

## Evaluation of the effects of ethosomes in the delivery of transdermal drugs

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### Abstract

The purpose of drug administration through the skin is to treat skin disorders on a topical level or to deliver drugs to the systemic circulation via transdermal absorption due to the variability in peak plasma concentration following oral and parenteral delivery. Ethosomes lipid-based nanovesicles with improved softness, deformability, and elasticity, are the most investigated vesicular system. Ethanol, cholesterol, and lecithin are used to prepare ethosomes. The loose hair follicles and Stratum Corneum (SC) percutaneous route allowed the ethosomes to permeate the epidermis. During percutaneous penetration, the vesicles were released into the superficial layer of the skin, allowing the therapeutic substances to penetrate while the phospholipids remained in the upper epidermis.

**Keywords:** Ethosomes, ethanol, skin, vesicles, Stratum Corneum

Received on: 03. 05. 2022

Revised on: 20. 05. 2022

Accepted on: 30. 05. 2022

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### 1. Transdermal drug delivery systems (TDDS):

Skin, the biggest organ in the body, was not recognized as a route of drug delivery for systemic medications until the late twentieth century (El-Menshawe *et al.*, 2019).

In the last decade, transdermal medication delivery has attracted much attention. According to experts, By 2025, the global transdermal drug delivery market is expected to reach \$95.57 billion (Shewaiter *et al.*, 2021).

The SC, a 10 m-thick layer of dead, keratinized epidermal cells that act as a barrier for drug permeation, is the most typical way to absorb drugs through the skin.

The purpose of drug administration through the skin is to treat skin disorders on a topical level or to deliver drugs to the systemic circulation via transdermal absorption. Because peak plasma

concentrations differ between oral and parenteral administration, overdosing becomes a common problem, making it difficult to efficiently monitor plasma concentration (Yu, Yang, *et al.*, 2021).

There are many advantages to (TDDS). For example, medications can avoid hepatic first-pass metabolism and factors that modify pharmacokinetics in the gastrointestinal tract, improving systemic bioavailability and lowering the risk of drug concentration-related side effects because the topically applied drugs are released in a predetermined range over a long time. This often increases patient compliance because it is easy to use with a low dose frequency (Ita, 2020). Moreover, the topical route provides a large and varied application surface and ease of self-administration. It is an available alternative to both oral delivery and hypodermic drug injection.

Skin physiology, drug physicochemical factors,

and the delivery system determine the frequency and degree of drug absorption through the skin. The present transdermal dosage forms, such as patches, ointments, and creams, are associated with several limitations. One of the most unpleasant side effects of transdermal patches is skin irritation, caused by their occlusive properties, which block sweat ducts, preventing water drainage from the skin surface. Other disadvantages include difficulties applying to curved surfaces, pain while peeling away, and a lack of aesthetic appeal (Belikov *et al.*, 2015).

Semisolid treatments, such as creams and ointments, may overcome some of these difficulties, but they also have limitations. Such forms do not maintain long-term contact with the skin and are wiped away by the patient's clothing. As a result, the repeated application is required in chronic conditions such as athlete's foot, ringworm, and candidiasis. Furthermore, their use may leave a sticky and greasy after application, resulting in poor patient compliance (Pereira *et al.*, 2018).

A dosage form that allows for less frequent administration while maintaining direct contact with the skin for an extended period is required to improve patient compliance (Kathe and Kathalia, 2017).

### 1.1. Advantages of transdermal drug delivery:

- Transdermal medication administration avoids the difficulties of gastrointestinal absorption, including enzymatic and pH-related inactivation.
- The metabolism of the first pass is bypassed.
- Immediate medication warnings in the case of emergency and the ability to quickly reduce drug side effects by removing the patch.
- Avoid incompatibility with the gastrointestinal tract.
- Unwanted adverse effects are avoided.
- It prevents drug levels from fluctuating.
- It is simple to stop therapy at any moment.
- Easiness of self-administration.
- They are non-invasive, thus avoiding the discomfort of parenteral therapy.
- This is of great benefit in nauseated or unconscious patients.
- Transdermal therapy is a better approach to delivering drugs broken down by the stomach's acidic pH, not effectively absorbed by the intestine, or degraded by the liver (Shewaiter *et al.*, 2021).

### 1.2. Disadvantages of transdermal drug delivery:

- It is unable to achieve high serum drug levels.
- It could not be made for drugs with huge molecular weights.
- Pulsatile delivery of the drugs is not possible.
- Drugs or formulations that irritate the skin are not acceptable. In general, local irritation at the application site is a possibility
- High possibility of causing an allergic reaction.
- A specific range of drug lipid versus aqueous solubility, namely a partition coefficient (PC) value between 1 and 3, is required to allow drug permeation of the transverse SC and the underlying aqueous layer.
- Because of the intrinsic limitations of drug entrance imposed by the skin's impermeability, only potent drugs are suitable for transdermal therapy.
- Long-term adherence is difficult.

## 2- Lipid-based nanovesicles

Lipid-based nanovesicles are spherical vesicles with an aqueous inner core and one or more lipid bilayers, with hydrophilic medications encapsulated in the internal core and hydrophobic drugs integrated into the external lipid bilayers.

Liposomes, the most well-known and well-developed lipid-based nanovesicles, comprise phospholipid molecules that stabilize the formulation (Chacko *et al.*, 2020).

The phospholipid component can interact with the lipids in the SC, causing a fusion mechanism and a transdermal effect. It has also been discovered that deformable liposomes pass through SC with intact structure. (Siler-Marinkovic, 2016).

However, because of its poor fluidity, its penetration into the deeper layers of the skin is limited, and accumulation is mainly seen in the epidermis (Yu, Meng, *et al.*, 2021). so, significant efforts have been made to improve skin penetration.

Ethosomes and transfersomes, lipid-based nanovesicles with improved softness, deformability, and elasticity, are the most investigated vesicular system (Natsheh and Touitou, 2020).

Ethosomes are multilamellar nanovesicles that are

consisted of phospholipid and ethanol. Ethanol increases the fluidity of phospholipid bilayers, breaks down the SC membrane barrier, and thus enhances penetration (Mousa *et al.*, 2022).

### 3- Ethosomal system types

(Figure.1) obtained the classification of ethosomal systems based on their compositions (Abdulbaqi *et al.*, 2016).

#### 3.1. Classical ethosomes

Classical ethosomes are a development of liposome that contains phospholipids, ethanol, and water.

Classical ethosomes had many advantages over classical liposomes in transdermal drug delivery as they had a negative charge which established stability to vesicles and had smaller vesicles to achieve high entrapment efficiency % (Mousa *et al.*, 2022).

#### 3.2. Binary ethosomes

Binary ethosomes were developed by adding a different type of alcohol as Propylene glycol (PG) and isopropyl alcohol (IPA) to the classical ethosomes (Li *et al.*, 2012; Shen *et al.*, 2014).

#### 3.3. Transethosomes

The essential components of classical ethosomes are present in this ethosomal system, and an additional component, such as a penetration enhancer or an edge activator (surfactant) in their composition.

These novel vesicles were created to combine the benefits of classical ethosomes and deformable liposomes into a single formula to create transethosomes.

Many studies have found that transethosomes have better qualities than classical liposomes (Chen *et al.*, 2014; Song *et al.*, 2012).

## 4. Effects of materials used on ethosomal system properties:

### 4.1. Ethanol

Ethanol is a powerful penetration enhancer, and it helps ethosomes by giving particles unique properties such as small size, negative electric potential, stability, entrapment efficacy, and improved skin permeability. (Ascenso *et al.*, 2015). Ethanol concentrations in ethosomes ranged between ~10%–40% (Puri and Jain, 2012). Many researchers concluded that when ethanol concentrations rise, the size of the ethosomes decreases (Li *et al.*, 2012; Patel *et al.*, 2012).

Bendas and Tadros (Garg *et al.*, 2016) observed that ethosomes containing 40% ethanol had a 44.6 % smaller mean vesicle diameter than

classical liposomes containing no ethanol (Nainwal *et al.*, 2019).

However, raising the ethanol concentration over 40% causes the bilayer to leak, resulting in a minor increase in particle size and a significant reduction in encapsulation efficacy (EE). Elevating the ethanol concentration further would solubilize the vesicles (El-Menshawe *et al.*, 2019).

According to certain research, Interpenetration of the ethanol hydrocarbon chain occurs at high ethanol concentrations, resulting in a decrease in vesicular membrane thickness and, as a result, a decrease in vesicular size. (Abdulbaqi *et al.*, 2016).

Other researchers believe that ethanol alters the charge of the ethosomes, resulting in a good degree of stability and a reduction in mean particle size (Mishra *et al.*, 2012; Verma and Pathak, 2012). The vesicular charge is a critical parameter that affects vesicular properties like stability and vesicle-skin contact. Because of the increased ethanol concentration in ethosomes, the vesicular charge has changed from positive to negative (Zhou *et al.*, 2010). The negative charge of simple ethosomes increases as the concentration of ethanol rises. (Abdulbaqi *et al.*, 2016).

Because ethanol gives a negative charge on the surface of ethosomes, it prevents the vesicular system from aggregating due to electrostatic repulsion. Besides, it has also been reported to have stabilizing properties (Abdulbaqi *et al.*, 2016).

Ethanol also affects ethosomes properties as entrapment efficiency (Abdulbaqi *et al.*, 2016).

### 4.2. Phospholipids

Choosing the right phospholipid type and concentration for the formulation is crucial during the ethosomes development. They will affect the vesicles' size, encapsulation efficacy, electric potential, stability, and penetration into the skin layers (Natsheh and Toutou, 2020).

In formulating ethosomes, Prasanthi and Lakshmi used three types of phospholipid (Phospholipon 90H and 80H, and soy phosphatidylcholine).

In an ethosomal formulation, phospholipid concentrations typically vary from 0.5% to 5%. Finally, increasing the concentration of phospholipids increases vesicular size slightly or considerably but does not significantly improve EE% (Ahad *et al.*, 2013).

### 4.3. Cholesterol

Cholesterol is a rigid steroid molecule that increases drug stability and EE% in ethosomes. It lowers vesicular permeability vesicular fusion and prevents leakage. It is usually used at a concentration of <3% (Zhu *et al.*, 2013). However,

it contributed to up to 70% of the overall phospholipid concentration in some formulations.

Cholesterol increases the particle size of ethosomes in several studies. (Limsuwan and Amnuakit, 2012). Scientists found that ethosomal size rises from  $136 \pm 42$  nm to  $230 \pm 27$  nm when 25.87 mm of cholesterol was incorporated in the formulation (El-Menshawe *et al.*, 2019; Nainwal *et al.*, 2019).

The addition of cholesterol to the ethosomes boosted vesicular stability and rigidity. Other researchers have seen increased rigidity (i.e., decreased elasticity) of the ethosomal vesicles when cholesterol is added (Abdulbaqi *et al.*, 2016).

#### 4.4. Diacetyl phosphate

Diacetyl phosphate is commonly added to avoid vesicle aggregation and improve the formula's stability. The ethosomal formulation is used in concentrations ranging from 8% to 20% of the total phospholipid concentration (Hasan *et al.*, 2013). All ethosomes, including diacetyl phosphate, formed vesicles with sharply negative potential (Abdulbaqi *et al.*, 2016).

#### 4.5. Stearylamine

Stearylamine induces a positive charge in ethosomes formulations. The first trial used an ethosomal system with a 2:1:1 molar ratio of phosphatidylcholine, cholesterol, and stearylamine; this combination was loaded with mycophenolic acid (Limsuwan and Amnuakit, 2012). Stearylamine addition leads to a rise in particle size, a decrease in encapsulation efficiency, and a change

in the potential charge from negative to positive, resulting in vesicle aggregation within one week.

The transdermal flux and the quantity of the drug delivered after 12 hours of the negatively charged ethosomes were significantly higher than the positively charged ethosomes (El-Menshawe *et al.*, 2019).

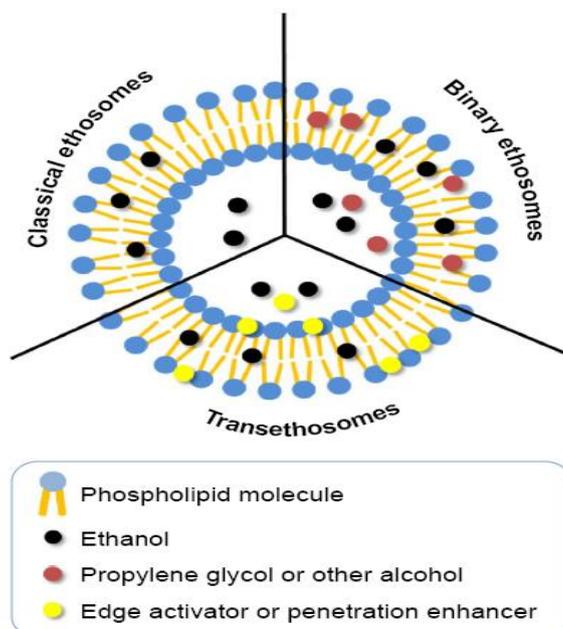
#### 4.6. Propylene glycol

Penetration enhancers like PG are widely used. It has been discovered to alter the ethosomal properties of size, encapsulation efficiency, permeability, and stability when used to prepare binary ethosomes at concentrations ranging from 5% to 20% (Limsuwan *et al.*, 2017).

Incorporating PG into ethosomal systems will result in even smaller particle sizes than systems without it (Amr Gamal *et al.*, 2020). When the PG concentration was increased from 0% to 20% v/v, the VS decreased significantly from  $103.7 \pm 0.9$  nm to  $76.3 \pm 0.5$  nm (Zhang *et al.*, 2012).

#### 4.7. Isopropyl alcohol

The effect of isopropyl alcohol (IPA) on a diclofenac-loaded ethosomal system's EE% and skin permeation was investigated. This study created classic ethosomes with 40% ethanol, binary ethosomes with 20% IPA and 20% ethanol, and ethosomes with 40% IPA (Dave *et al.*, 2010). According to the transdermal drug-flux measurements through mouse skin, IPA significantly impacted EE% but minorly impacted drug release (Dave *et al.*, 2010).



**Figure 1.** Different types of ethosomal systems (Abdulbaqi *et al.*, 2016).

## 5. Mechanism of skin permeation by ethosomes

(Figure.2) shows that the drug penetration pathways through the intact SC are available via intercellular and transcellular routes (Abdulbaqi *et al.*, 2016). Many factors influence the transport of medicines from topically applied vesicles into the skin. The size of the vesicle and the encapsulation quality are two essential factors that influence the topical administration of drugs. Smaller vesicles can quickly enter the deeper layers of the skin (Mbah *et al.*, 2014).

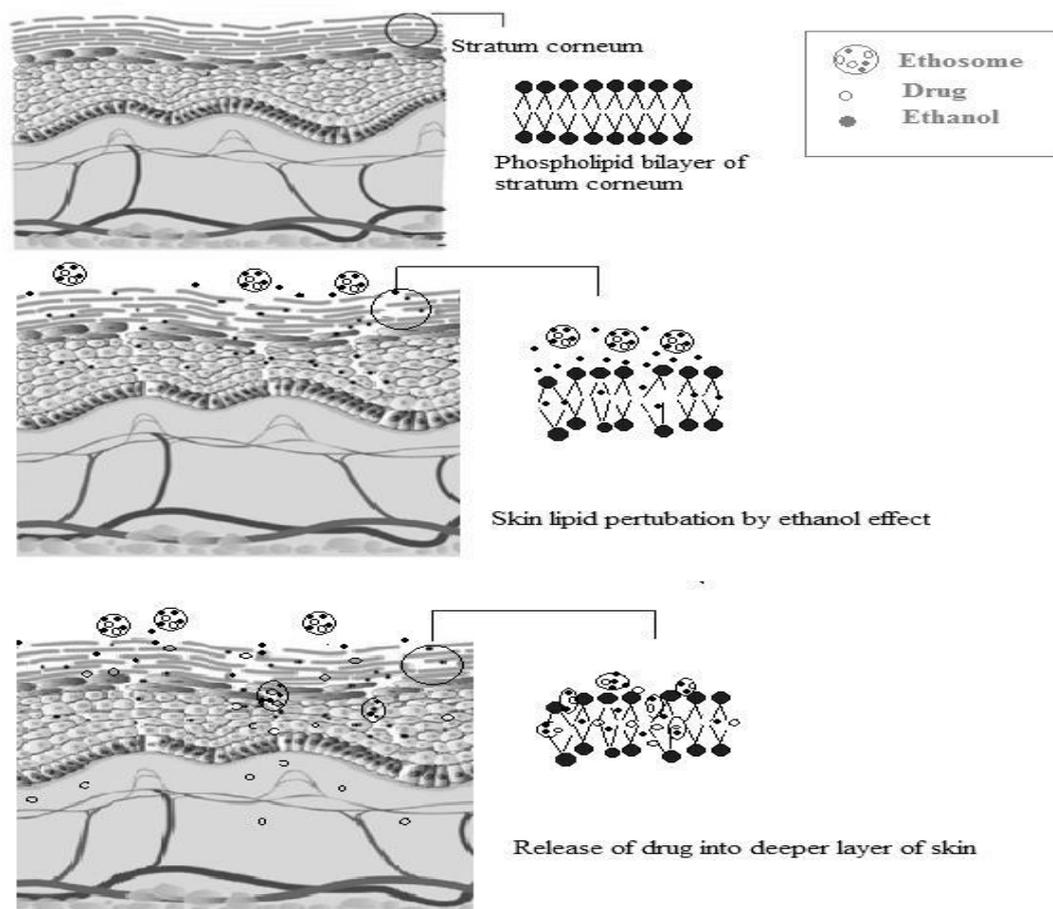
The size of the ethosomes is influenced by the amounts of phospholipids and ethanol. The size of the ethosome was shown to decrease as the concentration of ethanol increased, while the size of the vesicle increased with the concentration of phospholipids increased (Yang *et al.*, 2017).

The loose hair follicles and SC percutaneous route allowed the ethosomes to permeate the epidermis. The vesicles were released into the superficial layer

of the skin during percutaneous penetration, allowing the therapeutic compounds to penetrate while the phospholipids remained in the upper epidermis progressively. (Yang *et al.*, 2017). The reported mechanism for enhancing drug permeability is based on the ethosomal system's synergistic effects of ethanol and phospholipids. (Akhtar and Pathak, 2012).

Ethanol works as an effective penetration enhancer. At physiological temperature, the SC lipid multilayer of the skin is tightly packed and organized orderly. Ethanol raises the fluidity of SC lipids. The lipid bilayer arrangement in the skin is disrupted, and the density of skin lipids is reduced.

The vesicle bilayer may become flexible and malleable as an effect of ethanol. These soft and flexible ethosomal vesicles more easily penetrate the disorganized SC lipid bilayers, and the fusing of these vesicles in the deeper layer of the skin allows medications to be released. (Abdulbaqi *et al.*, 2016).



**Figure 2.** Proposed mechanism of drug delivery from ethosomes through the skin (Abdulbaqi *et al.*, 2016).

## Conclusion:

Ethosomes are multilamellar nanovesicles that are consisted of a phospholipid, cholesterol, and ethanol. Ethanol increases the fluidity of phospholipid bilayers, breaks down the SC membrane barrier, and thus enhances the penetration of drugs into the deepest layers of the skin.

## Conflict of interest

There is no conflict of interest.

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