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ETHOSOMES A NEW TREND IN HERBAL FORMULATION

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ABSTRACT:

Transdermal drug delivery system was first introduced more than 20 years ago. Transdermal drug delivery system is a type of convenient drug delivery system where drug goes to the systemic circulation through the protective barrier i.e. skin is the main target of topical and transdermal preparations. Major aim of transdermal drug delivery system is to cross the stratum corneum. Ethosomes are the ethanolic phospholipid vesicles which are used mainly for transdermal delivery of drugs. Ethosomes have gained importance in the area of research, because of their intensified skin permeation, better delivery of drug and increased drug entrapment efficiency. Ethosomes are brand-new lipid vesicular carriers with a reasonably high ethanol content that are used as a transdermal drug delivery system to test the effectiveness of a targeted medication at thesite of action. Ethosomes are soft, malleable vesicles composed mainly of phospholipids,ethanol (relatively high concentration) and water. Several approaches have been developed to weaken this skin barrier. One of the approaches for increasing the skin penetration of drugs and many cosmetic chemicals is the use of vesicular systems such as ethosomes. Ethanol is known as an efficient permeation enhancer and has been addedin the vesicular systems to prepare elastic nanovesicles. Ethosomal dispersions are addedto gels, patches, and creams for ease of use and stability. The ethosomes efficacy in dermal/transdermal administration is evaluated via clinical studies as well as a wide rangeof in vivo models. The present review focuses mainly on the various aspects of ethosomesincluding their mechanism of penetration, preparation, composition, characterization, advantages, applications and marketed product of ethosomes.

KEYWORDS: Transdermal ,Ethosomes , Ethanol, Skin, Penetration, Vesiclar

INTRODUCTION:

Using the skin is the most versatile and extensive way to deliver both topical and systemic drugs. When applied topically, the stratum corneum, the skin's outermost layer, serves as the most durable barrier to drug penetration, lowering the bioavailability of prescribed drugs. Therefore, to get beyond the skin's natural barrier, research and assessment of the many carriers needed for systemic medication distribution are crucial. Transdermal medication administration is a less intrusive method of pharmaceutical delivery that prevents first pass metabolism, minimizes dosage frequency, ensures patient compliance, and controls drug distribution [1-2]. Many benefits, including as higher safety, better patient compliance, and increased effectiveness, can be obtained by transdermal administration. Bypassing the risks and inconvenience of parenteral treatment, this method of medication delivery enhances patient compliance.[3] In this regard, the transdermal method is an intriguing choice because it is both practical and secure. [4] Only lipophilic medicines with a molecular weight of less than 500 Da may pass through the stratum corneum, which is a barrier encountered by the transdermal drug delivery mechanism. Other therapeutic benefits of TDD include the bypass of the first pass metabolism impact for drugs with low oral bioavailability, and continuous drug administration to produce a steady state plasma profile and hence lessen systemic adverse effects, perhaps improving patient compliance. [5–6] Ethosomes are novel drug delivery systems that provide the necessary requirements for the effective and secure administration of hydrophilic or lipophilic medications [7,8, 9]. The composition, shape, mode of action, and delivery characteristics of ethosomes set them apart from liposomes and other lipid vesicles. Unlike liposomes, the ethosomal carrier may carry chemicals transdermally or into the different layers of the skin since it is built on phospholipid soft vesicles in a hydroethanolic environment [7]. According to several publications, ethosomes have great promise for improving the efficacy of transdermal distribution of different medicines. Additionally, an excellent option for the

non-invasive administration of tiny, medium, and large sized drug molecules is provided by ethosomes. Ethosome preparation is simple and requires no sophisticated equipment, therefore it can be scaled up to an industrial level. In vitro and in vivo, animal and clinical investigations have shown that these vesicular networks are very efficient carriers for the conveyance of compounds with different lipophilicities into and through the skin [10].

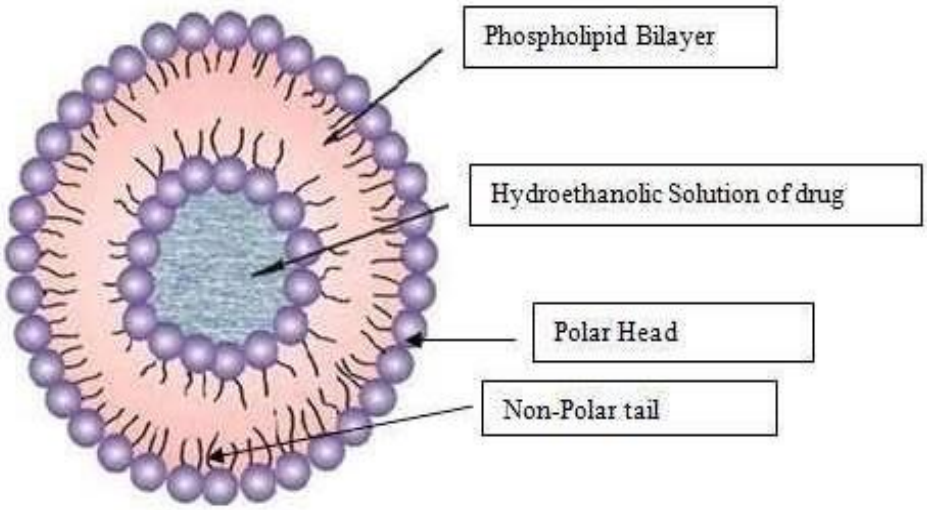


FIG: 1 ETHOSOMES [11]

ETHOSOME COMPOSITION:

By changing the ratio of alcohol to water or alcohol to polyol to water, ethosomal medication delivery may be controlled. The hydro alcoholic or hydro/alcoholic/glycolic phospholipid that makes up ethosomes is a vesicular carrier in which the concentration of alcohols or their combination is relatively high [12,13].

ADVANTAGES:

1. Transdermal and dermal distribution of the medication is improved by ethosomes.[14]
2. High patient compliance: The semisolid gel or cream form in which the ethosomes medications are administered is used.
3. There are several uses for ethosomal drug delivery systems in the veterinary, cosmetic, and pharmaceutical industries.
4. The Ethosomal system can be commercialized right away and is non-invasive and passive.
5. Relatively smaller in size than typical vesicles.[14,15]

DISADVANTAGES:

1. Ethosomal administration is often intended to provide gradual, sustained drug delivery; it is not a method for achieving quick bolus-type drug intake.
2. Poor-quality ethers may group together, causing precipitation.
3. Product loss results from the movement of ethosomes from the organic to the aqueous layer.
4. Medication that needs high blood levels cannot be given; only strong medications (daily dose -10 mg or less) can be used.[16]

TYPES OF ETHOSOMAL:

- Classical ethosomes
- Binary ethosomes
- Transethosomes

Classical ethosomes:

Modified ethosomes, or classical ethosomes, are made up of phospholipids, water, and a high ethanol content of up to 45% w/v. The findings indicate that classical ethosomes exhibit superiority over classical liposomes because to their smaller size, higher entrapment efficiency, and negative zeta potential. Medications with molecular weights between 130.077 and 24 k Da are the best choices for those trapped in traditional ethosomes. In comparison to classical liposomes, classical ethosomes have superior skin penetration and stability characteristics. [17]

Binary ethosomes:

Zhou et al introduced binary ethosomes, which were essentially created by combining a different kind of alcohol with conventional ethosomes .Propylene glycol (PG) and isopropyl alcohol (IPA) are the most often utilized alcohols in binary ethosomes.[18]

Transethosomes:

Transethosomes, a novel type of ethosomal system, were created to incorporate the benefits of transfersomes and traditional ethosomes into a single formulation. They are composed of the same fundamental elements as standard ethosomes plus a surfactant, which acts as an edge activator or penetration enhancer [19].

MECHANISM OF DRUG PENETRATION:

The enhanced drug penetration of ethosomes over liposomes is their primary benefit. Uncertainty surrounds the mechanism of medication absorption from ethosomes. There are likely two stages in which medication absorption takes place.

1. Ethanol effect
2. Effect of Ethosomes

Ethanol effect:

Through the skin, ethanol improves permeation. Its penetration-enhancing effect's mechanism is widely understood. Ethanol permeates intercellular lipids, causing the lipids in the cell membrane to become more fluid and the density of the lipid multilayer to decrease.

Ethosome effect:

Skin permeability increases as a result of the ethanol of ethosomes increasing the lipid fluidity of cell membranes. Thus, the ethosomes enter the deep skin layers with great ease, where they combine with skin lipids to release the medicines into the skin's deep layer [20].

Fig 2: Mechanism of ethosomes [21]

ETHOSOME PREPARATION TECHNIQUES:

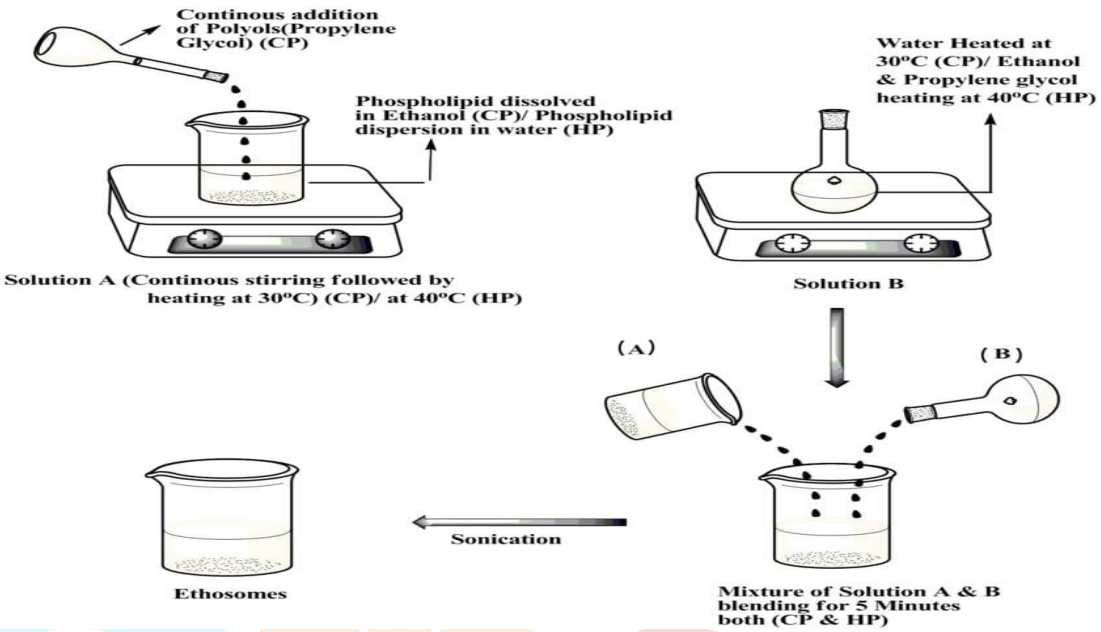
The first two methods, which are the most popular, are comparatively easier than the others since they don't require a lot of advanced technology.

Cold method:

This is the most widely used technique of all. Drugs, phospholipids, and other lipid ingredients are dissolved in room-temperature alcohol (usually ethanol) in a covered jar, and the mixture is vigorously stirred afterward. At 40°C, polyols such as polyethylene glycol are added while the mixture is being stirred.The setup is permitted to be heated to 300C in a water bath.300°C water that has been heated separately. is added to a covered pot and stirred for five minutes. the method of using extrusion and sonication to reduce vesicles' size to the appropriate levels. It is crucial to utilize the right temperature to meet the requirements of the preparation. It suggests the requirement for cold storage. Aqueous phases such as water, buffer solutions, or regular saline can be utilized. [22]

Hot method:

Phospholipids are dissolved in water and heated on a water bath to 40°C in this process. Ethanol and propylene glycol are combined and heated in a different vessel. The drug's hydrophilic and hydrophobic qualities determine which phases it enters. The organic phase is introduced to the aqueous phase once both phases have reached 40°C. Furthermore, sonication or extrusion can reduce the ethosome vesicle size [23]



Schematic representation of method of preparation of ethosomes by (A) Cold method and (B)Hot method. [24]

Classic mechanical dispersion method:

In a round-bottom flask (RBF), phospholipids are first dissolved in a blend of organic solvents. After that, the organic solvent is eliminated by forming a thin lipid coating on the RBF using a rotary vacuum evaporator. By placing the contents under vacuum for the whole night, even residues of solvents can be eliminated. A water-ethanolic solution is used to further hydrate the lipid coating that has been deposited. The lipid film is heated for 30 minutes while being spun in the RBF at a temperature that varies according to the kind of phospholipid. [25]

Ethanol injection sonication method:

In a glass bottle that is hermetically sealed and fitted with a syringe to allow the addition of ethanol without it evaporating, phospholipids are dissolved in ethanol. Separate drug dissolves in double-distilled water. Following the addition of the ethanolic lecithin solution to the aqueous drug solution at a flow rate of 200 µL/min, the mixture is homogenized for five minutes using an ultrasonic probe. Afterwards, the drug-loaded ethosomes are collected by filtering the ethosomal solution via 0.45µm filters. [26]

Thin-film hydration technique:

An organic solvent will be used to dissolve the lipids in a round-bottom flask, and a rotary evaporator will be used to evaporate the organic solvent above the lipid transition temperature. To create an ethosome suspension, the thin film that has developed around the inner walls of the round-bottom flask will be hydrated using an ethanolic mixture and scattered using a probe sonicator. [27]

Optimation method:

Take the phospholipid 90 and dissolve it in methanol :chloroform (3:1) ratio. At 600 rpm and above the lipid transition temperature of 550C, remove the organic solvent from the rotator flask evaporator. By keeping the temperature constant for thirty minutes, further eliminate the organic solvent. After a thin layer is created, hydrate it with a 1% w/v hydroethanolic mixture at 60 rpm for an hour. Sonication occurs in three cycles of five minutes each, with a five-minute break in between. The formulation should be kept in the container at 40C.[28, 29]

EVALUATION TEST:

- Filter Membrane: Vesicle Interaction Study by Scanning Electron Microscopy
- Drug Uptake Studies
- HPLC Assay:
- Vesicle-Skin Interaction Study by TEM and SEM

- Statistical Analysis
- Vesicle-Skin Interaction Study by Fluorescence Microscopy

Filter Membrane:

Investigating Vesicle Interactions Using Scanning Electron Microscopy Take a 0.2 mL vesicle solution and a 50 nm-pore-size filter membrane. The filter membrane is coated with the formulation before being placed in diffusion cells. The filter membrane's bottom side is in touch with the phosphate buffer solution (pH 6.5), while the top side was exposed to the air. After an hour, the filter membranes were taken out and ready for SEM research. They were first fixed for the night at 4°C in Karnovsky's fixative, then they were dehydrated using ethanol solutions varying in volume (30%, 50%, 70%, 90%, 95%, and 100% v/v in water). Ultimately, filter membranes were SEM-examined after being coated with gold. [30, 31]

Drug uptake study:

Drug uptake was assessed by evaluating the drug content using an HPLC test after 100 µl of the drug solution in phosphate buffer saline solution (pH 7.4), ethosomal formulation, or commercial formulation was incubated with MT-2 (T-lymphoid cell lines) cells.[30, 32, 33]

HPLC assay:

Using a methanol-based HPLC analysis, the quantity of drug that penetrated the receptor compartment during in vitro skin penetration assays and in MT-2 cells was ascertained: a combination of distilled water and acetonitrile (70:20:10 vol/vol), supplied at a rate of 1 mL/min by an LC 10AT vp pump (Shimadzu, Kyoto, Japan)[34]

Vesicle-Skin Interaction Study by TEM and SEM:

The animal is chopped into extremely thin pieces, such to those seen in Vienna, Austria, and Ultra chopped. The sections are then collected onto coated grids and examined under a transmission electron microscope. The skin pieces should be dehydrated before being mounted on stubs using adhesive tape and coated with gold palladium using a fine coat ion sputter coater for SEM examination. The portions underwent scanning electron microscopy analysis. [32]

Statistical Analysis:

ANOVA was used to assess the statistical significance of all the data produced, and then a studentized range test was performed. Using the PRISM program, a confidence criterion of $P < .05$ was set for the results' interpretation.[30, 35]

Vesicle-Skin Interaction Study by Fluorescence Microscopy:

Fluorescence microscopy was conducted in accordance with the SEM and TEM investigation methodology. Skin slices 5 µm thick were cut with a microtome and viewed using a fluorescence microscope. tiny The MT-2 cells, which are lymphoid cell lines used in the Cytotoxicity Assay, were grown at 37°C in an environment of 5% CO_2 using Dulbecco's modified Eagle media supplemented with 10% fetal calf serum, 100 U/ml penicillin, 100 mg/Ml streptomycin, and 2 mmol/L L glutamine. The cytotoxic dosage 50 (CD50) that caused a 50% decrease in absorbance at 540 nm was used to represent cytotoxicity. [29, 36]

APPLICATION:

Delivery of Anti-Viral drugs:

An antiviral medication called acyclovir is used to treat Herpes labialis. Because of its limited skin penetration, the traditional marketed formulation of acyclovir has a low level of therapeutic effectiveness. The medication was added to ethosomes to get around these drawbacks. This delayed the medication release and transdermal flux while also enabling appropriate zero order delivery.[37,38].

Ethosomes for menopausal syndromes:

Due to significant first pass metabolism, buspirone hydrochloride (BH) has an extremely low oral bioavailability of no more than 3.9 percent when administered intravenously.[39] Because of its short 2.5-hour half-life, BH also requires dosages often.[40, 41] Since BH is a hydrophilic cationic molecule, it cannot properly pass through the skin to reach the therapeutic level in the blood. Ethosomes formulations have been developed to improve BH's skin permeability. Additionally, this aids in improving the pharmacologic and pharmacokinetic efficacy of menopausal syndrome treatment. The results show that BH ethosomes are safe and effective in treating menopausal symptoms. [42]

Transdermal delivery of hormones:

Hormones administered orally have a number of drawbacks, including limited oral bioavailability, many dose-dependent adverse effects, and a high first pass metabolism. Comparing an ethosomal formulation including hormones like testosterone to other commercially available oral preparations, the ethosomal formulation exhibited roughly 30 times better skin penetration (Testoderm patch, Alza).[43]

Delivery of anti-arthritis drug:

Topical application of anti-arthritis medication can overcome issues related to oral traditional treatment and is a superior choice for site-specific drug delivery. By enhancing skin penetration and accumulation, the ethosomal version of cannabidol exhibits noticeably enhanced anti-inflammatory action. Similar to this, using piroxicam orally for rheumatoid arthritis can have serious adverse effects include bleeding in the stomach and ulcers. An alternate delivery method for systemically active drugs like piroxicam that prevents drug breakdown by enzymes is transdermal medication administration using ethosomal formulation .[44]

Delivery of antibiotics:

Topical antibiotic medication has the potential to mitigate the adverse effects and severe allergic responses associated with conventional oral antibiotic therapy. Ethosomes can avoid these issues by distributing a sizable amount of medication into the skin's deeper layers. Erythromycin ethosomes were developed by E. Touitou et al., who demonstrated a better inhibitory effect on Staphylococcus aureus compared to traditional oral antibiotic preparations. [45]

Delivery of problematic drug molecules:

Large biogenic compounds, such as insulin, are difficult to give orally because the gastrointestinal system fully breaks them down. Thus, the production of such big molecular weight medicines into ethosomes significantly boosts therapeutic effectiveness and penetration. [46]

Cosmeceutical Applications of Ethosomes:

Since they provided a variety of benefits, including improved transdermal permeability, especially in elastic forms, and reduced skin irritation from irritating cosmetic chemicals, ethersomes have been employed successfully in cosmetic formulations. To achieve these benefits of elastic vesicles for cosmeceuticals applications, the primary elements to be taken into account are their sizes and composition. Curcuma longa extract-containing ethosomal creams have also been developed and tested for their anti-aging and photoprotective qualities. In both investigations, ethosomal creams containing C. longa extract shown encouraging outcomes when used as photoprotective [47] or antiwrinkle [48] agents on human subjects. A new cellulite lotion called Lipoduction was created by the American firm Osmotics Inc. It works by penetrating lipid transporters and delivering components straight to fat cells. In less than 60 days, ingredients in lipoduction reduced the appearance of cellulite by up to 80%. It was discovered that Yeh et al.'s transethosome hair dye was superior to the hydroethanolic solution of the same extract in terms of delivering and boosting absorption of black tea extracts to the hair surface.[49]

Ethosome for peptides delivery:

Macromolecules that can't get past the SC (subcutaneous) layer are peptides and proteins. They are thought to be delivered via the I. V. and S. C. routes because of their low oral bioavailability. Because insulin is an oligomeric protein, individuals with insulin-dependent diabetic mellitus (IDDM) can receive intravenous administration of insulin, which has a molecular weight of 6000 Dalton per monomer. Numerous research concentrating on insulin delivery that is nonpassive by physical techniques like phonophoresis, iontophoresis, and so on, through the skin. [50,51]It has been demonstrated that augmentation with a deformable phospholipid vesicle and its passive distribution enhances percutaneous insulin absorption.[52]

PATENTED AND MARKETED FORMULATION OF ETHOSOME:

Professor Elka Touitou and her Pharmaceutics department students at the Hebrew University School of Pharmacy created and patented ethosomes. Hebrew University's Novel Therapeutic Technologies Inc. (NTT) has been successful in launching many medicines using the ethosomal delivery technology. Currently available in Japan, Noicellex TM is an anti-cellulite version of Ethosome. Currently on the market in the USA, Lipoduction TM, a different formulation that contains pure grape seed extracts (antioxidants) is used to treat cellulite. In a similar vein, Skin Genuity anti-cellulite gel is marketed by Physonics in London. Sinere sells nanominoxc, a hair tonic that contains monoxidil and encourages hair growth .[53, 54, 55]

CONCLUSION:

A review of the published data suggests that topically used ethosomes prove to be superiorwhen compared with conventional formulations and offer improved safety and efficacy.

Ethosomes are soft malleable potential carrier for the transportation of drugs, which has opened various challenges and opportunities for the development of improved drug therapies.Transdermal route is promising alternative to drug delivery for systemic effect. Application of ethosomes provides the advantages such as improved permeation through skin and targeting to deeper skin layers for various skin diseases. Ethosomes are interesting and innovative vesicular systems that have appeared in the field of pharmaceutical technology and drug delivery in recent years. High patient compliance as it is administrated in semisolid form (gel or cream) and various application in Pharmaceutical, Veterinary, Cosmetic field.

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