TITLE: ETHOSOMES FOR DRUG DELIVERY OF NATURAL PRODUCTS IN DIABETES

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ABSTRACT

Diabetes mellitus (DM) is the most common metabolic disorder worldwide, brought on by either decreased pancreatic insulin secretion, diminished insulin action in the body, or both. Approximately about 200 million people are currently affected globally with diabetes. Over the past decades, advancements have been madefor the delivery of herbal products through novel approaches such as “Ethosomes”. Ethosomes are composed of phospholipid, alcohol, polyglycol and water. Due to their ease of surface modification, lack of immunogenicity, and ability to efficiently encapsulate both hydrophilic and lipophilic medicines, ethosomes may be a better alternative to liposomes for various therapeutic molecules, including natural products. The unique combination of phospholipids and ethanol in ethosomes provides a stable and biodegradable nanocarrier system that minimizes adverse effects and maintains the integrity of the skin barrier. Ethosomes have demonstrated significant potential for delivering a wide range of drugs, including small molecules, peptides, proteins, and even genetic materials. The purpose of this review is to outline ethosomes for delivery of natural product for Diabetes mellitus.

KEYWORDS: Ethosomes, Diabetes mellitus, Herbal drugs

I. INTRODUCTION

In the realm of pharmaceutical research, continuous efforts are being made to enhance drug delivery methods and improve the therapeutic outcomes for various medical conditions. Among the latest innovations in this field are "ethosomal drug delivery systems" and "ethosomes," which have garnered significant attention for their potential to improve drug absorption through the skin.

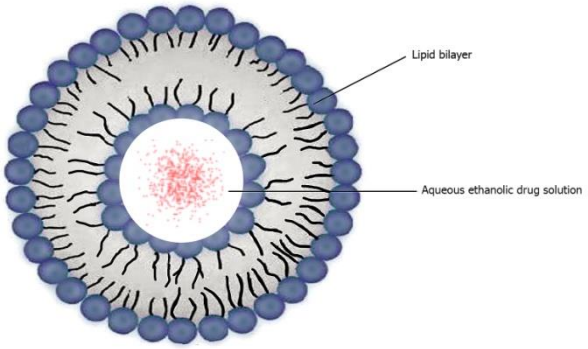

Figure 1: Structure of ethosomes

Ethosomal drug delivery systems utilize specialized lipid-based carriers known as "ethosomes" to facilitate the penetration of active pharmaceutical ingredients (APIs) into deeper layers of the skin and supporting tissues. These vesicles are composed of phospholipids, ethanol, and water, which impart unique properties to them. Ethanol, a key component of ethosomes, confers increased fluidity to the vesicles' lipid bilayers, thereby enhancing their ability to permeate through the skin effectively. The advantages of ethosomes are multi-faceted. They exhibit efficacy in delivering both hydrophilic and lipophilic medicines, making them suitable for a wide range of pharmacological substances. By disabling the barrier qualities of the skin's outermost layer, the stratum corneum, ethosomes significantly improve the ability of medications to penetrate

this barrier, increasing drug bioavailability.[1] This heightened bioavailability allows for administration at lower doses, reducing the potential for systemic side effects. Furthermore, ethosomes offer a non-invasive alternative to traditional oral or injectable approaches, making them particularly valuable for medications that may degrade in the gastrointestinal tract or have low oral bioavailability. However, the presence of ethanol in ethosomes can cause skin dryness and irritation, which might limit their application in individuals with sensitive or damaged skin. Despite their promise, ethosomes do pose challenges that require careful consideration. They can be susceptible to physical and chemical instability, leading to drug leakage or vesicle fusion. Additionally, the production of ethosomes demands specialized equipment and techniques, potentially increasing manufacturing costs compared to conventional drug delivery systems. Current research has explored the potential of ethosomes in facilitating the penetration of insulin and other antidiabetic medications through the skin, demonstrating promising results in preclinical investigations. However, more extensive clinical studies are needed to ascertain their safety, effectiveness, and practicality in real-world settings.[2] In comparison to conventional insulin formulations, ethosomal insulin formulations have demonstrated increased transdermal distribution and enhanced therapeutic benefits in preclinical investigations. To assess the safety, effectiveness, and practicability of ethosomes in clinical settings, more study is required. It is crucial to keep in mind that these investigations are still in the experimental stage. Ethosomes have also been investigated for the delivery of other antidiabetic medications, such as metformin, over the skin in addition to insulin. Enhancing drug absorption, bioavailability, and therapeutic results are the goals. It's important to point out that research is actively taking place in the creation of novel drug delivery methods, including ethosomes.For the most recent information on the use of ethosomes in the management of diabetes, it is crucial to review the most recent research updates and scientific literature.[1] [3]

Advantages and Disadvantages:

Table 1: Advantages and Disadvantages of ethosomes

Advantages	Disadvantages
Delivery of large molecules	May not be economical
It contains non-toxic raw material in formulation.	Ethosomes with poor shells may clump together and leads to precipitation.
Enhanced permeation of drug through skin for transdermal drug delivery.	Transfer of ethosomes from organic to aqueous layer leads to loss of product
High patient compliance	Poor practical yield.
The Ethosomal system is passive, non-invasive	Drugs that require high blood levels cannot be administered

II. Methods of preparation of ethosomes

1) Hot method*:*

A solvent (such as ethanol or propylene glycol) must first be used to dissolve the medication before the solvent can be added to the phosphate dispersion in water (40°C). The product is sonicated using a probe sonicator for 3 cycles of 5 minutes each after 5 minutes of mixing, with a 5 minute break in between each cycle. To produce nano-sized ethosomes, the formulation is homogenised (15,000 psi pressure) over the course of three cycles in a high pressure hydrogenizer. [3][2]

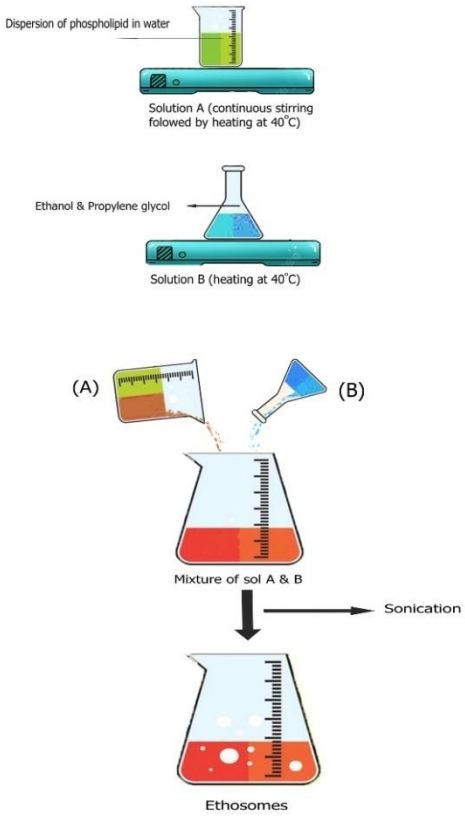

Figure 2: Hot method

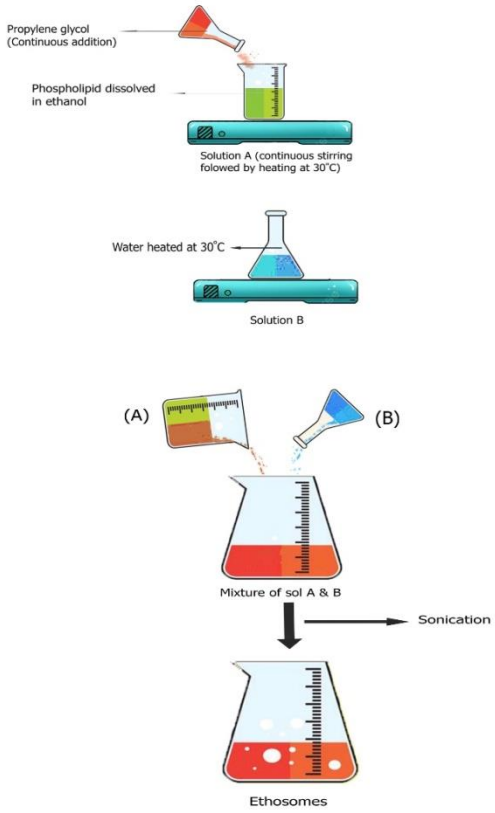

Figure 3: Cold method

2) Cold method:

The most well-liked and frequently applied ethosomal preparation technique is this one. At room temperature, ethanol is dissolved in the phospholipid, medication, and other lipid materials in the covered vessel and vigorously agitated. In the water bath, warm the mixture to 30 °C. In a separate vessel, heat the water to 30 °C. Add it to the previously specified mixture, and stir for 5 minutes with the lid on. If necessary, the formulation can be extended by reducing the size of the vesicles through extrusion, sonication, etc. The formulation needs to be carefully refrigerated stored.[4]

3) Thin-Film Hydration Method:

Weigh the appropriate amount of lipids (phospholipids such as phosphatidylcholine) and a drug (if required) and dissolve them in an organic solvent (e.g., ethanol or chloroform). Evaporate the solvent under reduced pressure to obtain a thin lipid film on the container walls. Hydrate the lipid film with an aqueous phase (e.g., phosphate-buffered saline) and subject it to sonication or vortexing to obtain a homogenous suspension. The resulting suspension is then subjected to further sonication or extrusion to reduce the vesicle size and

improve uniformity. The prepared ethosomes can be stored at an appropriate temperature until further characterization.[5]

III. Composition of Ethosomes

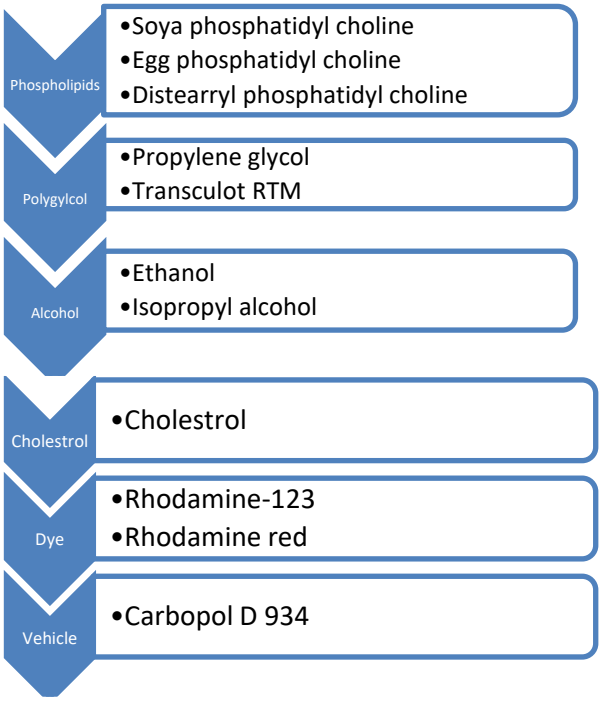

Figure 4: Composition of ethosomes

IV. Mechanism of drug penetration

1. **Penetration Enhancement**: Ethosomes are highly deformable vesicles due to the presence of high concentrations of ethanol. This deformability allows them to squeeze through the narrow spaces between skin cells, which helps in improving drug penetration through the skin. The ethosomes can bypass the stratum corneum (the outermost layer of the skin) and reach the deeper layers where they release the drug.[4]

2. **Lipid Bilayer Fusion**: Ethosomes can fuse with the lipid bilayers of the skin cells, facilitating the direct transfer of drugs into the cells. This fusion process helps in efficient drug delivery across the skin barrier.[5]

3. **Drug Solubility and Stability**: Ethosomes can enhance the solubility of poorly soluble drugs by incorporating them into the lipid bilayers. This increased solubility improves the drug's availability for absorption. Moreover, the encapsulation of drugs within ethosomes can protect them from degradation, thus improving their stability.[6][5]

4. **Targeting and Controlled Release**: Ethosomes can be modified to include targeting ligands on their surface, allowing them to specifically bind to receptors on target cells or tissues. This targeted approach increases the drug's concentration at the desired site and reduces systemic side effects. Additionally, the lipid composition and formulation parameters of ethosomes can be optimized to achieve controlled release of the drug over a desired period.[7][4]

The following two phases are probably when the medication is absorbed.

Effect of ethanol: Alcohol improves product penetration through the skin. Its penetration-enhancing effect has a well-known mechanism. Ethanol permeates intercellular lipids, increasing their fluidity and decreasing the density of the cell membrane's multilayer of lipids.

Effect of ethosomes: Ethosomes increase the fluidity of cell membrane lipids, which increases skin permeability. As a result, the ethosomes easily penetrate the deep skin layers, where they fuse with skin lipids and release the medicines.[5][6]

V. Characterization of Ethosomes

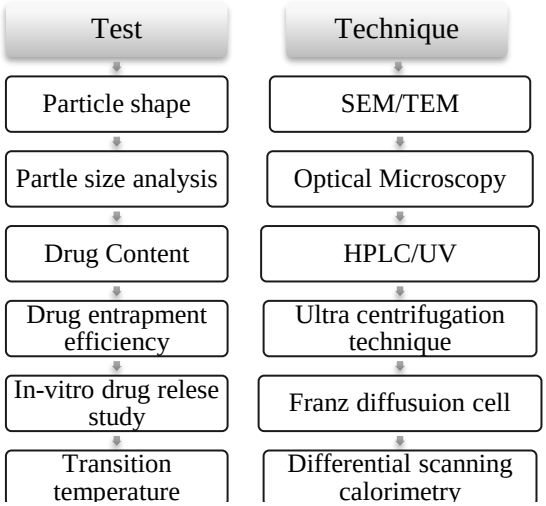

Figure 5: Characterization of Ethosomes

Shape and size of vesicle: Visual characterisation of the ethosomes can be conducted using Transmission electron spectroscopy and Scanning electron microscopy. The particle size of the ethosomes is determined using dynamic light scattering and photon correlation spectroscopy. The size of ethosomes might vary based on the formulation and technique of manufacture. The vesicle size is often in the nanometer range. Ethosomes are considered submicron vesicles, with average sizes ranging from 100 to 1000 nanometers (nm). Ethosomes are typically between 100 and 300 nm in size, making them suited for topical use due to their small size and potential for deeper skin penetration.The small size of ethosomes is favourable for medication administration because it allows for improved diffusion into the stratum corneum, the skin's outermost layer. Smaller vesicles' greater surface area-to-volume ratio improves skin contact, potentially leading to enhanced medication absorption.The size and form of the vesicle can be determined using techniques such as Dynamic Light Scattering (DLS) or Nanoparticle Tracking Analysis (NTA). These approaches can assess the size distribution of ethosomes and provide useful information about their physical features, which is important for determining their efficacy as drug delivery carriers.[6][3]

Transition temperature: Differential scanning calorimetry (DSC) can be used to determine the transition temperature of vesicular lipid systems. The phase transition temperature of the lipid bilayer within the vesicles is referred to as the ethosomes transition temperature. This temperature is also known as the gel-to-liquid crystalline phase transition temperature or the primary phase transition temperature. It is an important factor influencing the stability and drug release properties of ethosomes. The composition of the lipids used in the formulation of ethosomes essentially determines their transition temperature. Ethosomes are typically made up of phospholipids, and the phospholipids used determine the transition temperature. Phospholipids' acyl chain lengths and degrees of saturation can vary, affecting their fluidity at different temperatures. For instance, phospholipids with longer and more saturated acyl chains tend to have higher transition temperatures, while phospholipids with shorter and more unsaturated acyl chains have lower transition temperatures. The inclusion of ethanol in the formulation of ethosomes also lowers the transition temperature due to its fluidizing effect on the lipid bilayers. The transition temperature is essential because it determines whether the ethosomes exist in a gel phase (more ordered and less fluid) or a liquid crystalline phase (more disordered and more fluid). The gel

phase can reduce drug release rates, while the liquid crystalline phase is more conducive to drug release and skin penetration.For drug delivery applications, ethosomes are typically designed to have a transition temperature close to or slightly below room temperature (around 25°C).This ensures that the vesicles remain stable during storage but become fluidic and release their payload efficiently upon application to the skin. [7][3]

Drug entrapment: The entrapment efficiency of ethosomes can be measured by the ultracentrifugation technique and HPLC. In an eppendrof tube an aliquots from each formulation was taken and was subjected to centrifugation at 20000 rpm for 1hr. The supernatant was collected, filtered and the amount of the free drug was determined using HPLC method. The percent entrapment efficiency (EE) of the herbal product in the prepared vesicles can be calculated by using following equation:[8][7]

$$\% \text{ EE} = \left[\frac{(Total\ amount\ of\ drug\ used - Amount\ of\ free\ drug)}{Total\ amount\ of\ drug\ used}\right] \times 100 \ldots\ldots\ldots\ldots\ldots\ldots (1)$$

Drug content: A UV spectrophotometer can be used to determine the drug content of the ethosomes. A modified high performance liquid chromatographic method can also be used to quantify this. The amount of active pharmaceutical ingredient (API) or medication molecule enclosed within the vesicles is referred to as the drug content of ethosomes. Ethosomes are lipid-based vesicles that can encapsulate both hydrophilic and lipophilic medicines efficiently, making them appealing drug delivery carriers for topical and transdermal applications. The drug content of ethosomes is a critical parameter that has a direct impact on the efficacy of the drug delivery system. A high drug content means that a large amount of the medicine is available for distribution to the target site, maximising therapeutic impact while lowering needed dose. On the other side, a low drug content may limit the ethosomes' usefulness as a drug carrier. Several factors influence drug content in ethosomes, including formulation composition, preparation process, and the physicochemical properties of the drug molecule itself. The drug content is quantified using the encapsulation efficiency, which measures the proportion of drug encapsulated within the vesicles.

The encapsulation efficiency of ethosomes is calculated using the following formula:

Encapsulation Efficiency (%) = (Amount of drug encapsulated / Total amount of drug used) x 100……..(2)

It is crucial to highlight that attaining high drug content and encapsulation efficiency can be difficult for some medications, particularly those with poor solubility in the ethosomes' lipid bilayer. During the formulation process, many methods and techniques such as solvent injection, thin-film hydration, and sonication are used to optimise drug encapsulation. Experiments are frequently conducted by researchers and formulators to optimise the drug content and encapsulation efficiency of ethosomes by altering the lipid composition, drug-to-lipid ratio, and production circumstances. To achieve consistency and reproducibility of the drug delivery system for pharmaceutical and therapeutic purposes, the drug content should be rigorously characterised and confirmed.[9][3]

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. Surface tension measurement of ethosomes can provide valuable information about the stability and behavior of these lipid-based vesicles. Surface tension is a property of liquids that quantifies the force acting at the interface between the liquid and its surrounding medium. For ethosomes, the surrounding medium is typically water or an aqueous solution. There are various methods available for measuring surface tension, and the most commonly used techniques for ethosomes include:

- **Wilhelmy Plate Method**: In this method, a solid plate or ring is used to measure the force exerted by the ethosome solution on the plate's surface as it is withdrawn from or immersed into the liquid. The force is directly related to the liquid's surface tension. This method is commonly used for relatively large liquid samples.
- **Du Nouy Ring or Wilhelmy** Plate Method: This method is similar to the Wilhelmy Plate method but uses a ring or a loop instead of a solid plate. The ring is submerged into the ethosome solution, and the force required to lift it from the liquid surface is measured. The force is proportional to the surface tension.
- **Drop Shape Analysis**: In this method, a small droplet of the ethosome solution is placed on a solid surface, and the shape of the droplet is analyzed using image processing techniques. The shape of the droplet is influenced by the liquid's surface tension. This method is particularly useful for small sample sizes.
- **Pendant Drop Method**: In this technique, a droplet of the ethosome solution is suspended from a needle or a capillary tube. The shape of the droplet is analyzed, and the surface tension is calculated based on the droplet's geometry.

When measuring the surface tension of ethosomes, it's essential to consider the effect of temperature and other environmental factors on the vesicle's stability and surface properties. Surface tension can provide insights into the interaction between the ethosomes and the surrounding medium, which is relevant for understanding their behavior during topical application or transdermal drug delivery.[10][9]

Stability studies: The stability of vesicles can be measured by measuring their size and structure over time. DLS measures mean size, and TEM detects structural changes. Ethosome stability studies are critical for determining the long-term integrity, effectiveness, and safety of these lipid-based vesicular drug delivery systems. Under diverse settings, stability tests are carried out to assess the physical, chemical, and biological stability of ethosomes over time. These investigations' findings can aid in determining the shelf life and storage conditions of the formulation.

Here are some key aspects and parameters considered in stability studies of ethosomes:

- Physical Stability: Changes in the appearance, size, and form of ethosomes over time are referred to as physical stability. The size distribution, shape, and visual appearance of the vesicles are studied during stability investigations utilising techniques such as Dynamic Light Scattering (DLS), Transmission Electron Microscopy (TEM), and optical microscopy. Any significant changes in these properties could suggest vesicle instability or aggregation.
- Chemical Stability: Chemical stability entails tracking the degradation or interaction of the encapsulated medication and ethosome components over time. HPLC (high-performance liquid chromatography) is often used to analyse medication content and identify degradation products. To detect any chemical interactions between the medicine and the formulation components, Fourier Transform Infrared Spectroscopy (FTIR) and other spectroscopic approaches can be performed.
- Encapsulation Efficiency: An important criterion in stability studies is encapsulation efficiency, which evaluates the fraction of the drug encapsulated within the ethosomes. Changes in encapsulation efficiency can suggest drug leakage or structural changes in the vesicle.
- Zeta Potential: Zeta potential is a measure of ethosome surface charge and is critical for their stability. A sufficient zeta potential value is often found in a stable formulation. Any considerable shift in zeta potential could imply ethosome aggregation or destabilisation.
- Drug Release Kinetics: The drug release profile of ethosomes is examined in stability tests to verify that the formulation retains its targeted drug release characteristics throughout time.
- pH and Viscosity: During stability studies, the pH and viscosity of the ethosome formulation should be monitored, as changes in these parameters may alter the formulation's stability and efficacy.
- Temperature and Light Exposure: During storage and transportation, ethosomes may be exposed to a variety of temperature and light conditions. Stability studies involve subjecting the formulation to various temperature circumstances, such as accelerated stability testing and real-time stability testing, in order to evaluate the effect of temperature on the formulation's stability.
- Microbial Contamination: To ensure safety during storage and use, ethosomes intended for pharmaceutical or cosmetic use should be tested for microbial contamination.[11][5]

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). Skin permeation studies of ethosomes are conducted to evaluate the ability of these lipid-based vesicles to deliver drugs or active compounds through the skin. Ethosomes are designed to enhance the transdermal delivery of drugs by improving their skin penetration and permeation compared to conventional formulations. Skin permeation studies provide valuable insights into the efficiency and potential applications of ethosomes in topical and transdermal drug delivery. Here's an overview of the key aspects and methods involved in skin permeation studies of ethosomes:

- In Vitro Permeation research: A synthetic membrane or excised animal/human skin is employed as a barrier in this research to simulate the permeation capabilities of the skin. The ethosome formulation is applied to the surface, and the amount of medication that permeates the membrane or skin at particular time intervals is quantified. Cellulose-based membranes (e.g., cellulose acetate, cellulose nitrate) and synthetic polymer membranes (e.g., polyethylene terephthalate) are common synthetic membranes.
- .Ex Vivo Skin Permeation investigations: In ex vivo investigations, the barrier is freshly excised animal or human skin (typically obtained through surgical procedures). The skin is placed in a diffusion cell system, and the ethosome formulation is administered to the surface of the skin. Over time, the amount of medication that seeps through the epidermal layers is

measured. Ex vivo investigations, as opposed to synthetic membranes, provide a more accurate portrayal of the skin's genuine physiology.

- The Franz diffusion cell system is the most often utilised configuration for in vitro and ex vivo skin permeation research. It is made up of two compartments that are divided by a skin or synthetic membrane. The formulation is applied to one side (donor compartment), and the receptor fluid is collected from the other.
- Sampling of Receiver Fluid: Samples are collected from the receiver compartment at predefined time intervals during the permeation research. Analytical procedures such as high-performance liquid chromatography (HPLC) or UV spectrophotometry are used to determine the concentration of the drug in the samples..

- Permeation data is analysed to determine metrics such as permeation flux, cumulative permeated amount, and lag time. The rate of medication penetration per unit area of skin is represented by permeation flux. The cumulative penetrated amount indicates the overall amount of medication that has passed through the epidermal barrier over time. Lag time refers to the amount of time it takes for the drug to enter the skin and become detected in the receiver compartment.[12][10]

VI. Ethosomes as a Potential Delivery System in Diabetes

According to the World Health Organisation (WHO), diabetes complications would affect over 366 million people worldwide by 2030. Diabetes is a serious health problem. Type 1 diabetes (diabetes that requires insulin), type 2 diabetes (diabetes that does not require insulin), and gestational diabetes are the three main types of diabetes, with type 2 diabetes making up 90% of all cases. There are several ways to manage diabetes, including insulin therapy and islet transplantation. Despite the fact that several of these methods provide significant challenges.[6].The bulk of currently available diabetic therapies hinge on maintaining adequate control of blood sugar and lipid levels as well as minimising complications. Researchers' focus has been focused

SL NO	Title of the research	Name of herbal product	Delivery System	MOA	Reference
1	Curcumin loaded Ethosomal Gel for improved topical delivery: Formulation,characterization and Ex-Vivo studies	Curcumin	Ethosomal Gel	Permeate through the skin barriers	[14]
2	Development and assessment of phytophospholipid nano vesicular systems for treatment of diabetic neuropathy	*Curcuma longa* and B*oswellia serrata*	Ethosomal gel	Permeate through the skin barriers	[15]
3	Corn Silk Based Ethosomal Gel: A New Treatment for Periodontitis in Diabetic Albino Rats a Preliminary Study	Corn silk	Ethosomal gel	Permeate through the skin barriers	[16]
4	Development, Characterization ans Stability Evaluation of Topical Gel Loaded with Ethosomes Containing *Achillea millefolium* L. Extract	*Achillea millefolium* L. Extract	Ethosomal gel	Permeate through the skin barriers	[17]

by advances in pharmaceutical science to the use of drug administration systems and the intriguing potential of ethosomes in developing drug compositions and delivery strategies for the effective management of diabetes.[13][9]

Table 2: Ethosomes encapsulated herbal formulations

VII. NEED FOR NATURAL REMEDIES

Deficiencies in insulin production are among the primary factors that result in Diabetes Mellitus. Lately, several herbal plants have shown promise in managing diabetes by controlling the release of insulin. Since the extended use of glibenclamide in diabetic individuals can lead to harm to beta cells due to excessive stimulation of pancreatic islets.Prolonged duration therapy of hypoglycemic drugs resulting in substantial need for effective, reduced adverse reactions and cost-effective substances for the management of diabetes.
The majority of research on herbal and natural remedies have indicated superior anti-diabetic properties, at a reduced expense and with fewer adverse reactions compared to artificial medications.[18][14]

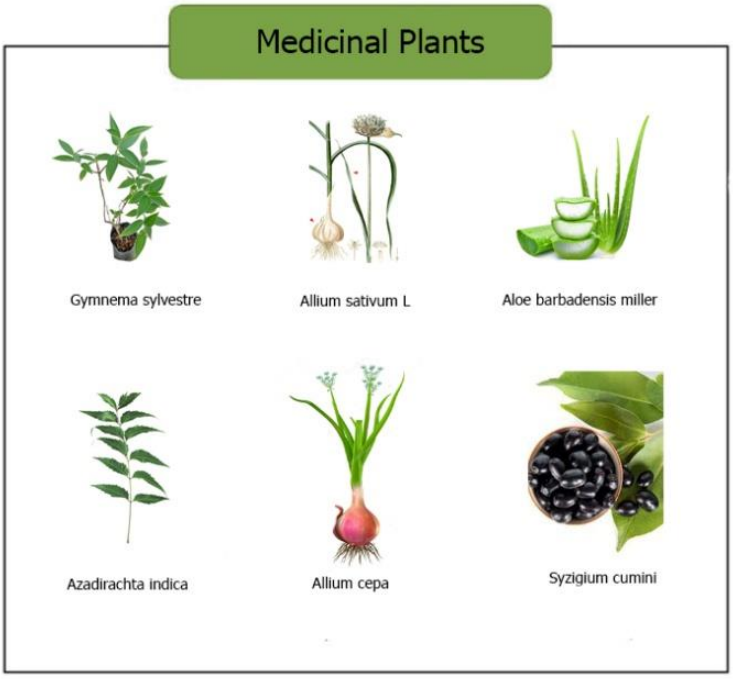

Figure 6: Examples of medicinal plants

Syzygiumcumini (Jamun)

Eastern traditional medicine has long made use of the fruit and seeds of the Jambul tree. After intake, the jamun pulp extract showed a reduction in blood sugar levels in just 30 minutes, however the seeds of the same fruit took an entire day. Additionally, blood insulin levels increased, and the extract also reduced insulinase activity in the liver and kidney.[19]

Aloe barbadensismiller (Aloe vera)

The popular indoor plant aloe vera has a long history as a versatile traditional remedy. Sap and substance are the two basic components of a plant. Aloe sap, sometimes known as "aloe liquid," is a sour yellow secretion from the pericyclic tubules just below the outer covering of the leaves. Aloe Vera material is the leaf pulp or gel. Aloe gum solutions effectively improve glucose tolerance in healthy people and people with diabetes.[20]

Nigella sativa

It was evaluated how long-term use of Nigella sativa might affect people with T2DM who are on common hypoglycemic drugs. When compared to the group that did not receive Nigella sativa, the one-year therapy with this herb led to higher levels of total antioxidant activity in the blood as well as higher levels of GSH and SOD. Additionally, those who received Nigella sativa treatment experienced a significant decrease in fasting blood glucose and glycosylated haemoglobin as well as an improvement in insulin resistance and -cell function. These results imply that supplementing with Nigella sativa may be advantageous as an alternate treatment for those with T2DM.[21]

Allium sativum

Both antioxidative and antihyperglycemic effects can be found in aged garlic extract. Consuming aged garlic extract increased endothelial dysfunction in people while reducing oxidative stress. A 4-week treatment with aged garlic extract at a daily dosage of 1200 mg on body weight, blood pressure, lipids, insulin resistance, and biomarkers of endothelial dysfunction, oxidative stress, and inflammation did not have any appreciable positive effects in a study on patients with type 2 diabetes mellitus (T2DM) and a high risk of cardiovascular events (30% risk in the next 10 years). The authors did, however, speculate that enrolling patients with a higher cardiovascular risk or giving aged garlic extract for a longer period of time would provide more observable results. It is necessary to conduct additional research to comprehend the mechanism, dosage, and safety of this natural product in future research.[22]

Figure 7: Marketed herbal formulation for diabetic treatment

VIII. Challenges Associated with Ethosomes

1. Stability: Ethosomes can be prone to physical and chemical instability, which can affect their performance and shelf life. Issues such as vesicle aggregation, leakage of encapsulated drugs, or changes in vesicle size and structure may occur during storage or formulation processes.[23][21]

2. Ethanol content: Ethosomes typically contain high amounts of ethanol to enhance their fluidity and skin permeation. However, the presence of ethanol can cause skin irritation, especially in individuals with sensitive skin. The use of ethanol also raises concerns about its potential systemic absorption and adverse effects.[9][4]

3. Vesicle size and distribution: The size and distribution of ethosomes can significantly impact their performance. Large vesicles may have limited skin penetration, while very small vesicles might be

prone to aggregation or rapid drug release. Achieving a uniform size distribution of ethosomes can be challenging.[24][7]

4. Scalability: Scaling up the production of ethosomes can be complex. Maintaining the desired vesicle characteristics and ensuring batch-to-batch consistency can be challenging during large-scale manufacturing processes.[25][8]

5. Regulatory considerations: Ethosomes are considered as innovative drug delivery systems, and their regulatory approval might require additional studies and evaluations. Regulatory agencies may require comprehensive safety, efficacy, and stability data before approving ethosome-based products for commercial use.[26]

6. Limited research and commercial availability: Despite the potential benefits of ethosomes, their use in clinical practice is still limited. Further research and development efforts are needed to explore their application in various therapeutic areas, including diabetes treatment, and to overcome the associated challenges.[27][22]

IX. Application of ethosomes

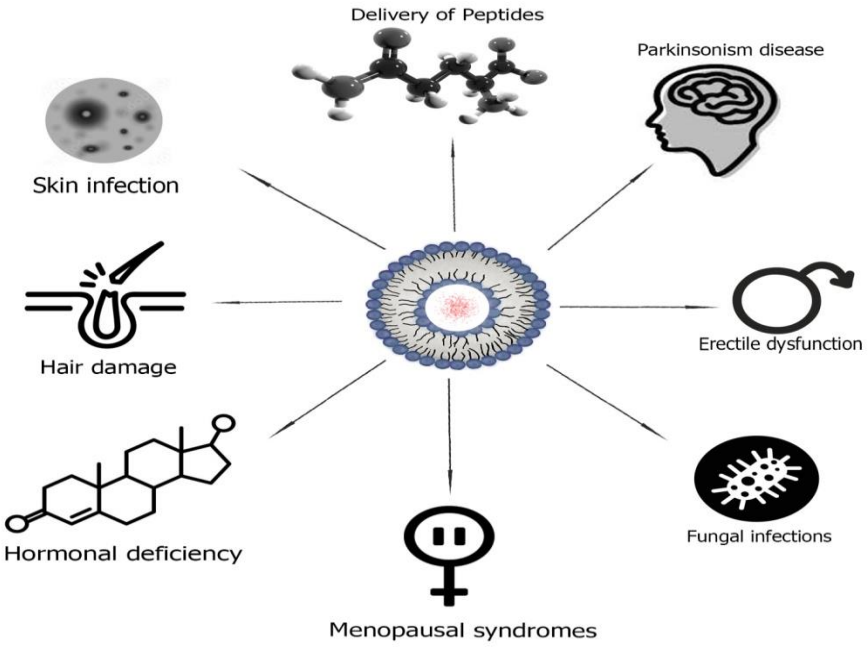

Figure 8: Application of ethosomes

Ethosomes for microbial and viral skin infection

The use of ethosomes has proven to be highly successful in delivering different antibiotics for effectively treating skin infections. The treatment of skin infections has been examined in animal models to study the impacts of antibiotics. The staphylococcus aureus is treated with ethosomal erythromycin compared to the treatment with a hydroethanolic erythromycin solution the mice that were infected showed effective healing of skin infections with no increase in bacterial growth. The research examines how bacitracin and fluorescently labeled bacitracin (FITC-Bac) ethosome permeate the skin in laboratory and living system. The measurement of the results has been performed through the use of CLSM (confocal laser scanning microscopy) and FACS

(fluorescent- activated cell sorting) experiments. The entry of compounds into the skin and improved their absorption compared to conventional liposomes, penetration of medications through the skin suffers with mild to moderate conditions exhibited significant improvement when treated with an ethosomal gel combining clindamycin and salicylic acid mild acne vulgaris without experiencing any adverse effects.[28] [29]

Ethosomes for skin disorder

Nanolipid carriers (solid lipid nanoparticles, nanostructured lipid carriers, liposomes and ethosomes) were prepared and evaluated for antipsoriatic activity in a mouse tail model. Ethosomes have not been shown to be particularly effective in treating superficial skin conditions such as psoriasis. The antitumor activity of 5-fluorouracil (5-FU) ethosomes was evaluated in nude mice using two skin cancer models, i.e., intradermal injection of TE.354.T cells and intradermal injection of TE.354.T cells injection of ES2 cells. The results showed significant inhibition of tumor growth in both models compared to the commercial product.[30] [31]

Minoxidil ethosomes for hair loss

Currently, there are significant numbers of people worldwide experiencing hair issues such as seborrhea, excessive hair loss, and acne. As a result, aiming to deliver the particular medication tothe designated area.The proper functioning of hairfollicles plays a crucial role in effectively treating pilosebaceous conditions. The drug Minoxidil, which has an affinity for fats, is applied directly on the scalp to treat hair loss. [32]

Delivery of Peptides through ethosomes

Peptides and proteins being large molecules, are unable to passthrough the outer layer of the skin stratum corneum) and due to their limited ability to be absorbed in the digestive system they are typically administered through intravenous (IV) or subcutaneous (SC) routes. Insulin, a protein made up of a few subunits, has a weight of 6000 Dalton per individual unit. It is administered through intravenous route to treat diabetes mellitus that requires insulin for management. Different scientists have directed their attention to delivering insulin into the body through the skin actively, instead of using passive methods. This has been accomplished by physical techniques such as iontophoresis, phonophoresis and other similar approaches. Vesicles have demonstrated efficacy in facilitating the transdermal absorption of insulin. An insulin patch containing ethosomes has been created and tests have been carried out on both normal and diabetic rats to observe the impact of the patch on blood glucose levels when compared to a patch of insulin that is not in the form of ethosomes. Duration of action compared to the control group treated with a regular patch effect that persisted for a minimum of 8 hrs.[33] [34]

X. Future aspects of ethosomes

The future of ethosomes holds several exciting possibilities and potential advancements in various areas of drug delivery.some future aspects and developments that researchers and scientists are exploring:

1. Enhanced stability and shelf life: Improving the stability of ethosomes is a crucial area of research. Scientists are investigating strategies to enhance the long-term stability of ethosomes, including the development of novel lipid compositions, stabilization techniques, and packaging methods to prevent vesicle degradation and improve shelf life.[9]

2. Targeted delivery: Efforts are being made to develop ethosomes with target-specific ligands or surface modifications that can enhance their ability to target specific cells or tissues. By incorporating targeting moieties, such as antibodies or peptides, onto the surface of ethosomes, researchers aim to achieve site-specific drug delivery and improve therapeutic outcomes.[35]

3. Combination therapies: Ethosomes can serve as a platform for combination therapies, where multiple drugs or bioactive compounds can be encapsulated within a single vesicle. This approach allows for synergistic effects, improved drug interactions, and enhanced therapeutic efficacy. Future research may

focus on optimizing the encapsulation of multiple drugs in ethosomes for combination therapy in various disease conditions.[36]

4. Personalized medicine: Ethosomes hold potential for personalized medicine approaches. By tailoring the composition and characteristics of ethosomes to specific patient needs, such as skin type or drug response, personalized ethosome-based formulations could be developed. This may lead to improved treatment outcomes by considering individual variations in drug absorption, metabolism, and skin permeability.[37]

5. Advanced characterization techniques: Researchers are exploring advanced characterization techniques to better understand the structure, behavior, and interaction of ethosomes. Techniques such as cryogenic electron microscopy, atomic force microscopy, and spectroscopic methods are being employed to gain insights into the morphology, size distribution, and drug release kinetics of ethosomes.[38][34]

6. Clinical translation and commercialization: As the research on ethosomes progresses, efforts are being made to translate promising findings into clinical applications. Regulatory aspects and guidelines for the development, evaluation, and approval of ethosome-based formulations are expected to be further refined to facilitate their clinical translation and commercial availability.[38][37]

Overall, ethosomes have a bright future because of continuing research that addresses their problems, improves their functionality, and considers new uses. These developments could revolutionise medication delivery methods and enhance therapy results for a range of medical situations.

XI. Conclusion

In conclusion, there is tremendous potential for ethosome-based medication delivery of natural ingredients for the treatment of diabetes. increased skin penetration, increased medication solubility and stability, targeted distribution, and the capacity to encapsulate both hydrophilic and lipophilic medicines are just a few benefits offered by ethosomes. For the transport of natural substances like curcumin, maize silk, and other substances with antidiabetic effects found in plants, ethosomes have been studied. The therapeutic effects and better drug penetration demonstrated by these investigations are encouraging.

But there are a number of difficulties with ethosomes that must be resolved. These difficulties include stability issues, worries about ethanol concentration, the dispersion of vesicle sizes, scalability, regulatory limitations, and a lack of research and commercial availability. The stability and shelf life of ethosomes are being improved, and research is also being done to create targeted delivery systems, investigate combination therapy, and improve characterization methods. Ethosomes' future also includes clinical translation for larger uses and personalised treatment strategies.Establishing the effectiveness, safety, and viability of ethosomes in clinical settings will require additional research and development initiatives. For regulatory authorities to authorise ethosome-based medicines for commercial use, extensive data on stability, efficacy, and safety are required. Ethosomes have the potential to transform medication delivery methods and enhance therapeutic results, notably in the management of diabetes mellitus.

Reference:

1. N. Akombaetwa , A.B. Ilangala , L.Thom , P.B. Memvanga, B.A. Witika , A.B. Buya," Current advances in lipid nanosystems intended for topical and transdermal drug delivery applications". Pharmaceutics, vol.15;15(2), pp.656, February 2023.
2. R. Bajracharya, J.G. Song, S.Y. Back, H.K. Han, "Recent Advancements in Non-Invasive Formulations for Protein Drug Delivery", Computational and Structural Biotechnology Journal, vol.17, 2019.
3. P. Verma, K. Pathak, "Therapeutic and cosmeceutical potential of ethosomes: An overview", J Adv Pharm Technol Res., vol. 1(3), pp. 274-82, July 2010.
4. R.B. Saudagar1, S. Samuel,"Ethosomes: Novel noninvasive carrier for Transdermal Drug Delivery" Asian J. Pharm. Tech., vol. 6(2), pp.135-138, 2016.
5. M. Sguizzato, F. Ferrara, S.S. Hallan, A. Baldisserotto, M. Drechsler, M. Malatesta, M. Costanzo, R. Cortesi, C. Puglia, G. Valacchi, "Ethosomes and Transethosomes for Mangiferin Transdermal Delivery", Antioxidants vol. 10, pp. 768, 2021.
6. A.Eric, K. Phoebe, "Differential Scanning Calorimetry Studies of Phospholipid Membranes: The Interdigitated Gel Phase'. Applications of Calorimetry in a Wide Context - Differential Scanning Calorimetry, Isothermal Titration Calorimetry and Microcalorimetry", InTech, 2007.
7. P.F. Yue, X.Y. Lu, Z.Z. Zhang, H.L. Yuan, W.F. Zhu, Q. Zheng, M. Yang, "The study on the entrapment efficiency and in vitro release of puerarin submicron emulsion"., AAPS PharmSciTech, vol. 10(2), pp. 376-83, April 2009.
8. S.A.T. Opatha, V. Titapiwatanakun, R. Chutoprapat, "Transfersomes: A Promising Nanoencapsulation Technique for Transdermal Drug Delivery" Pharmaceutics., vol. 9;12(9), pp. 855, September 2020.
9. S. Patel, " Ethosomes: A promising tool for transdermal delivery of drug"., Pharma Info., vol. 5(3), 2007.
10. M. Danaei, M.Dehghankhold, S. Ataei, D.F. Hasanzadeh, R. Javanmard, A. Dokhani, S. Khorasani, M.R. Mozafari, "Impact of Particle Size and Polydispersity Index on the Clinical Applications of Lipidic Nanocarrier Systems" Pharmaceutics, vol. 18;10(2), pp. 57, May 2018.
11. P. Verma, K. Pathak, "Therapeutic and cosmeceutical potential of ethosomes: An overview", J Adv Pharm Technol Res., vol. 1(3), pp. 274-82, July 2010.
12. D.K. Patel, R. Kumar, D. Laloo, S. Hemalatha, "Diabetes mellitus: an overview on its pharmacological aspects and reported medicinal plants having antidiabetic activity", Asian Pac J Trop Biomed., vol. 2(5), pp. 411-20, May 2012.
13. A.M. Vargason, A.C. Anselmo, S. Mitragotri, "The evolution of commercial drug delivery technologies" Nat Biomed Eng 5, pp. 951–967, 2021.
14. B. Kumar, P.K. Sahoo, S. Manchanda, "Curcumin loaded ethosomal gel for improved topical delivery: formulation, characterization and ex-vivo studies", Pharmaceutical Nanotechnology, vol. 1;9(4), pp. 281-7, August 2021.
15. G.Tiwari, D. Yadav, B. Singh, A. Kumar, P. Wal, R. Tiwari, "Development and assessment of phytophospholipid nanovesicular systems for treatment of diabetic neuropathy", Pharmacognosy Research, vol. 14(4), 2022.
16. IE R, YR K, ANA T, JS U, NS D, MH A. "Corn Silk Based Ethosomal Gel: A New Treatment for Periodontitis in Diabetic Albino Rats a Prelimenary Study", Indian Journal of Public Health Research & Development, vol.1;11(1), January 2020.
17. M. Andleeb, H.H.K. Shoaib, M. Daniyal, "Development, characterization and stability evaluation of topical gel loaded with ethosomes containing Achillea millefolium L. extract", Frontiers in pharmacology., vol.12;12, pp. 603227, April 2021.
18. D.K. Patel, S.K. Prasad, R. Kumar, S. Hemalatha, "An overview on antidiabetic medicinal plants having insulin mimetic property", Asian Pac J Trop Biomed, vol. 2(4), pp. 320-30, April 2020.
19. M.K. Rizvi, R. Rabail, S. Munir, M. Inam-Ur-Raheem, M.M.N. Qayyum, M. Kieliszek, A. Hassoun, R.M. Aadil, "Astounding Health Benefits of Jamun (Syzygiumcumini) toward Metabolic Syndrome", Molecules., vol. 24;27(21), pp. 7184, October 2022.
20. J.H. Hamman, "Composition and applications of Aloe vera leaf gel", Molecules., vol. 8;13(8), pp. 1599-616, August 2008.
21. A. Hamdan, R.I. Haji, M.H. Mokhtar, "Effects of Nigella Sativa on Type-2 Diabetes Mellitus: A Systematic Review", Int J Environ Res Public Health, vol. 5;16(24) pp. 4911, December 2019
22. J. Wang, X. Zhang, H. Lan, W. Wang, "Effect of garlic supplement in the management of type 2 diabetes mellitus (T2DM): a meta-analysis of randomized controlled trials", Food Nutr Res., vol. 27;61(1), pp.1377571, September 2017.
23. Rai S, Pandey V, G. Rai, "Transfersomes as versatile and flexible nano-vesicular carriers in skin cancer therapy: the state of the art", Nano Rev Exp., vol. 7;8(1),June 2017.
24. P. Verma, K. Pathak, "Therapeutic and cosmeceutical potential of ethosomes: An overview", J Adv Pharm Technol Res., vol. 1(3), pp. 274-82, Jul 2010.
25. A.K. Barupal, V. Gupta, S. Ramteke , "Preparation and Characterization of Ethosomes for Topical delivery of Aceclofenac", Indian J Pharm Sci. Vol. 72(5), pp. 582-6, September 2010.
26. N. Chauhan, P. Vasava, S.L. Khan, F.A. Siddiqui, F. Islam, H. Chopra, T.B. Emran, "Ethosomes: A novel drug carrier" Ann Med Surg (Lond), vol.8, pp. 82:104595, September 2022.
27. B. Godin, E. Touitou," Erythromycin ethosomal systems: physicochemical characterization and enhanced antibacterial activity", Curr Drug Deliv, vol. 2 (3), pp.269–275, 2005.
28. B. Godin, E. Touitou, E. Rubinstein, A. Athamna, and M. Athamna, "A new approach for treatment of deep skin infections by an ethosomal antibiotic preparation: An in vivo study", J. Antimicrob. Chemother, vol. 55, pp. 989-994, 2005.
29. K. Razaa, B. Singh, S. Lohan, G. Sharma, P. Negi, Y. Yachha, O.P. Katare, "Nano-lipoidal carriers of tretinoin with enhanced percutaneous absorption, photostability, biocompatibility and anti-psoriatic activity", International Journal of Pharmaceutics, vol. 456, pp. 65-72, 2013.
30. D. Ainbinder, E. Touitou, "A new approach for skin tumor treatment: from delivery system characterization to in vivo evaluation", Drug Deliv Transl Res.vol. 1 pp. 53–65, 2011.
31. B. Godin, M. Alcabez, E. Touitou, "Minoxidil and erythromycin targeted to pilosebaceous units by delivery systems (abstract)", ActaTechnol Legis Medic, vol. 10, pp.107, 1999.
32. G. Cevc, "Transferosomes, liposomes and other lipid suspensions on the skin: permeation enhancement, vesicle penetration, and transdermal drug delivery", Crit Rev Ther Drug Carrier Syst., vol.13, pp. 257–388, 1996.
33. I. Dkeidek, E. Touitou, "Transdermal absorption of polypeptides", AAPS Pharm Sci, vol. 1, 1999.
34. A.K. Barupal, V. Gupta, S. Ramteke, "Preparation and Characterization of Ethosomes for Topical delivery of Aceclofenac", Indian J Pharm Sci.,vol. 72(5), pp. 582-6, September 2010.
35. A. Yusuf, A.R.Z. Almotairy, H. Henidi, O.Y. Alshehri, M.S. Aldughaim, "Nanoparticles as Drug Delivery Systems: A Review of the Implication of Nanoparticles' Physicochemical Properties on Responses in Biological System", Polymers, vol. 15, pp. 1596, 2013.

36. I.M. Abdulbaqi, Y. Darwis, N.A. Khan, R.A. Assi, A.A. Khan, "Ethosomal nanocarriers: the impact of constituents and formulation techniques on ethosomal properties, in vivo studies, and clinical trials", Int J Nanomedicine, vol. 25;11, pp. 2279-304, May 2016.
37. S. Das, "Nanoparticles-advanced-characterization-techniques-A-view-point", vol. 7, pp. 1091–1098, 2017.
38. N. Akhtar, A. Varma, K. Pathak, "Ethosomes as vesicles for effective transdermal delivery: from bench to clinical implementation", Current clinical pharmacology, vol. 1;11(3), pp. 168-90, August 2016.