WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.453
Volume 13, Issue 13, 1689-1702. Review Article ISSN 2277–7105

AN UPDATED REVIEW ON NANOVESICLES - ETHOSOMES, AS A NOVEL DRUG DELIVERY SYSTEM

Yogita Chunchuwar–Mandlik*[1], Dr. Rahul H. Kasliwal[2], Dr. Yogesh N. Gholse[3] and Dr. Dinesh R.Chaple[4]

*[1]Research Student, Priyadarshini J.L. College of Pharmacy, Nagpur, Maharashtra, India.
[2]Associate Professor, Priyadarshini J.L. College of Pharmacy, Nagpur, Maharashtra, India.
[3]Assistant Professor, Priyadarshini J.L. College of Pharmacy, Nagpur, Maharashtra, India.
[4]Principal, Priyadarshini J.L. College of Pharmacy, Nagpur, Maharashtra, India.

Article Received on
24 May 2024,
Revised on 13 June 2024,
Accepted on 03 July 2024
DOI: 10.20959/wjpr202413-32585

***Corresponding Author**
Yogita Chunchuwar–Mandlik
Research Student,
Priyadarshini J.L. College of Pharmacy, Nagpur,
Maharashtra, India.

ABSTRACT

Nanoparticles have various potential applications in drug delivery, clinical medicine, research, and other sciences, making them a promising technology in the field of nanotechnology. Ethosomes are noninvasive delivery carriers that enable drugs to reach the deep skin layers and the systemic circulation. Ethosomes are soft, malleable vesicles tailored for enhanced delivery of active agents. Ethosomes are an improved version of liposomes commonly used to transport drugs. Ethosomal vesicles are structurally composed of a phospholipid bilayer and an inner aqueous core containing drugs. Ethosomes can range in size from tens of nanometers to microns, and is influenced by the composition of the formulation. The concentration of phospholipid and ethanol affect the size of ethosomes. Because of their unique structure, ethosomes can encapsulate and deliver through the skin highly lipophilic molecules. Ethosomes are innovative carriers that meet the essential criteria for efficient and safe lipophilic or hydrophilic drug administration One of the unique properties of ethosomes is their ability to efficiently encapsulate molecules with different physicochemical characteristics. For enhanced application convenience and improved stability, ethosomal dispersions can be incorporated into creams, patches, and gels. The lack of toxicity, good stability, and ease of manufacturing make ethosomal carriers a valuable tool for efficient dermal application. Another benefit of these new therapies is they could reduce treatment

costs. Ethosomes can efficiently deliver challenging biotechnological agents through the skin and cellular membranes. Using these carriers, new noninvasive therapies could be designed to meet unmet needs. These include improved treatments of deep skin microbial, viral infections, skin cancers, and new antirheumatic products.

KEYWORD: Vesicles, Transdermal, Ethanol, Ethosomes, penetration, carrier.

INTRODUCTION

The outermost layer of our skin, known as the stratum corneum, acts as a strong barrier that prevents drugs from easily penetrating the skin. This limits the effectiveness of transdermal drug delivery. To overcome this natural skin barrier, specialized carriers are required to transport drug molecules with varying physicochemical properties into the bloodstream. Ethosomal systems are novel lipid vesicular carriers that contain a high percentage of ethanol. These nanocarriers are designed to deliver therapeutic agents with varying physicochemical properties into deep skin layers and across the skin efficiently. Different preparation techniques are used in the preparation of these novel carriers. For ease of application and stability, ethosomal dispersions are incorporated into gels, patches, and creams.[1] Ethosomes are effective for delivering drugs topically as they are limited to the upper layer of the stratum corneum (SC). Ethanol is a well-known permeation enhancer that provides ethosomes with distinct characteristics, such as high elasticity and deformability, enabling them to penetrate deeply through the skin and enhance drug permeation and deposition. cholesterol is usually included in order to modulate the membrane permeability and the vesicle stability.[2,3] The effectiveness of topical antifungal treatment depends on drug penetration into the target tissue.[4] Ethosomes are the preferred carriers for topical drug delivery due to their simplicity in manufacture, non-irritating nature, effectiveness in encapsulating a wide range of drug compounds, and superior stability than alternative vesicular systems. Vesicles would also allow to control the release rate of drug over an extended time period. This review aims to provide an overview of ethosomes, including their mechanism of penetration, preparation, advantages, composition, and applications in drug delivery.[5]

SKIN BARRIER AND PERMIABILITY

The skin is the largest organ of the human body and has a complex structure. It's made up of three major tissue layers: the epidermis, dermis, and hypodermis. The epidermis and dermis are responsible for the process of percutaneous absorption. The skin has many histologic layers, but these three are the most important ones.[6] The epidermis results from an active

epithelial basal cell population and is approximately 150 micron thick. Below this layer are the other layers of the epidermis - the stratum lucidum, stratum granulosum, stratum spinosum and stratum germinativum. Together, these other layers constitute the viable epidermis.[7] The outermost layer of the epidermis, the stratum corneum, comprises insoluble keratin and lipids, forming a strong barrier against microorganisms, UV radiation, chemicals, and water loss from the body.[8] The stratum corneum is the outermost layer of the epidermis. It is comprised of 10 to 25 layers of dead, elongated, fully keratinized corneocytes, which are embedded in a matrix of lipid bilayers. It has been discovered that the stratum corneum acts as the primary barrier to the penetration of substances through the skin. The passage of drugs through the epidermis layer can occur through intercellular, transcellular, and appendageal routes. When a topical formulation is applied to the skin, the active drug must first penetrate through the stratum corneum to reach the visible tissue beneath it.[9] Various mechanisms have been investigated to improve the permeation of drugs through the skin. These mechanisms include the use of chemical or physical enhancers such as iontophoresis or sonophoresis. Liposomes, neosomes, transferosomes, and ethosomes have also been found to enhance the permeability of drugs through the stratum corneum. Permeability enhancers increase the permeability of the skin, making it easier for the drug to cross through the skin. Ethosomes, in particular, have been found to enhance permeation through the stratum corneum barrier.[10]

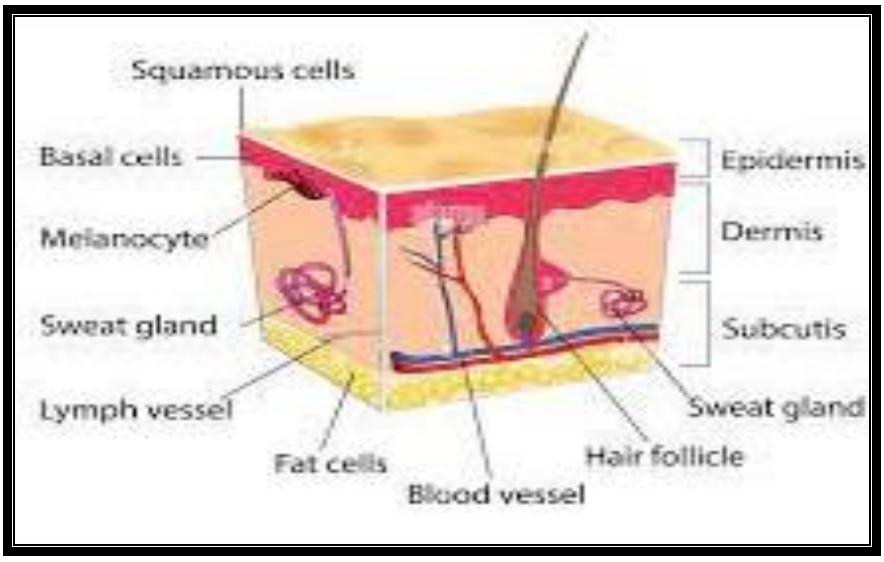

Figure 1: Structure of Skin.

ABOUT ETHOSOMES AND ITS COMPOSITION

Ethosomes are hydroalcoholic or hydro/alcoholic/glycolic vesicular carriers that have relatively high concentrations of alcohols or their combinations. Ethosomes can encapsulate drug molecules with varying physicochemical characteristics, including hydrophilic, lipophilic, or amphiphilic properties. The size of ethosomes can range from tens of nanometres to microns. Ethosomes were shown to enhance permeation through the stratum corneum barrier.[11,12] The unique characteristic of ethosomes is their high concentration of ethanol, which is known for disrupting lipid bilayer organization. This property allows the vesicle to penetrate the stratum corneum. Due to the high ethanol concentration, the lipid membrane is packed less tightly than conventional vesicles, but still maintains equivalent stability. As a result, the structure is more malleable, which enhances the drug distribution ability in the stratum corneum lipid.[13] Typically, ethosomes may contain phospholipids with various chemical .To provide continuous drug infusion through an intact skin, several transdermal therapeutic systems have been developed for topical application onto the intact skin surface to control the delivery of drug and its subsequent permeation through the skin tissue. Transdermal route is promising alternative to drug delivery for systemic effect. Ethosomes are the ethanolic phospholipid vesicles which are used mainly for transdermal delivery of drugs. Ethosomes have higher penetration rate through the skin as compared to liposomes hence these can be used widely in place of liposomes. Ethosomes have become an area of research interest, because of its enhanced skin permeation, improved drug delivery, increased drug entrapment efficiency etcstructures like phosphatidylcholine (PC), hydrogenated PC, phosphatidic acid (PA), phosphatidylserine (PS), phosphatidylethanolamine (PE), phosphatidylglycerol (PPG), phosphatidylinositol (PI), hydrogenated PC, alcohol (ethanol or isopropyl alcohol), water and propylene glycol (or other glycols). Delivery of high concentration of active ingredients through the skin is possible by using this composition. The delivery of the drug can be adjusted by changing the ratio of alcohol to water or alcohol-polyol to water.[14,15]

Table 1: Different Additives Employed In Formulation of Ethosome.

Class of Polymer	Example	Use
1. Phospholipid	Soya phosphatidyl choline,Egg phosphatidyl choline, Dipalmitylphosphatidyl choline Distearylphosphatidyl choline	Vesicles forming component
2. Polyglycol	Propylene glycol,Transcutol RTM	As a skin penetration enhancer
3. Alcohol	Ethanol	For providing the softness for

	Isopropyl alcohol	vesicle membrane. As a penetration enhancer
4. Cholesterol	Cholesterol	For providing the stability to vesicle membrane
5. Dye	Rhodamine-123 Rhodamine red FluoresceneIsothiocynate (FITC) 6- Carboxy fluorescence	For characterization study
6. Vehicle	Carbopol D934	As a gel former

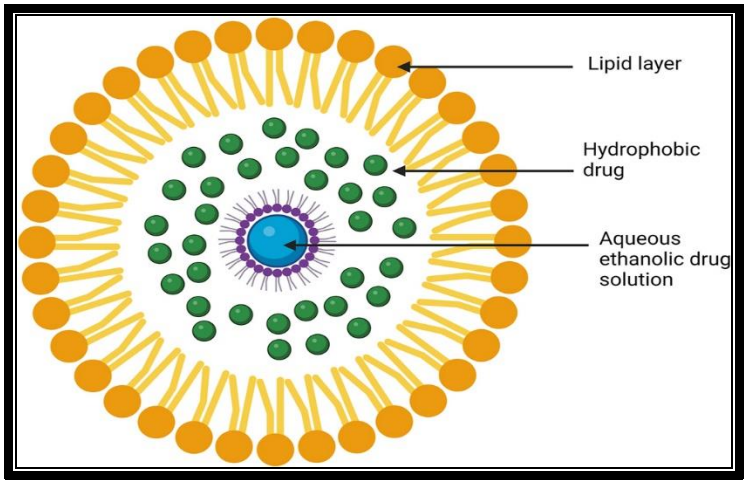

Figure 2: Structure of Ethosomes.

TYPES OF ETHOSOMES BASED ON COMPOSITION.[16]

1. **Classical ethosomes-** These are modified versions of classical liposomes that contain a high alcohol content of 45% w/w. They have an improved entrapment efficiency and a higher negative zeta potential as compared to classical ethosomes. Their molecular weight ranges from 130.07 Da to 24 kDa, which provides greater stability and increased permeation.
2. **Binary ethosomes:** In their initial publication, Zhou et al. introduced binary compounds that are formed by adding another alcohol to the formulation in order to enhance the ideal properties. The alcohols commonly added to these compounds are propylene glycol and isopropyl alcohol.
3. **Transethosomes-** In 2012, Song et al developed a new generation of vesicular systems. These systems are similar to classical preparations, but they contain an additional component in the form of an edge activator (usually a surfactant) and/or penetration enhancer. The novel delivery system is called "transethosomes" and combines the ideal properties of classical ethosomes, such as the ability to carry drugs, with the elasticity and deformability of transferosomes. Transethosomes have been reported to have superior and

beneficial characteristics compared to classical ethosomes. They are capable of entrapping drugs with a molecular weight ranging from 130.077Da to 200-235kDa. This makes them a promising candidate for the development of new drug delivery systems in the pharmaceutical industry.

ADVANTAGES OF ETHOSOMAL DRUG DELIVERY

1. Delivery of large molecules (peptides, protein molecules) is possible.
2. It contains non-toxic raw material in formulation.
3. Enhanced permeation of drug through the skin for transdermal drug delivery.
4. Ethosomal drug delivery system can be applied widely in Pharmaceutical, Veterinary, Cosmetic fields.
5. High patient compliance: The ethosomal drug is administrated in semisolid form (gel or cream) hence producing high patient compliance.
6. Simple method for drug delivery in comparison to Iontophoresis and Phonophoresis and other complicated methods.
7. The Ethosomal system is passive, non-invasive and is available for immediate commercialization.[3,13]
8. Ethosomes provide the controlled drug delivery and accordingly, it reduces the dosing frequency.[17]

DISADVANTAGES OF ETHOSOMAL DRUG DELIVERY

1. Skin irritation or dermatitis due to excipients and enhancers used in this drug delivery systems.
2. It give poor practical yield.
3. Transfer of ethosomes from organic to aqueous layer can leads to product loss.
4. Adhesive used in the drug delivery system may not adhere well to all types of skin.[18]
5. Administration of Ethosomal system is not a means to achieve rapid bolus type drug input, rather, it usually designed for slow, sustained drug delivery.[8]
6. It may not be cost-effective.[19]

ETHOSOME PREPARATION METHODS

Among the available techniques the first two techniques commonly used are simpler, without sophisticated technology**.**

1. **Hot method**- According to this method, in water phospholipid was dispersed by heating in a water bath at 40°C until a colloidal solution is obtained. Ethanol, propylene glycol

and drug was mixed in a separate vessel and heated up to 40°C. To aqueous phase organic phase was added and stirred for 5 min. The vesicle size of the ethosomal formulation was decreased to the desired extent using sonication**.** The storage was done properly afterward.[13, 20]

2. **Cold method-** In this method, in a covered vessel phospholipid, drug and other lipid materials are dissolved in ethanol 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 30^0C in a water bath. The water heated to 30^0C in a separate vessel is added to the mixture, which is then stirred for 5 min in a covered vessel. Using sonication or extrusion method the vesicle size of ethosomal formulation can be decreased to desire extend. The formulation is stored under refrigeration.[21]
3. **Classic method** - The phospholipid and drug are dissolved in ethanol and heated to 30°C±1°C in a water bath. To this lipid mixture Double distilled water is added in a fine stream, with constant stirring at 700 rpm, in a closed vessel. The resulting vesicle suspension is homogenized by passing through a polycarbonate membrane using a hand extruder for three cycles.[13]
4. **Ethanol injection-sonication method-** The organic phase consists of an ethanolic solution of phospholipids which is injected into the aqueous phase using a syringe system. The flow rate is maintained at 200 µL / minute and homogenization is achieved using an ultrasonic probe for 5 minutes.[14]
5. **Classic Mechanical Dispersion Method-** In a round bottom flask, soy phosphatidylcholine is dissolved in a 3:1 mixture of chloroform and methanol. A thin layer of lipids forms on the flask wall during evaporation of organic solvents in a rotating vacuum evaporator above the lipid transition temperature. The lipid layer is deposited and then cleaned of any remaining solvent by subjecting the container to a vacuum overnight. By rotating the flask at the appropriate temperature, hydration is accomplished using various concentrations of a hydroethanolic mixture containing the medication.[4,22]
6. **Reverse phase evaporation technique:**

   This method is rarely used and is mainly employed for producing large unilamellar vesicles. In this method, phospholipids are dissolved in diethyl ether, which is used as the organic phase. This organic phase is then mixed with an aqueous phase in a 3:1 ratio in an ultrasonic bath for 5 minutes, resulting in the formation of water-in-oil emulsion. The pressure is then reduced to a minimum to remove the organic phase, which leads to the

formation of a colloidal dispersion when the mixture is mechanically agitated vigorousl.[18]

SKIN DELIVERY FROM ETHOSOMAL SYSTEM

The mechanism of the drug absorption from ethosomes is not so clear. The drug absorption probably occurs in following two phases:

1. Ethanol effect
2. Ethosomes effect

1. Ethanol effect - Ethanol is known to act as a penetration enhancer when applied to the skin. Its mechanism of action is well understood, Interaction between ethanol and lipid molecules in the polar head group region reduces the transition temperature of lipids in the stratum corneum, resulting in increased fluidity and decreased density of the lipid multilayer. Ethanol disrupt intercellular lipid structure of stratum corneum by the phospholipids in their content Ethanol penetrates the intercellular lipids, leading to an increase in the fluidity of cell membrane lipids and a decrease in the density of the lipid multilayer of the cell membrane.[7,]

2. Ethosomes effect - The ethanol in ethosomes increases the fluidity of the cell membrane, which in turn increases skin permeability. This allows the ethosomes to easily penetrate the deeper layers of the skin, where they fuse with skin lipids and release drugs into the deep skin layer.[23]

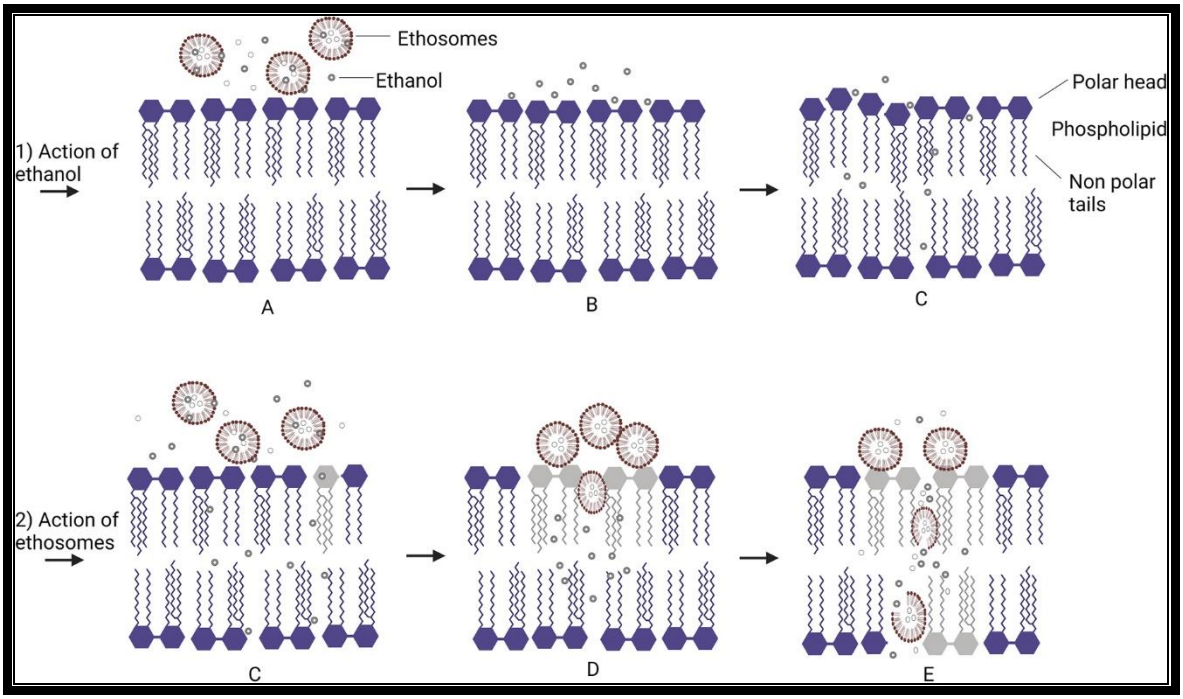

Figure 3- Mechanism of action of Ethosomes.

FLOW CHART SHOWING ACTION OF ETHOSOME – Mechanism of action of ethosomes is given below-

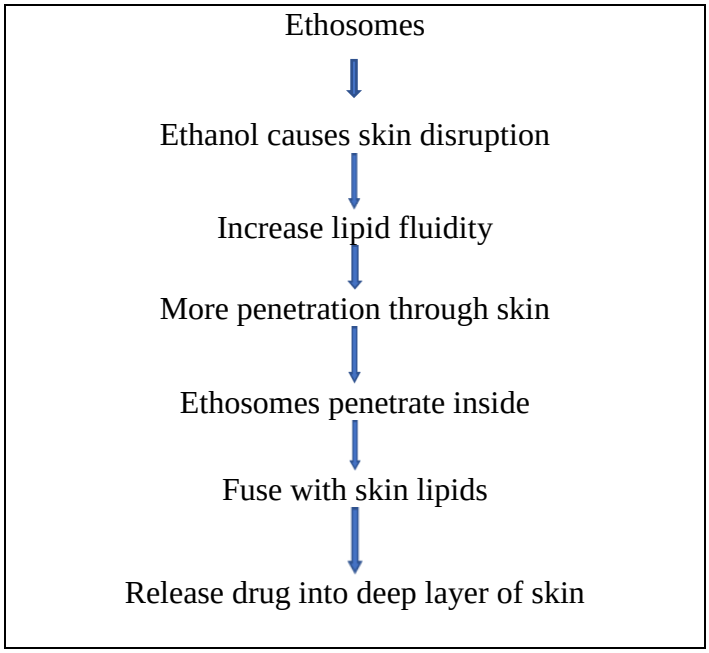

Figure 4: Flowchart Mechanism of action of Ethosome.

CHARACTERIZATION STUDY OF ETHOSOMES

1. **Vesicle size and Zeta potential** - Dynamic light scattering (DLS) and photon correlation spectroscopy (PCS) can be used to determine particle size and zeta potential with a computerized inspection system. Colloidal stability of the formulation find out by measuring zeta potential.[11,16]
2. **Vesicle shape -** The visualization of ethosomes can be achieved through transmission electron microscopy (TEM) and scanning electron microscopy (SEM). When viewed under electron microscopy, the ethosomal formulation appears as vesicles with a diameter of 300-400 nm. The vesicles appear to be malleable, as their shape is imperfectly round.[21]
3. **pH -** pH of the formulation is determined by using direct method,with the help of pH meter. The stable readings should be noted.[24]
4. **Scanning electron microscopy -** To determine the surface morphology and shape of ethosomes, the scanning electron microscopy (SEM) was used. One drop of Ethosomal formulation was placed on a clear glass stub. After air-drying, it was coated with Polaron E 5100 Sputter coater and observed under SEM.[25]
5. **Entrapment Efficiency** - ultracentrifugation technique used to measure the entrapment efficiency of drug by ethosomes. The vesicles are separated in a high-speed cooling

centrifuge at temperature maintained at 4°C. The sediment and supernatant liquids are separated; amount of drug in the supernatant is determined by UV-Visible spectrophotometry. From this, the entrapment efficiency is determined by the following equation.[22,26]

%entrapment efficiency = Amount of entrapped drug recovered /Total amount of drug * 100

6. **Differential scanning calorimetry (DSC) -** The Transition temperature (T) of vesicular lipids is measured in duplicate by DSC using a Mettler TA 4000DSC in an aluminium pan at a heating rate of 10°C per min, under a constant nitrogen stream.[6,20]
7. **Drug Content** - Drug content in ethosomes can be determined by UV spectrophotometer or a modified high-performance liquid chromatographic method.[21]
8. **In vitro drug release study and Drug Deposition study -** In vitro drug release study and drug deposition of ethosomal preparation can be performed using Franz diffusion cell with an artificial or biological membrane, or dialysis bag diffusion.[21,27]
9. **Stability studies** - The drug-retentive behaviour of ethosomal preparations can be checked by storing them at various temperatures such as room temperature (25 ± 2°C), 37 ± 2°C, and 45 ± 2°C for different durations ranging from 20, 40, 60, 80 and 120 days. The preparations should be kept in sealed vials (with a capacity of 10 ml) after flushing them with nitrogen.[8]

APPLICATION OF ETHOSOMAL DRUG DELIVERY SYSTEM[5,23,28,29]

1. **Transdermal delivery**

As ethosomes increase the permeability of drugs through the stratum corneum barrier, they can be used to administer drugs that have poor skin permeation, low oral bioavailability, and first-pass metabolism. They can also dose the skin and suppress infections at their root.

2. **Delivery of anti-arthritis drug**

Cannabidiol (CBD) is a drug candidate that has recently been developed for treating rheumatoid arthritis. However, its oral administration comes with several issues, such as low bioavailability, first-pass metabolism, and GIT degradation. To address these problems, Lodzki et al. prepared a CBD-ethosomal formulation for transdermal delivery.

3. **Transdermal delivery of hormones:**

When hormones are taken orally, it can lead to issues like low oral bioavailability, high first pass metabolism, and several dose-dependent side effects. Touitou et al. conducted a study to compare the skin permeation potential of testosterone ethosomes (Testosome) and a marketed

transdermal patch of testosterone (Testoderm¨ patch, Alza) on rabbit pinna skin. The results showed that the skin permeation of testosterone from the ethosomal formulation was nearly 30 times higher than that of the marketed formulation.

4. Delivery of antibiotics

Topical delivery of antibiotics is a more effective option to enhance the therapeutic efficacy of these agents. Conventional oral therapy often results in allergic reactions and several side effects. A study has shown that the use of ethosomal formulation of antibiotics could be highly efficient and can overcome the problems associated with conventional therapy.

5. Delivery of antifungal drugs

As a vesicular carrier system, ethosomes was found to have incredible capability of improving transdermal permeation of Ketoconazole. Ethosomes offers advantages of rapid onset and maximum release of drug with reduction of side effects. Furthermore, ethosome do not damage the architecture of skin and so, drug is transported into the systemic circulation across theundamaged skin.

6. Cosmeceutical Applications of Ethosomes

The use of ethosomes in cosmeceuticals not only increases the stability of cosmetic chemicals and reduces skin irritation, but also enhances transdermal permeation, particularly in elastic forms.

7. Delivery of problematic drug molecules

Delivery of large biogenic molecules such as peptides or proteins and insulin through oral route is difficult because they a completely degraded in the GIT tract hence transdermal delivery is a better alternative. But conventional transdermal formulation of biogenic molecules such as peptides or protein and insulin has shown poor permeation. Formulating these above molecules into ethosomes significantly increase permeation and therapeutic efficacy.

CONCLUSION

The main challenge of transdermal drug delivery is the epidermal barrier, but this can be overcome to a significant extent with the use of ethosomes. Ethosomes are advantageous over transdermal and dermal delivery methods as they allow drugs to reach deep layers of skin and enter the systemic circulation. They are non-invasive drug delivery carriers that can even deliver large molecules such as peptides and proteins. Ethosomes are administered in semi-solid forms like gel or cream, which makes it easier for patients to comply with the treatment. Ethosomes have various applications in the pharmaceutical, veterinary, and cosmetic field.

FUTURE PERSPECTIVES

The introduction of ethosomes has opened up a new field of research in vesicular science for transdermal drug delivery. Various reports indicate a promising future for ethosomes in making the transdermal delivery of different agents more effective. Further research in this area will allow better control over drug release in vivo, which will enable physicians to make therapy more effective. Ethosomes offer a good opportunity for the non-invasive delivery of small, medium, and large-sized drug molecules.

REFERENCES

1. Abdulbaqi, I. M., Darwis, Y., Khan, N. A. K., Assi, R. A. & Khan, A. A. Ethosomal nanocarriers: The impact of constituents and formulation techniques on ethosomal properties, in vivo studies, and clinical trials. International Journal of Nanomedicine, 2016; 1: 2279–2304.
2. Dave, V., Kumar, D., Lewis, S. & Paliwal, S. Ethosome for enhanced transdermal drug delivery of aceclofenac. International Journal of Drug Delivery, 2010; 2: 81–92.
3. Hallan, S. S. Maddalena S, Paolo M, Rita C, Nicolas H, Fanny S.*et al.* Design and characterization of ethosomes for transdermal delivery of caffeic acid. Pharmaceutics, 2020; 12: 1–18.
4. Jin-guang, LAI Wei,JIANG Yu .Preparation of curcumin ethosomes. African Journal of Pharmacy and Pharmacology, 2013; 7: 2246–2251.
5. Mishra, S. Sonia P, Divya D, Himanshu, Himanshu S, Himanshu P. *et al.* A research on formulation and evaluation of herbal ethosomal gel for analgesic activity. *JETIR* 2023; 10.
6. Godin, B. & Touitou, E. Ethosomes: New Prospects in Transdermal Delivery. Crit Rev Ther Drug Carrier Syst., 2003; 20: 63–102.
7. Patrekar, P. V, Suhel J. I, Sachin S M., Mulla TM, Amita Ahir, Avinash H .H. Ethosomes as novel drug delivery system: A review. The Pharma Innovation Journa, 2015; 4: 10–21.
8. Zhou, Y., Wei, Y.-H., Zhang, G.-Q. & Wu, X.-A. Synergistic penetration of ethosomes and lipophilic prodrug on the transdermal delivery of acyclovir. Arch. Pharm. Res., 2010; 33: 567–574.
9. Zahid, S. R, Neeraj U, Surendra D, Sudhir Kumar R, Prabhat J, Geeta P. Ethosome: a novel vesicular carrier for transdermal drug delivery. *J. D*rug Delivery Ther., 2018; 8: 318–326.

10. Jaiswal, P. K., Kesharwani, S., Kesharwani, R. & Patel, D. K. Ethosome: a new technology used as topical & transdermal delivery system. J. Drug Delivery Ther., 2016; 6: 7–17.
11. Parashar, T. Soniya, Roopesh S, Vishal S, Gaurav S, Satyanand T.*et al.* ETHOSOMES: a recent vesicle of transdermal drug delivery system. Int. J. Res. Dev. Pharm. L. Sci., 2013; 2: 285–292.
12. Bhalaria, M. K., Naik, S. & Misra, & A. N. Ethosomes: A Novel Delivery System for Antifungal Drugs in the Treatment of Topical Fungal Diseases. Indian Journal of Experimental Biology, 2009; 47: 368–375.
13. Sheo D. M, Sunil K. P, Anish K. G,yanendra K. Sand Ram C.D. Formulation Development and Evaluation of Ethosome of Stavudine. Indian J.Pharm. Educ. Res., 2010; 44: 102–108.
14. Rajendar, M., Chandrashekar, K. B. & Srinivas, D. A. Ethosomes as novel drug delivery carriers – a review. *IAJPS*, 2016; 3: 1639–1643.
15. Barupal, A. K., Gupta, V. & Ramteke, S. Preparation and characterization of ethosomes for topical delivery of aceclofenac. Indian Journal of Pharmaceutical Sciences, 2010; 72: 582–586.
16. Devaki, J., Pavuluri, S. & Suma, N. Ethosomes: A Vesicular Carrier as a Novel Tool for Transdermal Drug Delivery System. Journal of Drug Delivery and Therapeutics, 2023; 13: 159–164.
17. Shitole, M., Nangare, S., Patil, U. & Jadhav, N. R. Review on drug delivery applications of ethosomes: Current developments and prospects. TJPS, 2022; 46: 251-265.
18. Nainwal, N., Jawla, S., Singh, R. & Saharan, V. A. Transdermal applications of ethosomes – a detailed review. Journal of Liposome Research, 2019; 29: 103–113.
19. Chauhan, N. *et al.* Ethosomes: A novel drug carrier. Annals of Medicine & Surgery, 2022; 82.
20. Kumar Verma, N. & Kumar Yadav, K. Formulation and Evaluation of Ethosome (Mefenamic Acid) Using Hot Method. Journal of Chemical and Pharmaceutical Research, 2018; 10: 4–15.
21. Anuradha P, R.K. Sharma, Mahesh T, Shivaprakash, Anjana P. Ethosomes: A Novel Tool for Transdermal Drug Delivery Research J. Pharm. and Tech., 2013; 6: 838-841.
22. Aute, P. P., Kamble, M. S., Chaudhari, P. D. & Bhosale, A. V. A comprehensive review on ethosomes. Int. J. Res. Dev. Pharm. L. Sci., 2012; 2: 218–224.

23. Güngör, S., Erdal, M. S. & Aksu, B. New Formulation Strategies in Topical Antifungal Therapy. Journal of Cosmetics, Dermatological Sciences and Applications, 2013; 03: 56–65.
24. Shelke, O. & Kulkarni, A. Formulation, Development and Evaluation of Nano Ethosomal Gel of Tramadol Hydrochloride. J Nanomed Nanotechnol, 2018; 09: 514.
25. Shetty, S., Jose, J., Kumar, L. & Charyulu, R. N. Novel ethosomal gel of clove oil for the treatment of cutaneous candidiasis. Journal of Cosmetic Dermatology, 2019; 18: 862–869.
26. Singh, S. P. & Tripathi, D. M. Formulation and Evaluation of Posaconazole Drug Loaded Ethosomal Gel for Antifungal Activity. ijppr, 2021; 23: 34–46.
27. Mahmood, A., Rapalli, V. K., Waghule, T., Gorantla, S. & Singhvi, G. Luliconazole loaded lyotropic liquid crystalline nanoparticles for topical delivery: QbD driven optimization, in-vitro characterization and dermatokinetic assessment. Chemistry and Physics of Lipids., 2020; 234: 1–63.
28. Raut, S., Koli, P., Desai, H., Shelake, S. & Chougule, N. An Overview of Ethosomes as Novel Vesicular Carrier: Its Principle, Preparation and Applications. Int J Pharm Sci Rev Res., 2023; 79: 50–55.
29. V. Sankara, v. Wilsona, K. Sirama, A. Karuppaiaha, S. Hariharan,Topical Delivery of Drugs Using Ethosomes: A review. Indian Drugs, 2019; 56: 7-20.