing mixture of chloroform: methanol (3:1) Soya phosphatidylcholine is dissolved. The removal of organic solvents is done by using rotary vacuum evaporator above lipid transition temperature to create of a thin lipid film on the wall of the flask. Lastly, the residues of solvent mixture are eliminated by allowing the contents under vacuum overnight. Hydration is done with using distinct concentration of hydroethanolic mixture containing drug by rotating the flask at appropriate temperature**. [21,22]**

Classic method

In this method, in ethanol phospholipid and drug are dissolved and kept in water bath for heating (30°C±1°C). With continuous stirring, in the lipid mixture the double water was added in a fine stream. After that the recovered vesicle suspension is pass through a polycarbonate membrane using a hand extruder for the three cycles to homogenize [23].

6. Evaluation of ethosomes

i. Organoleptic properties

Organoleptic properties of ethosomes such as physical appearance, colour texture and consistency of gel were assessed visually.

ii. Scanning electron microscopy and transmission electron microscopy

The visualization of the shape of vesicle could be done by utilizing transmission electron microscopy (TEM), photomicrograph, or scanning electron microscopy (SEM) micrographs. [24,25]

iii. Vesicle size and zeta sizer

Size of vesicle and zeta potential of ethosomal preparation could be assessed through zeta meter [26]. Scale of size is approximately tens of nanometres (nm) to micrometres,

the constituents used in the formulation also alter the size. There are several factors which can influence the zeta potential and size. Decrease in the average diameter of vesicle is result of ethanol's presence, because it is the reason behind the system's net charge alteration and give it certain extent of stearic equilibrium which result in the reduction of average size of vesicle,[27] whereas the increase in the concentration of phospholipid leads to vesicle size increase. This could be described in expression of tendency of lipid coalesces, at high concentration of lipid [28,29]. instant dilution of ethosomes by using buffer saline solution. The mean of particle size was computed on the basis of the data obtain from the five batches of ethosomes.

iv. Differential scanning calorimetry

Differential scanning calorimetry is utilized to evaluate the transition temperature of the vesicular lipid systems, it can also able to identify the ethanol-skin phospholipid association, a distinctive credit to the fluidizing effect of ethanol on the phospholipid bilayers.[30]

v. Entrapment efficiency

Ultracentrifugation technique is able to assess the entrapment efficacy of ethosomes. The ethosomes capability to effectively entrap hydrophobic and hydrophilic drugs can be described by mean of high degree of lamellarity and, the presence of ethanol in the

vesicles. Furthermore, ethosomal preparations acquire greater entrapment ability in comparison to liposomes.[31]

vi. The efficiency of ethosomes to effectively entrap drugs was calculated by using centrifugation process [32]. The vesicles (2ml) were centrifuged at 4C with 14,000 rpm for 3 hours. The supernatant and sediment recovered, was analysed for drug content via HPLC. The entrapment efficiency was computed by the equation given below.

Entrapment Efficiency (%) = (D/DT) x 100%

Where, D = Amount of drug in sediment

DT = Total amount of drug in supernatant and sediment

vii. Drug content and uniformity

An aliquot of gel (0.1g) was isolated with 10ml of methanol and after that centrifuged with 1,000 rpm at 4C for 20 minutes. The supernatant attained was further examined by utilizing HPLC [32].

viii. PH measurements

The pH of ethosomal preparations were assessed by utilizing the pH meter. The electrode was immersed into the vesicles as long as it is enclosed by the vesicles.

ix. In vitro drug release study

The capability of the ethosomal formulations to diffuse into the layers of skin could be evaluated through confocal laser scanning microscopy. In vitro and in vivo skin permeation analyses have established the efficiency of the ethosomal preparations to improve permeation of both hydrophobic and hydrophilic molecules relative to the conventional liposomes. Several reports have stated a 5 – 10-fold better skin permeation of drugs formulated in ethosomes, relative to the conventional liposomal formulation. [33,34]

In vitro drug release analysis of drug in ethosomes were done by utilizing Franz diffusion cell. A fixed concentration of gel preparation was spread on the cellulose acetate membrane at the donor compartment. The receptor compartment was filled with PBS as receptor solution. Sample solution (0.5mL) was withdrawn at 1-hour interval for 8 hours and instantly substituted with the equivalent volume of receptor solution. The sample was assessed by utilizing HPLC technique [35].

x. In vitro skin permeation study

A fragment of freshly excised rat skin was dipped in the isotonic solution (0.9g sodium chloride dissolved in 100mL of R.O water). Ethosomal vesicles and gel were on rat skin and placed on top of the donor compartment of Franz diffusion cell. The dermal side of the skin should nearly touch the receptor liquid surface for permeation. All other analysis circumstances were as in vitro release study [35]. And skin retention of drug was assessed by HPLC method [36].

xi. Stability study

xii. Ethosomal vesicles stability was evaluated by determining the alteration in the entrapment ability of the drug. at different temperature the vesicles were kept, 4°C and 25□Cμ2□C. After that, the drug content of the vesicles was assessed every 15 days for 45 days.

Conclusions

In the modern approaches of topical and trans dermal delivery of drug ethosomes are the one of the best approaches for good drug delivery to the site of affected area, so it will be easily found that ethosomes are better than liposomes and many other drug delivery system .ethosomes can easily help to cross large molecules to cross striatum corneum with the help of ethanol as penetration enhancer. All these things make ethosomes an better drug delivery system.

REFERENCE

1.Bendas ER, Tadros MI. Enhanced transdermal delivery of salbutamol sulphate via ethosomes. AAPS Pharm Sci Tech 2007; 8:1-7.

2. Touitou E. - Composition for applying active substances to or through the skin. - US Patent 5,716,638, 1998

3. Touitou E. - Composition for applying active substances to or through the skin. - US Patent 5,716,638, 1998.

4. 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, 403-418, 2000

5.Schreiner V., Gooris G.S., Pfeiffer S., Lanzendorfer G., Wenck H., Diembeck W., Proksch E., Bouwstra J. - Barrier characteristics of different human skin types investigated with X-ray diffraction, lipid analysis, and electron microscopy imaging. -J. Invest. Dermatol., 114, 654-660, 2000.

6. Schaefer H., Redelmeier T.E. (Eds.) - Skin Barrier, Principles of Percutaneous Absorption. - Karger AG, Basel, Switzerland, 1996

7. Gangwar S., Singh S., Garg G., Ethosomes: A Novel tool for Drug Delivery through the Skin, Journal of Pharmacy Research 2010;3,4:688-691.

8. Kumar KP., Radhika PR., Sivakumar T., Ethosomes: A Priority in Transdermal Drug Delivery, International Journal of Advances in Pharmaceutical Sciences 2010;1:111-121.

9. Godin B., Touitou E. - Erythromycin ethosomal systems: physicochemical characterization and enhanced antibacterial activity. - Cur. Drug Deliv., 2, 269-275, 2005.

10. Dayan N., Touitou E. - Carriers for skin delivery of trihexyphenidyl HCl: ethosomes vs. liposomes. - Biomaterials., 21, 1879-1885, 2000.

11. Touitou E. - Drug delivery across the skin. - Expert Opin. Biol. Ther., 2, 723-733, 2002.

12. Harris R.A., Burnett R., McQuilkin S., McClard A., Simon F.R. - Effects of ethanol on membrane order: fluorescence studies. - Ann. N. Y. Acad. Sci., 492, 125-135, 1987.

13. Elsayed MA, Abdallah YO, Naggar FV, Khalafallah NM. Lipids vesicles for skin delivery of drugs: Reviewing three decades of research. Int J Pharm 2006;332:1-16.

14. Jain H., Patel J., Joshi K., Patel P., Upadhyay UM., Ethosomes: A Novel Drug Carrier, International Journal of Clinical Practice 2011;7:1:1-4.

15. Upadhyay N., Mandal S., Bhatia L., Shailesh S., Chauhan P., A Review on Ethosomes: An Emerging Approach for Drug Delivery through the Skin, Recent Research in Science and Technology 2011;3,7:19-24.

16. Sivakranth M., AnjumaAra P., Krishnaveni C., Venkatesh E., Ethosomes: A Novel Vesicular Drug Delivery System, International Journal of Advances in Pharmaceutical Research 2012;2,1:16-27.

17. Kumar R., Aslam MD., Tripathi A., Prasad D., Chaudhary V., Jain V., Mishra SK., Singh R., Ethosomes: Novel Vesicular Carriers in Transdermal Drug Delivery, Journal of Global Pharma Technology 2010;2,6:1-7.

18. Rathore AR., Khambete H., Jain S., Preparation and Characterization of Repaglinide Loaded Ethosomal Gel for the Treatment of NIDDM, International Journal of Pharmaceutical and Biological Archives 2013;4,2:385- 390.

19. Shahwal V., Samnani A., Dubey B., Bhowmick M., Ethosomes: An Overview, International Journal of Biomedical and Advance Research 2011;2: 161-168

20. 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.

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

22. 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 54.

23. Jain S, Tiwari AK, Sapra B, Jain NK. Formulation and evaluation of ethosomes for transdermal delivery of lamivudine. AAPS Pharm Sci Tech 2007; 8:1-9

24. Fang YP, Tsai YH, Wu PC, Huang YB. Comparison of 5-aminolevulinic acid-encapsulated liposomes versus ethosomes for skin delivery for photodynamic therapy. Int J Pharm 2008; 356:144-52.

25. Godin B, Touitou E. Erythromycin ethosomal systems: Physicochemical characterization and enhanced antibacterial activity. Curr Drug Del 2005; 2:269-75.

26. Rao Y, Zheng F, Gao J. In vitro percutaneous permeation and skin accumulation finasteride using vesicular ethosomal carrier. AAPS Pharm Sci Tech 2009; 9:860-5.

27. Fang JY, Hwang TL, Leu HY. Effect of enhancers and retarders on percutaneous absorption of flurbiprofen from hydrogel. Int J Pharm 2003; 250:313-25.

28. Lopez-Pinto JM, Gonzalez-Rodriguez ML, Rabasco AM. Effect of cholesterol and ethanol on dermal delivery from DPPC liposomes. Int J Pharm 2005; 298:1 12.

29. Maghraby M, Campbell M, Finnin BC. Mechanism of action of novel skin penetration enhancers phospholipids versus skin lipids liposomes. Int J Pharm 2005; 305:90-104.

30. Hu G, Liu J. Advances in studies of phospholipids as carriers in skin topical application. J Nanjug Med Univ 2007; 21:349-53.

31. Godin B, Touitou E, Rubinstein E, Athamna A, Athamna M. A new approach for treatment of deep skin infection by an ethosomal antibiotic preparation: An In vivo study. J Antimicro Chemother 2005; 55:989-94.

32. Kumar V, M.R, Abdul Hasan Sathali A, Arun K. Formulation and evaluation of diclofenac potassium ethosomes. International Journal of Pharmacy and Pharmaceutical Sciences. 2010; 2(4): 82-86.

33. Verma DD, Verma S, Blume G, Fahr A. Ethosomes increases skin penetration of entrapped and non-entrapped hydrophilic substances into human skin: A skin penetration and confocal laser scanning microscopy studies. Eur J Pharm Biopharm 2003; 55:271-7.

34. Vivek D, Dhirendra K. Ethosomes for enhanced transdermal drug delivery of aceclofenac. Int J Drug Del 2010; 2:81-92.

35. Touitou E, Alkabes M, Dayan N. Ethosomes: Novel lipid vesicular system for enhanced delivery. Pharm. Res. 1997; 14: 305-306.

36. Navjot Kaur,1 Richa Puri,1 and Subheet Kumar Jain, Drug- Cyclodextrin-Vesicles Dual Carrier Approach for Skin Targeting of Antiacne Agent. AAPS PharmSciTech 2010; 11 (2): 528-537