“Nano medicine in Dermatology: Exploring the Potential of Ethosomal Gels for Enhanced Topical Drug Delivery”

Abstract:

Introduction: Ethosomal gels are a novel drug delivery system that combines the benefits of gel and unique properties of Ethosomes for topical administration. Ethosomes are composed of phospholipids, Nano vesicles with a high ethanol concentration (20-45%) and water, which enable them to penetrate the stratum corneum more effectively than other conventional. This makes ethosomal gels an ideal platform for delivering a wide range of therapeutics, including both hydrophilic and lipophilic drugs, directly to the site of action on the skin.

Objectives: The incorporation of Ethosomes into gel matrices enhances the stability, controlled release, and while also providing ease of application and improved skin retention. Ethosomal gels have shown great promise in the treatment of dermatological conditions such as psoriasis, fungal infections, and localized pain management.

Methods: Ethosomes were prepared using different concentrations of phospholipid PLH90, alcohol, propylene glycol, and carbapol and characterized by particle size, zeta potential, and entrapment efficiency. Furthermore, in-vitro, in-vivo, ex-vivo, pharmacokinetic studies were done.

Conclusion: The combination of ethosomal technology with gel systems can offer improved therapeutic efficacy, patient compliance, and enhanced skin bioavailability, making it a promising approach for topical drug delivery. It is advantageous to address the issue of frequent dosing caused by the shorter half-life of medications.

Keywords: Ethosomal gel, lipid based Nano vesicles, Transdermal drug delivery, encapsulation efficiency, Bioavailability.

Introduction:

Ethosomes, the lipid vesicular carrier systems, also called as alcoholic liposomes are composed of phospholipids, alcohol (ethanol and isopropyl alcohol) in relatively high concentration and water. Ethosomes are suitable carrier systems for both hydrophilic and lipophilic drugs. The small particle size of Ethosomes (microns to nanometer) facilitates their potentiality in carrying the drug through the skin into systemic circulation. The ease of preparation, non- irritant nature, efficiency to encapsulate wide range of drug molecules and higher stability than any other vesicular systems makes the Ethosomes the most opted carriers for topical delivery of drugs. Ethosomes contain phospholipids entrapping alcoholic drug solutions. The phospholipids may vary from 0.5 to 10%. The alcohols which can be a softener, vehicle and penetration enhancer along with glycol, constitute 22-70% of Ethosomes. Through various studies, it was reported that varying the compositions of alcohol and water, the drug delivery can be modulated and thus the bioavailability can be enhanced.[(1)]

Ethosomes are novel lipid-based vesicular systems that are used for transdermal drug delivery. Ethosomes are similar to liposomes but contain a higher concentration of ethanol (usually between 20-45%), which helps to increase the permeability of the skin and enhance drug absorption. This makes them an ideal system for delivering both hydrophilic and lipophilic drugs transdermally. Ethosomes are highly favored due to their ability to enhance drug delivery and improve therapeutic outcomes for localized and systemic treatments.

Ethosomes, made from phospholipids and high content of ethanol, enhance skin permeability by boosting lipid fluidity, thereby enabling the drug to penetrate more deeply through the stratum corneum in transdermal. The process may employ both hot and cold techniques, along with size reduction methods such as sonication and extrusion to refine the Ethosomal carriers. Evaluating the Ethosomal gel will involve assessing factors such as size, shape, drug content, and zeta potential to confirm stability and effectiveness. The ultimate goal of the Ethosomal gel is to improve the bioavailability, which could lead to better therapeutic results for conditions like angina, while also ensuring patient comfort and adherence.

Ethosomes are more effective than liposomes or hydro-alcoholic solutions at delivering drugs to the skin. Ethosomes can penetrate deeper into the skin, and can deliver more drugs than other methods. Ethosomes are flexible and can deform to pass through cell gaps. The ethanol in Ethosomes helps the vesicles travel through the skin by increasing fluidity and lowering density. Ethanol also makes the vesicles negatively charged, which improves stability.

Ethosomes are better than other prepration because, Ethosomes are able to penetrate the skin more easily than other methods, allowing the drug to reach deeper layers of the skin and potentially enter the bloodstream.

An ethosomal gel is a semi-solid. Ethosomes designed for topical or transdermal application. Combining Ethosomes with a gel base helps to improve the stability, patient compliance, and controlled release of the drug over a prolonged period.[2]

Key Components in Ethosomal Gel:

1. **Phospholipids**: Phospholipids form the bilayer structure of the Ethosomes. These are the primary components of Ethosomes and typically include phosphatidylcholine, phosphatidylserine, other lipid molecules.
2. **Ethanol**: Ethanol is crucial for increasing the fluidity of the lipid bilayer and enhancing the skin penetration of drugs. It facilitates the drug to cross the skin barrier more efficiently.
3. **Water**: Water acts as a solvent and helps in the of ethosomal dispersions.
4. **Active Pharmaceutical Ingredient (API)**: The drug to be delivered is typically incorporated into the ethosomal dispersions. The API can be lipophilic, hydrophilic, or amphiphilic.
5. **Gel Base**: The gel base usually comprises gelling agents like carbopol, hydroxypropyl methylcellulose (HPMC), or sodium alginate. The gel base provides a semisolid consistency that allows for easy application, enhances drug stability, and ensures controlled release.[3]

Advantages of Ethosomal Gel:

1. **Enhanced Skin Penetration:** Ethosomes possess the ability to carry drugs through the skin more effectively due to the high ethanol content, which disrupts the skin's lipid structure.
2. **Improved Bioavailability:** The enhanced permeability results in increased drug bioavailability, especially for poorly soluble drugs.
3. **Controlled Drug Release:** The gel helps control the release rate of the drug, which can be advantageous for chronic treatments requiring prolonged drug action.
4. **Patient Compliance:** Gels are easy to apply and do not leave residues, providing improved patient comfort compared to other topical like creams, ointments.
5. **Localized Treatment:** Ethosomal gels can be used to deliver drugs to specific areas, which is beneficial for treating localized conditions such as skin infections, pain, and inflammation.[4]

Disadvantages of Ethosomal Gel:

1. **Stability Issues:**

   Ethanol Evaporation: Ethosomes rely on ethanol to enhance skin penetration, but prolonged exposure to air or improper storage conditions can lead to the evaporation of ethanol. This can compromise the integrity of the ethosomal vesicles, reducing their effectiveness and stability.

- **Physical Instability**: Ethosomal dispersions may experience changes in size or aggregation of vesicles over time, which can impact their performance, leading to reduced drug delivery efficiency.

2. Skin Irritation:

- The presence of high ethanol concentrations in Ethosomes can lead to skin irritation, dryness, or burning sensations, particularly in sensitive skin areas. Ethanol can act as a solvent, disrupting the skin barrier, and while this is beneficial for enhancing drug penetration, it may also lead to irritation in some cases, especially with prolonged use.

3. **Complex Manufacturing Process**:

- The preparation of ethosomal systems requires specific expertise and equipment, especially for homogenization and sonication to reduce particle size and ensure uniform distribution of the drug. The use of ethanol, in particular, adds complexity to the process, as it requires careful control of ethanol concentration to maintain the stability of the system.

4. Limited Drug Selection:

- Although Ethosomes can carry a wide range of drugs**,** highly hydrophilic drugs or those with poor solubility may not be easily incorporated into Ethosomes. The nature of the drug (lipophilic or hydrophilic) plays a significant role in the efficiency of ethosomal drug delivery. For hydrophilic drugs, other approaches may need to be considered, by using different vesicular systems.

5. Cost of Raw Materials and Production:

- The raw materials for preparing ethosomal gels, such as phospholipids, ethanol and gelling agents, can be expensive. In addition, the manufacturing process (which requires special equipment for homogenization, sonication, and precise) may increase the overall cost of production. This could be a limiting factor for commercialization, especially for large scale applications.[5]

Nanomedicines:

Nanomedicines represent an exciting and rapidly growing field at the intersection of nanotechnology and medicine. This technology involves using engineered nanoparticles to improve the delivery, targeting, and efficacy of therapeutic agents, as well as to develop innovative diagnostic tools. Here's a more detailed look at the key aspects of nanomedicines:

What Are Nanomedicines?

Nanomedicines are pharmaceutical formulations that utilize nanotechnology to enhance the effectiveness of treatment and diagnostics. These nanomaterials, usually particles with diameters between 1 to 100 nm, can be designed to deliver drugs more precisely to specific locations within the body, improving the therapeutic outcome and minimizing unwanted side effects.

Key Components of Nanomedicines

- **Nanoparticles:** These are the primary carriers in nanomedicine. They are typically composed of materials such as lipids (liposomes), polymers (polymeric nanoparticles), or metals (gold or silver nanoparticles). Their size, surface characteristics, and shape can be finely tuned to achieve specific therapeutic goals.
- **Drug Encapsulation/Delivery Systems:** Nanomedicines can encapsulate drugs inside nanoparticles or attach drugs to their surfaces. This allows for controlled release, enhanced bioavailability, and reduced side effects by targeting drugs to specific cells or tissues.
- **Diagnostic Tools:** Nanoparticles are used in imaging and diagnostic applications, such as MRI or PET scans, where they can be functionalized to improve the contrast and specificity of imaging, allowing for better detection and monitoring of diseases.

Applications of Nanomedicines

Nanomedicines have broad applications across various medical fields:

- **Cancer Treatment:** Nanoparticles can target tumor cells more precisely, delivering chemotherapy or gene therapy directly to the cancer cells, minimizing damage to healthy tissues and reducing systemic toxicity. Nanomedicines like Doxil (liposomal doxorubicin) are already in clinical use for cancer treatment.

- **Gene Therapy:** Nanoparticles can be used to deliver genetic material such as DNA, RNA, or CRISPR systems to specific cells to treat genetic disorders. This can be especially beneficial for diseases with a genetic basis, such as cystic fibrosis or sickle cell anemia.
- **Infectious Diseases:** Nanomedicines can help deliver antimicrobial agents directly to infection sites, increasing drug efficacy and reducing the risk of drug resistance. They can also be used in vaccine development, enhancing immune responses.
- **Neurodegenerative Disorders:** Nanoparticles have the potential to cross the blood-brain barrier, enabling the delivery of therapeutic agents for diseases like Alzheimer's and Parkinson's, which are difficult to treat with conventional methods.
- **Diagnostic Imaging and Biosensing:** Nanomedicines are used in imaging techniques, enhancing the visibility of specific tissues or organs and improving the accuracy of diagnostic tools. They can also be used in the early detection of diseases such as cancer.

Advantages of Nanomedicines

- **Targeted Delivery:** Nanoparticles can be engineered to specifically target diseased cells or tissues, improving the precision of drug delivery and reducing off-target effects.
- **Enhanced Solubility and Bioavailability:** Drugs that are poorly soluble in water or have low bioavailability can be encapsulated in nanoparticles, improving their effectiveness.
- **Controlled Release:** Nanoparticles can release their drug payloads in a controlled manner, ensuring that the drug is delivered at the right time and in the right amount, which is especially beneficial for chronic conditions.
- **Reduced Toxicity and Side Effects:** By targeting the drug more specifically to the disease site, nanomedicines can reduce the harmful side effects typically associated with conventional treatments like chemotherapy.

Challenges and Limitations

Despite the vast potential of nanomedicines, there are several challenges:

- **Toxicity Concerns:** The small size and surface properties of nanoparticles can potentially cause toxicity. These particles may accumulate in organs like the liver or spleen, leading to long-term health risks.
- **Regulatory Issues:** The regulatory approval process for nanomedicines is complex. Due to their novel nature, there are uncertainties about how to assess their safety and effectiveness compared to traditional drugs.
- **Manufacturing and Cost:** The synthesis and scale-up of nanoparticles for commercial production can be expensive and technically challenging.
- **Long-Term Effects:** The long-term impact of nanoparticles on human health and the environment is still not fully understood, raising concerns about their widespread use.

Examples of Nanomedicines in Clinical Use

- **Doxil:** A liposomal formulation of the chemotherapy drug doxorubicin used in the treatment of cancers like breast cancer and ovarian cancer. It reduces side effects by encapsulating the drug in nanoparticles, allowing for targeted delivery.
- **Abraxane:** An albumin-bound nanoparticle formulation of paclitaxel used in the treatment of cancers such as breast cancer and non-small cell lung cancer.
- **Onivyde:** A liposomal formulation of irinotecan, used to treat pancreatic cancer, which improves the drug's pharmacokinetics and reduces side effects.

The Future of Nanomedicines

The future of nanomedicines is very promising. As research advances, the potential for more personalized, efficient, and less invasive treatments grows. Nanomedicine holds the promise of revolutionizing treatments for conditions that are currently difficult to treat or have limited therapeutic options. Additionally, advances in nanomaterials, along with a better understanding of their interactions with biological systems, will likely address many of the current challenges, such as toxicity and regulatory concerns.

In conclusion, nanomedicines have the potential to significantly improve health care by offering more targeted, effective, and less toxic treatments. However, continued research, regulatory advancements, and clinical trials are necessary to ensure their safe and widespread use.

Material and Method:

Material:

1. **Phospholipid (Phosphatidylcholine)** – 1-10% w/w
    - Acts as the primary lipid component forming the vesicular structure of Ethosomes.
2. **Ethanol** –20-45% v/v
    - Enhances the skin penetration of the drug by disrupting the skin's lipid barrier.
3. **Active Pharmaceutical Ingredient (API)** – 0.5-5% w/w (depending on drug potency)
    - The drug to be delivered, which can be either hydrophilic or lipophilic.
4. **Water (Purified Water or Distilled Water)** – 40-60% v/v
    - Solvent used for preparing the ethosomal dispersion.
5. **Gel Base**:
    - **Carbopol 940** – 0.5-2% w/w
        - Carbopol is a commonly used gelling agent that helps in creating a gel-like consistency.
    - **Triethanolamine (TEA)** – 0.1-0.2% w/w
        - Used to neutralize carbopol and adjust the pH of the gel.
    - **Glycerin or Propylene Glycol** – 2-5% w/w
        - Humectants that provide moisture to the gel and improve its spreadability.[6]

Method:

Composition:

Ethosomes are vesicular carriers composed of hydro-alcoholic or hydro/alcoholic/glycolic phospholipid in which the concentration of alcohols or their combination is relatively high.

Preparation of Ethosomal Gel:

1. **Preparation of Ethosomal Dispersions**:
    - **Hydration of Phospholipids**: Phosphatidylcholine is dissolved in a mixture of ethanol and water. The mixture is kept under stirring at a temperature (typically 40-50°C) to ensure complete dissolution of the lipid component.
    - **Incorporation of the Active Ingredient (API)**: The drug is dissolved in the ethanol-water mixture. For lipophilic drugs, the ethanol content helps solubilize the drug.
    - **Preparation of Ethosomal Suspension**: The mixture is stirred and allowed to cool to room temperature to form the ethosomal dispersion. If required, additional homogenization or sonication can be performed to reduce the size of the vesicles.

2. **Preparation of Gel Base**:
    - **Hydration of Carbopol**: Carbopol is dispersed in purified water with gentle stirring. The dispersion is left to hydrate for a few hours or overnight.
    - **Adjusting pH**: After Carbopol hydration, Tiethanolamine (TEA) is added to neutralize the gel base and adjust the pH to the desired level (usually pH 5.5-7).
    - **Addition of Humectants**: Glycerin or propylene glycol is added to the gel base to improve its spreadability and maintain moisture content.
3. **Incorporation of Ethosomal Dispersion into Gel Base**:
    - Once the ethosomal dispersion and gel base are prepared separately, the ethosomal dispersion is gradually added to the gel base with continuous stirring to ensure uniform distribution.
    - Mixed until a smooth, homogeneous gel is obtained.
4. **Storage and Packaging**:
    - The ethosomal gel is then stored in air tight containers to prevent evaporation of ethanol. It should be kept in a cool, dry.[6]
5. **Vesicle Prepration:**

Cold Method:

In this method phospholipid, drug and other lipid materials are dissolved in ethanol in a covered vessel at room temperature by vigorous stirring with the use of mixer. Propylene glycol or other polyol is added during stirring. This mixture is heated to 300°C in a water bath. The water heated to 300°C in a separate vessel is added to the mixture, which is then stirred for 5min in a covered vessel. The vesicle size of Ethosomes can be decreased to desire extend using sonication or extrusion method. Finally stored under refrigeration.[7]

Hot Method:

In this method phospholipid is dispersed in water by heating in a water bath at 400C until a colloidal solution is obtained. In a separate vessel ethanol and propylene glycol are mixed and heated to 400°C. Once both mixtures reach 400°C, the organic phase is added to the aqueous one. The drug is dissolved in water or ethanol depending on its hydrophilic/ hydrophobic properties. The vesicle size of Ethosomes can be decreased to the desire extent using probe sonication or extrusion method.[8]

Classification:

SR. NO.	INGREDIENS	ROLE	EXAMPLE
1.	Phospholipids	Act as the membrane-forming component of the Ethosomes.	Soya Lecithin, Phosphatidylcholine
2.	Alcohol	A key component that enhances skin penetration by reducing the rigidity of the lipid bilayer and increasing the fluidity of the skin's stratum corneum.	Ethanol
3.	Gelling Agent	Converts the liquid Ethosomes dispersion into a gel.	Carbopol, Hydroxypropyl Methylcellulose (HPMC), Sodium Alginate
4.	Preservatives	To prevent microbial contamination.	Methylparaben, Propylparaben
5.	pH Adjuster	To adjust the pH of the gel for skin compatibility and optimal gel formation.	Triethanolamine
6.	Stabilizers	To ensure the stability of the formation , such as antioxidants	Ascorbic acid
7.	API	The therapeutic agent intended for transdermal delivery, such as a drug or a bioactive compound.	
8.	Vehicle	Acts as the solvent and medium.	Distilled water, purified water

Table no.1: Classification of ethosomal gel

Mechanism of Ethosomal Gel Drug Delivery:

The mechanism of drug delivery using ethosomal gels is primarily based on the unique properties of Ethosomes and the benefits of transdermal drug delivery systems. The mechanism involves several key stages:

1. Penetration Enhancement through Ethanol:

Ethanol plays a crucial role in the mechanism of drug delivery from ethosomal gels. The high concentration of ethanol in the ethosomal gel reduces the structural integrity of the stratum corneum, which is the outermost layer of the skin. This disruption of the skin's lipid structure facilitates the permeation of Ethosomes and, consequently, the entrapped drug into the deeper layers of the skin or even the bloodstream for systemic circulation.

- **Skin Permeation**: The ethanol acts as a penetration enhancer by altering the lipid bilayer of the stratum corneum, increasing its permeability. It disrupts the tightly packed lipids in the skin, allowing the ethosomal vesicles to more easily penetrate through the skin barrier and release the drug.
- **Vesicle Fusion**: Once Ethosomes come in contact with the skin, they can undergo fusion with the skin's lipid layers. This process helps deliver the drug to the targeted site more effectively.[9]

2. Enhanced Drug Diffusion:

The ethosomal gel system is designed to allow for a controlled release of the drug. The gel matrix ensures that the drug is released slowly over time, preventing rapid degradation and maximizing therapeutic effects. The lipid bilayer of the Ethosomes, along with the gel matrix, governs the rate of drug release, ensuring a prolonged therapeutic effect.

The drug is initially encapsulated within the ethosomal vesicles, and as the gel is applied to the skin, the vesicles slowly release the drug into the skin layers. This ensures both localized action at the site of application and, if necessary, systemic absorption.

3. Vesicular Drug Delivery and Retention in the Skin:

Once the ethosomal gel is applied to the skin, the vesicles are able to reach the deeper layers of the skin due to their small particle size and the presence of ethanol. Ethosomes can interact with the skin cells and, through their lipid bilayer, may fuse with the cell membrane, allowing the drug to enter the cell. This vesicular drug delivery mechanism enhances the retention of the drug within the skin or can promote systemic absorption for drugs requiring circulation. Additionally, the gel base helps the Ethosomes adhere to the skin for a longer period, thereby ensuring a prolonged drug release.

4. Controlled Drug Release:

The gel matrix plays an essential role in controlling the release rate of the drug. It ensures that the Ethosomes do not release the active ingredient too quickly, thereby providing a sustained release profile. This controlled release can be particularly beneficial for drugs that need to maintain constant plasma levels for therapeutic efficacy or for drugs that require prolonged skin exposure (e.g. treating chronic skin conditions).

5. Therapeutic Outcomes:

The mechanism of ethosomal gel delivery ensures improved bioavailability, localized treatment, and systemic absorption for drugs that may not otherwise be effectively delivered via other routes. The penetration enhancement via ethanol allows drugs to bypass the skin's barrier, reaching deeper layers of the skin or entering the bloodstream for systemic effects.[10]

Challenges in the development of ethosomal gels:

Here is a detailed list of challenges faced in the development of ethosomal gels for transdermal drug delivery, along with corresponding references for further reading:

1. Stability Issues

- **Vesicle Instability**: Ethosomal .s can suffer from vesicle aggregation, size instability, or drug leakage over time, which can reduce the effectiveness of the drug delivery system.
- **Ethanol Evaporation**: Ethanol plays a crucial role by enhancing skin penetration. However, its volatility can lead to changes in the ethosomal structure.

2. Skin Irritation

- **Ethanol-Induced Irritation**: Ethanol, although essential for enhancing the permeation of drugs across the skin, can cause skin irritation, dryness, or even allergic reactions in some individuals. This poses a significant concern for long-term or daily use of ethosomal gels.

3. Drug Release Control

- **Sustained Drug Release**: Achieving a controlled release of the drug over a prolonged period is one of the most significant challenges. The ethosomal vesicles must be combined with a gel matrix that facilitates a steady release rate. This becomes difficult when trying to balance the gel's viscosity with the ethosomal structure.

4. Scalability of Production

- **Manufacturing at Scale**: The preparation of Ethosomes typically requires high-pressure homogenization or ultrasonication**,** which are not easy to scale up for large-scale manufacturing. This presents challenges in uniformity**,** drug encapsulation efficiency, and maintaining consistency in product quality during large-scale production.

5. Regulatory and Quality Control Challenges

- **Regulatory Approval**: Given that ethosomal gels are a relatively novel drug delivery system, obtaining regulatory approval can be complex. Regulatory bodies such as FDA or EMA require comprehensive documentation on safety**,** efficacy, and quality, including detailed clinical data and toxicity studies, which can be costly and time-consuming.[(11)]

6. High Manufacturing Costs

- **Cost of Raw Materials**: The phospholipids, ethanol, and other ingredients required for ethosomal gels can be expensive. This, coupled with the specialized equipment required for production, can lead to high manufacturing costs, which may hinder the commercial viability of Ethosomes, especially for mass-market applications.

7. Limited Drug Selection

- **Incompatibility with Hydrophilic Drugs**: Ethosomal systems are particularly effective for lipophilic drugs but face challenges with highly hydrophilic drugs. The encapsulation efficiency of hydrophilic drugs is generally lower in Ethosomes, limiting the range of drugs that can be effectively incorporated into the gel.

8. Ethosomal Gel Viscosity and Compatibility

- **Viscosity Issues**: The gel matrix's viscosity must be optimized to ensure that the ethosomal vesicles are uniformly dispersed without compromising the drug release rate. If the gel is too thick, it may slow down drug release, and if it is too thin, it may cause rapid drug release, leading to a loss of controlled delivery.

9. Ethosomal Gel Penetration Issues

- **Penetration Enhancement**: While ethanol helps in skin penetration, excessive ethanol concentration may not always be beneficial, as it can disrupt the skin barrier excessively, causing toxicity. Balancing the ethanol concentration to enhance penetration without causing damage remains a challenge.[12]

Evaluation of Ethosomal Gel:

Sr. No.	Parameter	Importance	Method
1.	Vesicle size and shape	Determine Skin penetration and stability.	SEM, TEM, DLS
2.	Zeta potential	Stability of vesicle	Zeta meter
3.	Entrapment efficiency	Suitability of method	Ultracentrifugation
4.	Drug content	Important in decinding the amount of vesicle preparation to be used.	UV, HPLC
5.	Stability studies	To determine shelf life of vesicle.	SEM, TEM, HPLC
6.	In-vitro dissolution	Determine drug release rate from vesicle.	Franz diffusion cell

Table no.2: Evaluation of Ethosomal Gel[16]

Characterization of Ethosomal Gel:

- **Particle Size**: A critical parameter that affects the penetration ability of Ethosomes. Particle size is usually measured using Dynamic Light Scattering (DLS).
- **Zeta Potential**: Determines the stability of the ethosomal dispersion. A higher zeta potential usually correlates with improved stability of the ethosomal gel.
- **Entrapment Efficiency**: This measures the percentage of the active drug encapsulated within the ethosomal vesicles.[13]

1. **In-Vitro Drug Release Studies**: These studies are conducted to determine the release profile of the drug from the ethosomal gel. The diffusion rate can be measured using diffusion cells. Studies on drug diffusion or release were carried out utilizing a dialysis membrane. A dialysis tube with a molecular weight cutoff ratio of 12000–14000 Dalton was used. The membrane was sliced into a specific size and let soak in a buffer solution of pH 7.4 for 24 hours. The membrane can be activated by immersing it in a solution that causes the pores to open. The membrane's one side was knotted with thread once activated. Following the addition of 1 ml of the other edge of the dialysis membrane was knotted with the aid of thread to create a tiny size pocket. All six tests were identically put into the membrane pockets. The paddle of the USP paddle equipment was then used to secure these, containing pouches. 7.4 pH buffer was used as the release medium, and the temperature of the medium was maintained at 37°C throughout the process. All Baskets of the dissolution apparatus were filled to the mark. The equipment was used for 12 hours. At predetermined intervals, samples were collected, and a new medium was added in their place. Using a UV-visible spectrophotometer, samples were examined at 240 nm. The readings were taken in a triplicate manner and Calculated drug diffusion over time. Statistical kinetic models were employed to release data to ascertain the rate and mechanism of drug release. Higuchi, Korsmeyer Peppas, zero order, and first order models were used.

2. **Ex-vivo Permeation Analysis:** On the skin of the rats, the betamethasone-loaded ethosomal gel was allowed to permeate. For the investigation, male albino rats were chosen, and the abdomen skin was meticulously dissected. Male rats were chosen because they had less adipose tissue under their abdomen skin than female rats. Following the dissection, ethanol was used to wash away any adipose tissues that had stuck to the abdomen skin. Skin was stored in the refrigerator until it was needed for a test analysis. The Franz diffusion cell was used to conduct a permeation study in pH 7.4 buffer at 32 °C. The buffer was placed in the Franz cell, which had rat skin attached between the donor and receiver compartments so that the dermal layer of the skin faced the receiver medium. The test was done on the skin for 24 hours at a speed of 300 rpm using 0.5 g of the test sample. At regular intervals, 2ml of each sample was removed from the receiver chamber and replenished with fresh buffer. The control sample underwent the same process. A gel containing 0.05% of the drug was mixed immediately to create the control. The penetrated medication was examined using a UV-visible photometer in triplicate on both the test and control samples. Results were plotted against the amount of cumulative medicines that soaked via rat skin over time. The enhancement ratio of penetration was computed using the test sample's and the control sample's flux over the membrane. [14]

3. **Skin Permeation Studies**: These studies use Franz diffusion cells or other similar methods to evaluate the permeation of the drug through the skin.

4. **Stability Studies**: Stability tests are conducted to assess how well the ethosomal gel maintains its efficacy, appearance, and consistency over time under various environmental conditions (e.g. temperature, humidity).
5. **Rheological Studies**: To ensure that the gel has an appropriate viscosity for easy application, rheological measurements are performed to evaluate the flow behavior.
6. **In-Vivo Evaluation**: This includes assessing the pharmacokinetics of the drug, as well as skin irritation, histopathological examinations, and clinical efficacy. [15]

Parameters:

1. **Vesicle shape:** Ethosomes can be easily visualized by using transmission electron microscopy (TEM) and by scanning electron microscopy (SEM).

2. **Vesicle size and zeta potential:** Particle size of the Ethosomes can be determined by dynamic light scattering (DLS) and photon correlation spectroscopy (PCS). Zeta potential of the Ethosomes can be measured by Zeta meter.

3. **Transition temperature:** The transition temperature of the vesicular lipid systems can be determined by using differential scanning calorimetry(DSC).

4. **Drug entrapment:** The entrapment efficiency of Ethosomes can be measured by the ultracentrifugation technique.

5. **Drug content:** Drug content of the Ethosomes can be determined using UV spectrophotometer. This can also be quantified by a modified high performance liquid chromatographic method.

6. **Surface tension measurement:** The surface tension activity of drug in aqueous solution can be measured by the ring method in Du Nouy ring tensiometer.[16]

Future aspects:

- **Enhanced Skin Permeation and Therapeutic Efficacy:** Ethosomal gels have demonstrated improved skin penetration, leading to enhanced therapeutic effects. For instance, studies have shown that quercetin-loaded ethosomal hydrogels exhibit significant anti-inflammatory activity, suggesting their potential in treating inflammatory skin conditions.[17]
- **Cosmetic and Dermatological Applications:** In the cosmetic industry, ethosomal gels are being explored for delivering active ingredients aimed at treating conditions such as acne, hair loss, and hyperpigmentation. Their ability to encapsulate various drugs, including retinoid and benzoyl peroxide, positions them as promising candidates for advanced skincare treatments.[18]
- **Treatment of Skin Disorders:** Ethosomes have shown promise in managing skin disorders like psoriasis. Recent research involved developing vitamin D3-loaded ethosomal gels, which demonstrated effectiveness against chronic skin conditions, highlighting their potential in dermatological therapies.[19]
- **Transdermal Vaccination:** Beyond therapeutic applications, ethosomal gels are being investigated for vaccine delivery. Studies have explored their use in percutaneous immunization, offering a needle-free alternative for vaccine administration and potentially improving patient compliance.[20]

Conclusion:

Ethosomal gel offer promising results in the development of an efficient, novel drug delivery system. Ethosomes, which are phospholipid based vesicular carriers, exhibit enhanced skin penetration, stability, and controlled drug release, making them an excellent choice for transdermal drug delivery.

Ethosomal gels suggest that can effectively incorporate drugs into a gel matrix, enhancing their bioavailability and therapeutic effect. Various parameters such as particle size, zeta potential, encapsulation efficiency, in vitro release, and skin permeation have shown that ethosomal gels possess superior performance compared to traditional drug delivery systems.

It was observed that a well-optimized ethosomal gel provides a high degree of stability, skin penetration, and controlled drug release over an extended period. These attributes are beneficial for chronic treatments and minimizing side effects. The texture, spreadability, and drug release kinetics of the gel also suggest that ethosomal gels can improve patient compliance due to their easy application and long-lasting effects.

In conclusion, ethosomal gel are a promising approach for enhancing drug delivery through the skin, offering advantages such as improved stability, enhanced drug permeation, and a controlled release profile. Ongoing research and development are expected to further optimize their potential for treating various dermatological conditions and improving patient outcomes.

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