Ethosomes as pharmaceutical novel drug delivery technique:

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Abstract:

Skin serves as a barrier against local and systemic effects and is one of the largest organs. The outermost layer of the skin, the Stratum Corneum (SC), is impermeable to hydrophilic and high molecular weight drugs.

Drugs can infiltrate deeper layers of the skin's blood circulation through ethosomes without requiring surgical intervention. As new vesicular carriers for the transfer of active compounds to/through the skin, "smooth vesicles" known as ethosomes function. Most of them are made up of phospholipids, water, and ethanol (phosphatidylcholine, phosphatidylserine, and phosphatidic acid).

Ethosomes can serve as a capsule for the release and transportation of both hydrophilic and lipophilic medications via the skin because of their amphiphilic properties. Comparing other vesicles that serve as drug delivery systems, ethanol is present in ethanolosomes at a rate of 45 percent, which is the greatest concentration. Ethosomes are liposomes that are heavily ethanol-contained. Tens of nanometers to microns are the sizes of ethosomes. By piercing the dermal layers of the skin, they can transfer drugs to the deep skin or systemic circulation.

Keywords: Ethosomes, skin, liposome, vesicles, systemic effects and etc.

الخلاصة -:الجلد ، وهو أكبر عضو في الجسم ، يعمل كطريق محتمل لتوصيل الأدوية للتأثيرات الموضعية والجهازية. ومع ذلك ، فإن الطبقة الخارجية من الجلد ، تعمل الطبقة القرنية (SC) كحاجز قوي يمنع تغلغل الأدوية المحبة للماء وذات الوزن الجزيئي العالي.

الإيثوسومات هي مركبات غير جراحية لتوصيل الأدوية تسمح للأدوية بالوصول إلى طبقات أعمق من الجلد و/ أو الدورة الدموية الجهازية الإيثوسومات هي "حويصلات طرية" تعمل كناقلات حويصلية جديدة لتوصيل عوامل نشطة إلى / من خلال الجلد. تشكل الفوسفوليبيدات (فوسفاتيديل كولين ، فوسفاتيديل سيرين ، حمض الفوسفاتيديك) ، والإيثانول ، والماء معظمها.

يمكن أن تغلف الإيثوسومات وتحسن نقل كل من الأدوية المحبة للماء والأدوية المحبة للدهون على الجلد بسبب طبيعتها البرمائية. بالمقارنة مع أنظمة توصيل الأدوية الحويصلية الأخرى ، تحتوي الإيثوسومات على أعلى تركيز من الإيثانول (20-45٪).

الإيثوسومات هي جسيمات شحمية ذات تركيز عالٍ من الإيثانول. يبلغ حجم الإيثوسومات عشرات من النانومتر إلى الميكرونات في المتوسط. لديهم القدرة على التسلل عبر طبقات الجلد وتوصيل الأدوية إلى الجلد العميق أو الدورة الدموية الجهازية.

Introduction

The skin is the biggest and most flexible organ in the body. Devices used to administer transdermal medications are made to pass through the stratum corneum. Several methods have been used to boost drug penetration rates. The most sophisticated kind of vesicular delivery, ethanolsomes, have a high ethanol content that improves drug penetration into the deeper layers of skin. The primary use of ethosomes is the delivery of medications through the skin. When applied to the skin, the self-contained, distinctive dose form of transdermal medication delivery gradually distributes the medication into the bloodstream (1).

Transdermal drug delivery systems have many features over other drug delivery systems. It is a better alternative to obtain steady state plasma concentration with less frequent dosing regimens (2).

Advantages such as improved patient acceptance, reduced side effects and utility of medications with short half-lives, prevention of extensive FPM, expected and prolonged action, enhancement of physiological and pharmacological response, and prevention of drug level fluctuations are all touted. The fundamental issue with drug transport over the skin is the barrier function controlled by the stratum coneum. The lipid layers that surround the corneocytes that make up the stratum corneum are crucial to the stratum corneum's ability to function as a barrier (3).

Novel drug delivery systems must be created to enhance the number of medications supplied through transdermal route. These systems include the use of physical techniques like sonophoresis, iontophoresis, microneedles, etc. as well as chemical techniques such as penetration enhancers (example; organic solvents and surfactants) and biochemical techniques using liposomes, niosomes, transferosomes, and ethosomes to increase drug permeability through the stratum corneum (4).

For many years, the vesicles' significance in cellular communication and particle transportation has been well understood. In order to improve medication delivery via their cavities and tag the particles for cell specificity, researchers have gained an understanding of the features of vesicle structure. A significant development in vesicle research was the discovery of vesicle derivatives, often known as an ethosomes (3).

More than two decades ago; the first transdermal drug delivery device was introduced. Transdermal drug delivery is a practical delivery technology in which the medicine enters the systemic circulation through the protective barrier of the skin (4). The skin is used as an alternate delivery route for systemically active medicines in transdermal medication delivery (5).

Skin acts as a prominent target and barrier for topical/transdermal drug administration. One of the main problems of transdermal delivery of drug is the skin's low permeability, which restricts the range of drugs that can be used in this route (6).

Drug permeability in human skin is selective. Medications that are lipophilic in nature can pass through the skin, whereas hydrophilic drugs cannot. Permeation of water-soluble medicines is either minimal or non-existent (7).

Layers of skin

The epidermis is the outer layer of the skin. Corneum stratum Granulosum stratum Spinosum stratum Layer at the bottom Papillary dermis layer of the dermis The reticular dermis layer is a type of dermis that has a The layer beneath the skin (8).

Possible routes for a penetrant to pass through the skin barrier.

(1) Through the intact horny layer.
(2) Hair follicles with associated sebaceous glands.
(3) sweat glands (9).

A drug's penetration (passive diffusion) via the stratum corneum is the most common way for it to be absorbed percutaneously. Drug molecules can penetrate through the stratum corneum and into the dermis after leaving the stratum corneum. The medication is ready for absorption into the general circulation once it reaches the vascularized dermal layer. These layers act as barriers to prevent external substances from penetrating the body and causing water loss. The dermis and subcutaneous layers of the skin contain sebaceous glands, sweat glands, and hair follicles that rise to the surface (8).

Only lipophilic medicines with a molecular weight of less than 500 daltons pass through the stratum corneum (SC), which functions as a barrier. Several strategies have been tested to increase permeation, with lipid vesicles being the most effective of them. These strategies include the use of physical enhancers like iontophoresis, sonophoresis, microneedles, and electroporation as well as chemical enhancers like surfactants and organic solvents. Big molecular weight drugs can be delivered into the skin or even the bloodstream using vesicles, which act as carrier systems (8).

The horny layer, which consists of dead epidermal cells, is known as the stratum corneum. It's made up of 40% protein (mostly keratin), 40% water, and 20% lipids. The stratum corneum is a semipermeable membrane made up of keratinized tissue. Drugs can enter through hair follicles and gland ducts quickly, but their relative surface area is so little compared to the overall epidermis that they have little influence on drug absorption (10).

Transdermal drug blood levels can be measured (by calculating the AUC) and compared to a standard formula, but this is not the case with topical nonsystemic products. The therapeutically effective medication concentration in the skin for topical formulations is unknown; hence treatment is dependent on qualitative criteria (10).

Drugs can enter deeper skin layers and/or the general circulation through ethosomes, which are non-invasive drug delivery systems. "Soft vesicles" called ethosomes are used as new vesicular carriers to transfer active ingredient to or through the derm.

Most of them are constituted of alcohol, H2O, and lipid bilayers (phosphatidylcholine, phosphatidylserine, and phosphatidic acid) (10).

Ethosomes can act as transporter and transport of hydrophilic and hydrophobic drugs over the skin as a result of their amphiphilic properties. In comparison to other vesicles which act as carrier. ethosomes have the highest concentration of ethanol reaching to 45%. Ethosomes are liposomes with a high ethanol concentration. Ethosomes are tens of nanometers to microns in size on average. They have the ability to infiltrate through the dermal layers of the skin and deliver drugs to the deep skin or systemic circulation. Ethosomes are liposomes with a high ethanol concentration, to put it another way. Ethosomes are from nano-micro in size average. They have the ability to infiltrate through the dermal layers of the skin and deliver drugs to the deep skin or systemic circulation (11).

Novel lipid carriers known as Ethosomes can improve medicine administration via the skin. Lipid, ethanol, and water make up the ethosomal system. 5. The amount of ethanol in a liposome versus an ethosome is the difference. In the case of ethosome, it contains a lot of ethanol, which helps with penetration. Ethosomes can encapsulate a variety of substances, including lipophilic drugs6. Unlike liposomes, ethosomes increase drug delivery by the skin in both occlusive and non-occlusive states (12).

Touitou devised ethosomes, which are particularly adapted vesicular carriers, in answer to the requirement for effective drug delivery via topical application on the skin. 2 Phospholipids, ethanol (up to 50%), and water make up the majority of this system. Ethosomes, which are unique vesicular carriers, differ from conventional lipid nanocarriers in a variety of ways, including the bilayer fluidity of the vesicles (13).

Ethosomes differ from other nanoparticles in amount of alcohol, fluidity, mechanism of skin breakthrough, manufacturing methodology, and lack of side effects. It differ from liposomal formulations, that may not contain more than 10% of ethanol, ethosomes have far higher ethanol content (20-45%). Ethanol acts as a penetration booster, increasing the transport of therapeutic compounds to the deeper layers of the epidermis and into the systemic circulation simpler and more effective (11).

The systemic action and deeper distribution and penetration in the skin lipid bilayers are due to mixture of phospholipids and a higher percentage of alcohol in the vesicular formulation. Ethosomes can entrap medicinal molecules with different physiochemical properties, such as hydrophobic, lipophilic, or amphiphilic. Drug permeability across the stratum corneumbarrier has been found to be improved by liposomes, noisomes, transferosomes, and ethosomes. The permeability of the skin is increased by the permeationenhancer, allowing the medicine to pass through (14).

By exceptional and self-amplifying deformability, ethosomes are able to infuse through pores inside the stratum corneum. Ethosomes having a diameter of 200–300nm can easily puncture undamaged skin (15).

Increases in the percent of lipid in the system result in greater vesicles, but increases in the percent of ethanol at about the same lipid concentration result in smaller ethosomes, according to a thorough analysis of the influence of system content on vesicular size. 3 This relationship means that changes in percentage of any of system constituents will result in change in the system's overall characteristics (16).

Advantages of ethosoms as drug delivery system

Ethosomes have several advantages such as:

1. Ethosomes have the ability to deliver monumental molecules like peptides, macromolecule molecules, and so on.
2. Ethosomes are developed by utilizing biologically and eco- friendly chemicals rendering it non-toxic to the human body.
3. Ethosomal could be a sensible choice for transcutaneous delivery of drug because it enhances the penetration.
4. It will be carry out to numerous fields like Cosmetic, Pharmaceutical and Veterinary.
5. Ethosomal can be prepared as gel or cream, therefore achieving high patient compliance (9).

Composition of ethosomes

Ethosomes, which are categorized as GRAS, often contain ethanol, phospholipids, and water (generally regarded as safe). They may also add propylene glycol, isopropyl alcohol, and other surface modifiers to enhance the drugs solubility in the solvents and the penetration of pharmaceuticals through membranes. Many phosphatidylcholines and phosphatidylethanolamine-containing compounds have been used in ethosomes, including Phospholipid 90, Soya phosphatidylcholine (S-75), and Lipoid S 100 ,as explained in table(1) (17).

Numerous methods have been used in experiments to determine how excipients affect vesicle size. According to Touitou et al., the size of the vesicles diminishes (193–103 nm) as the amount of ethanol in the solution rises (20–45 percent), increasing the amount of medication that penetrates and permeates the skin. A rise in the zeta potential to more negative values may be the cause of a reduction in the size of the ethosomes. They also found that the ethosome particle size (118-249 nm) increased as the quantity of phospholipid (0.5-4 percent) was increased. Dayan and Touitou assert that the type of the medication can also be useful in determining particle size.

It was noticed a decrease in particle size from 154 to 90 nm when the percentage of trihexyphenidyl hydrochloride (0–3 percent), an anti-M1 muscarinic drug used to treat Parkinsonism, was raised. The compound's surface activity, according to the researchers, is what caused the smaller particle size (18).

Table(4): Composition of ethosom[18]

Chemical	Example	Use
Phospholipids	Soya phosphatidyl choline Egg phosphatidyl choline Dipalmityl phosphatidyl choline Distearyl phosphatidyl choline	Vesicles forming component
Polyglycol	Propylene glycol Transcutol	As a skin penetration enhancer
Alcohol	Ethanol Isopropyl alcohol	For providing the softness for vesicle membrane
Cholesterol	Cholesterol	to provide stability to vesicle membrane

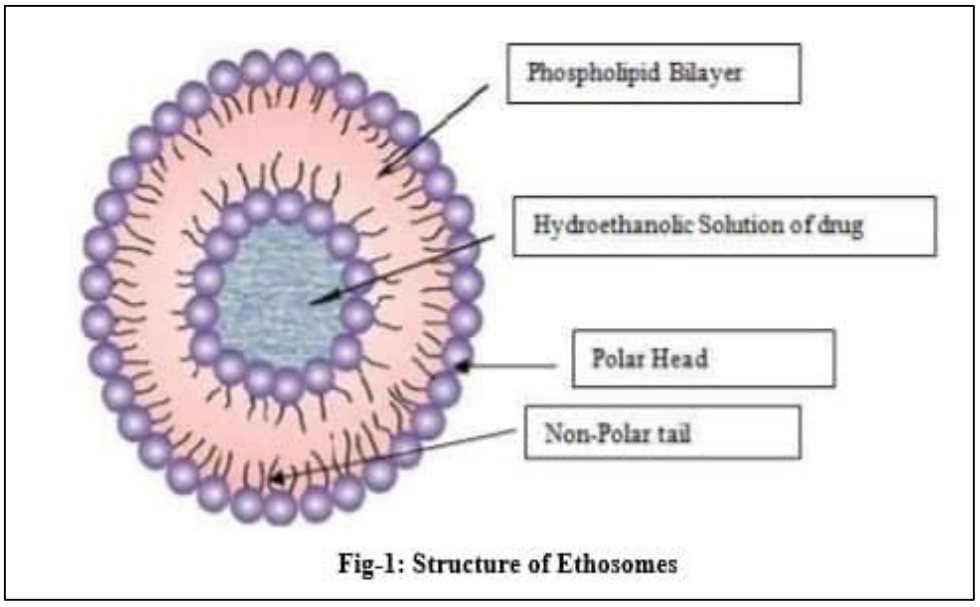

Fig-1: Structure of Ethosomes

Figur (4): Ethosome Composition (37)

Ethosomal types

The scientists classify ethosomes into three types:-

Classical ethosomes

Liposomes have been modified to create these ethosomes. They're made up of a lot of ethanol (about 45 percent by weight), phospholipids, and water. Because of their smaller size and higher entrapment efficiency, these ethosomes were regarded to be superior to liposomes for percutaneous distribution. When compared to liposomes, the stability and penetration qualities of classical ethosomes were superior. The classical ethosomes were used to encapsulate drugs with molecular weights ranging from 130.077 Da to 24kDa (19).

Binary ethosomes

Zhou et al. were the first to introduce binary ethosomes. They were produced by blending different type of alcohol with traditional ethosomes. The two alcohols most frequently utilized in binary ethosomes are PG and IPA (20).

Transfersomes

Nano-vesicles called transfersomes are stretchy. The majority of its components are phospholipids and edge activators like sodium (cholate and deoxycholate), Span (60, 65, 80), Tween (20, 60, 80) and dipotassium glycyrrhizinate (8). It is the first generation of UDV and was first found in 1992 by Cevc[9] (transfersomes, a trademark of IDEA AG, Munich, Germany). These vesicles easily penetrate skin due to a synergistic interaction between the carrier qualities and penetration enhancers. Transfersomes can penetrate the skin's layers in a variety of ways (10). They can readily change their form and pass the skin barrier by migrating inside vesicle to zones with smaller curvature because EA activity in response to mechanical stress allows them to do so. As a result, the membrane elastic energy is minimized. This process allows transfersomes to easily squeeze out of channels one-tenth the diameter of vesicles and cross the SC under the influence of an osmotic transdermal gradient (18).

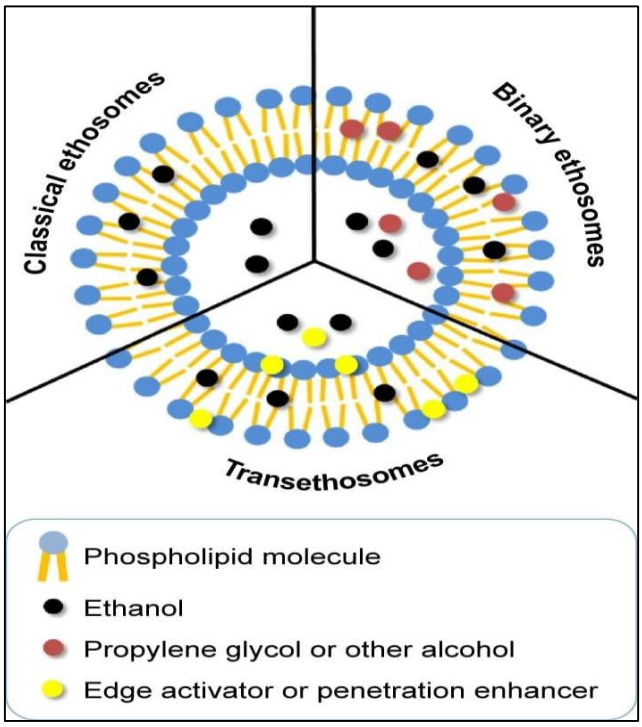

Figure (2): Different ethosomal system types are represented schematically. (16)

Methods of preparation

The formulation and preparation of ethosomes can be done in one of two ways. Both approaches are straightforward and convenient, and neither requires a specialized tool or a lengthy process (21).

1. Cold method
2. Hot method

Cold method

The most common method for creating ethosomal formulations is this one. This process involves the vigorous stirring and use of a mixer to dissolve phospholipids, medicines, and other lipid molecules in ethanol at room temperature. PG or another polyol is added while stirring is taking place. This mixture is cooked to 300°C in a water bath. The mixture is mixing for 5 minutes in a closed jar after the water has been heated to 300°C and added. The vesicle size of an ethosomal formulation can be reduced to required level via sonication or extrusion. The combination is then put in the refrigerator (22).

Hot method

In order to use this technique, phospholipid must be dissolved in water and heated in a water bath to 40°C until a colloidal solution forms. In a different tank, ethanol and propylene glycol are

combined, then warmed to 40 °C. The organic phase is introduced to the aqueous phase once both mixtures have reached 40°C. Depending on the drug's hydrophilic/hydrophobic properties, it dissolves in either water or ethanol. By utilizing probing sonication or extrusion, the vesicle size of an ethosomal formulation can be reduced to the required level (Touitou, 1998) (23).

Mechanism of drug penetration

The ethanol effect, which occurs when ethanol is intercalated into intercellular lipids to increase lipid fluidity and decrease lipid multilayer density, explains the first part of the mechanism. Following the ethosomal effects, which include inter-lipid penetration and permeation via creating new channels as a result of the ethosomes' malleability and fusing with the skin lipids, come the ethosome effects. It is yet unknown how ethosomes are integrated. The likelihood of medication absorption is highest over the next two times (24). Figure (3) presents a proposed method for how molecules from the ethosomal system pass through the skin (6).

Effect of ethanol: Ethanol improves skin penetration. The mechanism underlying its penetration-improving action is widely known. Ethanol penetrates intercellular lipid, increasing the fluidity of cell membrane lipids and decreasing the density of the lipid multilayer.

Ethosome effect: the process underlying its permeation-improving action is widely known. The fluidity of lipids in cell membranes is increased by ethanol's penetration of intercellular lipids, which also reduces the density of the lipid multilayer in the cell membrane (25).

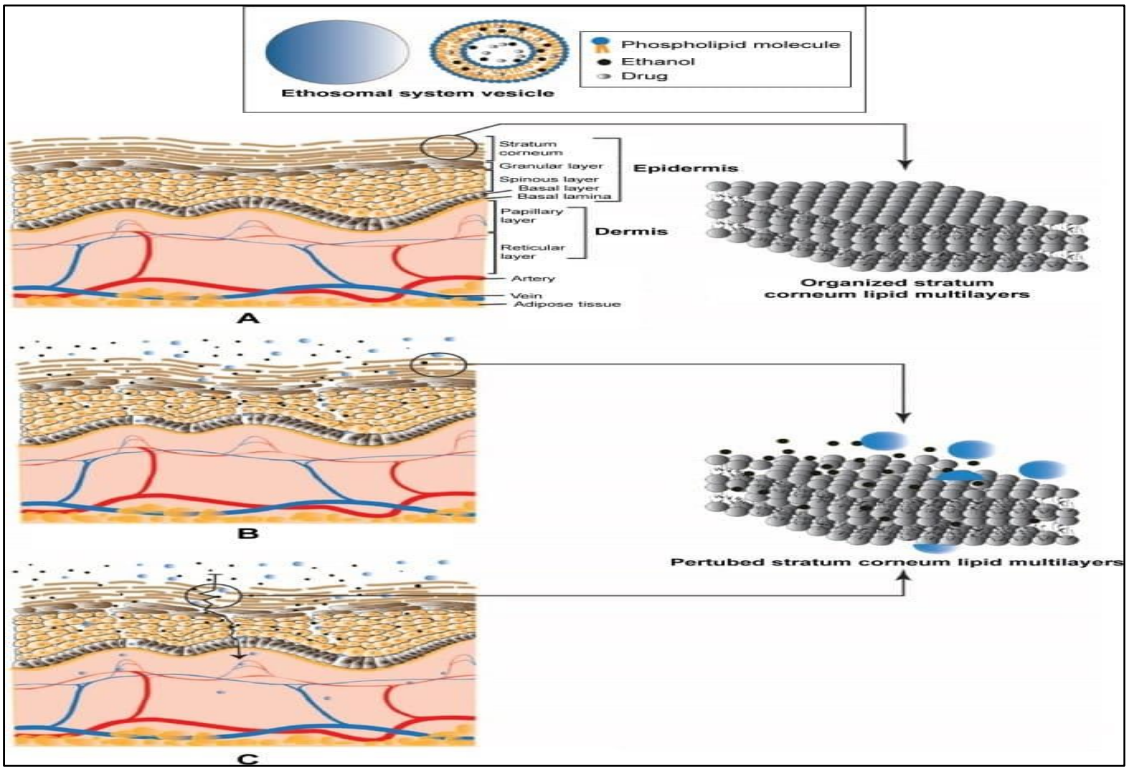

Figure (3): proposed way for ethosomal system molecules to pass through skin (16).

Advantages of ethosomal drug delivery

Ethosomes includes a several advantages:

1. Compared to alternative transdermal and dermal delivery approaches
2. Greater drug penetration through the skin for stratum drug delivery.
3. It is feasible to deliver huge molecules (peptides, supermolecules).
4. Its formulation includes non-toxic ingredients.
5. Very high patient adherence because ethosomal medicine is given as gel or cream (as semisolid), patient compliance is good.
6. The Ethosomal system is an immediately marketable passive, unobtrusive approach.
7. The ethosomal drug delivery method has a wide range of applications in the pharmaceutical, veterinary, and cosmetic fields.
8. Easy technique for drug delivery as compared to therapy and phosphophoresis and alternative sophisticated strategies.(26)

Disadvantages:

1. Product loss after switching from organic to water-based media;
2. Ethosomal delivery is ineffective for quick treatment because it delivers the medication at a steady pace.
3. The yield from this device is low.
4. The medicament must have an appropriate molecoular size for ethosomal delivery (35).

Ethosomal dosage forms

Ethosomal patches

Ethosomal patches are more challenging to manufacture and test than ethosomal gels because they require the use of molds. A literature search revealed that only seven studies reported the development of ethosomal patches for numerous drugs, including testosterone, 6-artesunate, febrifugine, 27-ligustrazine, 34,118 valsartan, 37 tizanidine hydrochloride, 119 and insulin. The polymers employed to create the ethosomal patches included acrylic resin, hydroxypropyl methylcellulose E15, and 121-Polyvinylpyrrolidone/vinyl acetate. As a plasticizer, triethyl citrate was applied to the mix (20).

Ethosomal gels

Ethosomal patches are more challenging to manufacture and test than ethosomal gels because they require the use of molds. A literature search revealed that only seven studies reported the development of ethosomal patches for numerous drugs, including testosterone, 6-artesunate, febrifugine, 27-ligustrazine, 34,118 valsartan, 37 tizanidine hydrochloride, 119 and insulin. The polymers employed to create the ethosomal patches included acrylic resin, hydroxypropyl methylcellulose E15, and 121-Polyvinylpyrrolidone/vinyl acetate. According to several authors, ethosomal gels function better than regular gels for a number of medications and agents (27).

Ethosomal creams

On the creation of ethosomal creams, only two studies have been released. Both of these investigations used Curcuma longa extract-loaded ethosomal systems as an anti-wrinkle and photoprotective treatment in a cream basis. (24)

According to all of the previously mentioned study, integrating ethosomal systems into suitable vehicles such patches and semisolids boosts the drug from the ethosomal systems' skin permeation. Among the vehicles described, gels are the best option for incorporating ethosomal systems, although ethosomal creams may be employed in aesthetics(27).

Is ethosome system safe?

Ethosomes are consisting of chemicals that are usually considered to be harmless (GRAS). Numerous studies, both in vitro and in vivo, have been conducted to determine the safety of ethosomal systems administered topically to the skin. In vitro cell culture experiments revealed that ethosomal systems are safe for skin cells. Skin Histology has been examined at the treatment area after single and chronic application of ethosomal systems containing different compounds (e.g., BH, ibuprofen, testosterone, CBD, etc.) revealed no changes in the structure or thickness of the horny layer, as well as no infiltration of inflammatory cells into the skin (13).

There was no evidence of cutaneous irritation in the rabbits.[3] After using transdermal ethosomal ibuprofen gel for five days, biochemical examination of rat blood indicated no statistically significant variations in liver, kidney, or muscle function indices between the treated and control groups (11).

In a research led by Paolino and Fresta, the skin acceptability of ethosomal systems on healthy human participants was examined using reflectance spectrophotometry. 10 The systems did not cause skin erythema 12 hours, 24 hours, or 48 hours after application, according to their findings. The administration of a hydroethanolic solution with the equal water to ethanol ratio as ethosomes, on the other hand, caused significant cutaneous erythema (11).

Furthermore, when several ethosomal systems containing clindamycin and salicylic acid, acyclovir, or PGE1 were used for skin of human participants in three clinical studies, there were no negative skin reactions. Furthermore, there have been no reports of skin irritation or security issues in the years when ethosomal carriers-based products have been in use (11).

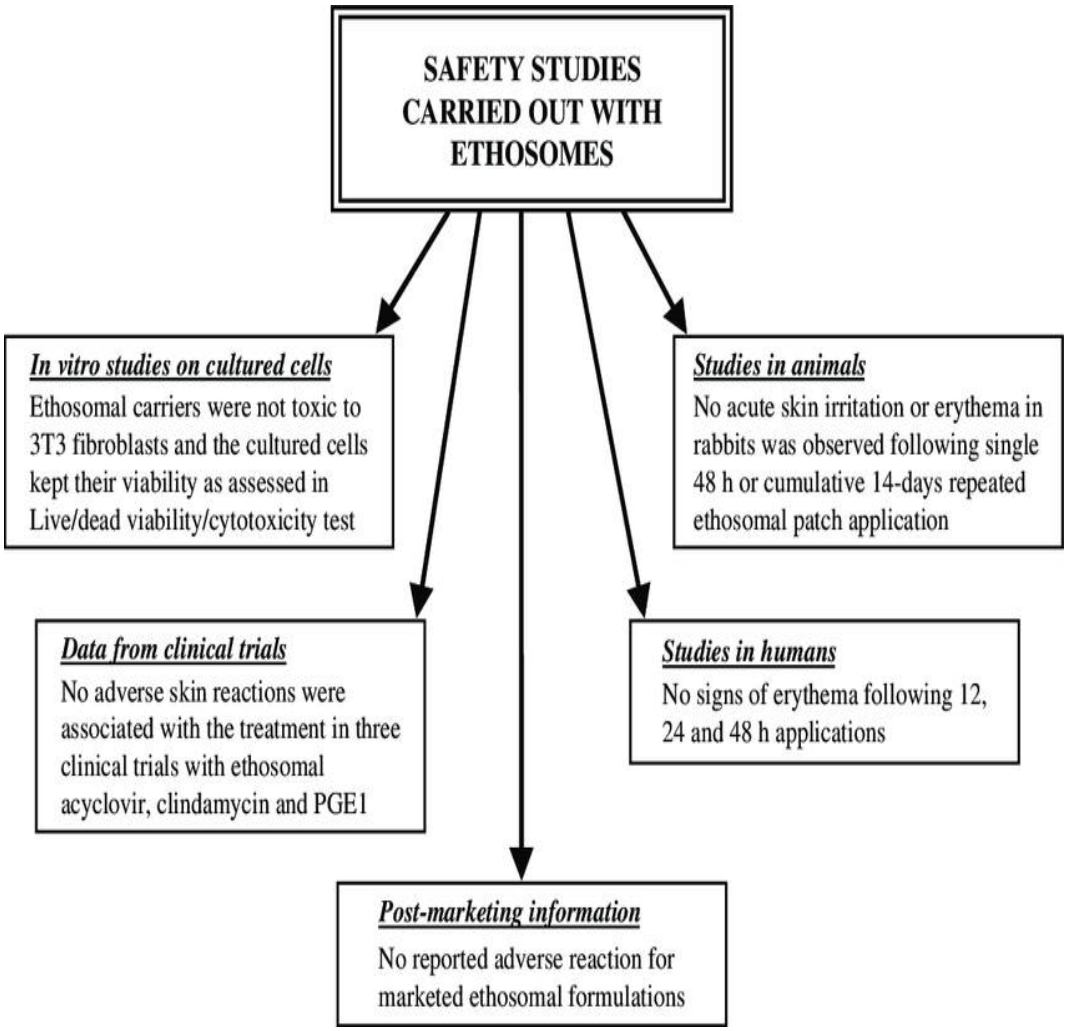

Figure (4): Safety studies carried out with ethosomes (11)

Stability of ethosomes:

Entrapment capacity and particle size were used to assess the ethosomal formulations' stability over time. Essentially, choosing the right lipid composition appears to be a key aspect in creating dispersions of stable ethosomes the best pharmacological and therapeutic properties. When liposomes are stored, they can undergo a variety of modifications (27).

Liposomes tend to merge and expand into larger vesicles during storage, and this fusion and rupture represent a significant risk of drug leakage from the vesicles. The lack of electrostatic repulsion is believed to account for the neutral liposome's tendency to assemble, however in the case of ethosomes, ethanol ghange the system charge and gives some degree of steric stabilization, which results in increase dispersibility and stability and decrease average ethosomal size (27).

Boosting percentage of ethanol from 15%- 45% enhances entrapment efficiency due to the enhanced membrane fluidity. The ethosomes' lipid part is generated from different type of phospholipid origin. Unsaturated fatty acid consisting of phospholipids is known to undergo oxidation. The products of oxidation may alter the permeability of ethosome (27).

Because the presence of lyso-PC increases the permeability of ethosomes, it is critical to limit its level in a particular preparation to a minimum (28).

The capacity of Ethosomal preparations to maintain medicine was tested by keeping the formulas at various temperatures for various amounts of time, namely 252°C (room temperature), 372°C, and 452°C. Ethosome stability may also be measured quantitatively using DLS and TEM to examine the size and appearance of the vesicles (28).

Evaluation of the various properties of ethosomes, transfersomes, and liposomes

Evaluation of the various properties of ethosomes, transfersomes, and liposomes is summarized below in table (2).

Table (2): Evaluation of the various properties of ethosomes, transfersomes, and liposomes [8]

Characters	Liposome	Transferosomes	Ethosomes
Vesicles	Bilayer Lipid vesicle	2nd generation elastic lipid vesicle carriers	3rdgeneration elastic lipid vesicle carriers
Composition	Phospholipids and Cholesterol	Phospholipids and edge activator	Phospholipids and Ethanol
Characteristics	Microscopic Spheres (Vesicles)	Ultraflexible Liposome	Elastic Liposome
Flexibility	Rigid in nature	High deformability due to surfactant	High deformability and elasticity due to ethanol
Permeation Mechanism	Diffusion/Fusion/Lipolysis	Deformation of vesicle	Lipid Perturbation
Extent of Skin Penetration	Penetration rate is very less as the stiff shape and size does not allow to pass through stratum corneum	Can easily penetrate through paracellular space by flexible structure	Can easily penetrate through paracellular space by ethanol effect
Route of administration	Oral, Parenteral, Topical and transdermal	Topical and Transdermal	Topical and Transdermal
Marketed products	Ambisome, DaunoXome, Doxil, Abelect	Transfersomes® (Idea AG)	Nanominox, Cellutight EF, Noicellex, Decorin Cream

Applications:

Ethosomes can successfully encapsulate and transfer highly lipophilic compounds like testosterone, cannabis, and ibuprofen, as well as hydrophilic medicines like clindamycin phosphate and buspirone hydrochloride, into the skin due to their unique structure. Peptides, hormones, antibiotics, prostaglandins, and antivirals have all been explored for transdermal and intradermal administration.Peptides, hormones, antibiotics, prostaglandins, antivirals, and antipyretics have all been (29).

The ingredients used to manufacture ethosomes have already been approved for use in medicinal and cosmetic products, and the vesicles are stable when kept. They can be used in gels, creams, emulsions, and sprays, among other medicinal preparations. As a result, pharmaceutical and cosmeceutical products are being produced. Ethosomal systems outperform other carriers in a number of ways.In terms of quantity and depth of chemical distribution, ethosomal systems outperform alternative carriers (30).

Pharmaceutical applications:

- **Transdermal drugs**

Due to their capacity to economically pass through healthy human skin, the use of ethosomes can result in a medicine delivery efficiency of more than 65 percent (Touitou et al., 2000, 2001). For the treatment of numerous skin conditions, ethosomes have successfully delivered drugs like ketotifen, bacitracin, minoxidil, and other chemicals through the skin (23).

- **Hormonal drugs**

Oral hormone delivery is associated with a number of issues, including:-

- Low oral bioavailability
- High first-pass metabolism
- A number of negative consequences that is dose-dependent.

In addition to these turn down effects, oral hormonal preparations also strongly rely on patient compliance. It recognized that the risk of treatment failure rises with each missed tablet. (Johnsen et al., 1974).Touitou et al. demonstrated the potential of ethosomes in hormone administration by comparing transdermal distribution of testosterone-loaded ethosomes (Testosome) to transdermal testosterone patch (Testoderm patch, Alza) across rabbit pinna skin. The ethosomal formulation showed roughly 30-times higher skin permeation of testosterone. The amount of medicine deposited in the ethosomal formulation was markedly higher. When Testosome was used instead of Testoderm, the area under the curve (AUC) and Cmax of testosterone increased considerably. As a result, both in vitro and in vivo experiments showed that the ethosomal formulation increased skin permeability and testosterone absorption. In a subsequent investigation, same group created a testosterone non-patch formulation to minimize the area of application. It was

observed that the area of application required by ethosomal testosterone formulation to provide the effective dose was ten times less than that required by marketed (AndroGel) formulation (31).

- **DNA delivery:**

Skin is an immunologically active organ that facilitates expression of genes and serves as a formidable barrier against microbes passing through the body's periphery.It aids in the transportation of chemicals via DNA in skin cells that are encased in protein i.e. GTP-cytomegalovirus (CMV) tended to focus by transfecting constructs into ethosome for gene expression, which has also been shown to be a necessary use of ethosomes.CLSM studies have demonstrated that applying the ethosomal formulations on the dorsal side of 5-week-old CD-1 male mice for 48 hours and then removing it from the skin after 48 hours assisted successful drug delivery. As a result, the GFP-Cytomegalovirus-driven transfecting construct allowed for efficient gene expression in skin cells (32).

- **Anti-viral drugs**:

Zidovudine ethosomal formulations have been created to boost transdermal flow and extend release to avoid the problem of zidovudine oral administration being accompanied with severe adverse effects (Jain et al 2004). The ethosomal formulation of acyclovir was created for cutaneous administration (Horwitz et al 1999).They compared it to a commercial formulation of acyclovir (Zovirax, Glaxo-Wellcome) in a double-blind, randomized study in terms of time to crust development, time to crust removal, and proportions of lesions not progressing beyond the popular stage (abortive lesions).When ethosomal formulation was used to treat the disease, there was a significant improvement in all clinical parameters compared to the marketed formulation. For ethosomal acyclovir and zovirax, the average time to crusting of lesions was 1.6 vs 4.3 days in the parallel arm and 1.8 vs 3.5 days in the crossover arm (P0.025).As a result, when acyclovir was loaded into ethosomes, there was a faster recovering and a higher percentage of abortive lesions (33).

- **Anti-arthritis and anti-inflammatory activity drugs:**

On volunteers with erythema caused by methyl-nicotinate, ethosomes loaded with Ammonium glycyrrhizinate (AG) were tested for their anti-inflammatory effects. To further understand the effects of ethosomes on erythema, a comparison was done between the drug's hydroethanolic solution and the anti-inflammatory action of ethosomes loaded ammonium glycyrrhizinate. The Erythema index was calculated using a Reflectance Visible Spectrophotometer. The ethosomes laden Ammonium glycyrrhizinate showed a reduction in the length and vividness of erythema as compared to hydroethanolic solution. Cannabidiol (CBD), a medication used to treat rheumatoid arthritis, has a high affinity for lipids.Poor BA due to hepatic metabolism, gastric pH instability, and limited aqueous solubility are just a few of the drug's adverse effects. In vivo permeation tests were used to test the skin permeability of ethomal CBD. The drug was discovered to have built up in the skin and tissues beneath it (19).

- **Parkinson disease drugs**:

For the treatment of parkinson's disease, Dayan and Touitou (2001) developed an ethosomal formulation of the psychoactive drug trihexyphenidyl hydrochloride (THP) and compared its distribution to that of a conventional liposomal formulation. Parkinson's disease is treated with THP, an antagonist of M1 muscarinic receptors. THP has a short biological half-life (3 hours), and due to movement impairments and neurological signs associated with parkinsonian disease, oral administration is challenging (29).

The THP ethosomal formulation looked like small phospholipid vesicles under transmission and scanning electron microscopes. In comparison to liposomes, phosphate buffer, and hydroethanolic solution, the transdermal flow of THP from ethosomes through naked mouse skin was 87, 51, and 4.5 times higher, respectively.

The amount of THP remaining in the skin after 18 hours following the application of ethosomes was significantly higher than it was following the application of liposomes or hydroethanolic solution (control). These results indicated that the ethosomal-THP formulation had a greater capability for skin penetration and might be used to more effectively manage Parkinson's disease (30).

- ## Cosmeceutical applications of ethosomes

The use of ethosomes in cosmeceuticals has a number of benefits, including boosting transdermal permeability, especially in elastic forms, and improving the stability of cosmetic chemicals as well as lowering skin irritation from irritating cosmetic chemicals (34).

The compositions and sizes of the vesicles, on the other hand, are the most important aspects to consider when using elastic vesicles for cosmeceutical applications. One of the various techniques to reducing oxidative harm in the skin for aesthetic and cosmeceutical uses is topical administration of various antioxidants (35).

Antioxidants, on the other hand, are rarely stable and c. One of the most frequently seen exogenous lipophilic antioxidants in tissues is vitamin E. The topical treatment for it can aid in shielding the skin from oxidants outside. When applied to cosmetics and several dermatological products, vitamin E has been shown to prevent UV exposure, some dangerous chemicals, and physical agents, as well as limit the production of lipid peroxides in the epidermis. In their study "Antioxidant Ethosomes for Topical Delivery Utilizing the Synergistic Properties of Vitamin A Palmitate, Vitamin E, and Vitamin C," Koli et al. (2008) found that the synergistic interaction of Vitamin C in the aqueous core and Vitamin A and E in the lipid bilayer provides total protection from oxidative stress. This indicates that while tocopherol cannot be delivered via the skin using either elastic or non-elastic liposomes, encapsulating the vitamin in either can increase its photo-stability when exposed to UVB rays (30).

Examples of ethosomal products:

Esposito et al. (2004) created liposomes and ethosomes of azelaic acid as a topical medium gel, and the results showed that ETHOS 40 might be accountable for a higher drug than liposomes and ETHOS 20 (30).

Osmotics Inc., a firm based in the United States, announced the launch of lipoduction, a novel cellulite cream that employed ethosome technology to penetrate the skin's lipid barrier and deliver chemicals straight to fat cells. In less than 60 days, ingredients and excipients in lipoduction reduced the look of cellulite by up to 80% (30).

Phenylethyl resorcinol (PR)-containing ethosome formulations were created. 0.5 percent w/v Phenylethyl resorcinol, 0.5 percent w/v cholesterol from lanolin, 3 percent w/v L—phosphatidylcholine from soybean, 30 percent v/v absolute ethanol, and water up to 100 percent v/v were used to make the formulation. It had a vesicular size of 389 nm, a low polydispersity index of 0.266, a zeta potential of mV, a high PR entrapment effectiveness of 71%, and good stability after 4 months of storage at 4 and 30°C at 75% RH. The penetration coefficient of PR from ethosomes was substantially greater than that of liposomes in in vitro tests utilizing pig skin. PR accumulation in pig skin after application of ethosome formulations was 7.4-, 3.3-, and 1.8-fold greater than that attained with liposomes, 20 percent propylene glycol solution, and 30 percent hydroethanolic solution, respectively, according to in vitro retention profiles. PR's antityrosinase activity in pig skin was shown to have an inhibition value of roughly 80In B16 melanoma cells, ethosomes consistently showed stronger tyrosinase inhibitory efficacy and melanin content decrease than other formulations. In albino rabbits, ethosomes did not produce acute cutaneous irritation. These results and findings show that this drug delivery are capable to effectively transporting phenylethyl resorcinol into the skin and have potential for topical lightening skin solutions (36).

Characterizations of ethosomes

1.Visualization

TEM (Transmission electron microscopy) (10) and SEM (scanning electron microscopy) could both visualize ethosomes (37).

2.Stability of vesicle

The shape and size of ethosomal particle could be assessed over time to identify the stability. The dynamic light scattering measures mean vesicle size, whereas TEM determines structural changes (38).

3.In vitro drug release study and drug deposition study

Franz diffusion cell with manufactured or biological membranes, Dialysis bag diffusion could be used for in vitro drug release studies and drug deposition of ethosomal formulation (39).

4.Particle size and zeta potential: size of the ethosomes particle

Dynamic light scattering (DLS) and photon correlation spectroscopy can be utilized to determine this (PCS). A Zeta meter can be used to determine the formulation's zeta potential (25).

5.Entrapment efficiency:

The ethosomal vesicles entrapment efficiency is measured using the centrifugation technique. A centrifuge of high-speed cooling of a speed 20000 rpm and a temperature of 40 C is employed in this process for around 90 minutes. The supernatant and sediment liquids are separated with the use of a centrifuge. By lysing the vesicles with methanol, the sediment recovered can be used to estimate the amount of drug present. We can calculate the entrapment efficiency using this equation (40).

$$Entrapment\ efficiency = \frac{DE}{DT}\ X\ 100$$

DE- the quantity of medication in the sediment

DT- medication used in formulation (equal to the drug amount in sediment and supernatant liquid) (40).

6.Permeation and penetration studies

Confocal laser scanning microscopy is being utilizing to determine the ethosome's penetration depth (CLSM) (41).

7.Transition temperature

DSC in an aluminum pan with a heating rate of 10 °C per minute, under a steady nitrogen stream, could be utilized to measure the transition temperature (T) of vesicular lipids in duplicate (42).

8.Measurement of surface tension

Surface tension test of medications in aqueous liquids can be performed using the ring technique via Du Nouy ring tensiometer (43).

Conclusion

To avoid harmful and undesirable side effects at other areas, medications might be administered directly to the area where they work. They can also be used to lower the dose of medication administered, increase the pharmacological action of the drug, and increase the bioavailability of medications with limited bioavailability. Because drug targeting to the site of action enhances overall efficacy, the vesicular system is advantageous for drugs with a narrow therapeutic index. Twenty years after its invention, ethosomes have already shown they have the ability to transport therapeutic chemicals via the skin without having any unwanted side effects.

The use of ethosomes in appropriate vehicles such lotions, gels, and patches improves skin permeability and therapeutic effects. There are a variety of ethosomal preparations on the market right now. However, more research is needed to improve the stability of ethosomes. The fundamental problem of transdermal drug administration is that most chemicals do not penetrate the human skin well. The stratum corneum, the skin's topmost layer, is home to the skin's principal barrier. In addition, study in this field will allow for improved regulation of medication release in vivo as well as long-term safety data, allowing for more effective therapy.

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