World Journal of Pharmaceutical Sciences
ISSN (Print): 2321-3310; ISSN (Online): 2321-3086
Published by Atom and Cell Publishers
Available online at: http://www.wjpsonline.org/
Review Article

Ethosomes: A Novel Deformable Carrier

Santosh Shelke[1]*, Sadhana Shahi[2], Suwarna Kale[1], Vandana Patil[1], Dipali Deshpande[1]

[1]Department of Pharmaceutics, Yash Institute of Pharmacy, Aurangabad-431134, Maharashtra, India.
[2]Department of Pharmaceutics, Government College of Pharmacy, Aurangabad – 431005, Maharashtra, India

Received: 26-07-2015 / Revised: 16-08-2015 / Accepted: 19-08-2015

ABSTRACT

Skin acts as a major target as well as a principal barrier for mucous/topical/transdermal drug delivery. Transdermal drug delivery engender major interest among large pharmaceutical firms as it provides the bypass to first-pass metabolism, avoid exposure to the chemical and biological conditions of the gastrointestinal tract, reduce adverse events and moreover improve patient compliance. Major objective of the transdermal drug delivery system is to cross the stratum cornea. One simple and convenient approach to achieve the permeation through the skin is to encapsulate the drug in ethanol based liposomes (ethosomes). Ethosomal carriers are systems containing soft vesicles, composed of hydroalcoholic or hydro/glycolic phospholipids in which the concentration of alcohols is relatively high. Ethosomes have higher penetration rate through the skin as compared to liposomes. The higher concentration of ethanol conveys fluidity of lipids which leads to increase in permeability of the skin/mucous membrane and ultimately helps to improve the drug permeation. Ethosomes have become an area of research interest, due to its potential enhanced skin permeation, improved drug delivery, increased drug entrapment efficiency etc. The purpose of this review is to focus on various aspects of ethosomes including their mechanism of penetration, preparation, composition, characterization, application and marketed product of ethosomes. Ethosomes can act as a carrier for large and diverse group of drugs with different physicochemical properties and found a number of applications in pharmaceutical, biotechnological and cosmetic fields.

Keywords: Ethosomes, Transdermal drug delivery, Stratum corneum, Vesicles, Hydroalcoholic phospholipid.

INTRODUCTION

The application of medicinal substances to the skin is an old concept. In recent years innovative techniques have been developed for the delivery drug through skin. Human skin is an effective, selective barrier for chemical permeation. Transdermal and intranasal drug delivery system is an successful substitute dosage form for delivery of drugs, as it offers several advantages over traditional drug delivery systems, including oral and parenteral drug delivery system, avoidance of gastrointestinal disturbances, first pass metabolism of the drug, lower fluctuations in plasma drug levels, targeting of the active ingredient for a local effect, and good patient compliance [1, 2]. Despite many advantages, lower diffusion rate of drug across the stratum corneum is the major hurdle in delivering the drug. As skin is a natural barrier to water it restricts the permeability of water soluble molecules. As shown in **Figure 1** the stratum corneum is composed of insoluble bundled keratins surrounded by a cell envelope, stabilized by cross-linked proteins and covalently bound lipids. Transdermal drug delivery systems involve a patch, in which the drug permeates through various layers of skin, via a passive diffusion pathway. However highly lipophilic and low molecular weight drugs are only able to permeate through the skin. Several methods and approaches have been assessed to increase the permeation rate of drugs. One of simple and convenient approach is application of drugs in formulation with elastic vesicles or skin enhancers, which includes use of chemical or physical enhancers, such as Iontophoresis, Sonophoresis, etc. Liposomes, Niosomes, Transferosomes and ethosomes have proved the potential of permeating the skin barrier [3]. In past few decades, topical delivery of drugs by liposomal formulations has evoked considerable interest. A recent study shows that they do not deeply penetrate skin but remain confined to upper layers of the stratum corneum. Microscopic studies have revealed that intact liposomes are not able to

***Corresponding Author Address:** Santosh Shelke, Yash Institute of Pharmacy, Aurangabad-431134, Maharashtra, India*

penetrate into the granular layers of the epidermis. Thus, the modification of vesicles (**ethosomes)** for drug delivery through skin, results in the development of a novel vesicular carrier, improving the skin delivery of various drugs [4]**.** To overcome problems of poor skin permeability Cevc et al. and Touitou et al **[5, 6]** introduced two new vesicular carrier systems transfersomes and ethosomes, respectively for non-invasive delivery of drugs into or across the skin **[7].** Transfersomes and ethosomes incorporated activators (surfactants) and penetration enhancers (alcohols and polyols), respectively, to influence the properties of vesicles and stratum corneum **[8].**

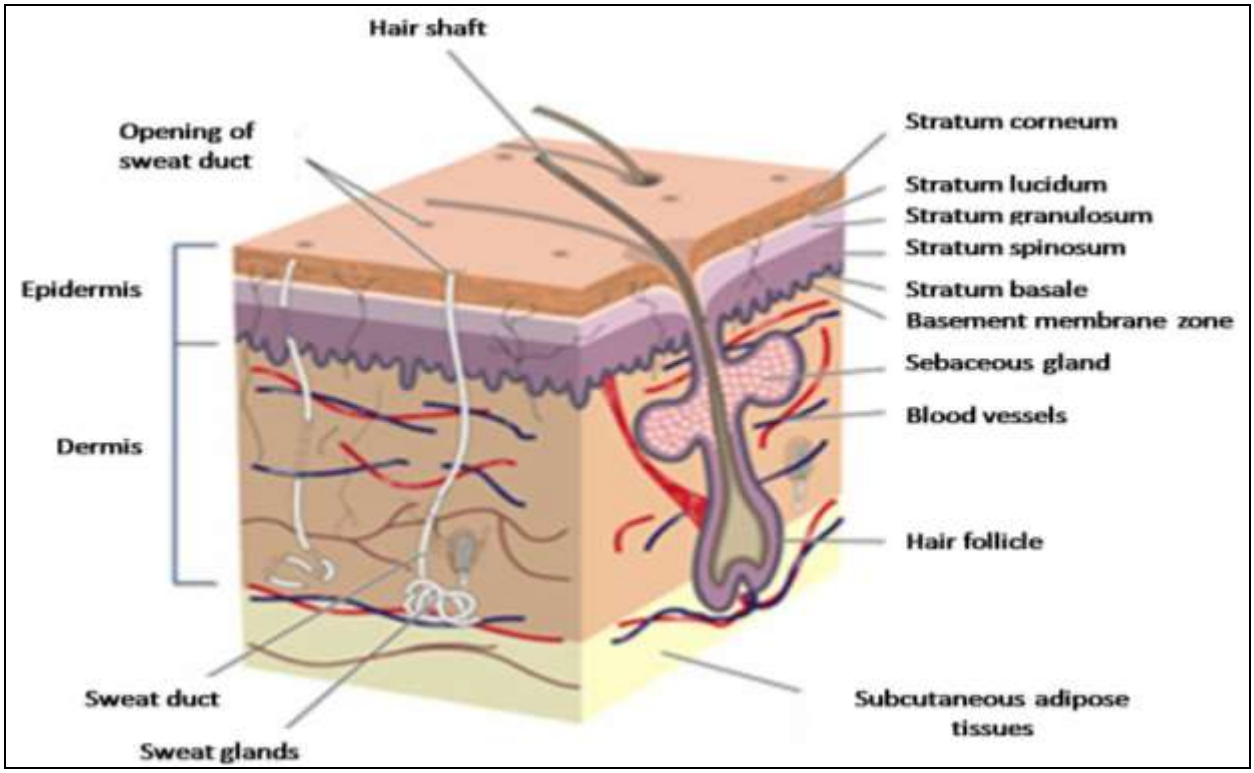

Figure 1: Structure of skin.

Ethosomes is second generation of elastic liposome having ability to permeate drug into the skin. In Ethosomes ethanol amalgamates with the lipid of stratum corneum resulting in increased fluidity and declining the density of the lipid multilayer. If the ethosomes are combined with the permeation enhancer like Oleic acid and propylene glycol, it will increase the penetration rate of drug to deeper skin tissue with desired systemic action**.** Vesicles can be used for encapsulating hydrophilic and lipophilic as well as low and high molecular weight drugs. Therefore, these lipid rich vesicles are essential to carry drugs across the skin thus, enhancing the systemic absorption of drugs [9]. Objective of the investigation was to focus on the current aspect of ethosomes and to craft special attention on its application. Moreover review is elaborated on methods of preparation, composition, and mechanism drug transport through the membrane, characterization and evaluation of ethosomes.

Ethosomes: These are soft, malleable lipid vesicles composed mainly of phospholipids, with higher concentration (20-45%) of alcohol (ethanol or isopropyl alcohol) than water. Ethosomes were first developed by Touitou et al., 1997, as additional novel lipid carriers composed of ethanol, phospholipids, and water. "Ethosomes are ethanolic liposomes", can be defined as noninvasive delivery carriers that enable to permeate the drug into deeper skin layers and/or the systemic circulation providing an effective intracellular delivery of hydrophilic, lipophilic or amphiphilic molecules [10] as shown in **Figure 2**. The high concentration of ethanol makes the ethosomes a unique formulation for delivery of drug into deep skin [11]. Ethosomes are known to play important role in controlling the release rate of drug over an extended time, keeping the drug shielded from immune response or other removal systems. In contrast to conventional liposomes, ethosomes shows smaller vesicle size, higher entrapment efficiency as well as improved stability. The size

range of ethosomes may vary from tens of nanometers (nm) to microns (μ) ethosomes permeate through the skin layers more rapidly and possess significantly higher transdermal flux , depending on method of preparation, composition and application techniques like sonication [12, 13].

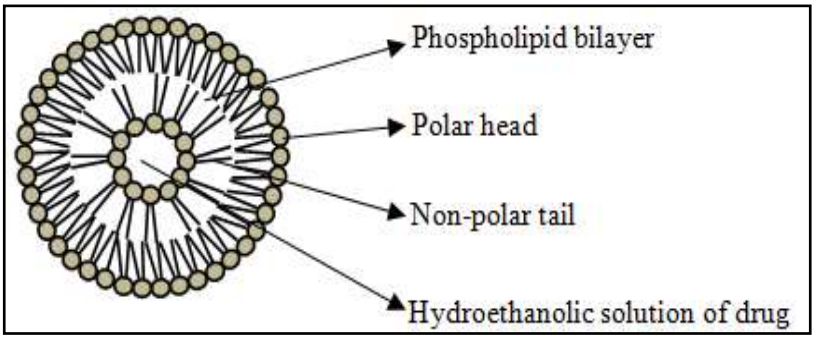

Figure 2: Proposed diagram of Ethosome.

Composition of Ethosomes: Basically, ethosomes exhibit lipid bilayer like liposomes; however they differ from liposomes in terms of composition (high content of ethanol). The ethosomes are composed of hydroalcoholic or hydro/glycolicphospholipid in which the concentration of alcohol is relatively high. Typically, ethosomes may contain phospholipids with various chemical structures like phosphatidylcholine (PC), hydrogenated PC, phosphatidic acid (PA), phosphatidylserine (PS), Phosphatidyl ethanolamine (PE), phosphatidyl glycerol (PPG), phosphatidyl inositol (PI), hydrogenated PC, alcohol (ethanol or isopropyl alcohol), water and propylene glycol (or other glycols). Some preferred 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% can also be added to the preparation. Alcohol, such ethanol and isopropyl alcohol; among glycols, propylene glycol and Transcutol are generally used which may range from 20 to 50% in the final product. In addition to non-ionic surfactants (PEG-alkyl ethers) and cationic lipids (cocoamide, POE alkyl amines, dodecylamine, cetrimide etc) can be combined with the phospholipids in the preparations [14]. The concentration of the non-aqueous phase (alcohol and glycol combination) may range between 22 to 70%. Various additives (table 1) which are used for formulation of ethosomes are listed in the **Table 1.**

Table 1: Different Additive 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	As a skin penetration enhancer
Alcohol	Ethanol Isopropyl alcohol	For providing the softness to 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 P934, HPMC	As a gel former

Advantages of Ethosomal Drug delivery [15]: In comparison to other transdermal and dermal drug delivery systems, advantages of ethosomal drug delivery system are:

- Ethosomal system is passive, noninvasive and is available for immediate commercialization.
- Provides the platform for the delivery of large and diverse group of drugs (peptides, protein molecules).
- Composition is safe and the components are approved for pharmaceutical and cosmetic use.
- 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.
- Patient compliance is considered as ethosomes are administrated in semisolid form (gel or cream).
- Acts as permeation enhancer for drug through skin for transdermal and dermal delivery.
- High market attractiveness for products with proprietary technology. Relatively simple to manufacture with no complicated technical investments required for production of ethosomes.
- Widely proved aplications in Pharmaceutical, Veterinary, and Cosmetic fields.
- Simple method for drug delivery in comparison to iontophoresis and phosphophoresis and other complicated methods.

Limitations of ethosomes [16]

- Poor yield.
- Loss of product during transfer form organic to water media.

Method for Preparing Ethosomes

Ethosomal formulation can be prepared by following method. All the methods are convenient, do not require any sophisticated equipments and are easy to scale up at industrial level.

Cold Method: Cold method is most common method used for the preparation of ethosomal formulations [17]. In this method phospholipid, drug and other lipid materials are dissolved in ethanol in a covered vessel at room temperature by vigorous stirring using mixer. During stirring Propylene glycol or other polyol is added to the mixture. 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 at 4^0C.

Hot method: In this method [18] phospholipids are dispersed in water by heating in a water bath at 400^0C until a colloidal solution is obtained. In a separate vessel ethanol and propylene glycol are mixed and heated to 400ºC. Once both the mixtures reaches 400ºC, the organic phase is added to the aqueous one. The drug is dissolved in water or ethanol depending on its hydrophilic/ hydrophobic properties.

Injection Method: Ethosomes were prepared using different concentrations of lecithin, ethanol, isopropyl alcohol and propylene glycol. Phospholipids and drug is dissolved in ethanol and propylene glycol. The mixture is heated to 30º on the thermoregulated magnetic stirrer. To the solution double distilled water is added slowly in a fine stream with the speed of 200µl/min with a constant mixing at 700 rpm in a closed vessel. The temperature is maintained at 30º C during the experiment. The mixing is continued for 5 minutes. The prepared ethosomes are stored at 4º C. Ethosomes prepared by this procedure are subjected to sonication at 4ºc using probe sonicator in 3 cycles of 5 minutes with 5 minutes rest between the cycles [19].

Mechanical dispersion method: Soya phosphotidylcholine is dissolved in a mixture of chloroform: methanol in round bottom flask (RBF). The organic solvents are removed using rotary vacuum evaporator above lipid transition temperature to form a thin lipid film on wall of the RBF. Finally, traces of solvent mixture are removed from the deposited lipid film by leaving the contents under vacuum overnight. Hydration is done with different concentration of hydroethanolic mixture containing drug by rotating the RBF at suitable temperature [20].

Routes of penetration: The penetrant permeates by 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.

These pathways are important for ions and large polar molecules that struggle to cross intact stratum corneum.

Mechanism of penetration

The enhanced delivery of drugs using ethosomes can be ascribed to an interaction between ethosomes and skin lipids. The first part of the mechanism is due to the ‘ethanol effect’ whereby

intercalation of the ethanol into intercellular lipids increasing lipid fluidity and decreases the density of the lipid multilayer. This is followed by the 'ethosome effect', which includes inter lipid penetration and permeation by the opening of new pathways due to the malleability and fusion of ethosomes with skin lipids (Figure3), resulting in the release of the drug in deep layers of the skin [21].

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.

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 get fused with skin lipids and releases the drugs into deep layer of skin.

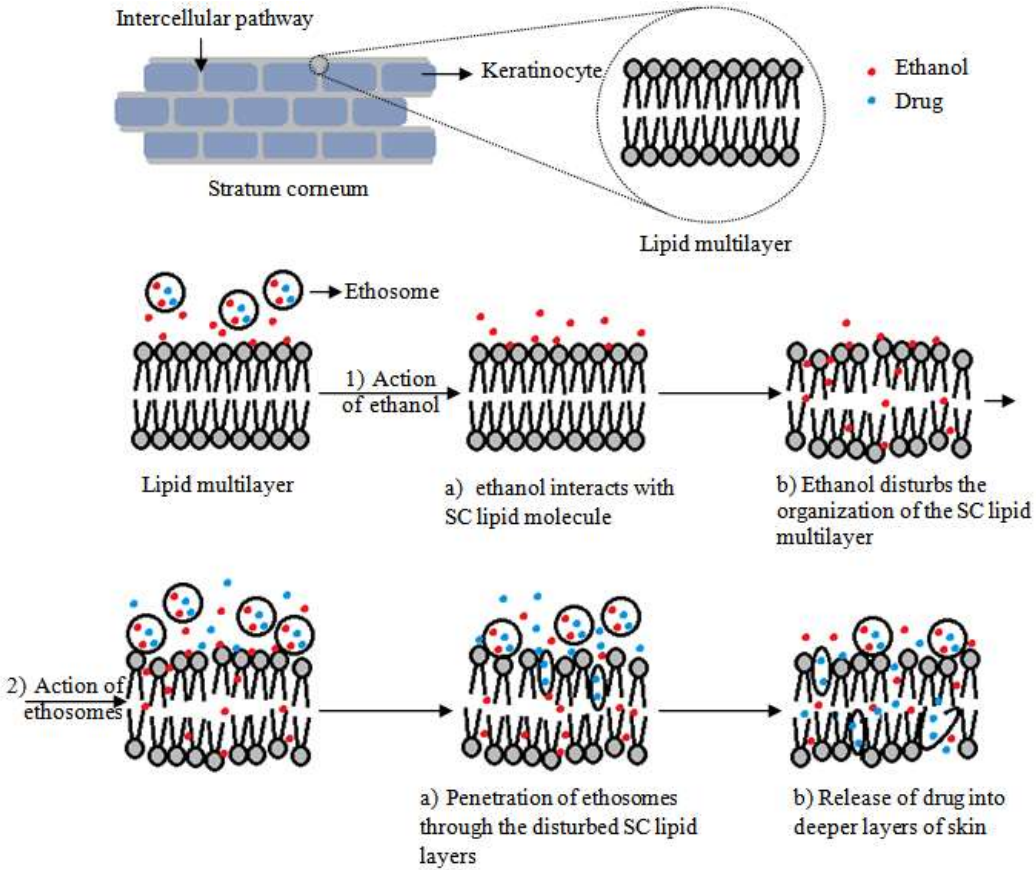

Figure 3: Proposed mechanism for skin delivery of ethosomal system.

Stability of ethosomes

Ethosomes offer better stability as compared to conventional liposomes [22]. In case of liposomes, upon storage they tend to fuse and grow into larger vesicles and this fusion and breakage of liposome vesicles on storage pose an important problem of drug leakage from the vesicles. The absence of electrostatic repulsion is likely to account for the tendency of neutral liposomes to aggregate, whereas in ethosomes, ethanol causes a modification of the net charge of the system (impart negative charge to the system) and confers it some degree of steric stabilization leading to increased stability of vesicles against agglomeration and drug leakage from vesicles. Increasing the concentration of ethanol from 20 to 45% increases the entrapment efficiency owing to an increase in the fluidity of the membranes. However, a further increase in the ethanol concentration (>45%) destabilizes the vesicles and probably makes the vesicle membrane more leaky, thus leading to a decrease in entrapment efficiency.

Characterization and evaluation of Ethosomes

Size analysis: Several techniques are available for assessing size and size distribution of ethosomes which include microscopy techniques, size-exclusion chromatography (SEC), and static or dynamic light scattering. Particle size of the ethosomes can be determined by dynamic light

scattering (DLS) and photon correlation spectroscopy (PCS). A recently developed microscopic technique known as atomic force microscopy (AFM) has been utilized to study ethosome morphology, size and stability. Ethosomes can be analysed without manipulations by AFM, scanning probe microscopes with dimensional resolution (0.1nm). AFM analysis is rapid, powerful and relatively noninvasive technique. It can provide information on morphology, size, as well as on the possible aggregation processes of ethosomes during their storage [23]. HPLC along with SEC can be used to separate and quantify ethosomes population under physiological conditions. This mechanism leads to separation based on large particles elution before smaller particles. Conventional SEC is frequently used for liposomes separation from unencapsulated materials as a final purification step, but the use of HPLC-SEC for analysis offers increased resolution of liposome populations and reduced sample size and enhances reproducibility [24]. Transmission electron microscopy and Scanning electron microscopy provided the morphology and detail size characterization by the methods [25]. Photon correlation spectroscopy (PCS), is broadly used in ethsomes size distribution analysis. Basically PCS measures the time-dependant fluctuations of light scattered from particles with brownian motion, which results from collisions between suspended particles and solvent molecules [26]. Measurement of particle size distribution could also be achieved using density gradient stabilized sedimentation whereby particles that are lower in density than the fluid in which they are suspended can be accurately analysed.

Zeta potential: The zeta potential is a physical property which is exhibited by overall charge of any particle in suspension. To measure the zeta potential, a laser is used to provide a light source of illuminating particles within the samples. The incident laser beam passes through the centre of the sample cell and the scattered light at an angle of about 13^0 is detected. When an electric field is applied to the cell, any particles moving through the measurement volume will lead to fluctuation of the detected light with a frequency proportional to the particle speed. This information is passed to a digital signal processor, then to a computer and hence potential zeta is calculated. Particles suspension with zeta potentials > +30 mV or < −30 mV are normally considered stable [27]

Drug entrapment Efficiency: Drug entrapment efficiency denotes the separation between the free drug and the encapsulated drug by using high speed centrifuge. The ultracentrifugation technique [28] was reported as a simple and fast method for the separation of drug-loaded liposomes from their medium. Drug loaded ethosomal nano-dispersion is subjected to centrifugation at 50,000 rpm for 50minutes at 4ºC using micro-ultracentrifuge (Thermo scientific Sorvall MX 150 Micro-Ultracentriguge, India) to estimate drug entrapment. Supernatant liquid was analysed for free drug UV, HPLC or LCMS and calculated by formula; Percent entrapment efficiency = (Amount of drug encapsulated / Total amount of drug used in formulation) x 100.

Transition temperature: The transition temperature of the vesicular lipid systems can be determined by using differential scanning calorimetry (DSC). The Mettler DSC 60 computerized with Mettler Toledo star software system (Mettler, Switzerland) is used. 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 [23].

Drug content: Method is developed to access the drug content present in the formulation. Drug content of the ethosomes can be determined by using UV spectrophotometer. This can also be quantified by a modified high performance liquid chromatographic method.

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). In another method skin of the test animal is separated from the underlying connective tissues. The excised skin is placed on the aluminium foil, by gntly teasing the dermal side of the skin for any adhering fat and/or subcutaneous tissue. The effective permeation area of the diffusion cell and receptor cell volume is 1.0 cm^2 and 10 mL, respectively. The temperature is maintained at 32°C ± 1°C. The receptor compartment contained PBS (10 mL of pH 6.5). Excised skin is placed in 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 [29].

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 100 μL RPMI medium was added. Cells were incubated with 100 μL 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.

Stability studies: A stable pharmaceutical dosages are designed to preserve the physical and integrity of the active ingredient during its shelf life. In designing a stability study, physical, chemical and microbial parameters must be considered and evaluated. This wisdom is also required for the ethosome dosage form. A stability study must include a section for product characterization and another section concerning the product stability during storage. 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. 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 [30].

Degree of deformability and turbidity: The degree of deformability of the ethosomal preparation can be performed by extrusion method and the turbidity of the preparation can be performed by using nephelometer [31].

Therapeutic Applications of Ethosomes

Pilosebaceous targeting: Pilosebaceous units has been interestingly used particularly for the treatment of follicle-related disorders suchas acne or alopecia. Maiden et al prepared and evaluated Minoxidil ethosomal formulation, which is used topically on the scalp for the treatment of baldness. Results showed possibility of better clinical efficacy [32].

Transdermal Delivery of Hormones: Touitou et al (2000) investigated the efficiency of ethosome carriers for transdermal delivery of testosterone hormone comparing the skin permeation potential of ethosomal formulation of testosterone (Testosome) across rabbit pinna skin with marketed transdermal patch of testosterone (Testoderm patch). They observed nearly 30 times higher skin permeation of testosterone from ethosomal formulation as compared to that of marketed formulation [33].

Delivery of anti-parkinsonism agent: Dayan and Touitou et al, 2002 prepared ethosomal formulation of psychoactive drug trihexyphenidyl·HCl (THP) used in treatment of parkinson disease and compared its delivery with that from classical liposomal formulation. The value of transdermal flux quantity of drug, skin retention and stability was found to be superior than that of conventional liposomes [34,35].

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. Sheo Datta Maurya in 2010 had developed indinavir sulfate ethosomes for anti-HIV therapy [36, 37].

Topical Delivery of DNA: Ethosomes is used 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 and applied topically to the 5 week male mice. Gupta et al. recently reported immunization potential using transfersomal formulation. From both the results it was suggested that ethosomes could be used as carriers for gene therapy and showed the possibility of using ethosomes for effective transdermal immunization [38].

Delivery of Anti-Arthritis Drug: 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 when tested by carrageenan induced rat paw edema model [39]. Antiarthritic efficacy of tetrandrine by topical was developed by Chao Fan et al, 2013 as ethosomes [40]. Further it is required for chronic use in the condition like rheumatoid arthritis. Therefore, Sujitha B et al formulated Piroxicam Loaded Ethosomal Gel, 2014 [41].

Delivery of Antibiotics: Ethosomes penetrate rapidly through the epidermis and bring appreciable amount of drugs into the deeper layer of skin and suppress infection at their roots. Bacitracin and erythromycin loaded ethosomal formulation for dermal and intracellular delivery were developed and the studies indicated the penetration of ethosomes into the cellular membrane and released the entrapped drug molecules within the cells [42].

Used in treatment of herpetic infection: 5% acyclovir ethosomal preparation compared to the 5 % acyclovir cream showed significant improvements in treatment of herpetic infections [43].

Delivery of Anti-Viral Drugs: Jain et al., 2004 concluded that ethosomes could increase the transdermal flux, prolong the release and present an attractive route for sustained delivery of zidovudine [44]. Horwitz et al., 1999 formulated the acyclovir ethosomal formulation for dermal delivery [43]. The results showed shorter healing time and higher percentage of abortive lesions. C.K. Sudhakar et al, 2014 had developed ethosomes by enhanceing permeability of lamivudine as antiviral agent [45]. Dubey et al, 2010 prepared an ethosomal formulation of Indinavir, an anti-HIV drug, and investigated their enhanced transdermal delivery potential. Ethosomal formulation showed better skin deposition profile and shortest lag time for indinavir.

Delivery of Problematic drug molecules: Dkeidek and Touitou investigated the effect of ethosomal insulin delivery in lowering blood glucose levels (BGL) 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 [46, 47].

Delivery of Anti funal agent: Rahul G.S. Maheshwari et al, 2012 had developed Ethosomes and ultra-deformable liposomes for transdermal delivery of clotrimazole [48]. Sarat Chandarn C et al 2012 formulated Ethosomes containing Ketoconazole [49].

Used for treatment of chemotherapy induced nausea and vomiting: Vipul Mogal in 2013 had developed granisetron Hydrochloride via Ethosomes to treat chemotherapy induced nausea and vomiting [50].

Delivery of NSAIDs agent: To evaluate the transdermal potential of novel vesicular carrier, ethosomes, bearing aceclofenac, Non-steroidal anti-inflammatory drugs (NSAIDs) agents having limited transdermal permeation Vivek Dave et al formulated ethosomes of aceclofenac [51]. The potential of ethosomes for delivering etodolace, a potent, water insoluble non-steroidal anti-inflammatory drug via skin to enhance skin permeation after topical application was developed by Bhale Shwetaet al in 2013 [52].

Treatment of acne and the dermatological diseases: Isotretinoin, a derivative of retinoic acid (13-cis-retinoic acid), has been developed by Sheba Rani Nakka David (2013). It is commonly used for the treatment of severe acne and the other dermatological diseases.**[53]** Verma and Fahr, (2004) reported the cyclosporin A ethosomal formulation for the treatment of inflammatory skin disease like psoriasis, atopic dermatitis and disease of hair follicle like alopecia areata etc. Paolino et al, 2007, investigated the potential application of ethosomes for dermal delivery of ammonium glycyrrhizinate, useful for the treatment of various inflammatory based skin diseases.

Delivery of anti-hypertensive agent: Ravindra Bhana et al. developed ethosomes bearing losartan potassium for transdermal drug delivery [54].

Used to treat Alzheimer's disease: For delivering a drug into the brain via the intranasal route using a liposomal Formulation Karthik Arumugam Ganesa et al Developed, Rivastigmine, which is used in the management of alzheimer's disease [55].

Delivery of Anti hyperlipidemic agent: Almost 95% of simvastatin is metabolized by the liver and excreted from bile. Less than 5% of the active structures were found in the blood circulation after oral administration. Therefore, Keyao An et al had prepared Simvastatin Ethosome and Evaluated In Vitro. It has shown to especially effective in reducing low-density lipoprotein cholesterol (LDL) and improving other conditions that are influenced by lipid levels, including coronary artery diseases. [56]

Used in angina pectoris: Ligustrazine plays a role in expanding blood vessels, increasing coronary and cerebral blood flow, preventing platelet aggregation, inhibiting thrombosis, and improving the microcirculation. Xingyan Liu et al in 2011 prepared a ligustrazine ethosome patch and its evaluation was carried out in vitro and in vivo [57].

Used as bronchodilator: Mina et al, 2007 formulated ethosomal formulation of salbutamol sulphate (SS); a hydrophilic drug used as bronchodilator, and compared its transdermal delivery potential with classic liposomes containing different cholesterol and dicetylphosphate concentrations. Study showed a significant decrease in vesicle size by decreasing cholesterol concentration and increasing dicetylphosphate and ethanol concentrations [58].

Herbal ethosomes [59]: Curcumin is easily susceptible to oxidization and low bioavailability, which is prevented by CHEN Jin-guang by developing curcumin ethosomes and further utilized in clinical practices [60]. Hair growth promoting activity of Moringa oleifera leaf extract formulated as an ethosome (MOE) had been investigated Philip F. Builders, 2014 [61]. Meng-I Yeh et al had developed Ethosomes in hair dye products as carriers of the major compounds of black tea extracts [62].

Application of ethosomes in cosmeceuticals: Many cosmetic preparations contain active ingredients which can only act when they penetrate at least the outermost layer of the skin, the stratum corneum. However, due to the resistance of the stratum corneum to the transport into the skin, the efficacy of topically applied requires to alter the formulation whereby its permeability is increased. Ethosomes provides an excellent carrier to supply wide range of ingredients [63]. Vesicular systems, such as liposomes and ethosomes, are used in cosmetic and pharmaceutical products to encapsulate ingredients to protect ingredients from degradation, to increase bioavailability, and to improve cosmetic performance. The advantage of ethosomes in cosmeceuticals is not only to increase the stability of the cosmetics and decrease skin irritation from the irritating cosmetic chemicals, but also for transdermal permeation enhancement, especially in the elastic forms. Topical administration of many antioxidants is one of the several approaches to diminish oxidative injury in the skin for cosmetic and cosmeceutical applications.

Future Perspective: For transdermal delivery of drugs, stratum corneum is the main barrier layer for penetration of drug. Various methods have been discovered to enhanced skin penetration of drugs lipid vehicle based enhancement approach has drawn considerable interest in recent past. Studies will continue further to improve skin delivery of drug using lipid vesicles. Introduction of ethosomes has initiated a new area in vesicular research. Ethosomes has shown promising result and potential for delivery of various agents more effectively. Better control over drug release, non – invasive delivery of small, medium and large size drug molecules can be achieved by ethosomes. Ethosomes can be the promising tool for dermal/transdermal delivery of various agents and can be an alternate formulation for problematic drugs.

CONCLUSION

Transdermal route is promising alternative to drug delivery for systemic effect. Ethosomes has initiated a new area in vesicular research for transdermal drug delivery. From the literature it has outlined to improve the permeation of drugs through the stratum corneum and thereby their efficacy. The versatility of ethosomes for transdermal as well as topical drug delivery is evident from the research reports of enhanced delivery. Ethosomes plays a crucial alternative to conventional transdermal permeation enhancement techniques by offering safety, efficacy, long term stability, simplified industrial manufacture as well as better patient compliance. Ethosomes provides better skin permeation than liposomes. Thus, it can be concluded that ethosomes can become a promising drug carrier in future for not only topical treatment of local and systemic disorders, but also for the cosmetic and cosmeceutical fields for the development of novel improved therapies.

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