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Review

Ethosomal Carriers: A Breakthrough in Skin Permeability and Drug Absorption

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ABSTRACT:

Delves into the evolving field of transdermal drug delivery, highlighting ethosomes as a breakthrough in overcoming the skin's natural barrier to drug absorption. Ethosomes are vesicular carriers enriched with high ethanol content, which enhances the penetration of drugs through the skin, leading to higher bioavailability compared to conventional liposomes. The article classifies ethosomes into three types: classical, binary, and transethosomes, each varying in composition to improve drug stability and skin interaction. Ethosomes are notable for their ability to carry a wide variety of drugs, including water-soluble, fat-soluble, and unstable compounds, with applications spanning pharmaceuticals, cosmetics, and biotechnology. Key benefits include improved patient compliance, enhanced drug efficacy, and a simpler production process. However, challenges such as potential skin irritation and the limited scalability of production remain. The article also explores the preparation methods and evaluates the clinical potential of ethosomes, with a focus on further research directions to optimize their use in therapeutic settings.

KEYWORDS: Ethosomes, Transdermal drug delivery, Skin permeability, Drug delivery system

INTRODUCTION

A popular issue in drug delivery research is transdermal drug delivery because of its simplicity, safety, and efficacy as a non-invasive method of administering medication. Better patient compliance, sustained and regulated release, decreased drug metabolism, and avoiding the first-pass impact associated with gastrointestinal absorption are just a few advantages it offers. However, transdermal administration of pharmaceuticals severely inhibits drug penetration and absorption due to the skin's natural barrier, thereby reducing the effectiveness of several medications. Researchers work to enhance medication permeability and absorption for efficient transdermal delivery in order to get over this restriction.

In recent years, the use of novel nanocarriers for drug delivery has shown enormous potential. Ethosomes form when a medicine and a carrier, typically alcohol or its derivatives, combine. The active alcohol component in this carrier offers superior permeability and drug loading capability compared to conventional liposomes. Ethosomes have demonstrated two primary benefits: they can easily adapt to a wide range of drug types, including unstable, fat-soluble, and water-soluble pharmaceuticals; additionally, they can enhance drug-skin interactions by enhancing drug penetration and absorption. Ethosomes can therefore improve drug stability while lowering systemic adverse effects and drug waste. Ethosomes also provide several advantages in the area of transdermal drug administration and might be used in a number of sectors, including the biotechnology, pharmaceutical, veterinary, cosmetic, and nutritional industries. Currently, medications make up the majority of the products marketed. One example is the Decorin cream, which is intended to address pigmentation and anti-aging concerns and is produced by Genomic Cosmetics, a company headquartered in Pennsylvania, USA. Topical medications Noicellex and Supravir were developed by Trima and Novel Therapeutic Technologies, respectively. The anti-cellulite cream Noicellex is made to increase the penetration of its active component, which increases its efficacy. Supravir is a cream that contains acyclovir, a drug that treats herpes infections by

rupturing lipids, while Cellutight EF is a topical anti-cellulite cream made by Hampden Health (USA). Through deeper skin penetration, the lotion's powerful blend of ingredients increases metabolic rates and reduces fat.
Ethosomes are a modern drug delivery technique used in the transdermal drug administration sector. This study's objective is to present a comprehensive analysis of the current status of the field's research. A significant portion of the review focuses on the many ethosome classifications, their underlying mechanisms, production processes, significant variables, and clinical research. During this discussion, we will examine the challenges and prospects associated with the development and improvement of ethosomes as a drug delivery system that can be applied topically. The aim of this research is to provide a comprehensive understanding of the literature on ethosome-based transdermal drug delivery while also offering insightful recommendations and ideas for further research in this area[1].

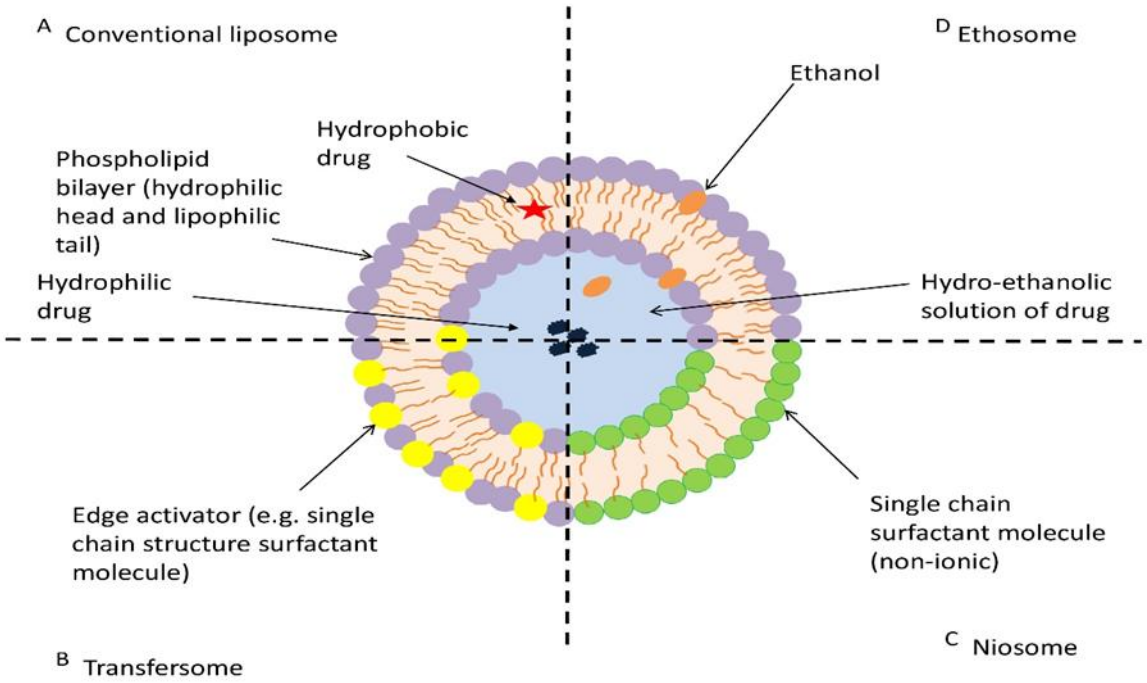

Fig.1 structure of Ethosome

TYPES OF ETHOSOMES

shows the three different kinds of ethosomal systems, which are categorized according to their compositions.

1. Classical Ethosomes

The components of classical ethosomes, a type of liposome, include water, phospholipids, and a significant amount of ethanol (up to 45% w/w). The smaller size, negative ζ-potential, and increased entrapment effectiveness of classical ethosomes made them superior to classical liposomes for transdermal drug delivery. In addition, classical ethosomes outperformed classical liposomes in terms of skin penetration and stability profiles. 6 to 8. Between 130.077 Da and 24 kDa, the molecular weights of medications trapped in traditional ethosomes have varied[2].

2. Binary Ethosomes

Binary ethosomes are created by improving on conventional ethosomes by substituting a combination of ethanol and propylene glycol for single ethanol throughout the production process. As a result, there is less ethanol and less volatility, which improves medication solubility, formulation stability, and drug penetration. Binary ethosomes were created by numerous researchers in an effort to improve skin penetration and formulation stability. As an illustration, Wu et al. made ethosomes, transfersomes, and binary ethosomes with terbinafine hydrochloride. A 7:3 (w/w) mixture of ethanol and propylene glycol was shown to be the most effective binary ethosome for improving medication penetration through the skin. Furthermore, when rhodamine B was administered via binary ethosomes as opposed to ethosomes plus transfersomes, it demonstrated a higher depth of penetration and fluorescent intensity. Binary ethosomal soy lecithin and binary combination (1:1) gel and ethosomal gel formulations of triamcinolone. These vesicles demonstrated higher zeta potential, EE ethosomal gel, and better Rhoamine B penetration than the reference[3].

3. Transethosomes

Song et al. initially described transethosomes, the newest class of ethosomal systems, in 2012. This ethosomal system contains an additional molecule along with the basic components of regular ethosomes, such as a penetration enhancer or edge activator (surfactant). In an effort to create transethosomes, these innovative vesicles were created by combining the benefits of deformable liposomes (transfersomes) and traditional ethosomes into a single composition. Transethosomes have been found to have better qualities than standard ethosomes by numerous researchers. Various kinds of penetration enhancers and edge activators have been studied in an effort to create ethosomal systems with improved properties. It has been reported that transethosomes can ensnare medications with molecular weights between 200 and 325 kDa and 130.077 Da[4].

ADVANTAGES OF ETHOSOMES[5]

1. The presence of enzymes improves the effectiveness of drug delivery through the skin, transdermal application, and intracellular delivery.
2. Offer a variety of macromolecules with unique physicochemical properties, such as proteins, peptides, hydrophilic and lipophilic compounds, etc.
3. The components of ethosomes are approved for use in pharmaceutical and cosmetic applications and are generally recognized as safe (GRAS) and non-toxic.
4. The toxicological profiles of the ethosome features are well-established in the scientific literature; hence, there is no risk associated with the large-scale pharmacological production of ethosome structures.
5. Due to its passive and non-invasive nature, the ethosomal system could be commercialized right away.
6. Ethosomal drug delivery methods can make a significant contribution to the veterinary, pharmaceutical, biotechnology, cosmetic, and nutraceutical industries.
7. Excellent patient adherence: Patients adhere to treatment plans when ethosomal medicine is applied as a gel or cream.
8. Unlike sonophoresis, iontophoresis, and other more complex methods, this is a simple drug delivery method.
9. Ease of industrial scale-up: Ethamome production is quite simple and doesn't require expensive technical inputs. Multiliter preparation of amounts is helpful for ethosomal formulation.
10. Etherosomes let medications absorb through the skin more efficiently, allowing them to enter the bloodstream or reach the targeted area of the skin.
11. It has been demonstrated that drugs are more effective at trapping than liposomes.
12. Over long periods of time, there is outstanding stability.
13. Since the alcohol in ethosomes serves as a natural preservative, no additional preservative is needed.

DISADVANTAGES OF ETHOSOMES[6]

1. If a patient is allergic to any ethosomal component, including ethanol, an allergic reaction can be detected.
2. Ethosomal carriers are crucial mainly for transdermal administration, in contrast to other carriers (solid lipid nanoparticles, polymeric nanoparticles, etc.) that can be utilized for a number of routes.
3. Ethanol must be prepared, applied, transported, and stored with sufficient prudence due to its propensity for burning.
4. Very low yield; possibly not economical.
5. Product loss during the transition from water to organic media.
6. It is limited to potent substances that require one or fewer doses per day.
7. Ethosomal administration frequently attempts to create steady, continuous drug delivery rather than speedy drug input in the form of a bolus.
8. To promote cutaneous microcirculation and vascular access, medications should be sufficiently soluble in both lipophilic and aqueous environments.
9. The size of the drug's molecules must be suitable for skin absorption..
10. Not every type of skin will react favorably to adhesive.
11. Excipients and penetration enhancers used in drug delivery systems can induce dermatitis or skin irritation.
12. Insufficient shell locking can cause ethosomes to cluster and disintegrate in water.

COMPOSITION OF ETHOSOMES

Phospholipids: The vesicular structure and other properties may be impacted by the type and amount of phospholipid used.Eggs and soy provide phosphatidylcholine, which is mostly used in lecithins. The size, Zeta potential, penetrating ability, and stability of the vesicles may also be impacted by changes in the source. Used soy phosphatidyl choline, phospholipon 90H, and phospholipon 80H to get a result that showed the phospholipid source had a major impact on ethosomal size and vesicular entrapment efficiency. According to Shen's research, vascular stability was considerably enhanced by a higher phospholipid concentration. The component's ideal range is determined to be 0.5% to 5%.When concentration increased, it was discovered that the size increased moderately to slightly. Only up to a certain point is this pattern of increasing size apparent. Phospholipid concentration increases entrapment efficiency up to a certain point, after which there are no more impacts observed[7].

Alcohol:

1. Ethanol: An effective penetration booster is ethanol. It is essential to ethosomal systems because it gives the vesicles special properties like size, potential, stability, entrapment efficiency, and enhanced skin permeability. It has been found that the range of ethanol concentrations in ethosomal systems is 10% to 50%. Numerous researchers have discovered that the size of the ethosomes will decrease as the formulation's ethanol concentration rises[8].

2. Propylene glycol: The penetration enhancer PG is widely used. When used to generate binary ethosomes at concentrations ranging from 5% to 20%, it has been shown to affect the ethosomal attributes of size, entrapment efficiency, permeability, and stability. Particle size is significantly decreased in ethosomal systems when PG is added as opposed to when it is not. PG is thought to improve viscosity and have antihydrolysis properties, which promotes ethosome stability[9].

3. Isopropyl alcohol: Dave and colleagues investigated how isopropyl alcohol affected the effectiveness of skin penetration and entrapment of ethosomes loaded with diclofenac. According to the results, IPA significantly impacted entrapment effectiveness but had little influence on drug release. Additional research is necessary to assess how IPA or other alcohols affect other aspects of the ethosomal system[10].

Cholesterol: Cholesterol plays a key role in ethosomal systems by enhancing the stability and drug entrapment efficiency of the vesicles. It works by reducing vesicular permeability, preventing fusion between vesicles, and minimizing leakage of the entrapped drug. Typically used in concentrations below 3%, cholesterol has been incorporated into certain formulations at much higher concentrations, even up to 70% relative to the phospholipid content. Studies have consistently shown that adding cholesterol increases vesicle size, with one study by López-Pinto et al. demonstrating that 25.87 mM of cholesterol increased ethosomal size from 136±42 nm to 230±27 nm. Another study reported a size increase from 102±13 nm to 152±12 nm when the cholesterol concentration was raised from 0% to 0.15% w/w.

However, there are varying reports on cholesterol's impact. While most research highlights the stabilizing effects of cholesterol, one study found no significant stabilizing impact when using 15% ethanol and phosphatidylethanolamine in the ethosomal formulation. In most cases, though, cholesterol has been found to improve vesicular hardness and durability. Despite these advantages, the increased rigidity can come with a downside. In vitro studies using Franz diffusion cells and confocal laser-scanning microscopy have shown that the stiffer ethosomal vesicles struggle to penetrate the stratum corneum, reducing the efficiency of drug delivery through the skin. Other studies have also noted that cholesterol makes vesicles less elastic, which may further limit the effectiveness of transdermal drug delivery systems. Therefore, while cholesterol significantly enhances the structural integrity of ethosomes, its impact on flexibility and permeability must be carefully considered in drug delivery formulations[11,12].

Dicetyl phosphate: In order to improve the stability of the system by preventing vesicle aggregation, diethyl phosphate is frequently added to ethosomal formulations at concentrations ranging from 8% to 20% of the total phospholipid content. Research has demonstrated that this addition produces vesicles with a noticeably negative ζ-potential, but it is still unclear how it will affect other ethosomal system properties[13].

Penetration enhancers/edge activator: Drug penetration is a key element of topical pharmaceutical administration techniques. The transethosomal preparation has the highest success rate for this type of delivery,

despite the fact that there are several ethosomal systems available. Unlike the conventional ethosomes, they use particular extra components called edge activators or penetration enhancers[14].

Oleic acid: The stratum corneum becomes more fluid and more effective at regulating vesicle size, elasticity, zeta potential, and skin permeability when oleic acid is present. When used at a modest concentration of 0.5%, it frequently enhances penetration. Better skin penetration, better drug disposition in the rat dermis and epidermis, and a negative zeta potential were seen in transethosomes containing oleic acid[15].

Tweens and spans: Tween 80 was usually used at a concentration between 10 and 50 percent of the total phospholipids used. It was claimed to enhance the stability and skin penetration qualities of the system while also reducing the size of the vesicles. Because of their solubilizing properties and innate ability to prevent vesicle fusion, the main mechanism has been clarified. A study found that transethosomes made with Tween 20 had ethosomes that were smaller, better at trapping, and penetrated human skin more effectively ex vivo than those made with Tween 80.The optimum ingredient for creating transethosomes with caffeine and vitamin E was found to be Span 20[16].

Polyethylene glycol 4000: Transethosomes containing mycophenolic acid have been demonstrated in experiments to significantly increase vesicular size while having no appreciable impact on other characteristics like permeability, entrapment efficiency, or vesicular stability[17].

L-menthol: These penetration enhancers have reportedly been used in transethosomes with 5% ascorbic acid.Through a human skin cadaver, it showed a more consistent release pattern and increased the drug's release rate. In comparison to the case of conventional ethosomes, a larger release of 36.5% was achieved after 24 hours. The increased release is caused by the eutectic mixture that forms between the medication and L-menthol, which alters the barrier characteristics of the stratum corneum layer and improves the drug's solubility[18].

MECHANISM OF DRUG PENETRATION:

Uncertainty surrounds the mechanism of medication absorption from ethosomes. The two phases listed below are probably when the drug is absorbed.

Ethanol Effect: Through the skin, ethanol improves permeation. Its penetration-enhancing action mechanism is well understood. Ethanol enters intercellular lipids, increases their fluidity, and lowers the density of the lipid multilayer that makes up the cell membrane[19].

Ethosomes Effect: The ethanol in ethosomes enhances the lipid fluidity of cell membranes, which in turn promotes skin permeability. So, the ethosomes easily enter the deep layers of the skin, where they combine with the lipids in the skin to release the drugs[20].

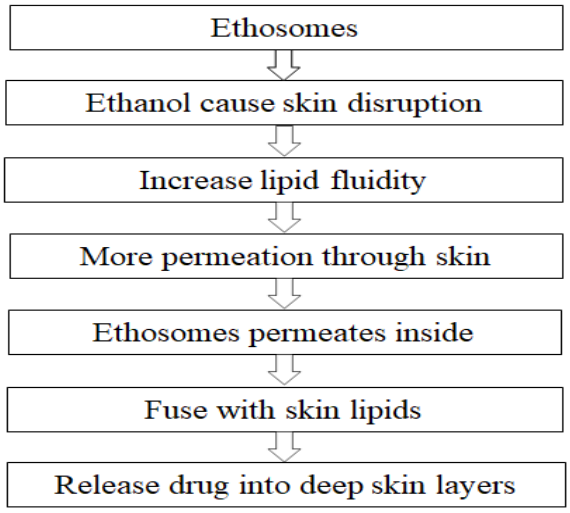

Fig.2 Mechanism of Ethosomes[21]

METHODS OF PREPARATION :

Ethosome preparation is based on quick and easy scale-up techniques that don't require complex instruments at the pilot and industrial levels. Ethosomes are prepared in two fundamental cold and hot methods.

Cold Method: The method most commonly employed to manufacture ethosomal formulation is this one. In a covered vessel at room temperature, phospholipid, medicine, and other lipid ingredients are dissolved in ethanol

using a mixer and rapid shaking. Another polyol, such as propylene glycol, is added while stirring. Heat this mixture to 300 °C in a water bath. The water heated to 300 °C in another vessel is added, and the mixture is covered and stirred for five minutes. The vesicle size of the ethosomal formulation can be decreased to the required degree by using the sonication or extrusion techniques. Lastly, the mixture is refrigerated for storage[22].

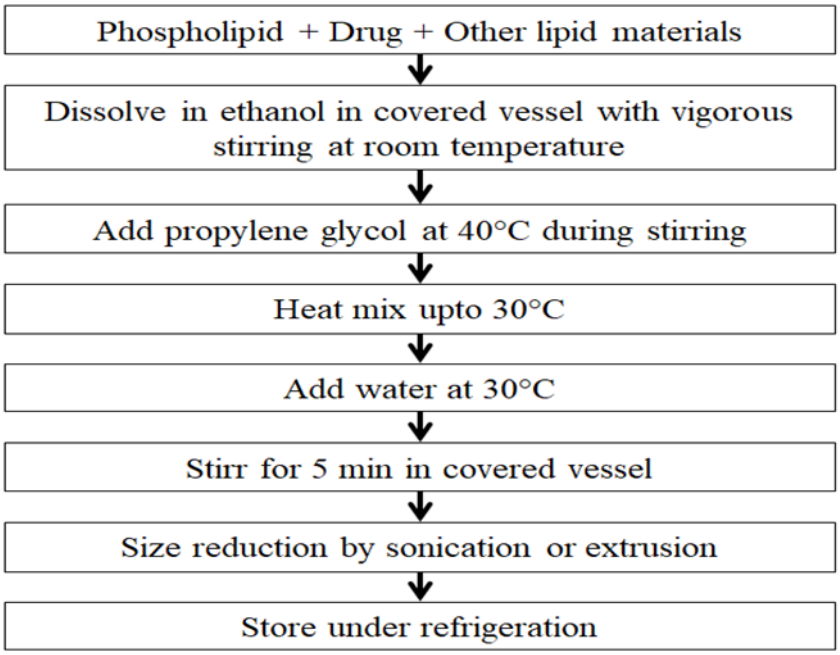

Fig.3 Cold Method

Hot Method: By heating it to 400°C in a water bath, phospholipid is dissolved in water and a colloidal solution is created. In a separate tank, propylene glycol and ethanol are mixed and heated to 400 °C. When the temperature of both solutions reaches 400 °C, the organic phase is added to the aqueous phase. Either water or ethanol will dissolve the medication, depending on whether it is hydrophilic or hydrophobic. The vesicle size of the ethosomal formulation can be decreased to the required extent by using the extrusion method or probe sonication[23].

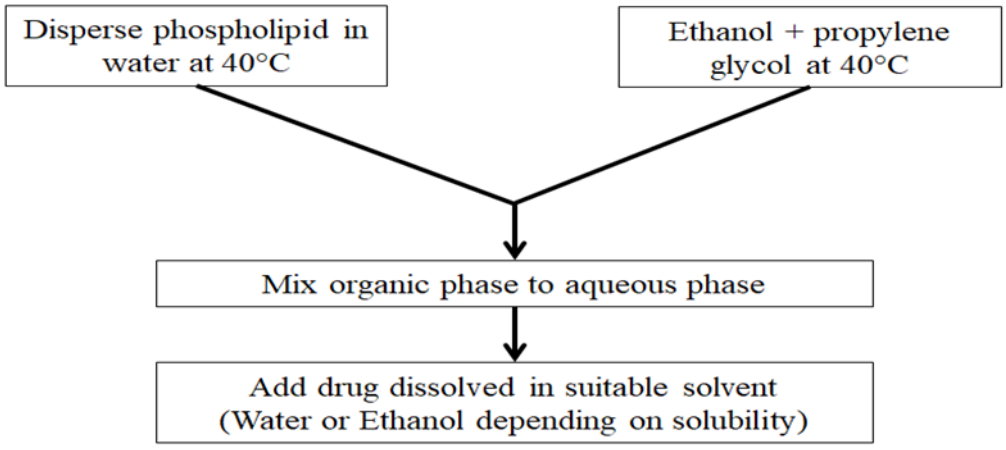

Fig.4 Hot Method

Classic Method: After dissolving the drug and phospholipid in ethanol, the mixture is heated to 30°C±1°C in a water bath. The lipid mixture is constantly spun at 700 rpm while being introduced to double-distilled water in a fine stream in a closed vessel. A manual extruder is used to force the resultant vesicle solution through a polycarbonate membrane three times in order to homogenize it[24].

Mechanical dispersion method: Methanol and chloroform are used to dissolve soy phosphatidylcholine in a round-bottom flask (RBF). A rotary vacuum evaporator is used to extract the organic solvents above the lipid transition temperature in order to produce a thin lipid coating on the RBF wall. Finally, the contents are placed under vacuum for an entire night in order to remove any remaining solvent mixture from the formed lipid layer. The RBF is spun at the right temperature to produce hydration with varying amounts of a hydroethanolic combination, including medication[25].

CHARACTERIZATION OF ETHOSOMES:

1. Size and Shape Analysis: The average size of ethosomes was ascertained through microscopic examination. We diluted a sample of ethosomes with distilled water such that individual vesicles could be seen. A drop of the diluted solution was placed on a glass slide covered with a cover slip and observed under a microscope (magnification: 15 × 45 X). A calibrated ocular micrometer with a stage micrometer was used to randomly determine the sizes of 150 vesicles[26].

The formula Average diameter (dav) = nd/n was used to determine the average diameter.

where n and d stand for the number and dimension of the vesicles, respectively.

2. Surface Morphological Study: We used a computerized inspection system to determine size and size distribution using dynamic light scattering (DLS). A drop of the material was placed on a carbon-coated copper grid to evaluate the surface morphology for TEM. The material was negatively stained with a 1% phosphotungustic acid aqueous solution after 15 minutes. A transmission electron microscope was used to analyze the samples once the grid had completely dried by air. Additionally, a drop of ethosomal system was placed on a clear glass stub, allowed to air dry, and then coated with Polaron E 5100 Sputter coater before being observed under a scanning electron microscope (SEM) to characterize the surface morphology of the ethosomal vesicles[27].

3. Entrapment efficency: Ultracentrifugation was used to measure the entrapment effectiveness of Etodolac by ethosomal vesicle. Ten milliliters of ethosomal formulation were vortexed for two cycles of five minutes each, with two minutes of rest in between. Fresh untreated ethosomal formulations and 1.5 ml of each vortexed sample were transferred into separate centrifugal tubes. For three hours, these materials were centrifuged at 20,000 rpm. The drug content in both vortexed and unvortexed samples was measured at 206 nm after the supernatant layer was removed and appropriately diluted with water[28].

This is how the entrapment efficiency was determined:

$$\%\ Entrapment\ Efficiency = \frac{Total\ drug - Free\ drug}{Total\ drug} \times 100$$

4. In Vitro Release: Franz-diffusion cells were used to conduct in vitro release tests on ethosomal preparation. The receptor compartment held 15 milliliters. There was a 1.43 cm gap between the donor and receptor compartments. The donor and receptor compartments were separated by a cellophane membrane used for dialysis. One side of the dialysis membrane was covered with a weighed quantity of ethosomal preparation. The pH 6.8 phosphate saline buffer served as the receptor medium. A water jacket was placed around the receptor chamber to keep the temperature at 37±10C. Heat was supplied via a magnetic stirrer attached to a thermostatic hot plate. The receptor fluid was stirred with a magnetic stirrer that was connected to a Teflon-coated magnetic bead. To stir the receptor fluid, a Teflon-coated magnetic bead was fastened to a magnetic stirrer. Every sampling interval, samples were removed and swapped out with equal volumes of fresh receptor fluid. At 206 nm, the extracted materials were analyzed using spectrophotometry[29].

5. In vitro permeation studies: It was determined how well ethosomal formulations of ethosolac penetrated using a Franz diffusion cell. The mice's shaved abdominal skin (2.17 cm of exposed surface area, 0.5±0.1 mm thick) was placed on the receptor compartment with the stratum corneum side facing up toward the donor compartment. A magnetic bar was used to spin 15 milliliters of pH 6.8 phosphate buffer, which was maintained at 33.8 °C, at 600 rpm within the receptor compartment. After applying one milliliter of the ethosomal formulation to the skin, the top of the diffusion cell was covered with paraffin paper. To maintain sink conditions, 1 milliliter aliquots of the receptor medium were taken at the specified intervals (0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, and 24 hours) and quickly replaced with an equivalent volume of fresh receptor solution. Following extraction, the materials were analyzed using spectrophotometry at 206 nm[30].

6. Transition temperature: When we talk about the transition temperature in ethosomes, we usually mean the temperature at which the lipid bilayer, which is primarily made up of phospholipids, changes from a gel (solid-ordered) state to a liquid-crystalline (liquid-disordered) state. Because it influences the fluidity and permeability of ethosomal vesicles, two properties essential to their role as drug delivery systems, this transition temperature is significant.

Lipid-based carriers called ethersomes change the characteristics of their bilayer by incorporating ethanol into their structure. Ethanol increases the vesicle membrane's fluidity and improves its capacity to encapsulate and transport medications through the skin by lowering the transition temperature of the phospholipids in ethosomes[31].

7. Drug content: Evaluate the drug content in ethosomes, two commonly used techniques are UV spectrophotometry and modified high-performance liquid chromatography (HPLC).

a. UV Spectrophotometer Method:

- Ethosomes containing the drug are disrupted using a solvent such as ethanol or methanol to release the drug.
- After suitable dilution, the absorbance of the drug is measured using a UV spectrophotometer at a specific wavelength characteristic of the drug.
- A calibration curve with known concentrations of the drug is used to quantify the drug content in the ethosomal formulation[32].

b. Modified High-Performance Liquid Chromatography (HPLC):

- HPLC involves separating the drug from the ethosomal formulation using a mobile phase (a mixture of solvents) and a stationary phase (usually a column with specific packing material).
- The method is modified to accommodate the nature of ethosomes, which contain lipids and phospholipids.
- The drug is detected by a UV detector or another suitable detector after separation, and its concentration is determined by comparing it with a calibration curve of the pure drug[32].

EVALUATION OF ETHOSOME:

1. TEM and SEM analysis of the vesicle-skin contact process: Transmission electron microscopy was used to investigate ultra-thin animal sections that were cut using Ultracut (Vienna, Austria), collected on formvar-coated grids, and evaluated. Adhesive tape was utilized to mount the dehydrated skin slices on stubs for SEM analysis, and a fine-coat ion sputter coater was employed to apply a coating of gold palladium alloy. An electron scanning microscope was used to analyze the sections[33].

2. Scanning electron microscopy analysis of the filter membrane-vesicle interaction: A 50 nm-pore filter membrane was covered with 0.2 mL of vesicle suspension and placed into diffusion cells. PBS (phosphate buffered saline solution), which has a pH of 6.5, was in contact with the lower side of the filter while the upper side was left exposed to the atmosphere. After an hour, the filters were removed and fixed overnight at 4°C in Karnovsky's fixative. To get them ready for SEM studies, they were then dehydrated using graded ethanol solutions (30%, 50%, 70%, 90%, 95%, and 100% vol/vol in water). After that, the filters were gold-coated and examined using an SEM[34].

3. Investigation of vesicle-skin contact using fluorescence microscopy: TEM and SEM studies were carried out using the same methodology as fluorescence microscopy. A fluorescence microscope was used to examine the 5-µm thick sections of paraffin blocks that had been cut with a microtome (Erma optical works, Tokyo, Japan). tiny The cytotoxicity To produce MT-2 cells (Tlymphoid cell lines), Dulbecco's modified Eagle media (HIMEDIA, Mumbai, India) was utilized. It contained 10% fetal calf serum, 100 U/mL penicillin, 100 mg/mL streptomycin, and 2 mmol/L Lglutamine. The culture was conducted at 37°C with 5% CO2. To demonstrate cytotoxicity, the cytotoxic dose 50 (CD50) was employed, which resulted in a 50% reduction in absorbance at 540 nm[35].

4. Skin permeation studies: The test animals' (rats') hair was carefully clipped to less than 2 mm with a pair of scissors, and the skin of the abdomen was cut off from the underlying connective tissue with a knife. Following the removal of the skin, it was spread out on aluminum foil, and any leftover fat or subcutaneous tissue was gently scraped away. Effective permeation areas were 10 mL for receptor cell volumes and 1.0 cm2 for diffusion cell volumes. An even temperature of 32°C ± 1°C was kept. The receptor compartment was filled with 10 milliliters of phosphate-buffered saline solution (pH 6.5). Between the donor and receptor compartments was

skin that had been removed. The epidermis of the skin received a 1.0 mL application of the ethosomal formulation. The epidermis of the skin received a 1.0 mL application of the ethosomal formulation. At 1, 2, 4, 8, 12, 16, 20, and 24-hour intervals, 0.5 mL of samples were extracted using the diffusion cell sampling ports and high-performance analysis assays for liquid chromatography[36].

5. HPLC Assay: The amount of medication that entered the receptor compartment in MT-2 cells was measured using the HPLC assay, and in vitro skin penetration tests were also employed[37].

6. Drug uptake studies: Following the addition of 100 µL of RPMI medium, 24-well plates (Corning Inc.) were used to test the drug's absorption into MT-2 cells (1×106 cells/mL). The drug content was measured using an HPLC technique to evaluate drug absorption after incubation with 100 µL of the drug solution in either ethosomal formulation, commercial formulation, or phosphate buffered saline solution (pH 7.4)[38].

7. Statistical analysis: All of the generated data were evaluated for statistical significance using the studentized range test and ANOVA. The PRISM software (GraphPad, Version 2.01, San Diego, CA) was used to analyze the results, and a P <.05 confidence level was used[39].

APPLICATION OF ETHOSOMES:

1. Delivery of Anti-Viral Drugs: Antiviral substance that targets the human immunodeficiency virus. Ethosomes may lengthen the release, boost the transdermal flow, etc. The zidovudine[40].

2. Delivery of Anti-Arthritis Drug: Recently, a medication candidate called cannabidol (CBD) was created to treat rheumatoid arthritis. Lodzki et al. created a CBDethosomal formulation for transdermal administration. The results indicate a significant increase in its skin penetration and, consequently, its activity[41].

3. Cosmaceutical Applications of Ethosomes: Ethosomes are used in cosmetics not only to increase the stability of the chemicals and lessen skin irritation from the irritating chemicals but also to provide percutaneous sweetening, especially in the stretchy forms. However, the most important considerations for obtaining these advantages of elastic vesicles for cosmetic applications are their compositions and sizes[42].

4. Delivery of Antibiotics: Ethosomes quickly pierce the epidermis, deliver a sizable quantity of medications to the skin's deeper layer, and stop infections at their source. Ethamomal formulations loaded with erythromycin and bacitracin were created for both cutaneous and intracellular delivery, and investigations showed that the ethosomes penetrated the cell membrane and liberated the drug molecules that were trapped inside the cells[43].

5. Delivery of Anti-Parkinsonism Agent: Trihexyphenidyl hydrochloride (THP) was given an ethosomal formulation by Dayan and Touitou, who then contrasted its administration with that of a traditional liposomal formulation. THP is an antagonist of M1 muscarinic receptors and is used to treat Parkinson's disease. According to the results, the ethosomal-THP formulation had a better ability to penetrate the skin and might be a more effective treatment for Parkinson's disease[44].

6. Delivery of problematic drug molecules: Large biogenic molecules like insulin and peptides or proteins are difficult to administer orally since the GIT tract totally breaks them down; transdermal distribution is a superior option. However, the traditional transdermal delivery of biogenic molecules, including insulin and proteins or peptides, has a low penetration rate. When these substances are converted into ethosomes, their penetration and therapeutic effectiveness are significantly enhanced. [45].

Conclusion: The conclusion of the article emphasizes the promising role of ethosomes as an advanced and effective system for transdermal drug delivery. Ethosomes offer numerous advantages, including improved drug penetration, higher bioavailability, and enhanced stability for various types of drugs, such as water-soluble, fat-soluble, and unstable compounds. These vesicles demonstrate significant potential in diverse fields, including pharmaceuticals, cosmetics, and biotechnology. However, some challenges remain, such as potential skin irritation, limited scalability, and the need for further optimization in formulation. The article suggests that, with continued research and development, ethosomes could further revolutionize transdermal drug delivery, improving therapeutic outcomes and patient compliance. Future research should focus on overcoming current limitations and expanding the applications of ethosomal systems for broader clinical use

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