

Ethosomes: a potential nanocarrier for transdermal drug delivery

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ABSTRACT

Ethosomal system is a lipid vesicular nanocarrier that holds a high concentration of alcohols. This nanocarrier is optimized for the dermal and transdermal delivery of medicinal drugs with various physicochemical features. Since its release in 1996, ethosomes have been subjected to subsequent studies to modify the original formula via the addition of different components, leading to the development of novel ethosomal system types. These new carriers are prepared via a variety of methods and characterized through different parameters, including vesicular size, zeta potential, entrapment efficiency, and skin permeation. The ethosomes efficacy in dermal/transdermal administration is evaluated via clinical studies as well as a wide range of in vivo models. Ethosomal dispersions are frequently incorporated into topical preparations, including gels, patches, and lotions, due to their stability and convenience. This article provides a thorough overview of ethosomal systems from the standpoint of ethosomal types, beginning with classical ethosomes and progressing to binary ethosomes and transethosomes. In addition, this work provides a comprehensive overview of the components of the ethosomal system and their contribution to the final properties of ethosomes, besides highlighting the different methods of preparation and the common dosage forms used as ethosomes' vehicles.

Keywords: Ethosomes; Transethosomes; Ethanol; Cold method; Skin permeation.

Introduction

The skin is the widest and most exposed organ of the body, and it offers a promising way for systemic drug administration via the transdermal route. Transdermal drug delivery systems have many benefits for patients because they are both self-administered and noninvasive carriers. On the other hand, this route of administration prevents the drug from undergoing first-pass metabolism in the liver, enhancing more precise dosing, reducing administration frequency, and increasing patient compliance. The transdermal bioavailability of drugs is restricted by the skin's outermost layer, the stratum corneum, which acts as a highly resistant barrier to drug penetration. To overcome the skin's natural barrier and reach the body's circulatory system, delivered compounds with distinct physicochemical qualities could be loaded into unique carriers (1, 2).

The development of liposomal formulae for the topical administration of drugs was the starting point for the creation of a broad variety of elastic lipid-based vesicular systems. Cevc and Blume described transfersomes as the first flexible liposomes (3), and subsequently, the novel research of Tuitou et al. led to the discovery of a new lipid vesicular system named ethosomes that are distinguished from liposomes by the presence of relatively large amounts of ethanol in addition to phospholipids and water (4, 5). Later, several modifications of the initial ethosomal systems were developed by incorporating various chemicals into the core ethosomal formula in an effort to improve vesicular properties and skin penetration.

This review article investigates the ethosomal system in depth, distinguishing the various types of ethosomes based on their chemical composition and the influence of these chemicals on ethosomal properties. In addition, this article discusses the different techniques that are used for the preparation of ethosomes and the pharmaceutical dosage forms that could be used as vehicles for the ethosomal formula.

Classification of ethosomal systems

The known ethosomal systems could be classified into three distinct types according to the components incorporated into their formula namely, classic or traditional ethosomes, binary ethosomes, and transethosomes as shown in **Figure 1**.

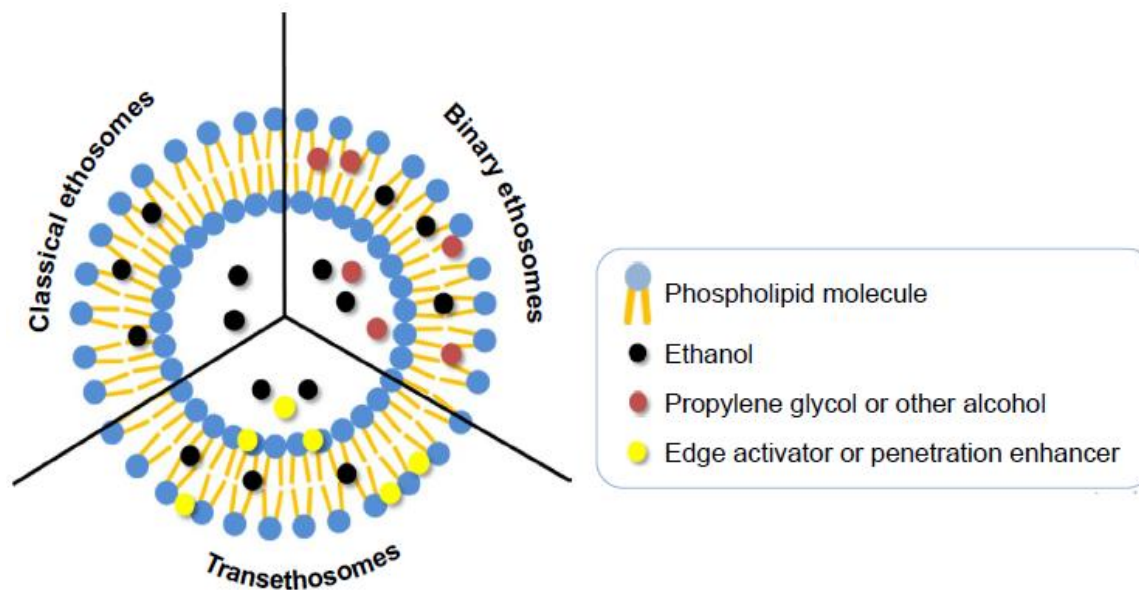


Figure 1: Different types of ethosomal systems and their composition (6).

Traditional ethosomes

Traditional or classical ethosomes are the initially developed ethosomal system that modified the liposomal composition via the incorporation of a relatively high amount of ethanol, up to 45%, along with phospholipids and water components. Traditional ethosomes showed a high potential for transdermal drug delivery when compared with traditional liposomes mainly due to their greater entrapment efficiency, smaller size, and negative surface charge (4, 7). Furthermore, the ethosomal system revealed greater stability in comparison with the classic liposomes.

Binary ethosomes

This type of ethosomal system was first described by Zhou et al. (8) and included modification of the traditional ethosomes via the addition of different kinds of alcohol. The binary ethosomes have been studied in different research that widely used propylene glycol/ethanol mixture (1, 9-13) or isopropanol /ethanol mixture (14-16).

Transethosomes

Transethosomal system is the latest generation of ethosomes that was first described by Song et al. (17). This system has the same components as traditional ethosomes, but with the inclusion of an edge activator or penetration enhancer into the vesicular structure. The development of these

vesicles was a trial to merge the benefits of traditional ethosomes with transfersomes (elastic liposomes) into a single vesicular carrier that was proved its significant superiority over the classic ethosomes as reported by several studies (18-24).

Composition of ethosomal system

Phospholipids

Phospholipids are the main building blocks of any lipid-based vesicles, including ethosomes. There are different types of phospholipids that impart various properties to the produced vesicles and affect their size, entrapment efficiency, permeation properties, and stability. Therefore, the types and concentrations of phospholipids should be carefully selected according to the main aim of the study. The most commonly used phospholipids in ethosomal formulations are phospholipon 90G (25-29), phospholipon 90H (30-32), and α -phosphatidylcholine (33-35). Phospholipids were reported in ethosomal formulations at concentration ranges between 0.5 and 5.0 percent (36). It was found that the increase in phospholipids concentration dramatically increased both the size of vesicles and entrapment efficiency (1, 37). But at a critical concentration, the effect on entrapment efficiency is diminished, as reported by Zhaowu et al. (38).

Ethanol

Ethanol is the unique component of the ethosomal system that acts as a potent permeation enhancer and is mainly responsible for the preferable properties of ethosomes. Ethanol concentrations in ethosomal systems have been observed to range between 10% and 50% (37). The incorporation of ethanol into the vesicular system imparts a significant reduction of the vesicular size (1, 39), an increase in entrapment efficiency (40, 41), and an improvement of both the zeta potential and stability of the produced vesicles (42, 43). The solubility of both lipophilic and amphiphilic agents is improved by ethanol, leading to higher drug loading. However, exceeding the optimal ethanol concentration would result in a leaky bilayer due to the solubility of phospholipids in ethanol, which would increase vesicular size somewhat while drastically reducing entrapment efficiency, and further raising the ethanol concentration would solubilize the vesicles (44, 45). According to some research, the hydrocarbon chains in ethanol may interpenetrate at high concentrations, resulting in a thinner vesicular membrane and a smaller

vesicle (46, 47). Other literature referred to the penetration power of ethanol as being due to the negative charge that it imparts on vesicles and may affect other characteristics, such as the stability and vesicular interaction with the permeable membrane (45). The charged surface of ethosomes prevents the vesicular system from clumping together owing to electrostatic repulsion. The negative charge of the empty ethosomes increases with increasing ethanol concentration, according to Dayan and Touitou (48).

Propylene glycol

Propylene glycol (PG) is another penetration enhancer that is incorporated into binary ethosomes at concentrations ranging from 5-20 % (49). It has been shown to alter ethosomal features such as entrapment efficiency, size, permeability, and stability. For instance, when PG is added to ethosomal systems, the particle size is reduced even more when compared to systems without PG (1, 50, 51). Other studies have proposed that the inclusion of PG and ethanol in ethosomes improves drug solubility, resulting in improved drug distribution throughout the vesicle and enhanced entrapment efficiency (52). In vitro drug permeation via Franz diffusion cells revealed the significant difference between the classical and binary ethosomes in drug deposition through the stratum corneum as reported by Abdelbary G. *et al.* (1). It was observed that the ratio of ethanol:PG should be optimized to obtain a great enhancement in drug permeation, as shown by several studies (1, 53). The binary ethosomes were revealed to be more stable than traditional ethosomes when stored at 4°C (8).

Other components of ethosomal system

The development of transethosomes forces the incorporation of a variety of ingredients into the ethosomal formula in order to improve their properties and enhance the penetration power of the entrapped agents. The most commonly added edge activators are tween 80 (17, 19-21, 54), oleic acid (55-57), and different types of bile salts (17, 58, 59). Tween 80 is employed in the ethosomal system at concentrations ranging from 10% to 50% of total phospholipid content and showed a potential to minimize vesicular size and improve system stability and skin-permeation qualities in ethosomal systems. Tween 80's effects on the ethosomal system are mostly related to its solubilizing characteristic and ability to prevent vesicle fusion (20, 54, 60). In a similar pattern, oleic acid modulates vesicular size, elasticity, zeta potential, and skin permeability via enhancing

the fluidity of the stratum corneum. Different studies revealed that the incorporation of oleic acid into the transethosomes produces more elastic vesicles of smaller vesicular size, higher entrapment efficiency (61), and also increased skin permeation and deposition of the loaded agents, besides enhancing the negative zeta potential of the vesicles (17). The bile salts are widely used permeation enhancer that could withstand alone such as bilosomes (62, 63), and could be included in transethosomes (55, 64). A study for instance, incorporated sodium deoxycholate in the transethosomal formula and it was found that sodium deoxycholate significantly increased both the entrapment efficiency and the vesicular size that was attributed to the electrostatic repulsion between the bilayers that increased the interbilayer distance (65). Furthermore, it was reported that sodium cholate and sodium taurocholate improve the stability of the vesicular system as a result of enhancing the negative zeta potential (17, 66). In other studies, various ingredients were added to transethosomes such as sodium stearate (67), Dicetyl phosphate (68), and stearylamine (69).

Advantages of ethosomal system

- The formulation's ingredients are non-toxic.
- The ability to load and deliver large agents (protein and peptides).
- The semisolid dosage forms facilitate ethosomal administration and enhance patient compliance.
- The ethosomal system is a noninvasive, passive technique.
- This could produce a prolonged action of the loaded drug and an extended half-life in systemic circulation.
- Transdermal delivery of the loaded agents is easy in comparison with other application methods such as Iontophoresis, Phonophoresis.
- Easy to prepare with acceptable stability.
- Could be applied to the delivery of pharmaceutical and cosmetics agents.

Disadvantages of ethosomal system

- The molecular weight of the loaded agents should be suitable for transdermal delivery.
- Ethosomal system is not appropriate for the delivery of large drug dose.
- Not appropriate for oral delivery due to the high alcoholic contents.
- Adhesion to the skin may differ according to the skin type.
- Could produce irritation or discomfort on the application due to formulation contents.

Theory of ethosomes permeation

Different processes were hypothesized to explain the remarkable penetration efficiency of ethosomes via the skin, as shown in **Figure 2**. At a healthy temperature, the SC lipid multilayer of skin is tightly packed and structured in an ordered form. Ethanol is a powerful penetration enhancer that is incorporated at a high concentration in the ethosomal system, functions as an efficient penetration enhancer that has a fluidizing impact on the lipid bilayers of the stratum corneum by lowering the stratum corneum's melting point (T_m) (70, 71). This results in a disruption of the organisation of the skin's lipid bilayer and a reduction in the density of the skin's lipids. Additionally, ethanol has the potential to impart the vesicle bilayer more softness and flexibility. These flexible ethosomal vesicles have the ability to break through the disordered lipid bilayers of the SC. Through the fusion of these vesicles in the deeper layer of skin, drugs are released (70, 72, 73). In conclusion, the impact of ethanol on the lipids of the SC as well as the fluidity of the vesicles, in addition to the potential of contact between ethosomes and the SC, may result in improved drug delivery.

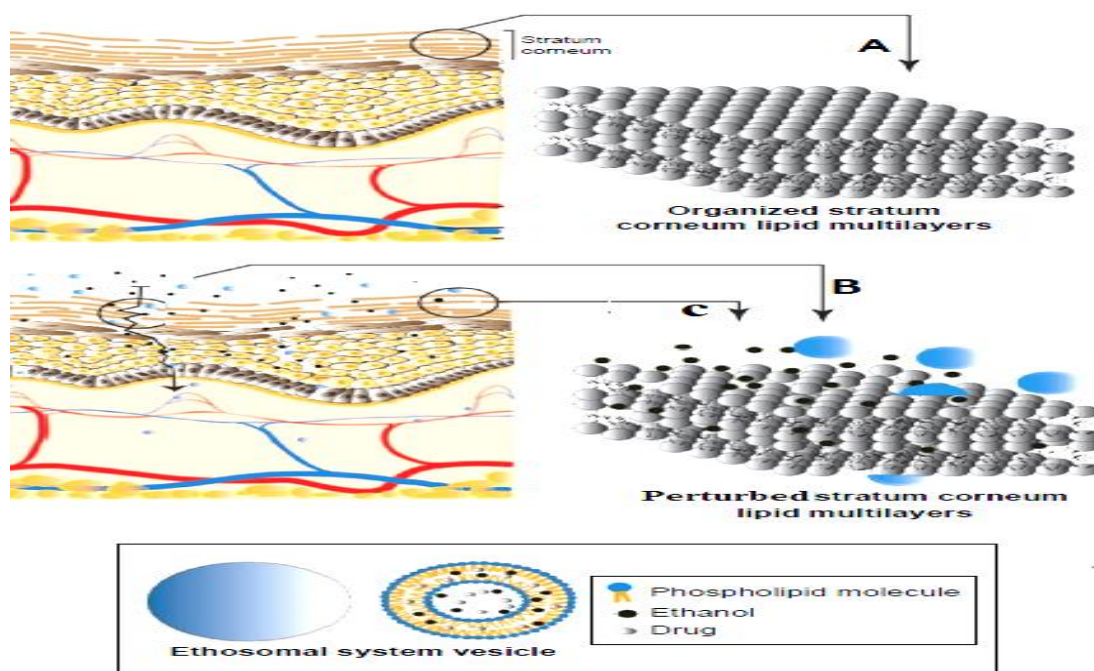


Figure 2: Schematic representation of different mechanisms of drug delivery from the ethosomal system. (A) Normal skin; (B) Penetration of the soft malleable ethosomal system vesicles; (C) Skin-lipid perturbation by ethanol effects (6).

Different methods for preparation of ethosomes

There are various methods for the preparation of the ethosomal system that include the cold method, the hot method, the thin film rehydration method, the ethanol injection method, the reverse-phase evaporation method, and the transmembrane pH-gradient method.

The classical cold method

The classical cold method is the easiest and most commonly used approach to preparing ethosomal systems that was developed by Touitou (4). The organic phase and the aqueous phase were prepared separately at 30°C, where the phospholipids (along with surfactants or penetration enhancers for transethosomes) dissolve in ethanol or a mixture of solvents (ethanol/PG) to produce the organic phase. Water, buffer solution, or normal saline solution are used as the aqueous phase and is slowly added to the organic phase, drop by drop. A magnetic stirrer is used to stir the mixture at a speed of 700–2,000 rpm. To get the right ethosomal suspension, the mixing is done for 5–30 minutes. Depending on its physicochemical properties, the drug could be dissolved in either the water phase or the oil phase (1, 74-76).

The hot method

The ethosomes' inventor described this approach in 1996 (77). Phospholipid is distributed in water and heated to 40°C to form a colloidal suspension. Using a mechanical or magnetic stirrer, ethanol is heated to 40°C and added dropwise to the phospholipid dispersion. Based on hydrophobic / hydrophilic characteristics, the drug is dissolved in organic or aqueous phases (78, 79).

The thin-film hydration method

This approach is an extension of the usual liposome-preparation process, but the hydration of the lipid film is conducted via hydroalcoholic liquid. In a dry, clean, round-bottom flask, the phospholipids are dissolved in a suitable organic solvent usually chloroform (80) or a mixture of chloroform/methanol (81). At temperatures above the lipid-phase transition, a rotating vacuum evaporator removes organic solvents. Then, the solvents are removed from the lipid film overnight under a vacuum. The lipid film is subsequently hydrated using a hydroalcoholic solution or phosphate buffered saline/ethanol mixture (12, 80, 81).

Ethosomal dosage forms

The ethosomal system has a high alcohol content; therefore, incorporating the system into an appropriate vehicle for dermal/transdermal administration prolongs skin contact time, reduces evaporation of ethanol, enhances drug effectiveness, increases stability and shelf life of the system, and improves patient compliance. The ethosmal system was reported to be loaded into various topical dosage forms, including gels, transdermal patches, and creams.

Ethosomal gels

Gel is a commonly used dosage form for loading the ethosomal system and is usually based on Carbopol (76, 82-84), or hydroxypropyl methylcellulose (85-87), as gel-forming agents. The pH, viscosity, spreadability, and extrudability of ethosomal gels are among their distinguishing features. These polymers have been demonstrated to be compatible with ethosomal systems, giving them the necessary viscosity and adhesive characteristics. The skin permeation and deposition of different drugs from ethosomal gels have been studied by many researchers and found to be superior to those of conventional or commercially available gels or creams (1, 84).

Ethosomal patches and creams

Patches or creams are less commonly used as a vehicle for ethosomal systems, often due to the ease of preparation and compatibility of gel bases with the high alcoholic content of ethosomes, acceptable patient compliance compared to creams, besides the difficulties associated with patch development where specific molds are required (88, 89). On the other hand, patches offer the delivery of the loaded agents under occlusive conditions that could improve the skin's permeation and deposition. However, in the case of the ethosomal system, the efficiency of delivering the loaded agents under occlusive and nonocclusive conditions showed no significant difference as reported by Godin and Touitou (90).

Conclusion

Several studies have demonstrated the ethosomal system's ability to transport therapeutic compounds through the skin for both local and systemic applications. Later, intense studies over many years led to the development of transethosomes, a novel class of ethosomal systems with

enhanced vesicular capabilities and skin permeation potential compared to those of standard ethosomes. By altering the edge activators and/or penetration enhancers, the characteristics of transethosomes could be modified in accordance with the study requirements. The incorporation of ethosomal systems into acceptable vehicles, such as gels, patches, and creams, is a critical step towards improving skin permeability and therapeutic efficacy. However, further investigations are required to improve the stability of the ethosomal system and force its commercial applications.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this review article.

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