REVIEW ON ETHOSOMAL GEL: FOR EFFECTIVE TRANSDERMAL DELIVERY

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Abstract: The skin, being one of the most extensive and accessible organs of the human body, offers a promising route for drug administration, providing advantages such as reduced plasma drug level fluctuations, avoidance of gastrointestinal and first-pass metabolism issues and improved patient compliance. Transdermal Drug Delivery Systems (TDDS) have evolved as self-contained dosage forms capable of delivering therapeutic agents into systemic circulation at controlled rates. Among these, ethosomes novel lipid vesicular carriers introduced by Touitou et al. in 1997 have gained significant attention due to their unique composition of ethanol, phospholipids and water, which enhances skin permeation by fluidizing stratum corneum lipids. Ethosomal dispersions prepared by hot or cold methods are evaluated based on vesicle size, morphology, zeta potential and entrapment efficiency. Incorporating these vesicles into gel matrices using suitable gelling agents further improves formulation stability, spreadability and sustained drug release. Ethosomal gels have shown promising applications in delivering various therapeutic molecules, improving dermal penetration and enhancing the bioavailability of poorly soluble drugs. This review presents an overview of Ethosomal gel formulation, characterization parameters and therapeutic potential, highlighting their growing significance as advanced non-invasive platforms for next-generation transdermal drug delivery systems.

Keywords: Ethosomes, Transdermal Drug Delivery Systems (TDDS), Lipid carriers, Skin permeation, Ethanol-based vesicles.

INTRODUCTION: The skin is one of the most comprehensive and readily approachable organs of the human body and the skin as a channel of drug delivery can offer many merits over conventional drug delivery systems including lower fluctuations in plasma drug levels, avoidance of gastrointestinal disturbances and first-pass metabolism of the drugs and high patient compliance.[1] Stratum corneum, represents the most resistible barrier to drug penetration across the skin, which limits the transdermal bioavailability of drugs. Therefore, special carriers are required to combat the natural skin barrier to deliver drug molecules with different physicochemical properties to the systemic circulation. Transdermal drug-delivery systems offer many advantages, such as avoidance of first-pass metabolism by the liver, controlled delivery of drugs, reduced dosing frequency and improved patient compliance, as they are non-invasive and can be self-administered.[2]

Transdermal drug delivery systems (TDDSs) are an innovative and patient-friendly approach for drug delivery and have several benefits over conventional oral and parenteral drug delivery systems. These systems are designed to transport medication through the skin membrane and into the bloodstream, maintaining constant drug levels for an extended period.[3] In transdermal methods of delivery, the drug traverses the skin layers and then enters the general blood circulation, subsequently reaching the target organ. The main barrier of drug traversing the skin is the outermost layer of skin known as the stratum corneum (SC). This layer includes corneocytes or dead skin cells. These cells are located in multi-layered lipids, which describe as a 'bricks and mortar' model. Overcoming this barrier is the major challenge faced by researchers in formulating drugs and tools of drug delivery to the skin.[4]

Ethosomes are one of the novel lipid vesicular systems that contain ethanol in relatively high concentration. This ethanolic vesicular system was developed by Touitou (Touitou 1996). Ethosomes contain mainly active pharmaceutical ingredients (API), ethanol, water and phospholipid (Touitou 1996, 1998). Ethosomal vesicles are structurally composed of a phospholipid bilayer and an inner aqueous core containing drug.[5]

Ethosomes are defined as non-invasive delivery carriers that enable drugs to reach deep into the skin layers or systemic circulation. These are soft, malleable vesicles tailored for enhanced delivery of active agents. Vesicles would also allow controlling the release rate of drug over an extended time, keeping the drug shielded from immune response or other removal systems and thus be able to release just the right amount of drug and keep that concentration constant for longer period of time.[6]

The size of ethosomes can be adjusted from tens to micron to nanometers. Due to their high deformability, ethosomes demonstrate an exceptional ability to permeate intact skin. The high ethanol concentration in ethosomes is what makes them unique, as ethanol disrupts the lipids bilayer organization. When incorporated into vesicle membrane, ethanol enhances the vesicle's ability to penetrate the stratum corneum. Additionally, the high ethanol content causes the lipid membrane to be less tightly packed than in conventional vesicles, resulting in a more flexible structure. This improves drug distribution within the stratum corneum lipids. Compared to classical liposomes, which primarily deliver drugs to the outer layer of the skin, ethosomes significantly enhance drug permeation through the stratum corneum barrier.[7]

Ethosomes are biologically attuned and biodegradable which provides larger surface area because of reduced vesicular size compared to other vesicular systems. Since incorporation of high ethanol concentration confers a negative charge to the liposomes which causes the size of vesicles to decrease, and that in turn ultimately leads to enhanced bioavailability of therapeutic agents. Ethosomes provides high patient compliance as they can be formulated in semisolid dosage forms (Gel or Cream) in contrast to complications associated with iontophoresis and phonophoresis.[8]

Composition Of Ethosomes

The ethosomal system is composed of phospholipids, ethanol, and water. The phospholipids used in the formulation can have diverse chemical structures, including phosphatidyl choline (PC), hydrogenated phosphatidyl choline, phosphatidyl ethanolamine (PE), phosphatidyl glycerol (PPG), phosphatidyl inositol (PI), and others. The proportion of the non-aqueous phase typically ranges from 22% to 70%. Ethanol or isopropyl alcohol can serve as the alcohol component. For characterization purposes, dyes or amphiphilic fluorescent probes, such as D-289, Rhodamine 123, Fluorescein Isothiocyanate (FITC), and 6-carboxyfluorescein are frequently incorporated into ethosomes.[1]

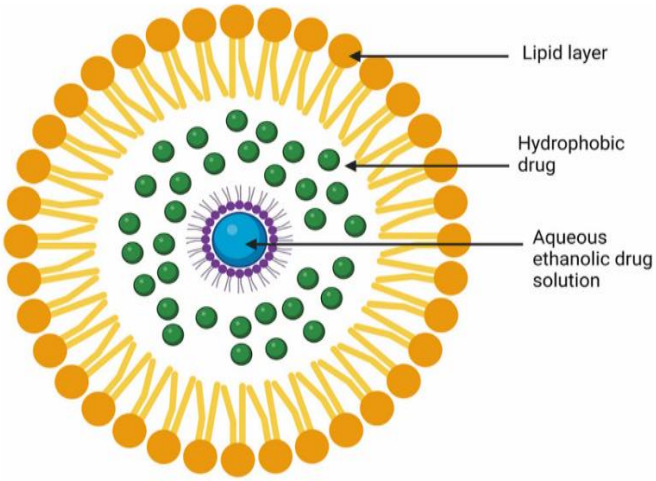

Figure 2. Structure of Ethosome

Ethanol typically reduced the mean diameter. Their formulation led to an increase of the percutaneous permeation of the active ingredient, both in vitro and in vivo, with good tolerability in human volunteers.[9]

MECHANISM

Ethanol effect: Ethanol works to improve the penetration of the skin. Its boosting action through absorption has a well-established mechanism. By penetrating intercellular lipids, ethanol increases the fluidity of cell membrane lipids while decreasing their density.[10]

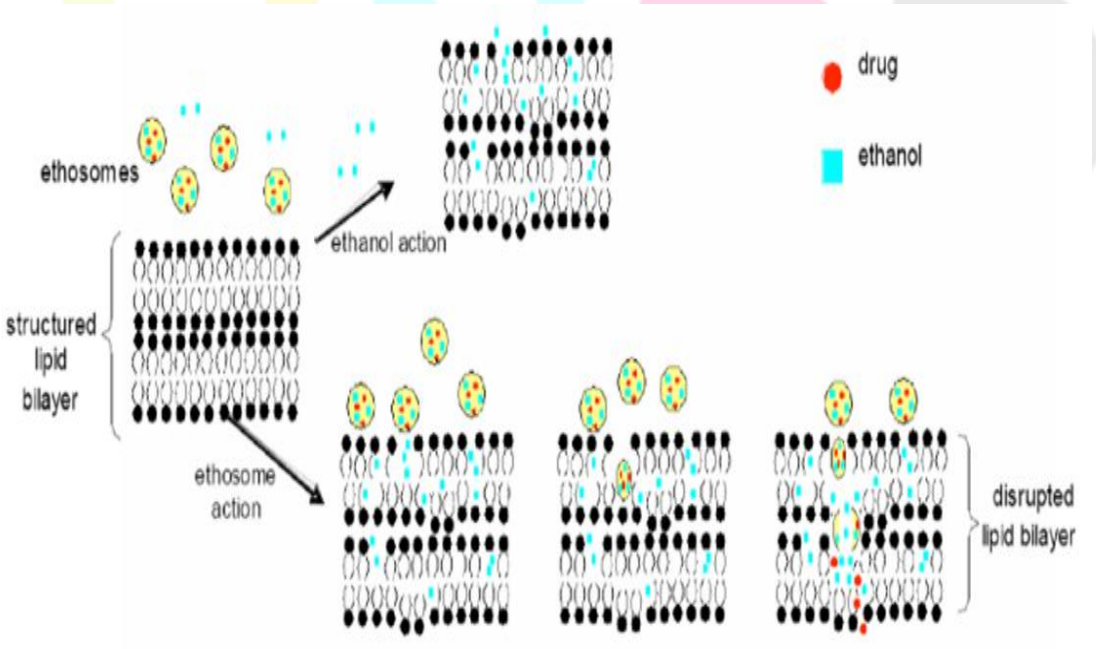

Figure 3. Drug Penetration through Ethosomes

Ethosome effect: An increase in skin permeability is the result of Ethosome ethanol's greater lipid fluidity in cell membranes. Ethosomes thus penetrate the deep skin layer relatively rapidly, where they interact with skin lipids to release medications into the deep skin layers.[10]

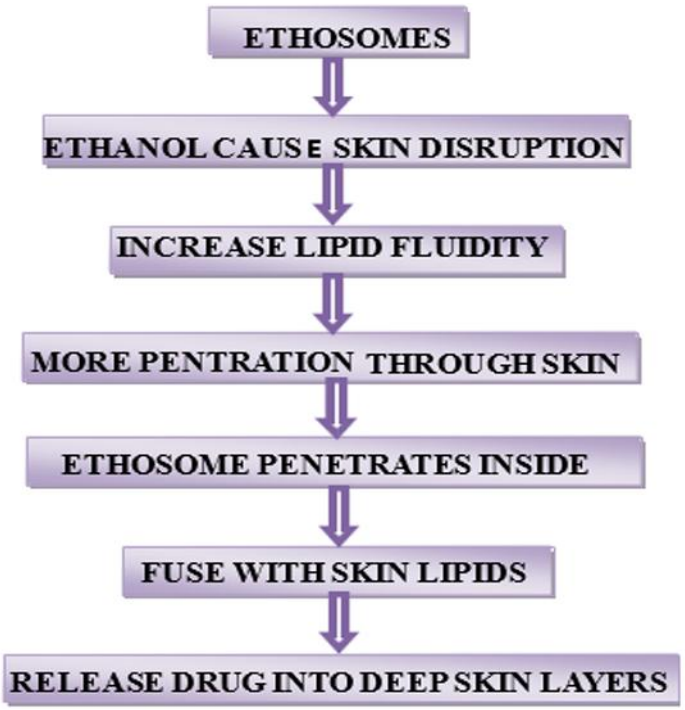

Figure 4. Mechanism of action of ethosomes

ETHOSOMAL SYSTEM TYPES

Their three types of Ethosomal systems, classified on the basis of their compositions.

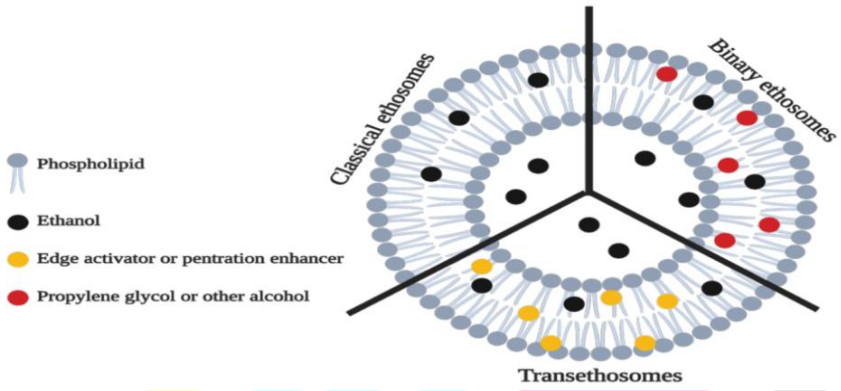

Figure 5. Schematic representation of the different types of ethosomal systems.

i. Classical Ethosomes

They are a new generation of conventional liposomes, ethanol of concentration up to 45% w/w, phospholipids, and water are the main ingredients of them. Classical ethosomes, according to the reports, were more effective than classical liposomes because they were small in size and had negative ζ(zeta)-potential and the higher ability for drug entrapment, and these are very important in transdermal delivery. Furthermore, skin penetration and stability profiles are higher compared to classical liposomes.[11]

ii. Binary Ethosomes

They were presented by Zhou et al. 13 using a different type of alcohol like propylene glycol added to the classical Ethosomes introduces the binary ethosomes. Alcohols used commonly in binary Ethosomes are isopropyl alcohol (IPA) and propylene glycol (PG).[11]

iii. Transethosomes

Transethosomes are recent vesicular nano-carrier systems that have the advantages of both transfersomes and Ethosomes.

Transethosomes are recently discovered ethosomal systems and considered a new generation and were first reported by Song et al. in 2012.16 these vesicles were designed to share the benefits of both classical ethosomes and deformable lip (transfersomes) to introduce transethosomes. Edge activators and permeability enhancers of different types have been used to produce transethosomal systems with better features. According to the reports, drugs of molecular weights of 130.077 Da to 200–325 kDa can be entrapped with transethosomes. Figure 5 shows the three types of ethosomal systems, according to their compositions.[11]

METHOD OF PREPARATION

1. Cold method: For ethosome preparation, the cold approach is one of the most popular techniques. First, phospholipid is vigorously stirred in ethanol at room temperature to dissolve it. Next, polyols such as propylene glycol are added gradually while being stirred frequently, and the mixture is heated to 30ºC in a water bath. The water is then heated to 30 degrees Celsius in a different vessel and the two combinations are combined. The mixture is then stirred for five minutes in a covered vessel. The Ethosomal formulation can have its size reduced to the necessary degree by employing the sonication technique.[10]

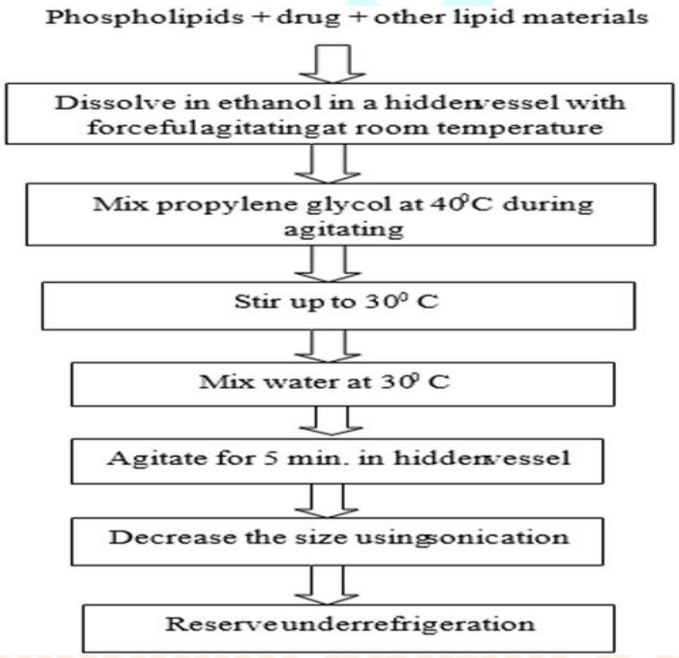

Figure 5. Formulation method of ethosomes by cold method

2. Hot method: In the hot process, phospholipid is added to water and heated on a water bath to 40ºC until an aqueous phase, or colloidal solution, is formed. In a separate vessel, ethanol and propylene glycol are properly combined and heated to 40ºC (Organic phase). Under continuous stirring, the organic phase is introduced to the aqueous phase. A desired degree of Ethosomal formulation size reduction can be achieved by employing the sonication technique.[10]

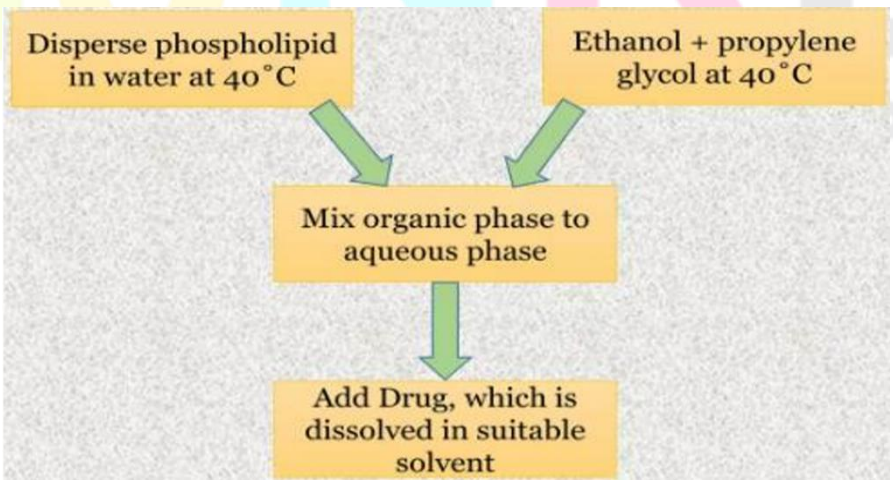

Figure 6. Formulation method of Ethosomes by hot method

3. Classic mechanical dispersion method: Using a round-bottom flask, this approach dissolves phospholipid in an organic solvent or a combination of organic solvents. To produce a thin layer of lipids on the RBF surface, the organic solvent is removed using a rotating vacuum evaporator. By keeping the contents under vacuum for the entire night, traces of the solvent are extracted from the lipid film that has formed. The drug's hydro-ethanolic solution is used to hydrate the lipid layer by spinning the flask at the proper temperature. Cool the resultant Ethosomal suspension at room temperature.[10]

4. The ethanol injection sonication method: This procedure involves injecting the organic phase, which contains the phospholipid dissolved in ethanol, into the aqueous phase using a 200-flow syringe system at a rate of 38µl per minute. An ultrasonic probe is then used to homogenize the mixture for five minutes.[10]

INCORPORATION INTO GEL

Carbopol 934 (1–3%w/v) was accurately weighed and dispersed into double distilled water (80 ml) in a beaker. This solution was stirred continuously at 800 rpm for 1 h, and then, 10 ml of propylene glycol was added to this solution. The obtained slightly acidic solution was neutralized by dropwise addition of 0.05 N sodium hydroxide solutions, and again, mixing was continued until gel becomes transparent. Volume of gel was adjusted to 100 ml and then sonicated for 10 min on bath sonicator to remove air bubbles. Final pH of the Gel base was adjusted to 6.5. Gel was also prepared with plain drug by adding 10 mg of drug and dispersed properly by following same procedure given above. Ethosomes preparation comparing to 0.05% w/w of drug was fused into the gel base to get the ideal concentration of drug in gel base.[12]

EVALUATION[1,6]

1) Vesicle shape: Ethosomes can be easily visualized by using transmission electron microscopy (TEM) and by Scanning electron microscopy (SEM).

2) Vesicle size and zeta potential: Particle size of the ethosomes can be determined by dynamic light scattering (DLS) and photo correlation spectroscopy (PCS). Zeta potential of the formulation can be measured by Zeta meter.

3) Transition temperature: The transition temperature of the vesicular lipid sys terms can be determined by using differential Scanning calorimetry (DSC).

4) Drug entrapment: The entrapment efficiency of Ethosomes can be me assured by the ultracentrifugation technique.

5) Drug content: Drug content of the Ethosomes can be determined u sing UV spectrophotometer. This can also be quantified by modified high performance liquid chromatographic method.

6) Surface tension measurement: The surface tension activity of drug in aqueous solution can be measured by the ring method in a Du Nouy ring tensiometer.

7) Stability studies: The stability of vesicles can be determined by asses sing the size and structure of the vesicles over time.

8.Skin permeation studies: The ability of the Ethosomal preparation to penetrate into the skin layers can be determined by using confocal laser scanning microscopy (CLSM).

EVALUATION OF GEL[12]

Ethosomal gel was characterized for their pH, viscosity, spreadability, Drug content and extrudability.

i. **pH**
The pH of selected optimized formulations was established with the help of digital pH meter. The pH meter was calibrated with the help of buffer solution of pH 4, pH 7 and pH 9. After calibration, the electrode was dipped into the vesicles. Then, pH of selected formulation was measured and readings shown on display were noted.

ii. **Viscosity**
Viscosity measurements of prepared topical Ethosomes based Gel were measured by Brookfield viscometer using spindle no. 63 with the optimum speed of 10 rpm.

iii. **Spreadability**
Spreadability of formulation is necessary to provide sufficient dose available to absorb from skin to get good therapeutic response. An apparatus in which a slide fixed on wooden block and upper slide has movable and one end of movable slide tied with weight pan. To determine spreadability, 2–5 g of Gel placed between two slides and gradually weight was increased by adding it on the weight pan and time required with the top plate to face the distance of 10 cm on adding 80 g of weight was noted. Good spreadability shows lesser time to spread.

$$\text{Spreadability (g.cm/sec)} = \frac{\text{Weight tide to upper slide} \times \text{length moved on the glass slide}}{\text{Time taken to slide}}$$

iv. Drug content

Accurately weighed 100 mg of topical Ethosomal Gel was taken in beaker and added 20 ml of methanol. This solution was mixed thoroughly and filtered by means of Whatman filter paper No. 1. Then, 1.0 mL of filtered solution was engaged in 10 mL capacity of volumetric flask; moreover, volume was ready up to 10 mL by means of methanol. This solution was analysed using UV spectrophotometer at λ max 351 nm.

v. Extrudability study

Extrudability was determined on the amount of the Gel extruded as of collapsible tube on appliance of certain load. More the quantity of Gel extruded shows better extrudability. It was determined by applying the weight on gel filled collapsible tube and recorded the weight on which Gel was extruded from tube.

ADVANTAGES[6]

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 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 for comparison of Iontophoresis and Phonophoresis and other complicated methods.
7. The Ethosomal system is passive, non-invasive and is available for immediate commercialization.

DISADVANTAGES[6]

1. They require high blood levels. It is limited only to potent molecules, those requiring a daily dose of 10mg or less.
2. It is not a means to achieve rapid bolus type drug input, rather it usually designed to offer slow, sustained drug delivery.
3. Adequate solubility of the drug in both lipophilic and aqueous environments to reach dermal microcirculation and gain access to the systemic circulation.
4. The molecular size of the drug should be reasonable that it should be absorbed percutaneously.
5. Adhesive may not adhere well to all types of skin.
6. It may not be economical.
7. Poor yield.
8. Skin irritation or dermatitis due to excipients and enhancers of drug delivery systems.

APPLICATION OF ETHOSOMES[6]

1. Treatment of microbial and viral skin infections.
2. Anti-inflammatory ethosomal systems.
3. Ethosomal Systems for Menopausal Syndromes.
4. Management of Erectile Dysfunction.
5. Analgesic and Antipyretic Ethosomal Systems.
6. Topical Delivery of DNA.

CONCLUSION

Ethosomes represent an advanced and promising drug delivery system, offering several advantages such as enhanced drug stability, improved skin penetration and increased therapeutic efficacy. Their unique lipid ethanol composition enables them to encapsulate and transport both hydrophilic and lipophilic drugs, thereby broadening the scope of transdermal drug delivery for various therapeutic agents. Additionally, the development of ethosomal gels has further strengthened their applicability by providing a more patient friendly, easily spreadable and sustained release topical formulation that enhances skin retention and overall treatment outcomes. However, continued research is essential to better understand their long-term stability, safety profile and clinical performance to fully harness their potential in pharmaceutical applications.

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