Journal of Biomedical and Pharmaceutical Research
Available Online at www.jbpr.in
CODEN: - JBPRAU (Source: - American Chemical Society)
NLM (National Library of Medicine): ID: (101671502)
Index Copernicus Value 2022: 83.05
Volume 13, Issue 6: 2024, 79-84
Review Article
ISSN (Online): 2279-0594
ISSN (Print): 2589-8752

Preparation and Characterization of Ethosomal Gel Drug Delivery; A Comprehensive Review

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Article Info: Received: 10-10-2024 / Revised: 14-11-2024 / Accepted: 28-11-2024
Corresponding author: Neeru Jain
DOI: https://doi.org/10.32553/jbpr.v13i6.1217
Conflict of interest statement: No conflict of interest

Abstract

Ethosomes are aqueous, phospholipid, and ethanol (in larger amounts) soft vesicles. Because it can penetrate human skin intact and has a high degree of deformability, this carrier has intriguing properties. Ethosomes have been demonstrated to improve medication delivery to the outer layers of the skin by penetrating the stratum corneum barrier more effectively than traditional liposomes. Ethosomal systems have been the subject of on-going study, which suggests that these carriers, in conjunction with penetration enhancers, may prove to be successful drug delivery vehicles in the form of gels, patches, and creams. However, more thorough research is required to advance the ethosomal system's stability. The goal of this review is to preparation and characterization of ethosomal gel drug delivery.

Key words: Ethosomes, Liposomes, Phospholipid etc.

Introduction

Ethosomes – Phospholipid nanovesicles called Ethosomes are utilized to transport chemicals both transdermally and topically. Touitou et al. (1997) created Ethosomes, which are further unique lipid carriers made of water, phospholipids, and ethanol. They are said to enhance the way different medications are delivered via the skin **[1]**. It is thought that the effective permeation enhancer ethanol works by altering the stratum corneum's intercellular area. Soft, pliable vesicles, Ethosomes are primarily made of water, phospholipids, and ethanol in relatively high concentrations. These soft vesicles are innovative carriers of vesicles for improved skin administration. Ethosomes vesicles can vary in size from tens of nanometers to microns. As a lipid carrier, Ethosomes have shown remarkable effectiveness in percutaneous medication delivery **[2].**

Additionally, they have better pharmaceutical qualities than conventional liposomes, such as room temperature stability, high trap performance, and improved compatibility with the SC. As a result, both hydrophilic and lipophilic medications can more easily pass through the stratum corneum (SC) and into the deep layers of the skin **[3]**.

Ethosome's Advantage: [3]

Deliver a range of molecules with distinct physicochemical characteristics, including

proteins, peptides, hydrophilic and lipophilic compounds, and other macromolecules.

The ethosomal system is appropriate for instant marketing since it is non-invasive and passive.

The pharmaceutical, biotechnology, veterinary, cosmetic, and nutraceuticals industries can all benefit greatly from the use of ethosomal drug delivery systems.

Drugs can more effectively penetrate the skin thanks to Ethosomes, which helps them get to the intended location in the skin or the blood.

Ethosome's Disadvantage: [3]

Ethosomal carriers are crucial just for transdermal application, in contrast to other carriers (solid lipid nanoparticles, polymeric nanoparticles, etc.) that may be employed for numerous routes.

Product loss while switching from organic to water medium.

Ethosomal administration is usually meant to give consistent, ongoing medication delivery rather than a quick drug intake in the form of a bolus.

Dermatitis or skin irritation brought on by medication delivery systems' excipients and penetration enhancers.

Planning, application, transportation, and storage all require extra caution since ethanol is combustible.

Ethosome's Types:-

Classical Ethosomes – A variant of classical liposomes, classical ethosomes are made up of water, phospholipids, and high ethanol concentrations (up to 45% w/w). Because they were smaller and possessed a negative ζ-potential for increased efficiency without clogging, classical ethosomes were said to be better than classical liposomes for transdermal medication administration. Furthermore, classical ethosomes showed better skin penetration and stability characteristics than classical liposomes. Drugs found in conventional ethosomes have molecular weights ranging from 130.077 Da to 24 kda **[3-4].**

Binary Ethosomes – Zhou et al. introduced binary ethosomes. In essence, we were made by combining the traditional ethosomes with another type of alcohol. The two most common ethosomes in binary alcohols are propylene glycol (PG) and isopropyl alcohol (IPA). **[20-21].**

Transethosomes – Song et al. (2012) made the first observation of transethosomes, the newest generation of ethosomal systems. The fundamental elements of traditional ethosomes are included in this ethosomal system, together with an extra substance like an edge activator (surfactant) or penetration enhancer. These innovative vesicles were created in an effort to create transethosomes by combining the benefits of traditional ethosomes with deformable liposomes (transfersomes) in a single recipe. Superior transethosomal qualities above conventional ethosomes have been observed by a number of studies. To improve the ethosomal systems' characteristics, various types of edge activators and penetration enhancers were studied. Drugs have been found to be entrapped by transethosomes with molecular weights ranging from 200–325 kda to 130.077 Da **[3-6].**

Ethosome's Compositions: - The composition of ethosomes can be used to categorize them. Propylene glycol (PG), phospholipids, ethanol, stabilizer, other alcohol, Isopropyl alcohol, edge activator (surfactant), penetration enhancer, Tweens and spans, Dicetyl phosphate, Stearylamine, oleic acid, l-menthol, Cremophor, Skin-penetrating and cell-entering peptide, charge inducer, water, and drug or agent are all present **[3-4].**

Ethosome's Methods: - Ethosomes preparation relies on rapid and simple scale-up methods that don't require any sophisticated pilot or industrial-level equipment. There are two basic "cold" and "hot" ways for preparing ether.

Cold Method – The phospholipids, medication, and other lipid components dissolve the ethanol when it is shaken vigorously at room temperature. After that, the jar is heated to 30 °C. This is known as the "cold approach" and is frequently employed. Water heated to 30 °C is added to another beaker and swirled constantly into the original mixture. After five minutes of churning, vesicles begin to appear. The generated vesicles must be kept cool **[3-4, 7].**

Hot Method – The drug is combined with ethanol and propylene glycol in the hot process. Phospholipid dispersion in water is produced at 40 °C. A previously made mixture is mixed with this dispersion. After heating this final mixture to 30 °C, size reduction is next achieved by sonication or extrusion. **[3-4, 7].**

How Are Ethosomes Operated? – In ethosome function, vesicles, ethanol, and skin lipids work in concert **[8]**. The dispersion of active substances is improved over liposomes by ethosomes and skin lipids because they interact more effectively. The transition temperature of the lipids in the stratum corneum is lowered when ethanol interacts with the lipid molecules in the polar head group area. These increase fluidity and decrease lipid multilayer density, which allows the medicine to enter the deep layers of the skin. Additionally, ethanol gives vesicles flexibility and smoothness, which promotes deeper penetration into the epidermal layer **[9].**

Characterization – Photomicrographs, transmission electron microscopy (TEM), and scanning electron microscopy (SEM) micrographs may all be used to assess the ethosomal vesicle formation **[10].** A zeta meter can be used to find the formulation's zeta potential **[11].** The amounts of phospholipid and ethanol can affect the mean vesicle diameter decrease **[12–14].** Differential scanning calorimetry, a technique for identifying ethanol-skin phospholipid interaction—a characteristic linked to the fluidizing effect of ethanol on the phospholipid bilayers—can be used to assess the transition temperature of the vesicular lipid systems **[15].** The degree of entrapment of the ethosomes may be evaluated using the ultracentrifugation technique. The ability of ethosomes to efficiently entrap hydrophilic and lipophilic medications can be explained by the high degree of lamellarity and the presence of ethanol in the vesicles. Furthermore, liposomes are less effective at trapping than ethosomal formulations **[16].**

Applications – [17]

Numerous studies have demonstrated that ethosomes are a successful therapy for microbial and viral skin infections. The bacitracin and erythromycin ethosomal systems were developed and tested using animal models of deep skin infections.

Ammonium glycyrrhizinate ethosomes were demonstrated to have an anti-inflammatory effect on human volunteer subjects' skin after manufacturing.

Ethosomal patches have adequately shown improved outcomes when tested in vivo on rabbits to treat menopausal symptoms in women and androgen deficiency in males.

Ethosome's and Ethosomal Gel Evaluation Parameters –

Ethosomes Evaluation Parameters – [3]

Vesicle Skin Interaction Study – Various imaging techniques, such as those used to evaluate the process of enhanced ethosomal formulation skin penetration. Fluorescence microscopy, laser microscopy (CSLM) confocal scanning, eosinhematoxyl staining, and transmission electron microscopy were all employed. When combined, these visualization techniques further improved our comprehension of how the structure and vesicle penetration paths are modulated. Traditional liposomes barely penetrated the stratum corneum, the topmost layer of skin. The deep penetration of alcohol-free liposomes was almost insignificant. In contrast, the ethosomal carrier was utilized to

observe enhanced depth and quantity (dermis-layer) distribution of 6-CF and Rhodamine 123.

Filter membrane-vesicle interaction study by scanning Electron microscopy – These calls for placing filter membranes in diffusion cells with a 50 nm pore size and introducing vesicle suspension (0.2 ml). While the lower side of the filter was in touch with a phosphate buffer saline solution (pH 6.5), the upper side of the filter was left open to the air. After an hour, the filters were taken out and prepared for SEM research by fixing them overnight at 4°C in Karnovsky's fixative and then dehydrating them with graded ethanol solutions (30%, 50%, 70%, 90%, 95%, and 100% v/v in water).

Skin Permeation Studies – A knife was used to remove the abdomen skin from the underlying connective tissue, and a pair of scissors was used to gently trim the test animals' (rats') hair to less than 2 mm. The removed skin was placed on aluminum foil, and the dermal side was carefully peeled off to remove any clinging fat and/or subcutaneous tissue. 1.0 cm2 and 10 ml, respectively, were the effective difusion cell and receptor cell volume permeation area. A temperature of 32 °C ± 1 °C was maintained. There was saline solution with phosphate buffer (10 ml pH 6.5) in the receptor compartment. It positioned the removed skin between the receptor compartment and the donor. Ethosomal formulation (1.0 ml) was applied to the skin's epidermal surface. Using the diffusion cell's sampling port, 0.5 ml samples were collected at 1, 2, 4, 8, 12, 16, 20, and 24 hour intervals. A high-performance liquid chromatography assay was used for analysis.

HPLC Assay – The amount of drug penetrated in the receptor compartment was ascertained by HPLC testing employing a methanol: distilled water: acetonitrile combination (70:20:10 v/v) as a mobile stage during in vitro skin permeation tests and in MT-2 cells.

Drug Uptake Studies – 100 µl of RPMI media was added to 24-well plates (Corning Inc.) to facilitate drug absorption into MT-2 cells (1,1106 cells/ml). Cells were treated with 100 µl of the drug solution in either the ethosomal formulation, phosphate buffer saline solution (pH7.4), or the marketed formulation. The drug material was then subjected to HPLC test analysis to determine drug absorption.

Stability Study – When the vesicles were maintained at 4 °C ± 0.5 °C, their stability was assessed. After 180 days, the previously described approach was used to calculate the vesicle size, zeta potential, and trapping effectiveness.

Ethosomal Gel Evaluation Parameters – [18]

Organoleptic Character – The ethosomal and non-ethosomal gels' organoleptic characteristics were identified. Through visual assessment, the color, odor, and homogeneity were verified.

Viscosity – The Brook field viscometer was used to measure the viscosity. At constant torque percentage, the temperature was set at 25°C and the r/min was set at 25 units. Spindle number 63 was used to take the readings in triplicate (LV-1). For more accurate findings, the averages of three readings were taken **[19, 20-21].**

pH – The gel's compatibility should be assessed in relation to the topical preparation's pH. The gels were initially diluted with distilled water at a dilution factor of 100 (gel: deionized water = 1:100) in order to assess the pH of the prepared gels. Following the formation of suspensions, each suspension's pH was measured using a pH meter (Sigma-27 DP) **[19-20].**

Spreadability – The spreadability of both gel types was also assessed by sandwiching the gel between two slides that were 6 cm apart, just like the ethosomes **[21].**

Tube Extruability – The foldable metal or aluminum tubes were used to fill the gel. The tubes' weight was measured. The tube was then loaded to extrude a minimum of 0.5 cm of ribbon of material in 10 seconds. Three duplicates of the test were run, and the average was determined **[22].**

Irritation Test – Simply applying the gel to the skin and watching for any changes was how the irritation test was carried out.

Stability Study – The stability research was a crucial factor in determining the storage temperature and shelf life. Examining the impact of environmental factors on product quality was essential. The therapeutic efficacy of the dosage form may result from a change in the product's quality. The ethosomes' entrapment effectiveness, diffusion study, pH, and viscosity were assessed on the first day, 30 days, and 90 days **[23-25].**

Future Aspects – Transdermal medication delivery has entered a new era with the introduction of ethosome. Better control over medication release in vivo will be possible with greater study in this field, enabling doctors to improve the effectiveness of therapy. It has favourable prospects for the non-invasive administration of therapeutic molecules of various sizes. Particular attention is paid to transcutaneous vaccination and the transfer of proteins and other macromolecules through the skin.

Conclusion – Over the course of two decades, ethosomes have been demonstrated to be a new and efficient carrier system. Over time, they have become an attractive and innovative carrier system due to their capacity to provide therapeutic effects both topically and systemically via the skin. Therefore, it is reasonable to assume that ethosomal formulations have promise for the effective transdermal and/or dermal administration of bioactive compounds. Ethosomal systems have been the subject of on-going study, which suggests that these carriers, in conjunction with penetration enhancers, may prove to be successful drug delivery vehicles in the form of gels, patches, and creams. However, more thorough research is required to advance the ethosomal system's stability.

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