IJPSR (2015), Vol. 6, Issue 9 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 13 February, 2015; received in revised form, 25 May, 2015; accepted, 22 August, 2015; published 01 September, 2015

ETHOSOMES - A PROMISING WAY FOR TRANSDERMAL DRUG DELIVERY

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Keywords:

Transdermal delivery, alternative approach, good penetrability, phospholipids, prolonged release

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ABSTRACT: One of the major advances in vesicle research was the finding that some modified vesicles possessed properties that allowed them to successfully deliver drugs in deeper layers of skin. Transdermal delivery is important because it is a noninvasive procedure for drug delivery. Further, problem of drug degradation by digestive enzymes after oral administration and discomfort associated with parenteral drug administration can be avoided. An alternative approach to overcome the low oral bioavailability is to administer the drug by non oral routes such as buccal, nasal, vaginal, transdermal and parenteral. Among the above routes the transdermal delivery of ethosome is advantageous. Because it has good penetrability, ease of administration, rapid termination of the therapy and administrating to unconscious patients. Ethosome mainly contain phospholipids with higher concentration of ethanol. It can be used for systemic delivery of drug. It is beneficial to overcome the problem of frequent dosing due to shorter half-life of drugs. Prolonged release of the drug and increased bioavailability leads to significant reduction in the dose and hence dose related side effects.

INTRODUCTION: Optimization of drug delivery through human skin is important in modern therapy. Recently, the transdermal route vied with oral treatment as the most successful innovative research area in drug delivery[1]. Transdermal delivery is an important delivery route that delivers precise amount of drug through the skin for systemic action. Improved methods of drug delivery for biopharmaceuticals are important for two reasons; these drugs represent rapidly growing portion of new therapeutics, and are most often given by injection. Discovery of new medicinal agents and related innovation in drug delivery system have not been only enabled the successful implementation of novel pharmaceutical, but also permitted the development of new medical treatment with existing drugs.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.6(9).3663-70

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.6(9).3663-70

Throughout the past two decades, the transdermal patches have become a proven technology holding the promise that new compound could be delivered in a safe and convenient way through the skin[2].

Transdermal route offers several potential advantages over conventional routes like avoidance of first pass metabolism, predictable and extended duration of activity, minimizing under able side effects, utility of short half- life drugs, improving physiological and pharmacological response, avoiding the fluctuation in drug levels, inter and intra patient valuations, and most importantly, it provides patient convince. But one of the major problems in transdermal drug delivery is the low penetration rate through the outer most layer of skin [3].

Vesicular Carriers for Topical Delivery:

Niosomes are also known as non- ionic surfactant vesicles, are microscopic unilamellar or multilamellar vesicular structures containing a non-ionic surfactant with or without cholesterol. These vesicles encapsulate solutes and are also

osmotically active and stable. But they have less skin penetration power. Transfersomes appears to be remotely related to lipid bi- layer vesicle, liposome. But in functional terms, transfersomes are much more flexible and adaptable. Because of flexibility they can squeeze themselves even through pores much smaller than their own diameter. It mainly consists of phospholipids and surfactants. Although it has high penetration power due to high deformability it cannot reach up to deeper skin layer. So, it is less effective for systemic effects [3].

In the early 1990s, a greater knowledge of vesicles was gained and many types of vesicles and vesicles derivatives have been tested for their abilities for transdermal delivery of drug. Most experiments however have centered on liposomes, since derivatives only add to their basic properties. Vesicles are closed, spherical membranes that separate a solvent core from the surrounding solvent.

They are typically composed of phospholipids, mainly phosphotidyl choline (PL) as in liposomes while it has been suggested that the external envelop of a liposome would allow it to pass through lipophilic skin. Most researches show that liposomal vesicles become trapped within the top layer of the stratum corneum cells. Vesicular systems are drug delivery system to deliver the drug dermally and transdermelly. Liposomes have the potential of overcoming the skin barrier, as these are bilayered lipid vesicles, consisting primarily of phospholipids and cholesterols [4].

Novel Vesicular Carrier-Ethosomes:

Classic liposomes are of little or no value as carriers for transdermal delivery because they do not deeply penetrate the upper layer of stratum corneum. Only specially designed vesicles were shown to be able to allow transdermal delivery. Ethanol is known as an efficient permeation enhancer. Touitou et al., 2000 discovered lipid vesicular system embodying ethanol in relatively high concentration, which was named ethosomes. He found that ethosomes penetrate skin and enhance compound delivery to deep skin strata or systemically and suggested that ethanol fluidizes both ethosomal lipids and bilayers of the mortar. The soft malleable vesicles then penetrate through the disorganized lipid bilayers.

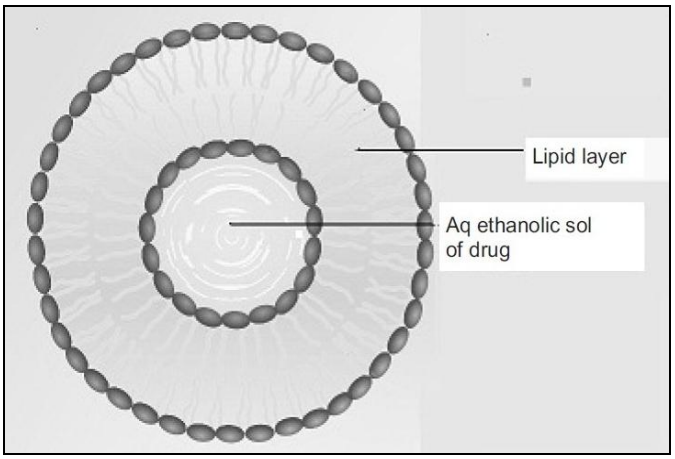

FIG. 1: VESICULAR DIAGRAM OF ETHOSOMES

The vesicles have been well known for their important in cellular communication and particle transportation for many years. Researchers have understood the properties of vesicle structures for use in better drug delivery within their cavities that would allow tagging the vesicle for cell specificity. Vesicles would also allow to control the release rate of drug over an extended time, keeping the drug shielded from immune response or other removal systems and would be able to release just the right amount of drug and keep that concentration constant for longer periods of time. One of the major advances in vesicle research was the finding a vesicle derivative, known as an ethosomes. Ethosomal carriers are systems containing soft vesicles and are composed mainly of phospholipid (Phosphotidyl choline; PC), ethanol at relatively high concentration and water. It was found that ethosomes penetrate the skin and allow enhanced delivery of various compounds to the deep strata of the skin or to the systemic circulation. [5, 6, 7]

Mechanism of Penetration:

Although the exact process of drug delivery by ethosomes remains a matter of speculation, most likely, a combination of processes contributes to the enhancing effect. The stratum corneum lipid multilayer at physiological temperature are densely packed and highly conformationally ordered. The high concentration of ethanol makes the ethosomes unique, as ethanol is known for its disturbance of skin lipid bilayers organization; therefore, when

integrated into a vesicle membrane, it gives that vesicles have the 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, giving it more freedom and ability to squeeze through small places such as the openings created in disturbing the stratum corneum lipid.

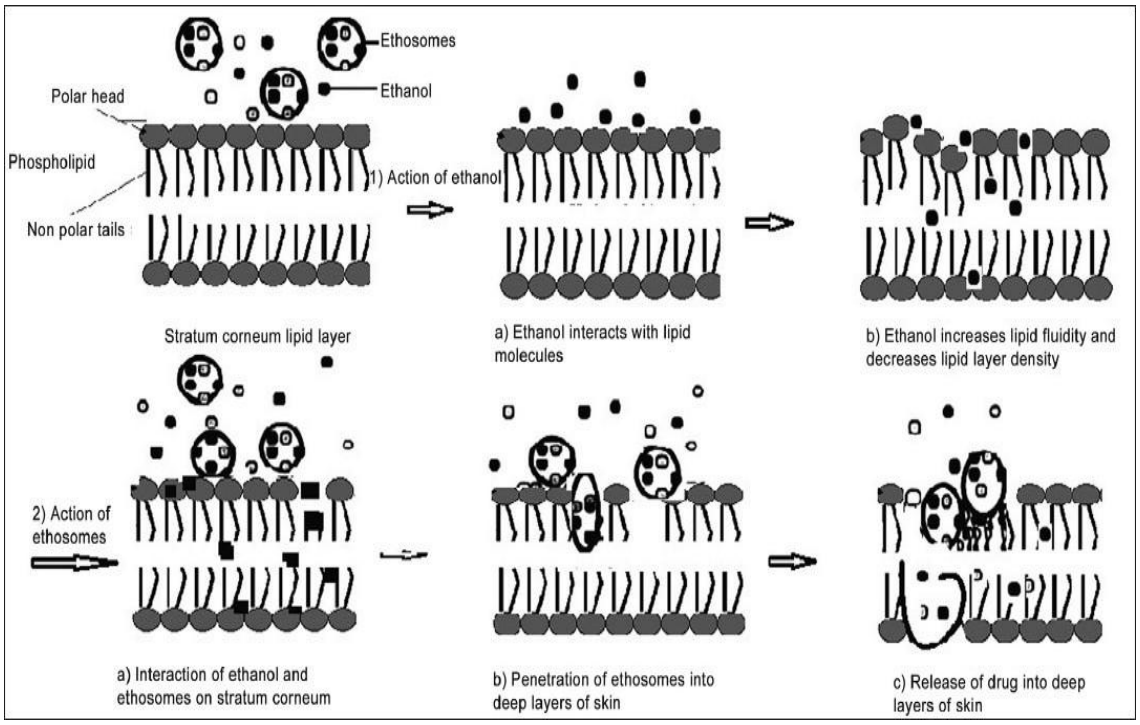

FIG.2: MECHANISM OF PENETRATION OF ETHOSOMAL DRUG DELIVERY SYSTEM

Ethanol interacts with lipid molecules in the polar hard group region, resulting in reducing the rigidity of the stratum corneum lipids, increasing their fluidity. The intercalation of ethanol into the polar head group environment can result in an increase in the membrane permeability. In addition to the effect of ethanol on stratum corneum structure, the ethosome itself may interact with the stratum corneum barrier. While encapsulated drug in classic liposomes remained primarily at the surface of the skin the ethosomal system was showed to be highly efficient carrier for enhanced drug delivery through the skin. The efficient drug delivery shown together with the long-term stability of ethosomes makes this system a promising candidate for transdermal delivery of drug. [7, 8]

Composition of Ethosomes:

The ethosomes are vesicular carrier comprise of hydroalcoholic or hydro/alcoholic/glycolic phospholipid in which the concentration of alcohols or their combination is relatively high. Typically, 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. Drug delivery can be modulated by altering alcohol: water or alcohol-polyol: water ratio. Some preferred phospholipids are soya phospholipids such as Phospholipon 90 (PL-90). It is usually employed in a range of 0.5-10% w/w. Cholesterol at concentrations ranging between 0.1-1 percent can also be added to the preparation. [9, 10]

Examples of alcohols, which can be used, include ethanol and isopropyl alcohol. Among glycols, propylene glycol and Transcutol are generally used. In addition, non-ionic surfactants (PEG-alkyl ethers) can be combined with the phospholipids in these preparations. Cationic lipids like cocoamide,

POE alkyl amines, dodecylamine, cetrimide etc. can be added too. 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% (**Table 1).**

TABLE 1: DIFFERENT ADDITIVES EMPLOYED IN FORMULATION OF ETHOSOMES

Class	Example	Uses
Phospholipid	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

Method For Preparing Ethosomes: [10, 11, 12]

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

Cold Method:

This is the most common method utilized for the preparation of ethosomal formulation. In this method phospholipid, 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 300ºC in a water bath. The water heated to 300ºC 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 desire extend using sonication or extrusion method. Finally, the formulation is stored under refrigeration.

Hot Method:

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

Characterization of Ethosomes: [12-15]

1. **Drug Entrapment Efficiency:**

Differential scanning calorimetry thermograms and anisotropy measurement of AVPC (a fluorescent analog of phosphatidylcholine), revealed that ethosomes possessed lower Tm compared to classical liposomes and that the bilayers had a high degree of fluidity. This imparted a soft and malleable character to the vesicles. The ability of ethosomes to efficiently entrap lipophilic and hydrophilic drugs can be explained by the high degree of lamellarity and by the presence of ethanol in the vesicles. In addition, ethosomal formulations possess greater entrapment capability than liposomes.

2. **Permeation Characteristics:**

In vitro and in vivo skin permeation studies have demonstrated the ability of ethosomal formulation to enhance permeation of both hydrophobic and hydrophilic molecules as compared to conventional liposomes. Different workers have reported 5-10 fold better skin permeation of drugs formulated in

ethosomes as compared to conventional liposome formulation. Ethanol has long been known to have permeation enhancement property. However, the permeation enhancement from ethosomes was much greater than would be expected from ethanol alone, suggesting some kind of synergistic mechanism between ethanol, vesicles and skin lipids. Thus, ethanol that was earlier considered harmful to conventional liposomal formulations, provided flexible characteristics to ethosomes, which allows them to easily penetrate into deeper layers of the skin.

3. **Vesicle Skin Interaction Study:**
For evaluating the mechanism of better skin permeation of ethosomal formulation different visualization techniques e.g. transmission electron microscopy, eosin-hematoxylin staining, fluorescence microscopy and confocal scanning laser microscopy (CSLM) have been used. Often, when used in combination these visualization techniques gave better idea about structure modulation and penetration pathways of vesicles. No ultrastructural changes were observed in cell layers below the stratum corneum indicating that rigid liposomal formulation did not induce any changes in the ultrastructure of stratum corneum and accumulated only in the top layer of the skin. These results illustrated that liquid state vesicles might act not only in superficial stratum corneum layers, but may also induce liquid perturbations in deeper layers of the SC, while gel state vesicles interacted only with the outermost layers in the SC.

This might explain the difference in drug permeation enhancement between ethosomal and conventional liposomal formulation. In addition, fusion of conventional liposomal vesicles on top of the stratum corneum might also act as additional barrier for diffusion of drugs and therefore inhibit skin permeation.

Applications: [16-23]

1. **Pilosebaceous Targeting:**
Hair follicles and sebaceous glands are increasingly being recognized as potentially significant elements in the percutaneous drug delivery. Interest in pilosebaceous units has been directed towards their use as depots for localized therapy, particularly for the treatment of follicle-related disorders such as acne or alopecia. Furthermore, considerable attention has also been focused on exploiting the follicles as transport shunts for systemic drug delivery. With the purpose of pilosebaceous targeting, Conventional topical formulation has very poor skin permeation and retention properties.

2. **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. In addition, along with these side effects oral hormonal preparations relying highly on patient compliance. The risk of failure of treatment is known to increase with each pill missed.

3. **Delivery of Anti-Parkinsonism Agent:**
Dayan and Touitou prepared ethosomal formulation of psychoactive drug trihexyphenidyl hydrochloride (THP) and compared its delivery with that from classical liposomal formulation. THP is a M1 muscarinic receptors antagonist and used in the treatment of Parkinson disease. The value of transdermal flux of THP through nude mouse skin from ethosomes was 87, 51 and 4.5-times higher than that from liposome, phosphate buffer and hydroethanolic solution, respectively. The quantity of THP remaining in skin at the end of 18 hr was significantly higher after application of ethosomes than after application of liposome or hydroethanolic solution (control). These results indicated better skin permeation potential of ethosomal-THP formulation and its use for better management of Parkinson disease.

4. **Transcellular Delivery:**
Touitou et al prepared ethosomes, hydroethanolic solution and liposomes, respectively. Fibroblasts viability tests showed that the ethosomal carrier was not toxic to the cultured cells. The penetration of these fluorescent probes into fibroblasts and nude mice skin was examined by CLSM (Confocal Laser Scanning Microscopy) and FACS (Fluorescent Activated Cell Sorting) techniques.

CLSM micrograph showed that significant quantity of probe was penetrated into the cells when incorporated into ethosomes as evident from the high intensity of fluorescence. In comparison, incorporation into hydroethanolic solution or

classic liposomes produced almost negligible fluorescence. Enhanced delivery of the hydrophilic calcein and lipophilic rhodamine red (RR) probe to nude mice skin was also observed when incorporated into ethosomes.

5. **Topical Delivery of DNA:**
Many environmental pathogens attempt to enter the body through the skin. Skin therefore, has evolved into an excellent protective barrier, which is also immunologically active and able to express the gene. On the basis of above facts another important application of ethosomes is to use them for topical delivery of DNA molecules to express genes in skin cells. It has been suggested that ethosomes could be used as carriers for gene therapy applications that require transient expression of genes. The results also showed the possibility of using ethosomes for effective transdermal immunization. Hence, better skin permeation ability of ethosomes opens the possibility of using these dosage forms for delivery of immunizing agents.

6. **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. Cannabidol (CBD) is a recently developed drug candidate for treating rheumatoid arthritis. Its oral administration is associated with a number of problems like low bioavailability, first pass metabolism and GIT degradation. Significantly increased in biological anti-inflammatory activity of CBD-ethosomal formulation was observed when tested by carrageenan induced rat paw edema model. So, it was concluded that encapsulation of CBD in ethosomes significantly increased its skin permeation, accumulation and hence it's biological activity.

7. **Delivery of Antibiotics:**
Topical delivery of antibiotics is a better choice for increasing the therapeutic efficacy of these agents. Conventional oral therapy causes several allergic reactions along with several side effects. Conventional external preparations possess low permeability to deep skin layers and subdermal tissues. Ethosomes can circumvent this problem by delivering sufficient quantity of antibiotic into deeper layers of skin. Ethosomes penetrate rapidly through the epidermis and bring appreciable amount of drugs into the deeper layer of skin and suppress infection at their root. The results of this study showed that the ethosomal formulation of antibiotic could be highly efficient and would overcome the problems associated with conventional therapy.

8. **Delivery of Anti-Viral Drugs:**
Zidovudine is a potent antiviral agent acting on acquired immunodeficiency virus. Oral administration of zidovudine is associated with strong side effects. Therefore, an adequate zero order delivery of zidovudine is desired to maintain expected anti-AIDS effect. From different studies, it was concluded that ethosomes could increase the transdermal flux, prolong the release and present an attractive route for sustained delivery of zidovudine. Acyclovir is another anti-viral drug that widely used topically for treatment of Herpes labialis. The conventional marketed acyclovir external formulation is associated with poor skin penetration of hydrophilic acyclovir to dermal layer resulting in weak therapeutic efficiency. To overcome the problem associated with conventional topical preparation of acyclovir, researchers have formulated the acyclovir ethosomal formulation for dermal delivery.

9. **Delivery of Problematic Drug Molecules:**
The oral delivery of large biogenic molecules such as peptides or proteins is difficult because they are completely degraded in the GI tract. Non-invasive delivery of proteins is a better option for overcoming the problems associated with oral delivery. Researchers have investigated the effect of ethosomal insulin delivery in lowering blood glucose levels in vivo in normal and diabetic SDI rats. The result showed that insulin delivered from this patch produced a significant decrease (up to 60%) in BGL in both normal and diabetic rats. On the other hand, insulin application from a control formulation was not able to reduce the BGL.

CONCLUSION: Introduction of ethosomes has initiated 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. Multiliter quantities of ethosomal formulation can be prepared very easily.

It, therefore, should be not before long that the corresponding drug formulation would have found their way into clinics to be tested for widespread usage. As mentioned above, numerous studies have been published showing that ethosomes can substantially improve the permeation of drugs through the stratum corneum and thereby their efficacy.

Several excellent phytochemicals and herbal extracts have been successfully delivered via ethosomes and showed some distinct advantages over conventional drug delivery systems. As an alternative to conventional transdermal permeation enhancement techniques, ethosomes are superior by offering safety, efficiency, long term stability, simplified industrial manufacture as well as better patient compliance. Thus, it can be a logical conclusion that ethosomal formulations possess promising future in effective dermal/transdermal delivery of bioactive agents. Transdermal route is promising alternative to drug delivery for systemic effect. This is an encouraging route for drugs, which are poorly absorbed from skin.

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How to cite this article:
Kulkarni S, Mishra KP, Sharma SB and Jain S: Ethosomes - A Promising Way For Transdermal Drug Delivery. Int J Pharm Sci Res 2015; 6(9): 3663-70.doi: 10.13040/IJPSR.0975-8232.6(9).3663-70.