

A review: The therapeutic potential of herbal ethosomes

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ABSTRACT:

Drug delivery systems have recently benefited from the development of novel technology. In comparison to other methods, using herbal formulations for innovative drug delivery systems is more beneficial and advantageous. The medicinal effects of plant extracts have been improved by the use of liposome, ethosome, phytosomes, emulsion, microsphere, and solid lipid nanoparticles in herbal formulation. By utilising all of these, tailored delivery of the formulation is accomplished, resulting in the formulation demonstrating action on the site and also increasing the formulation's bioavailability. The actives and extracts employed in herbal formulations exhibit increased stability, sustained release of formulation, protection against toxicity, and improved therapeutic efficacy using these innovative drug delivery vehicles. The primary goals of creating alternative medication delivery systems are to improve patient convenience, boost drug delivery efficiency, and ensure patient safety. Information on innovative herbal formulations is provided in the current paper.

Key Words: Ethosomes, Herbalmedicines

1.1 INTRODUCTION:

When compared to more traditional drug delivery methods like oral and parenteral, transdermal drug delivery has many advantages. One of the best ways to maintain stable plasma levels for extended periods of time is via the transdermal route, which may also be favourable due to fewer frequent dosing schedules^[1].

Increased patient acceptance, prevention of first pass metabolism, predictable and prolonged duration of activity, reduction of side effects and utility of medications with short half-lives, improvement of physiological and pharmacological response, and prevention of drug level fluctuations are benefits that are claimed^[2]. The stratum corneum-controlled barrier function is the principal obstacle to medication distribution over the skin. Corneocytes make up the stratum corneum, which is surrounded by lipid layers that are crucial to the

stratum corneum's ability to function as a barrier^[3, 4].

Novel drug delivery systems must be created in order to enhance the number of medications supplied via transdermal route. These systems use physical techniques like iontophoresis, sonophoresis, microneedles, etc., chemical techniques like penetration enhancers (surfactants and organic solvents), and biochemical techniques using liposomes, niosomes, transferosomes, and ethosomes to increase drug permeability through the stratum corneum.^[5]

For many years, the vesicles' significance in cellular communication and particle transportation has been well understood. In order to improve medication delivery within their cavities and tag the vesicle for cell specificity, researchers have gained an understanding of the structure and features of vesicles. The discovery of ethosomes, a vesicle derivative, was one of the most significant developments in vesicle research^[6].

1.1.1 Ethosomes

They are mostly employed in the transdermal mode of medication delivery. Ethosomes with different physicochemical properties, such as hydrophilic, lipophilic, or amphiphilic, can entrap drugs^[7,8].

Drugs are delivered using ethosomes, which are soft, pliable vesicles that can penetrate deep epidermal layers and/or the bloodstream. Ethosomes can range in size from nanometers to microns(μ)^[9].

Ethosomes are the modified forms of liposomes that are high in ethanol content. The ethosomal system is composed of phospholipid (Phosphatidylcholine, phosphatidylserine, phosphatidic acid), high concentration of alcohol (ethanol and isopropyl alcohol) and water. The high concentration of ethanol makes ethosomes unique because ethanol causes disturbance of skin lipid bilayer organization, hence when incorporated into a vesicle membrane, it enhances the vesicles' ability to penetrate the stratum corneum^[10].

1.1.2 Composition of Ethosomes: ^[11, 12]

The hydroalcoholic or hydro/alcoholic/glycolic phospholipid that makes up the ethosomes is a vesicular carrier with a relatively high concentration of alcohols or their combination. Phospholipids with different chemical structures, such as 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) are frequently found in ethosomes. Through the skin, a high concentration of active substances can be delivered by such a combination. 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 often used in a range of 0.5-10% weight per weight. Cholesterol may be included in the preparation at amounts ranging from 0.1% to 0.10%. Ethanol and isopropyl alcohol are two examples of alcohols that can be employed. Propylene glycol and Transcutol are the two most often utilised glycols. The phospholipids in these preparations may also be mixed with non-ionic surfactants (PEG-alkyl ethers). You can also include cationic lipids like cetrimide, cocoamide, POE alkyl amines, dodecylamine, etc. Between 20 and 50% of the finished product may contain alcohol. The concentration of the nonaqueous phase (alcohol and glycol combination) may range between 22 to 70%. Table 1.

Table 1: Different Additives Employed In Formulation of Ethosomes

Class of Polymer	Example	Uses
Phospholipid	Soya phosphatidyl choline Egg phosphatidyl choline Dipalmitylphosphatidyl choline Distearylphosphatidyl 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 Fluorence (FITC) 6-Carboxy fluorescence	For Characterization study
Vehicle	Carbopol 934	Gel forming agent

1.2 METHODS OF PREPARATION:

1.2.1 Cold method

The most popular technique for creating ethosomal formulations is this one. This method involves mixing phospholipid, medication, and other lipid components. While stirring, propylene glycol or another polyol is added. In a water bath, this mixture is heated to 300 °C. The mixture is then agitated for 5 minutes in a covered vessel while the water heated to 300°C in a pot is added to it. Using the sonication or extrusion methods, the vesicle sizes can be reduced to the desired extent. Finally, the formulation is kept chilled ^[13].

1.2.2 Hot method

This process involves heating phospholipid in a water bath at 400°C till a colloidal solution is produced. Propylene glycol and ethanol are combined and heated to 400°C in a

different vessel. The organic phase is introduced to the aqueous phase once both combinations have reached 400°C. Depending on whether the medication is hydrophilic or hydrophobic, it dissolves in either water or ethanol. Using the probe sonication or extrusion approach, the vesicle size of the ethosomal formulation can be reduced to the required level ^[14, 15].

1.2.3 Classic method

The medication and phospholipid are dissolved in ethanol and heated in a water bath to 30°C + 1°C. In a closed vessel, the lipid mixture is added to with double-distilled water in a thin stream while being constantly stirred at a speed of 700 rpm. Through three rounds of passing through a polycarbonate membrane using a hand extruder, the resulting vesicle suspension is homogenized ^[13].

1.2.4 Mechanical dispersion method

In a round bottom flask (RBF), soy phosphatidylcholine is dissolved in a solution of chloroform and methanol. A thin lipid coating is formed on the RBF wall by removing the organic solvents using a rotating vacuum evaporator above the lipid transition temperature. The deposited lipid layer is then cleaned of any remaining solvent combination by placing the container's contents under hoover for the night. Rotating the RBF at a proper temperature hydrates with varying concentrations of hydroethanolic mixture containing medication^[16].

1.3 Characterizations of Ethosomes

1. Visualization Visualization of ethosomes can be done using transmission electron microscopy (TEM) and by scanning electron microscopy (SEM)^[17].
2. Vesicle size and Zeta potential Particle size and zeta potential can be determined by dynamic light scattering (DLS) using a computerized inspection system and photon correlation spectroscopy (PCS)^[18].
3. Differential scanning calorimetry (DSC) Transition temperature (Tm) of the vesicular lipid systems was determined by using the Mettler DSC 60 computerized with Mettler Toledo star software system (Mettler, Switzerland). 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^[19,20].
4. Surface Tension

1.3.1 Activity Measurement

The surface tension activity of drug in aqueous solution can be measured by the ring method in a Du Nouy ring tensiometer^[19,20].

1. Entrapment Efficiency
2. The entrapment efficiency of drug by ethosomes can be measured by the ultra centrifugation technique^[20].
3. Penetration and Permeation Studies
4. Depth of penetration from ethosomes can be visualized by confocal laser scanning
5. Vesicle Stability
6. 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.
7. In vitro drug release study and Drug

Deposition study In vitro drug release study and Drug Deposition of ethosomal preparation can be performed by Franz diffusion cell with artificial or biological membrane, Dialysis bag diffusion

1.4 Advantages of ethosomal drug delivery

1. In comparison to other transdermal & dermal delivery systems
2. Enhanced permeation of drug through skin for transdermal drug delivery.
3. Delivery of large molecules (peptides, protein molecules) is possible.
4. It contains non-toxic raw material in formulation.
5. High patient compliance- the ethosomal drug is administered in semisolid form (gel or cream) hence producing high patient compliance.
6. The Ethosomal system is passive, noninvasive and is available for immediate commercialization.
7. Ethosomal drug delivery system can be applied widely in Pharmaceutical, Veterinary, Cosmetic fields.
8. Simple method for drug delivery in comparison to iontophoresis and phosphoresis and other complicated methods.

1.5 Applications of Ethosomes

1. Delivery of Anti-Viral Drugs
2. Topical Delivery of DNA
3. Transdermal Delivery of Hormones
4. Delivery of anti-parkinsonism agent
5. Transcellular Delivery
6. Delivery of Anti-Arthritis Drug
7. Delivery of Antibiotics

1.5.1 Therapeutic Applications of Ethosomes

According to Mishra et al.'s report from 2007, antigen-loaded ethosomes for transcutaneous immunisation against Hepatitis B were made and characterised. These ethosomes outperformed conventional liposomes in terms of entrapment efficiency, size range, and unilamellar, spherical shape. Studies using flow cytometry and spectral bio imaging shown that murine dendritic cells efficiently absorbed ethosomes loaded with HBsAg in vitro, with a peak uptake occurring after 180 minutes. When compared to conventional liposomes and soluble antigen preparation, the transcutaneous delivery capacity of the antigen-loaded antigen system showed much higher skin permeation of the antigen.

Comparatively to the topically applied hydroethanolic (25%) HBsAg solution, the intramuscularly injected alum-adsorbed HBsAg suspension, and the topically applied plain HBsAg solution, the HBsAg-loaded ethosomes in mice demonstrated a powerful systemic and mucosal humoral immune response. The creation of a transcutaneous vaccination against the Hepatitis B virus may benefit from the ability of ethosomes carrying HBsAg to elicit a protective immune response and from their capacity to cross the skin and target its immunological environment^[21].

Hormones taken orally can have side effects such as virilization, acne, and gynecomastia as well as difficulties like high first pass metabolism and low oral bioavailability. Oral hormonal preparations also rely heavily on patient compliance in addition to these negative effects. Each medication that is missed is known to raise the probability of treatment failure.

The skin penetration capacity of testosterone ethosomes (Testosome) across rabbit pinna skin was compared by Touitou et al. in 2000^[22] to that of the commercially available transdermal testosterone patch (Testoderm® patch, Alza corporation, California). The authors found that testosterone from the ethosomal formulation penetrated the skin roughly 30 times more than testosterone from the commercial formulation. After using Testosome as opposed to Testoderm®, the AUC and C_{max} of testosterone considerably increased.

As a result, tests conducted *in vitro* and *in vivo* showed that testosterone from the ethosomal formulation had increased skin penetration and bioavailability. In a subsequent investigation, same group created a testosterone non-patch formulation to minimise the area of application. They discovered that the ethosomal testosterone formulation required ten times less area of application than the commercial gel (AndroG, US) formulation to obtain the effective plasma concentration.

For the treatment of rheumatoid arthritis, Lodzki et al., 2003^[23] created the CBD-ethosomal formulation for transdermal distribution of cannabidiol. The application of CBD-ethosomal formulation to the abdomen of mice caused significant accumulation of Cannabidiol (CBD) in the skin and underlying muscles, according to the results of the skin deposition research. According to a plasma concentration investigation, the steady state level was attained in 24 hours and remained constant for 72 hours. When examined using a

model of rat paw edoema caused by carrageenan, it was found that the biological antiinflammatory activity of the CBD-ethosomal formulation had significantly increased. Finally, it was determined that the biological activity of CBD was greatly boosted by encapsulating it in ethosomes, which also increased its skin penetration and accumulation.

Dayan and Touitou, 2001, created an ethosomal formulation of the psychoactive medication trihexyphenidyl hydrochloride (THP) for the treatment of Parkinson's disease and compared its distribution to that of the traditional liposomal formulation. Parkinson's disease is treated with THP, an M1 muscarinic receptor antagonist. Due to the motor abnormalities and neurological symptoms linked to parkinsonian syndrome, THP has a short biological half-life (3 hours), making oral administration challenging. Transmission and scanning electron microscopy images of the THP ethosomal formulation revealed tiny phospholipid vesicles.

As compared to liposome, phosphate buffer, and hydroethanolic solution, the transdermal flow of THP through naked mouse skin from ethosomes was 87, 51, and 4.5 times higher, respectively. After applying ethosomes vs applying liposomes or hydroethanolic solution (control), the amount of THP still present in the skin after 18 hours was noticeably higher. These findings showed that the ethosomal-THP formulation had a superior skin penetration potential and might be used to treat Parkinson's disease more effectively.

Another study on methotrexate, a highly hydrosoluble anti-psoriatic, anti-neoplastic drug with restricted transdermal penetration. The skin permeation profile of the new formulation showed improved penetration of the rhodamine red-loaded formulation to the deeper layers of skin. The authors created optimised ethosomes-loaded methotrexate. The formulation's penetration capacity remained after storage, and the vesicle skin interface investigation demonstrated how ethosomes can enhance penetration through some visual pathways and corneocyte swelling.

Studies on cutaneous delivery have also been referenced in literature, in addition to ethosomes' better transdermal distribution. Paolino et al.'s 2005^[24] investigation into the potential use of ethosomes for ammonium glycyrrhizinate cutaneous administration. Ammonium is helpful in the treatment of a number of inflammatory skin conditions. A large quantity more medication has

cumulatively permeated from ethosomes (63.2%) than from the hydroalcoholic solution (22.3%) and aqueous solution (8.9%) of ammonium glycyrrhizinate, according to *in vitro* skin permeation studies. In 48 hours of treatment, ethosomal formulation demonstrated very good skin tolerability in human volunteers. When compared to the drug's ethanolic or aqueous solution, ethosomal formulation considerably increased biological anti-edema action.

The minoxidilethosomal formulation was created and assessed by Maiden et al. in 2004. A lipid-soluble medication called minoxidil is applied topically to the scalp to cure baldness. The skin penetration and retention qualities of the traditional topical formulation are extremely poor. When compared to the drug's ethanolic phospholipid dispersion, hydroethanolic solution, and ethanolic solution, each of which contained 0.5% of the drug, it was discovered that the amount of minoxidil accumulated into the skin of naked mice after application of its ethosomal formulation was 2.0, 7.0, and 5.0 times higher. These findings suggested that pilosebaceous targeting of minoxidilutilisingethosomes could improve therapeutic efficacy.

Many environmental pathogens attempt to enter the body through the skin. Skin has, therefore, evolved into an excellent protective barrier, which is also immunologically active and able to express the gene. On the basis of the above-mentioned facts another important application of ethosomes, is to use them for topical delivery of DNA molecules, to express genes in the skin cells. Touitou et al., 2003, in their study, encapsulated the GFP-CMV-driven transfecting construct into the ethosomal formulation. They applied this formulation to the dorsal skin of five-week-old, male CD-1 nude mice for 48 hours.

After 48 hours, the treated skin was removed and penetration of green fluorescent protein (GFP) formulation was observed by Confocal laser scanning microscopy (CLSM). It was observed that the topically applied ethosome-GFP-CMV-driven transfecting construct enabled efficient delivery and expression of genes in the skin cells. It was suggested that ethosomes could be used as carriers for gene therapy applications that required transient expression of genes. These results also showed the possibility of using ethosomes for effective transdermal immunization.

Gupta et al., 2004,^[25] recently reported the immunization potential of using transfersomal formulation. Hence, better skin permeation ability of ethosomes opens the possibility of using these dosage forms for the delivery of immunizing agents. Table 2 is a short compilation of research reports on ethosomes as a carrier for a variety of drugs researched of late.

1.6 Cosmeceutical Applications of Ethosomes

The advantage of applying ethosomes in cosmeceuticals is not only to increase the stability of the cosmetic chemicals and decrease skin irritation from the irritating cosmetic chemicals, but also for transdermal permeation enhancement, especially in the elastic forms. However, the compositions and sizes of the vesicles are the main factors to be considered to obtain these advantages of the elastic vesicles for cosmeceutical applications.

Topical administration of many antioxidants is one of the several approaches to diminish oxidative injury in the skin for antioxidants are usually not stable and can be degraded by exposing to light. These antioxidants include vitamin E, vitamin C, and flavonoids. Vitamin E is one of the major exogenous lipophilic antioxidants, which is usually found in tissues. Its topical application can enhance the skin protection from exogenous oxidants.

When vitamin E is added to cosmetics and many dermatological products, it is found to decrease the production of lipid peroxides in the epidermis as well as to protect against UV exposure and some destructive chemicals and physical agents. In order to deliver vitamin E into the deeper layer of SC, Koli et al., 2008, have formulated 'Anti-oxidant Ethosomes for Topical Delivery Utilizing the Synergistic Properties of Vitamin A Palmitate, Vitamin E, and Vitamin C,' and the findings have revealed that the synergistic interaction of Vitamin C in the aqueous core and Vitamin A and E in the lipid bilayer, provide complete protection from the oxidation of the ethosome formulations.

This has suggested that although elastic and non-elastic liposomes are not beneficial for the delivery of α -tocopherol through the skin, the entrapment of the vitamin either in elastic or non-elastic liposomes can increase its photo-stability under UVB irradiation^[29].

Table 2: A compilation of research reports on ethosomes as a carrier for topical and transdermal delivery of drugs

Drug	Aim of work	Formulation	Results
Lamivudine (Jain et al. 2007) ^[26]	To improve skin permeation and intracellular uptake of antiviral drug	Suspension	Better intracellular skin delivery, as the ethosomal formulation affected the normal histology of the skin by producing lipid perturbation and increased the intercellular lipid lamellar space in the stratum corneum
Erythromycin (Godin et al. 2005) ^[26]	To treat deep skin and soft tissue bacterial infections by dermal application	Gel	Ethosomal erythromycin applied to the skin of <i>S. aureus</i> infected mice was as effective as systemically administered erythromycin
Gold nanoparticles (Presa et al. 2009) ^[27]	Gold nanoparticles generated in ethosomes bilayers, as revealed by cryo electron tomography	Suspension	Gold nanoparticles encapsulated ethosomes offer a versatile platform for the enhancement of pharmacological efficacy in transdermal and dermal delivery systems
Colchicine (Singh et al. 2009) ^[28]	Elastic liposomal formulation for sustained delivery of colchicine: In vitro characterization and In vivo evaluation of anti gout activity	Suspension	This reveals that elastic liposomal formulation of colchicine possesses a greater potential to enhance skin accumulation, prolong release, and improve the site specificity of colchicine
Vitamin A palmitate, vitamin e, vitamin c (Koli et al. 2008) ^[29]	Development of anti-oxidant ethosomes of vitamin a palmitate, vitamin e, vitamin c for topical delivery	Gel	The anti oxidation of PC was found to increase due to the synergistic interaction of all three together, as compared to individual use

1.7 Herbal drugs

Herbal formulation means a dosage form consisting of one or more herbs or processed herb(s) in specified quantities to provide specific nutritional, cosmetic benefits, and/or other benefits meant for use to diagnose treat, mitigate diseases of human beings or animals and/or to alter the structure or physiology of human beings or animals.

Herbal preparations are obtained by subjecting whole plant, fragmented or cut plants, plants parts to treatments such as extraction, distillation, expression, fractionation, purification, concentration or fermentation. These include comminuted or powdered herbal substances,

tinctures, extracts, essential oils, expressed juices and processed exudates^[30-31].

1.7.1. Advantages of herbal drugs Herbal drugs possess following advantages^[32-33].

1.7.1.1. Low risk of side effects

Mostly herbal drugs are well tolerated by the patient, having fewer unintended consequences and fewer side effects than traditional medicine, and may be safer to use.

1.7.1.2. Effectiveness

Herbal drugs are more effective for long-standing health complaints that don't respond well to traditional medicine. One example is the herbs

and alternative remedies used to treat arthritis. Vioxx, a well-known prescription drug used to treat arthritis, was recalled due to increased risk of cardiovascular complications. Herbal treatments for arthritis, on the other hand, have lesser side effects. Such treatments include dietary changes like adding simple herbs, eliminating vegetables from the nightshade family and reducing white sugar consumption.

1.7.1.3. Lower cost

Cost of herbal drugs is much less than prescription medications. Research, testing, and marketing add considerably to the cost of prescription medicines. Herbs tend to be inexpensive compared to drugs.

1.7.1.4. Widespread availability

Herbs are available without a prescription. Simple herbs, such as peppermint and chamomile, can be cultivated at home.

1.7.2. Limitations of herbal drugs

Herbal drugs possess following limitations^[35-40].

1.7.2.1. Not suitable for many diseases

Modern medicine treats sudden and serious illnesses and accidents much more effectively than herbal or alternative treatments. An herbalist would not be able to treat serious trauma, such as a broken leg, nor would he be able to heal appendicitis or a heart attack as effectively as a conventional doctor using modern diagnostic tests, surgery, and drugs.

1.7.2.2. Lack of dosage instructions

Self-treatment with herbal drugs may consist of many risk factors. Moreover, with no proper direction of doses may lead to overdose.

1.7.2.3. Poison risk associated with wild herbs

Consumption of herbal drugs without correct identification of plant i.e., use of wrong part of plant may lead to poisoning.

1.7.2.4. Lack of regulation

Herbal products are not strictly regulated; consumers may buy inferior quality herbs. The quality of herbal products may vary among batches, brands or manufacturers. This can make it much more difficult to prescribe the proper dose of an herb. All herbal drugs are not safe; some may be poisonous or may cause allergenic reactions.

1.7.2.5. Longer duration of treatment

Curing period is usually longer in comparison to conventional medication. Immense patience while undergoing herbal treatment is needed.

Herbal ethosomes – a novel carrier for herbal drugs

- Ethosomes enable drugs to reach the deeper layer of skin or the systemic circulation⁸.
- They are non invasive drug delivery carriers.
- Ethosomes are composed of phospholipids, water and ethanol in high concentration.
- They are prepared as soft and malleable vesicles^[41].
- Ethosomes disturb the skin lipid bilayer due to high concentration of ethanol, Thus when prepared as vesicle it will penetrate into the stratum corneum.
- Than conventional vesicles, ethosome are loosely packed because of the ethanol content.

1.7.3 Advantages of herbal ethosomal drug delivery

Ethosomes possess many advantages when compared with transdermal or dermal drug delivery system, some of the advantages^[42, 43] are.

- Increased skin permeation of the drug.
- Large molecules like proteins, peptide molecule is possible.
- Good patient compliance.
- Compared with Iontophoresis and phonophoresis, ethosomes are simple method of drug delivery.
- It can be widely applied in cosmetic, veterinary, herbal drug technology.
- It is non invasive, passive and non toxic.
- It can entrap all types of drug molecules i.e. hydrophilic, lipophilic or amphiphilic.
- Permeation enhancer used in the formulation increase the permeability of the skin so that the drugs easily cross the skin.

1.7.5 Although ethosomes possess many advantages, there are certain disadvantages^[44] like.

- Very poor yield so may not be economical.
- Percutaneous absorption depends on the molecular size of the drug which should be reasonable.
- Ethosomal drug delivery system is limited to potent drugs and not for drugs that require high blood levels.

- Skin irritation or dermatitis may occur in some patients due to penetration enhancer or the excipients used.

1.7.6 Mechanism of drug delivery

The drugs get permeated through the skin into the systemic circulation. The mechanism of drug delivery of ethosomes through permeation is not clearly understood. There may be two reasons^[45, 46] for permeation.

- Effect of ethanol
- Effect of Ethosomes

1.7.6.1 Effect of ethanol

Ethanol basically is a permeation enhancer. Ethanol decreases the density of the lipid multi layer by penetrating into intercellular lipids thereby increasing the fluidity of lipid cell membrane.

1.7.6.2 Effect of ethosomes

Skin permeability is caused by ethanol of the ethosomes. Thus the ethosome can now easily permeate into the deep layer of the skin and when it

gets combined with skin lipids, release of drug into the deep layers of skin occurs.

1.7.6.3 Composition of ethosomes

Ethosomes already mentioned it is composed of Phospholipids, water and ethanol in high concentration.

- Various phospholipids which are used as vesicle forming component are employed in preparation. Examples are phosphatidylcholine^[47] (Soya phosphatidylcholine, Egg phosphatidylcholine, Dipalmitoyl phosphatidylcholine, Distearoyl phosphatidylcholine) Phosphatidic acid, Phosphatidylserine etc usually in the range of 0.5 % - 10% w/w^[48].
- Polyglycols like propylene glycol, transcutoyl RTM are used as skin penetration enhancer^[49].
- Ethanol, Isopropyl alcohol in the ethosome provide softness to the vesicle membrane
- Cholesterol used at a range of 0.1% - 1 % provide stability to the vesicle membrane^[50].

The final product contains 20% -50 % of alcohol^[51].

Table 3. System Application of Ethosomal formulations

Sr.no	Botanical	Active ingredients	Biological activity	Application of ethosomal formulations
1.	Sophora alopecuroides	Sophora alopecuroides ethosomes	Anti-endotoxic, anticancer and antiinflammatory	Ethosome enhances delivery of drugs through the stratum corneum barrier into the deep layer of the skin
2.	Sophora flavescens	Matrine	Antibacterial, antiinflammatory, antirheumatism and antitumour	Increase the percutaneous permeation and improve antiinflammatory effect
3.	Sesbania grandiflora	Sesbania ethosome	Anti-microbial	Enhance Transdermal permeation
4.	Glycyrrhiza glabra	Amonium Glycyrrhizinate Ethosomes	Anti inflammatory	Increases of in vitro percutaneous permeation and significantly enhanced anti inflammatory activity

5.	Podophyllumhex andrum	Podophyllotoxin	Purgative, antirheumatic, antiviral and antitumor	Higher entrapment efficiency and enhance its therapeutic effect
6.	Tripterygiumwilfordi	Triptolide	Anti inflammatory	high entrapment efficiency, good percutaneous permeability

Future perspectives

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 the 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.

The results of the first clinical study of the acyclovir-ethosomal formulation support this conclusion. Studies will continue to further improve the skin delivery of drugs using lipid vesicles. Special emphasis seems to be given to the skin delivery of proteins and other macromolecules and for transcutaneous immunization. The near future also holds the emergence of new commercial ethosome-based topical products. NTT, Novel Therapeutic Technology Inc., is a biopharmaceutical company with a portfolio of pharmaceutical formulations based on ethosome technology including formulations for the treatment of alopecia, deep skin infection, herpes, hormone deficiencies, inflammation, postoperative nausea, atopic dermatitis, and erectile dysfunction.

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