IJPSR (2013), Vol. 4, Issue 1 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 29 September, 2012; received in revised form, 12 November, 2012; accepted, 16 December, 2012

SOFT MALLEABLE VESICLES TAILORED FOR ENHANCED DELIVERY OF ACTIVE AGENTS THROUGH THE SKIN: AN UPDATE

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Keywords:
Ethosomes, Phospholipid, Ethanol, Non-invasive delivery

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QUICK RESPONSE CODE

IJPSR:
ICV- 5.07

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ABSTRACT

Ethosomes are noninvasive delivery carriers that enable drugs to reach the deep skin layers and/or the systemic circulation. These are soft, malleable vesicles tailored for enhanced delivery of active agents. They are composed mainly of phospholipids, high concentration of ethanol and water. The high concentration of ethanol makes the ethosomes unique, as ethanol is known for its disturbance of skin lipid bilayer organization; therefore, when integrated into a vesicle membrane, it gives that vesicle 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 and improves drug distribution ability in stratum corneum lipids. The Ethosomes were found to be suitable for various applications within the pharmaceutical, biotechnology, veterinary, cosmetic, and nutraceutical markets. These "soft vesicles" represents novel vesicular carrier for enhanced delivery to/through skin.

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.

Transdermal delivery is an important delivery route that delivers precise amount of drug through the skin for systemic action. Improved method of drug delivery for biopharmaceuticals is 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.

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. Since the first transdermal patch was approved in 1981 to prevent nausea and vomiting associated with motion sickness, the FDA has approved through the past 22 years more than 35 transdermal patch products spanning 13 molecules [1-2].

Routes of Penetration: At the skin, molecules contact cellular debris, microorganisms, sebum and other materials, which negligibly affect permeation. The penetrant has three potential pathways to the viable tissue - through hair follicles with associated sebaceous glands, via sweat ducts, or across continuous stratum corneum between these appendages (**Figure 1**).

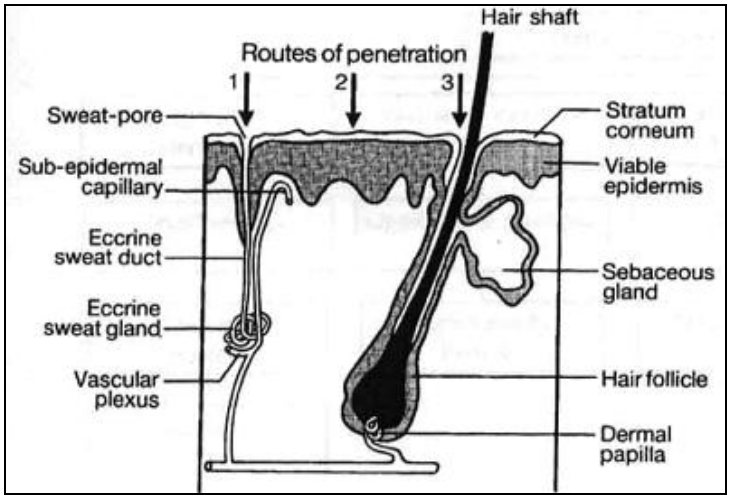

FIGURE 1: SIMPLIFIED DIAGRAM OF SKIN STRUCTURE AND MACROROUTES OF DRUG PENETRATION (1) via the sweat ducts; (2) across the continuous stratum corneum or (3) through the hair follicles with their associated sebaceous glands.

Fractional appendageal area available for transport is only about 0.1%; this route usually contributes negligibly to steady state drug flux. The pathway be important for ions and large polar molecules that struggle to cross intact stratum corneum. Appendages may be providing shunts, important at short times prior to steady state diffusion. Additionally, polymers and colloidal particles can target the follicle.

The intact stratum corneum thus provides the main barrier; its 'brick and mortar' structure is analogous to a wall (**Figure 2**). The corneocytes of hydrated keratin comprise of 'bricks', embedded in 'mortar', composed of multiple lipid bilayers of cermides, fatty acids, cholesterol and cholesterol esters. These bilayers form regions of semi crystalline, gel and liquid crystals domains. Most molecule penetrate through skin via this intercellular microroute and therefore many enhancing techniques aim to disrupt or bypass elegant molecular architecture.

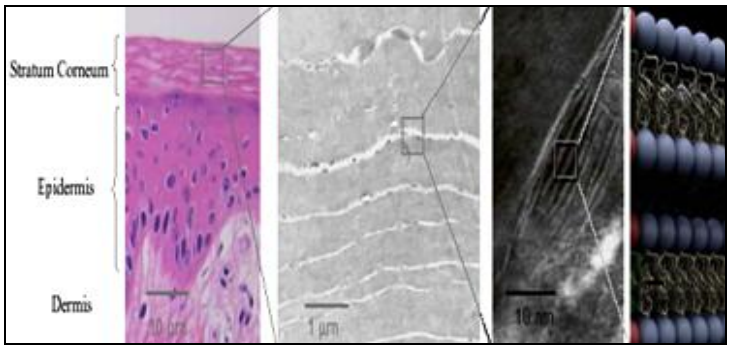

FIGURE 2: STRATUM CORNEUM (TOPMOST 15 µm LAYER) IS THE MAIN BARRIER

Viable layers may metabolize a drug, or activate a prodrug. The dermal papillary layer is so rich in capillaries that most penetrants clear within minutes. Usually, deeper dermal regions do not significantly influence absorption, although they may bind e.g. testosterone, inhitibiting its systemic removal [1].

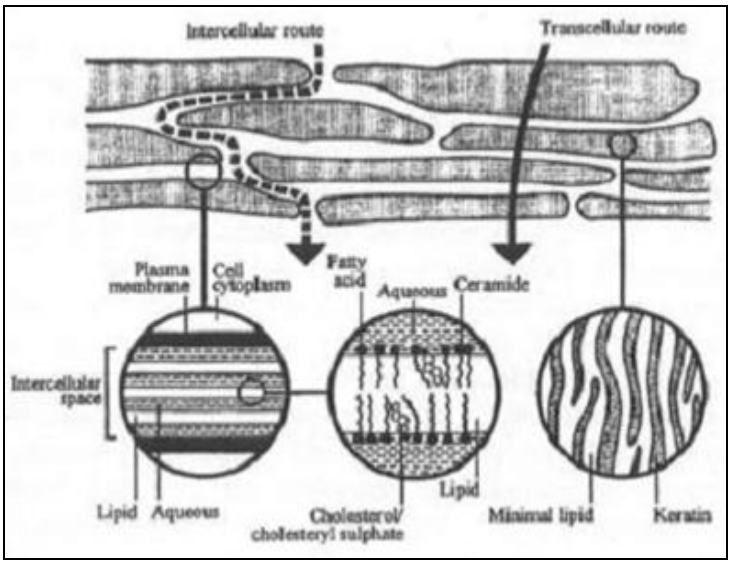

FIGURE 3: SIMPLIFIED DIAGRAM OF STRATUM CORNEUM AND TWO MICROROUTES OF DRUG PENETRATION

Optimising Transdermal Drug Delivery: 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.

The non-invasive approaches for providing transdermal drug delivery of various therapeutics substances are [5];

1) Drug and vehicle interactions
   a. Selection of correct drug or prodrug
   b. Chemical potential adjustment
   c. Ion pairs and complex coacervates
   d. Eutectic systems

2) Stratum corneum modification

   a. Hydration

   b. Chemical penetration enhancers

3) Stratum corneum bypassed or removed

   a. Microneedle array

   b. Stratum corneum ablated

   c. Follicular delivery

4) Electrically assisted methods

   a. Ultrasound (Phonophoresis, Sonophoresis)

   b. Iontophoresis

   c. Electroporation

   d. Magnetophoresis

   e. Photomechanical wave

5) Vesicles and particles

   a. Liposomes and other vesicles

   b. Niosomes

   c. Transfersomes

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.

Liposomes were discovered in the early 1960's by Bangham and colleagues (Bangham et al., 1965) and subsequently became the most extensively explored drug delivery system. In early 1960's a great knowledge of vesicle derivatives have been tested for their abilities.

Most experiments, however, have centered on liposomes,since derivations only add to their basic properties. Vesicles are closed, spherical membrane that separates a solvent from the surrounding solvent.

Possible use of liposomes in topical drug delivery vehicles for both water and lipid soluble drug has been investigated. While it has been suggested that the external envelop of a liposomes 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.

Generally liposomes are not expected to penetrate into viable skin, although occasional transport processes were reported [1]. This behavior is useful both for local treatment of skin disorders and for cosmetic formulations, but not promising for systemic effect.

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 al so 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 can not reach up to deeper skin layer. So, less effective for systemic effects [3-4].

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 to tag 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 t o the deep strata of the skin or to the systemic circulation [6].

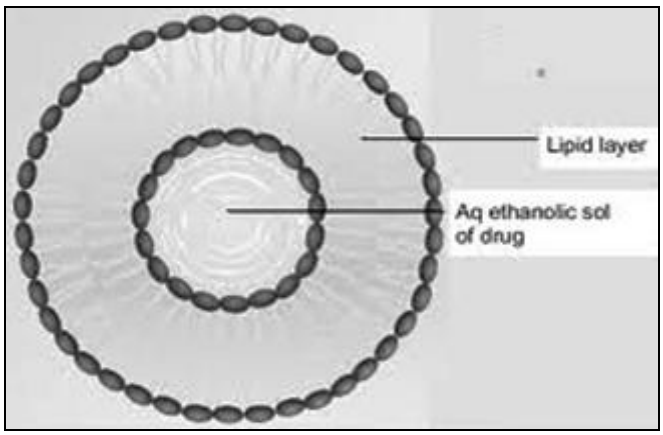

FIG. 4: STRUCTURE OF ETHOSOMES

- **Advantages of Ethosomal Drug Delivery**
  - Ethosomes are enhanced permeation of drug through skin for transdermal and dermal delivery.
  - Ethosomes are platform for the delivery of large and diverse group of drugs (peptides, protein molecules)
  - Ethosome composition is safe and the components are approved for pharmaceutical and cosmetic use.
  - Simple method for drug delivery in comparison tolontophoresis and Phonophoresis and other complicated methods.
  - 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.
  - Low risk profile- The technology has no large-scale drug development risk since the toxicological profiles of the ethosomal components are well documented in the scientific literature [7].

Mechanism of Penetration of Ethosomes: The main advantage of ethosomes over liposomes is the increased permeation of the drug. The mechanism of the drug absorption fromethosomes is not clear. The drug absorption probably occurs infollowing 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 multilayerof cell membrane.
2. **Ethosomes effect: S**kin Increased cell membrane lipid fluidity caused by the ethanol of ethosomes results increased permeability. So the ethosomes permeates very easily inside the deep skin layers, where it got fused with skin lipids.

The interdigitated, malleable ethosome vesicle can forge paths in the disordered stratum corneum. In the case of ethosomes encapsulating drugs, the higher positive zeta potential imparted by the drug can improve skin attachment of the vesicles. 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 make this system a promising candidate for transdermal delivery of drug [8].

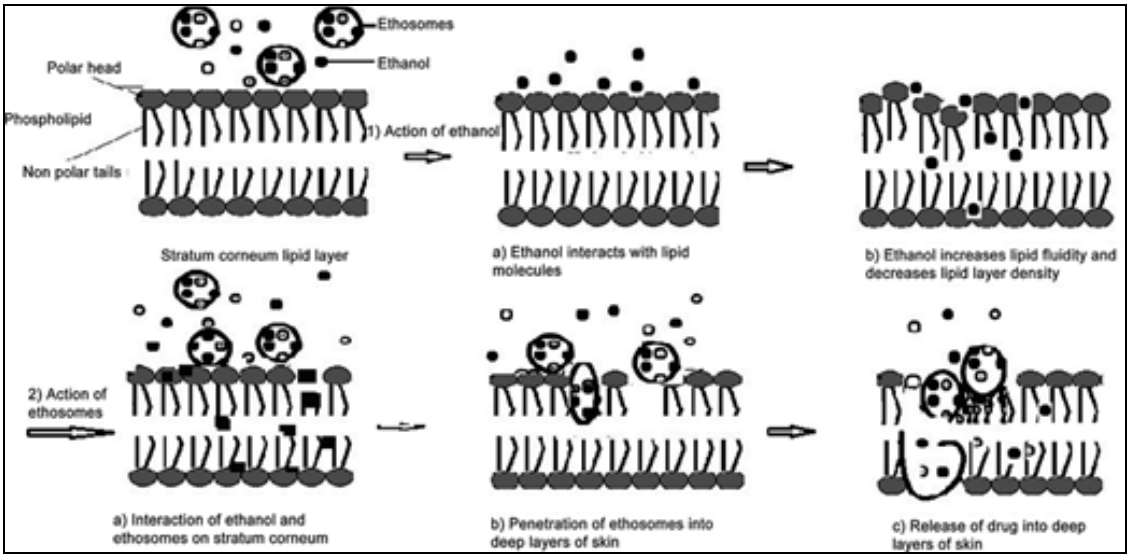

FIGURE 5: PROPOSED MODEL FOR SKIN DELIVERY ETHOSOMAL SYSTEMS

Table 1: Composition of Ethosomes for Transdermal delivery

Additives used in Ethosomal Preparation	Examples	Application
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 rigidity to vesicle membrane
Dye	Rhodamine-123, Rhodamine red Fluorescene Isothiocynate (FITC), 6- Carboxy fluorescence	For drug penetration studies
Vehicle	Carbopol 934	As a gel former

Method for preparation of Ethosomes:

1. **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 30°C in a water bath. The water heated to 30°C 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 [10].

2. **Hot method:** In this method phospholipid is dispersed in water by heating in a water bath at 40°C until a colloidal solution is obtained. In a separate vessel ethanol and propylene glycol are mixed and heated to 40°C. Once both mixtures reach 40°C, 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 [9].

Characterization of Ethosomes: Various methods of characterization of ethosomes are as follows,

TABLE 2: 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	Invitro dissolution	Determine the drug release rate from vesicle	Franz diffusion cell
7	Skin permeation	Determines rate of drug transport through skin	CLSM

1. **Visualization:** For the initial characterization of the vesicles, ethosomal preparation can be examined by negative stain electron microscopy (TEM). It also visualize the lamellar character of ethosomes. The three dimensional nature of phospholipid vesicle can be confirmed by further analysis by scanning electron microscopy (SEM) [10].

2. **Vesicle size and zeta potential:** Particle size of vesicle can be determined by dynamic light scattering (DLS). The charge of the ethosomal vesicle is an important parameter than can influence both vesicular properties such as stability as well as skin-vesicle interactions and it's zeta potential can also be determined using a computerized inspection system [11].

   The size of the vesicles can be characterized by light microscopy with an eye piece micrometer which is calibrated with a stage micrometer.

3. **Entrapment efficiency:** Separation of unentrapped drug and evaluation of entrapment efficiency can be measured by ultra-centrifugation.

   a. **Ultra-centrifugation:** Procedure was reported by touitou et al. Where ethosomal preparation was centrifuged at 4°C 40,000 rpm for 3 hours. The supernatant layer was removed and drug quantity was determined in both the sediment and the supernatant. The entrapment efficiency was calculated as follows.

$$\text{Entrapment Efficiency} = \frac{(T - C)}{T} \times 100$$

Where T is total amount of drug that is detected both in the supernatant layer and resident layer.

is the amount of drug detected only in the supernatant [12]

4. **Transition Temperature:** The transition temperature of the vesicular lipid systems can be determined by using differential scanning calorimetry [13].

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 [14].

6. **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.

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.

8. **Penetration and Permeation Studies:** Depth of penetration from ethosomes can be visualized by confocal laser scanning microscopy (CLSM). CLSM was used to investigate depth and mechanism of skin penetration of ethosomal preparation.

   The skin thickness was optically scanned at different increments through the z-axis of a confocal laser scanning microscope [19].

9. **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 [20].

10. **Phospholipids-ethanol Interaction:** The Phospholipid-ethanol interaction was studied by using Proton decoupled P-NMR and Differential Scanning calorimetry [21].

11. **Degree of deformability and Turbidity:** The Degree of deformability of the ethosomal Preparation was performed by Extrusion Method. and the turbidity of the preparation was performed by Using Nephalometer [22, 23].

12. ***In vitro* drug release study and Drug Deposition study:** In vitro drug release study and Drug Deposition of ethosomal preparation was formed by Franz diffusion cell with artificial or biological membrane, Dialysis bag diffusion [24].

13. **Storage-physical stability of ethosomes:** The ability of ethosomal preparations to retain the drug (i.e., drug-retentive behavior) was checked by keeping the preparations at different temperatures, i.e., 25 ± 2°C (room temperature,

RT), 37±2°C and 45±2°C for different periods of time (1, 20, 40, 60, 80 and 120 days). The ethosomal preparations were kept in sealed vials (10 ml capacity) after flushing with nitrogen. The stability of ethosomes was also determined quantitatively by monitoring size and morphology of the vesicles using DLS and TEM [25, 26].

Applications of Ethosomes: The ability of ethosomal system to deliver molecules to and through the skin was interigated using Franz and side by side diffusion cells. It was found that the drug penetrates the skin to a much greater depth from ethosomes than from classic liposome, hydroethanolic solution of drugs and ethanolic drug solution.

The different characteristics which decide the applications of ethosomes are its high encapsulation efficiency, small vesicle size and flexibility of vesicle membrane. Since ethosomes deliver the drug deep to and through the skin it has application area either in dermal delivery of drug molecules or transdermal delivery of drug molecules [27-34].

1) **Plosebaceous Targeting:** Hair follicles and sebaceous glands are increasingly being recognized as potentially significant elements in the percutaneous drug delivery. Furthermore, considerable attention has also been focused on exploiting the follicles as transport shunts for systemic drug delivery. With the purpose of pilosebaceous targeting, Maiden *et al*., prepared and evaluated minoxidil ethosomal formulation.

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. The risk of failure of treatment is known to increase with each pill missed. Touitou *et al*., compared the skin permeation potential of testosterone Ethosomes (Testosome) across rabbit pinna skin with marketed transdermal patch of testosterone (Testoderm¨ patch, Alza). They observed nearly 30-times higher skin permeation for testosterone from ethosomal formulation as compared to that marketed formulation.

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 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*., in their study demonstrated better intracellular uptake of bacitracin, DNA and erythromycin using CLSM and FACS techniques in different cell lines. Better cellular uptake of anti-HIV drug zidovudine and lamivudine in MT-2 cell line from ethosomes as compared to the marketed formulation suggested ethosomes to be an attractive clinical alternative for anti-HIV therapy.

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 [29]. 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. Touitou *et al*., in their study encapsulated the GFP-CMV-driven transfecting construct into ethosomal formulation. They applied this formulation to the dorsal skin of 5-week male CD-1 nude mice for 48 hr.

   After 48 hr, treated skin was removed and penetration of green fluorescent protein (GFP) formulation was observed by CLSM. It was observed that topically applied ethosomes-GFP-CMV-driven transfecting construct enabled efficient delivery and expression of genes in skin cells. It was suggested that ethosomes could be used as carriers for gene therapy applications that require transient expression of genes. These results also showed the possibility of using ethosomes for effective transdermal immunization. Gupta *et al*., recently reported immunization potential using transfersomal formulation.

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. Lodzki et al. prepared CBD-ethosomal formulation for transdermal delivery. Results shows significantly increased in biological anti-inflammatory activity of CBD-ethosomal formulation was observed when tested by carrageenan induced rat paw edema model. It was concluded 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 [30]. 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. With this purpose in mind Godin and Touitou prepared bacitracin and erythromycin loaded ethosomal formulation for dermal and intracellular delivery. The results of this study showed that the ethosomal formulation of antibiotic could be highly efficient.

TABLE 3: APPLICATION OF ETHOSOMAL DELIVERY

S.no.	Drug	Purpose of Ethosomal delivery	Application
1	Azelaic acid	Improves the sustained release	Treatment of acne
2	Diclofenac	Selective targeting the cells	NSAIDS
3	Testosterone	low oral bioavailability dose dependent side effects	Steroidal hormone
4	Trihexyphenidyl hydrochloride	4.5-times higher than that from liposome	Treatment of Parkinson's disease
5	Zidovudine and lamivudine	Better cellular uptake	Anti-HIV
6	Bacitracin	Better cellular uptake	Antibacterial
7	Erythromycin	Better cellular uptake	Antimicrobial
8	DNA	Expression into skin cells	Treatment of genetic disorders
9	Cannabidol	low bioavailability	Treatment of rheumatoid
10	Acyclovir	Poor skin permeation	Treatment of Herpes labialis
11	Insulin	GIT degradation	Treatment of diabetes
12	Cyclosporin	GIT degradation Poor oral	Treatment of Inflammatory skin disease
13	Ammonium glycyrrhizinate	Poor skin permeation Poor oral bioavailability	Treatment of inflammatory based skin diseases
14	Fluconazole	Poor skin permeation	Treatment of candidiasis
15	Methotrexate	Poor skin permeation	Treatment of psoriasis
16	Salbutamol	Enhanced drug delivery through skin with ethosomes	Anti-asthmatic
17	Minoxidil	Pilocebaceous targeting Accumulation in skin increased	Treatment of baldness
18	Proteins and Peptides	Large molecules	overcoming the problems asso-ciated with oral delivery
19	Enalapril maleate	Low oral bioavailability Major side effects in oral delivery	Treatment of Hypertension

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How to cite this article:
Parihar SK, Bhowmick M, Kumar R and Dubey BK: Soft Malleable Vesicles Tailored For Enhanced Delivery of Active Agents through the Skin: An Update. *Int J Pharm Sci Res*. 2013; 4(1); 172-180.