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# ETHOSOME: A Novel permeation enhancer for transdermal drug delivery system

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## Abstract

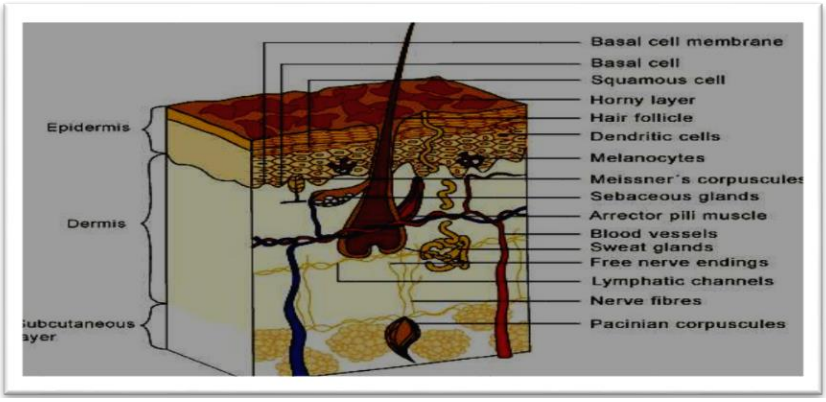
It is well established that the structure and function of the skin prevent penetration of many therapeutic molecules to the site of their action in the deep cutaneous strata. The use of nanotechnology has been considerably explored for developing efficient drug delivery systems for topical and transdermal applications. Ethosomes, a nano vasicular carrier designed to overcome the skin barrier(SC), so that new and advanceddermal and indigenous therapies can be achieved. Ethosomes are noninvasive delivery carriers that enable drugs to reach thedeep skin layers and/or the systemic circulation. Ethosomes constitute a vesicular nanocarrier containing a relatively high concentration of ethanol (20–45%),water and phospholipid. Ethosomes have higher penetration rate through the skin as compared to liposome's hence these can be used widely in place of liposome's. Ethosomes has enhanced skin permeability, improved drug delivery and increased drug entrapment efficiency etc. Ethosomes having an area of research interest, because of its cross the skin barrier due to ethonilic action and enhanced skin permeation, improved drug delivery, increased drug entrapment efficiency, etc.

## Keyword

Ethosome, Transdermal delivery, Nanocarrier vesicle, permeation enhancer.

## Introduction

The skin is the largest organ of the human body, calculating for more than 10% of body mass; it permit the body to interact more intimately with its environment[1,2,3]. Skin forms a protecting covering layer against the external environment and prevents water loss from the underneath tissue. It is more flexibility to resist permanent deformation from movement and thin enough to allow the perception of stimulus. It also performs many ancillary functions such as synthesis and metabolism and the production of sweat enables temperature control and excretion of waste products by means of sweating etc.[4,5,6] The skin can be considered to be composed of three main layers: subcutaneous tissue, dermis and epidermal layers[7] shown in **figure 1**




Stratum corneum (Sc) is the outermost layer of the epidermis. It composed of 10 to 25 layers of dead, elongated, fully keratinized corneocytes, which are sink in a matrix of lipid bilayers.[4,8,9] It has been shown that the stratum corneum( Sc) is the main dermal barrier to penetrate through the skin. The limiting factor for these processes is the slow diffusion through the dead keratinized horny layer of skin.[10,11] Stratum corneum act as a hydrophobic membrane. The rates of permeability of skin by low and high molecular weight organic non-electrolytes are mostly determined within the stratum corneum.[12,13] The main interest in dermal absorption assessment is related to: [1]

1. Local effects in dermatology[14]

2. Transport through the skin, seeking a systemic effect[14]

3. Surface effects[15,16]

4. Targeting of deeper tissues[17,18]

5. Unwanted absorption.[19,20]Routes of drug penetration.[1]

# Transdermal drug delivery system (TDDS)

Transdermal drug delivery systems (TDDS) have been recently developed, aiming to achieve the objective of systemic medication through topical application to the intact skin surface.[21,22] Transdermal therapeutic system is defined as self-contained individually seperate dosage forms which, when applied to the intact skin, delivery the drug, through the skin at controlled rate to the systemic circulation.[23] Transdermal delivery can provide a number of advantage including enhanced efficacy with increased safety and improved patient compliance. This route of drug administration avoids the hazards and disadvantage associated with parenteral therapy and improves patient compliance.[24] Transdermal route is an interesting option in this respect because transdermal route is convenient and safe.[25] Transdermal drug delivery system is it encounters the barrier properties of the dead keratinized horny layer (Stratum Corneum) and hence only the lipophilic drugs that have molecular weight <500 Dalton can pass through it.[26] TDDS has some other therapeutic benefits such as sustained drug delivery to provide a steady state plasma profile and hence reduced systemic adverse effect, thus developing the potential for improved patient compliance, Avoid the bypass of first pass metabolism effect for drug having poor oral bioavailability.[27] In order to enhance drug transdermal absorption, different methodologies have been investigated, developed, and patented.[28,29] Improvement in physical permeation enhancement technologies has led to renewed interest in transdermal drug delivery.[1] Some of these novel advanced transdermal permeation-enhancement technologies include iontophoresis, electroporation, ultrasound, microneedles to open up the skin, and more recently the use of transdermal nanocarriers,[30,31,32,] Now-adays liposomes, niosomes, transferosomes

and ethosomes (vesicular and non- invasive drug delivery) are used to increase the permeation of drug through the stratum corneum.[33]

**Ethosomes**

"Ethosomes are ethanolic Liposome ". Touitou invented a new vesicular system which was named ethosomes, due to the presence of ethanol in the vesicular structure.[34] Ethosomes were first developed by tauitou & her colleagues in 1997.[35] Ethosomes can be defined as noninvasive delivery carriers that enable drugs to reach deep into the skin layers and/or the systemic circulation. These are soft, malleable vesicles tailored for enhanced delivery of active pharmaceutical ingredients(API). The Nano carrier vesicles have been well known for their importance in cellular communication extended time, keeping the drug shielded from immune response or other removal systems and thus be able to release just the exact amount of drug and keep that concentration constant for longer periods of time. One of the major advances in vesicle research was the finding of a vesicle derivative, known as an Ethosomes.[36,37]

**Benefits of Ethosomal drug Delivery System**

Ethosomes includes a lots of benefits such as:

- Ethosomes are able to deliver various molecules like peptides, protein molecules, etc.
- Ethosomes are formulated by using biologically and eco- friendly chemicals rendering it non toxic to the human body.
- Ethosomal delivery is a exemplary option for transdermal delivery of medicament as it enhances the permeation.
- It can be implement to enormous fields like Cosmetic, Pharmaceutical, Veterinary fields.
- Ethosomal delivery can be formulated into gel or cream so as to generate high patient compliance.
- In contrast to various alternative techniques ethosomes are better technique.[38,39,40]

**Composition of Ethosome**

The ethosomes may contain phospholipids with various chemical structures like phosphatidylcholine (PC), hydrogenated PC, phosphatidic acid (PA), phosphatidylserine (PS), phosphatidylethanolamine (PE), phosphatidylglycerol (PPG), phosphatidylinositol (PI), hydrogenated PC, alcohol (ethanol or isopropyl alcohol), water and propylene glycol (or other glycols). Ethosomal delivery system deliver medicament very efficiently across the skin membrane. Ethosomal vesicles can be prepared by varying the concentration of alcohol, propylene glycol and phospholipids. Mostly preffered phospholipid is soya lecithin (phosphatidylcholine). It is utilized in the concentration range of 0.5-10% w/w. Mostly preferred alcohols involves ethanol and isopropyl glycol. Cholesterol is also occasionally utilized in the preparation in the concentrations range of 0.1-1%. In expansion, the non ionic surfactants (PEG-alkyl ethers) are utilized along with the phospholipids. The alcohol concentration in final product is may be about 20 to 50%. The range of non- aqueous phase concentration (alcohol and glycol mixture) is may be about 22 to 70%.[41]

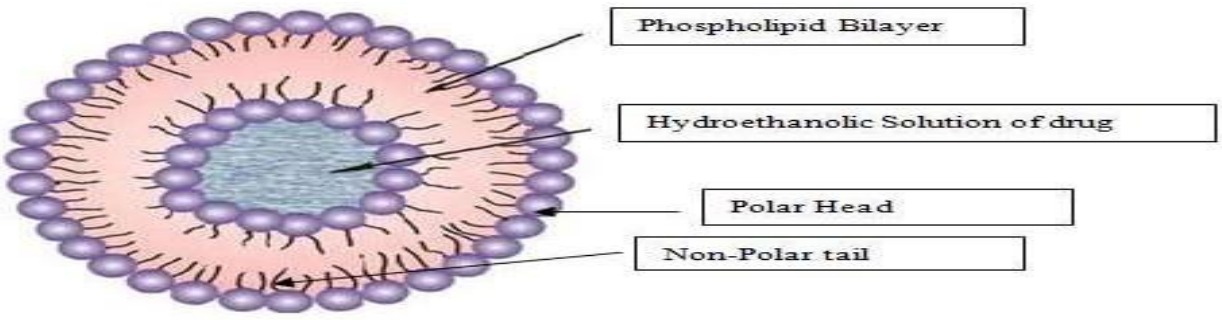



**Fig. 2: Structure of Ethosomes.[42]**

**Types of Ethosome**

**Classical Ethasome**

They are slight modifications of the conventional liposomes first prepared by Touitou et al. composed of Phospholipids and a relatively high concentration of ethanol (up to 45%).[42,43]

**Binary Ethasome**

They were first described by Zhou et al. [2]. They are just simple ethosomes the only difference between them and classical ethosomes is the type of alcohol, in classical ethosomes ethanol is the only alcohol used but in binary ethosomes alcohol used are propylene glycol(PG) and isopropyl alcohol(IPA).[44]

**Transethasome**

Transethosomes are a new generation of vesicular ethosomal systems first described by Song et al. [3] in 2012 for efficient delivery of the drug across skin as they combine the advantages of classical ethosomes and deformable liposomes (transferosomes).[45]

**Table 1. Different additives employed In formulation of ethosomes[42]**

| Material | Examples | Uses |
|---|---|---|
| Phospholipid | Soya phosphatidyl choline Egg phosphatidyl choline<br>Dipalmityl phosphatidyl choline Distearyl phosphatidyl choline | Vesicles forming component |
| Polyglycol | Propylene glycol Transcutol RTM | As a skin penetration enhancer |
| Alcohol | Ethanol Isopropyl alcohol | For providing the softness for vesicle membrane<br>As a penetration enhancer |
| Cholesterol | Cholesterol | For providing the stability to vesicle membrane |
| Dye | Rhodamine-123 Rhodamine red<br>Fluorescen Isothiocynate (FITC) 6-Carboxy fluorescence | For characterization study |
| Vehicle | Carbopol 934 | As a gel former |

# Methods of preparations of Ethosomes

Ethosomal formulation may be prepared by hot or cold method as described below. Both the methods are convenient, do not require any sophisticated equipment and are easy to scale up at industrial level.

## Cold Method

In this method Phospholipids, drug and other lipid materials are dissolved in ethanol in a covered vessel at room temperature by vigorous stirring with the use of mixer. Propylene glycol or other polyol is added during stirring. This mixture is heated to $30^0$C in a water bath. The water heated to $30^0$C in a separate vessel is added to the mixture, which is then stirred for 5 min in a covered vessel. The vesicle size of ethosomal formulation can be decreased to the desire extent using probe sonication or extrusion method. Finally, the formulation is stored under refrigeration.[46,47]

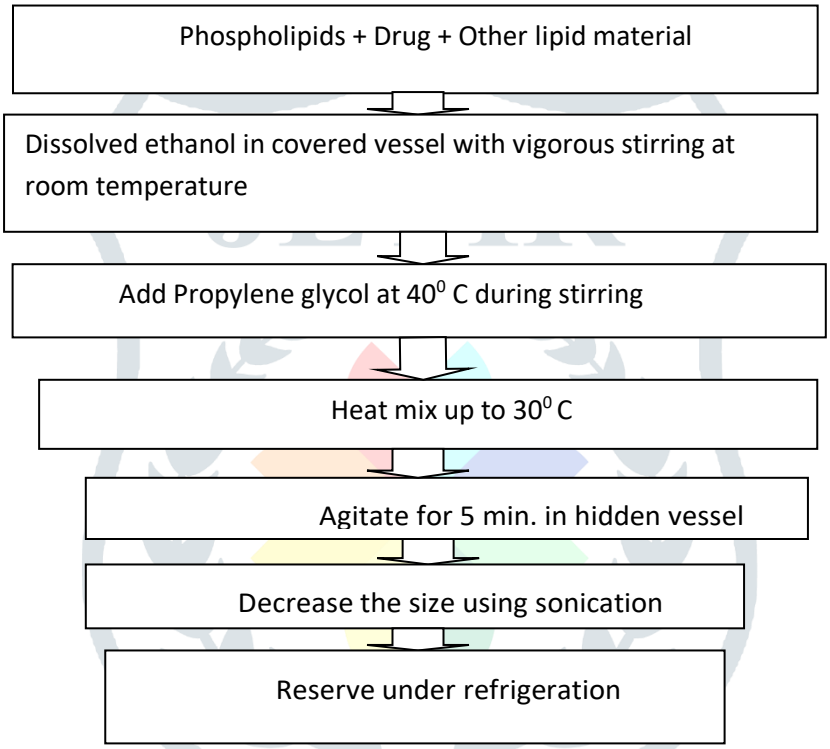



**Fig. 3: Formulation method of ethosomes by cold method.[48,49,50,51]**

## Hot Method

This method was first used by Touitou [7] in 1996 in this method phospholipid is dispersed in water by heating it in a water bath at 40°C until a colloidal solution is obtained. In a separate vessel, ethanol and propylene glycol are mixed and heated to 40°C. Once both mixtures reach 40°C, the organic phase is added to the aqueous phase. The drug is dissolved in ethanol or water based on its hydrophilic/ hydrophobic properties. The vesicle size of the ethosomal formulation can be modified to the desired extent using probe sonication orextrusion method.[42]

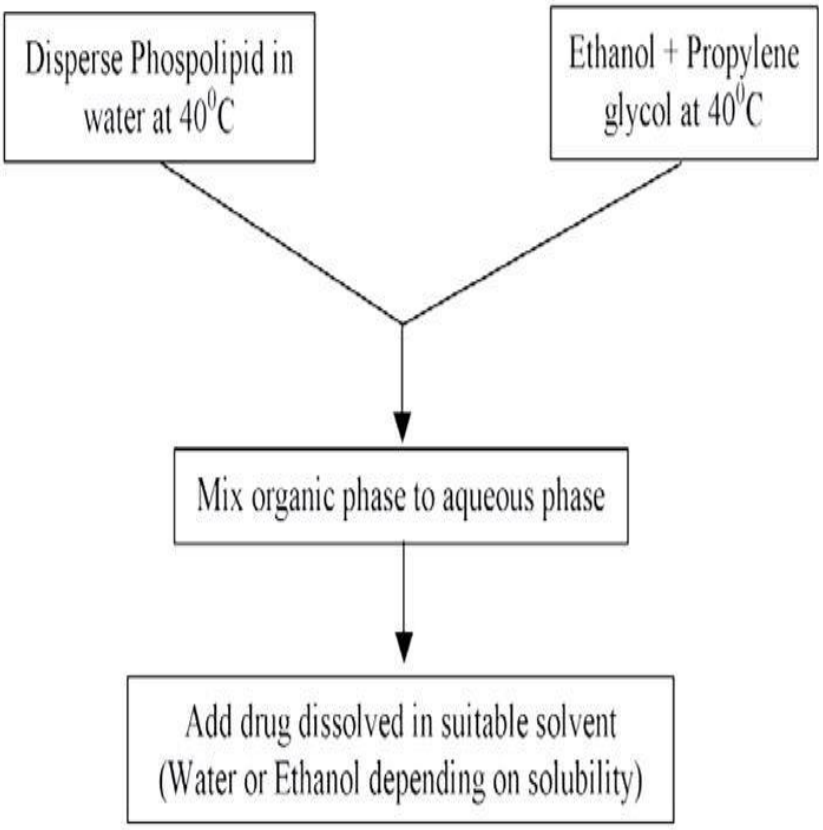



**Figure 4: Hot Method for Preparation of Ethosomes.**[52,53]

## Mechanism of Drug Penetration

The main advantage of ethosomes over liposomes is the increased permeation of the drug. The mechanism of the drug absorption from ethosomes is not clear. The drug absorption probably occurs in following two phases:

Ethanol effect

Ethosomes effect

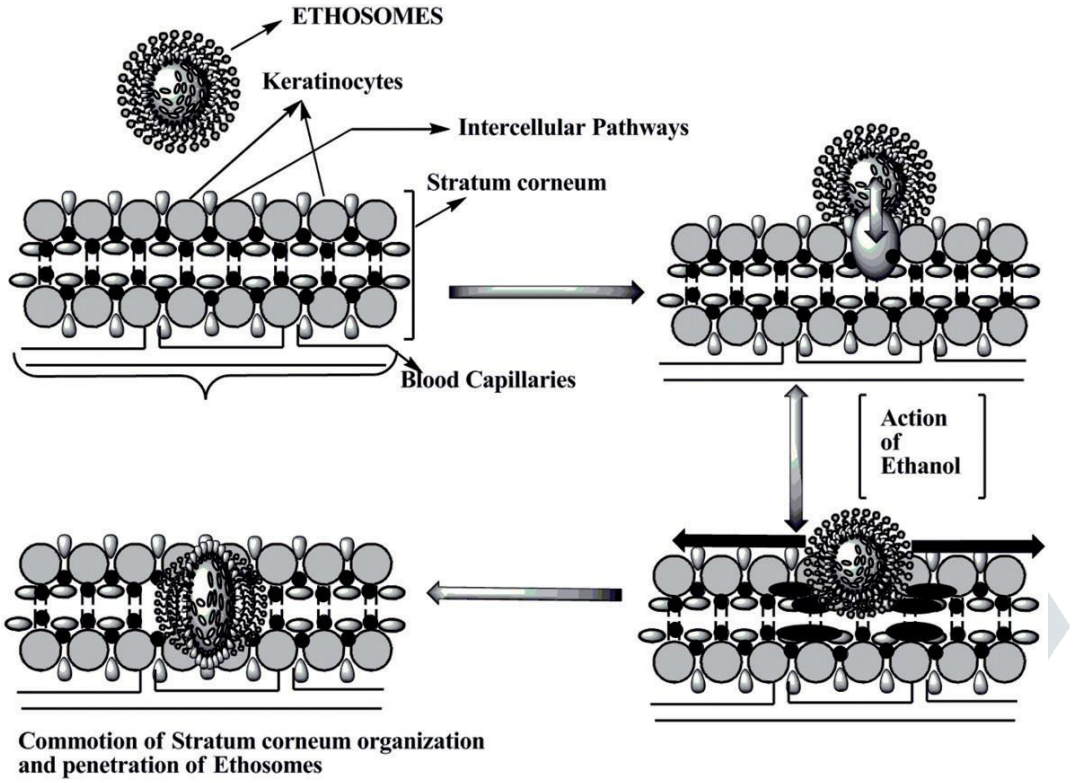
1. **Ethanol effect**

Ethanol acts as a penetration enhancer through the skin. The mechanism of its penetration enhancing effect is well known. Ethanol penetrates into intercellular lipids and increases the fluidity of cell membrane lipids and decrease the density of lipid multilayer of cell membrane.

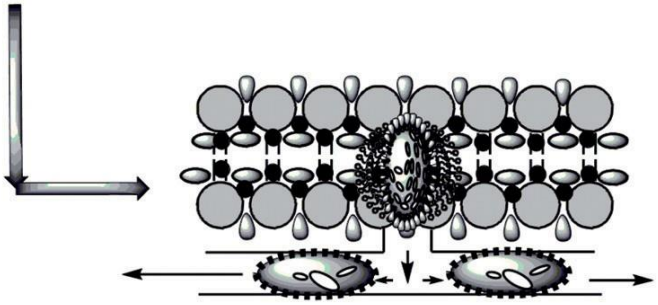
2. **Ethosomes effect**

Ethasome Increased cell membrane lipid fluidity caused by the ethanol results increased skin permeability. So the ethosomes permeates very easily inside the deep skin layers, where it got fused with skin lipids and releases the drugs into deep layer of skin.[37,54,]

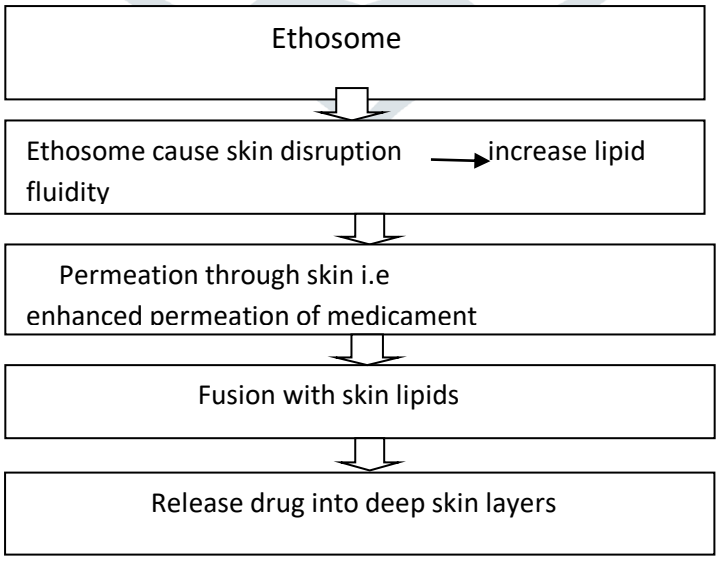
**Fig:5 & 6 Mechanism action of Ethasome for Transdermal drug delivery system.**[48, 55,56]




Commotion of Stratum corneum organization and penetration of Ethosomes

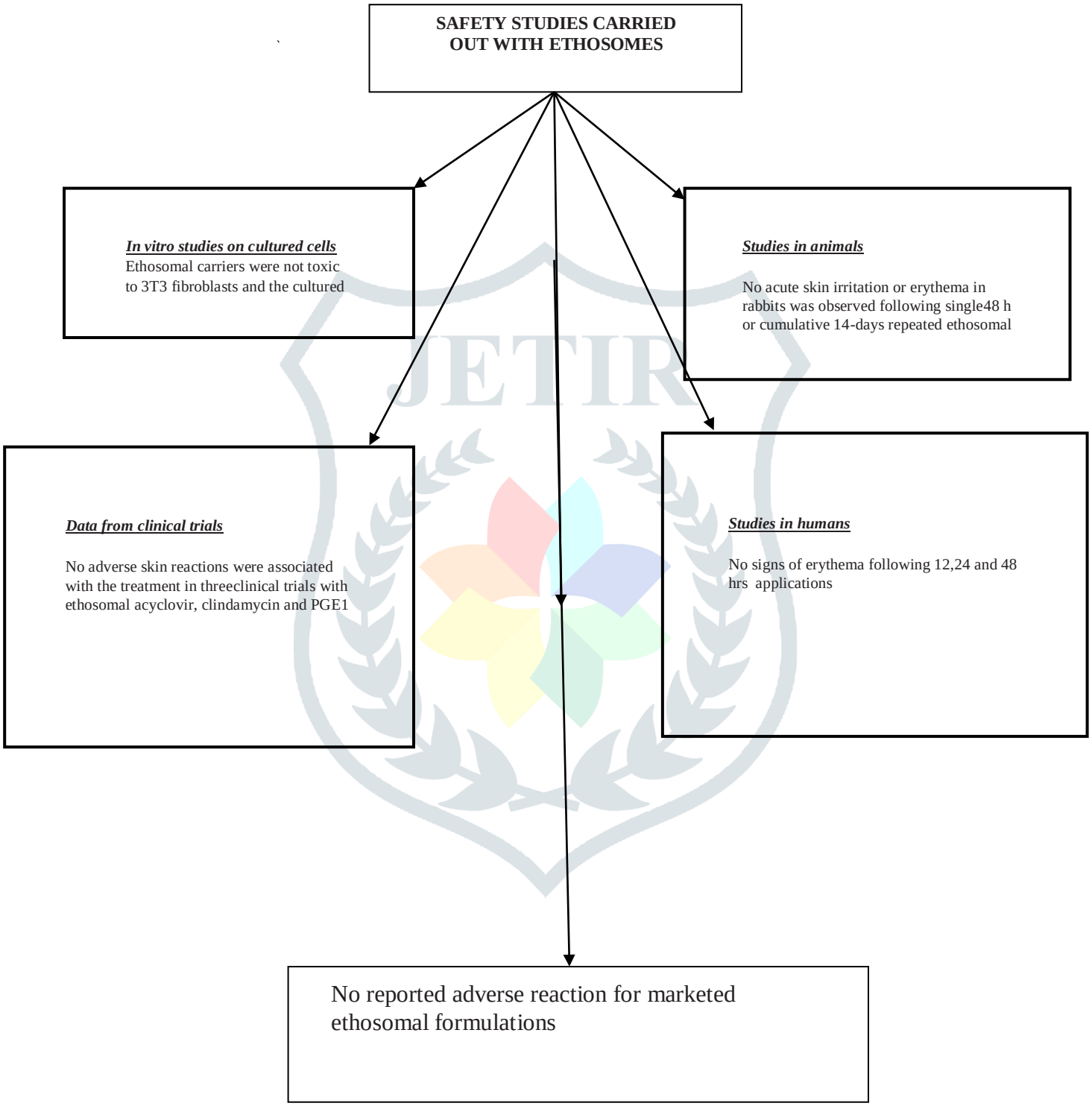


Absorption of Ethosomes in Blood capillaries



## SAFETY OF ETHOSOMAL SYSTEMS

Ethosomes are composed of ingredients generally regarded as safe (GRAS). The safety of ethosomal systems applied topically to the skin has been tested in numerous works, both *in vitro* and *in vivo*. *In vitro* studies on cell cultures showed that ethosomal systems are safe to skin cells.[57,58,59]



# Conclusion

Ethosome nano vesicular carrier open new challenge and opportunities for the development of Transdermal drug delivery system. Ethosome create alternative route for TDDS over the drug delivery for systemic effect. It can be easily concluded that ethosomes can provide better skin permeation than liposomes. . The main limiting factor of transdermal drug delivery system i.e. Stratum corneum barrier can be overcome by Ethasomes. Ethosomes are more advantages when compared to transdermal and dermal drug delivery system. . They are the noninvasive drug delivery carriers that enable drugs to reach the deep skin layers(Stratum Corneum) finally delivering to the systemic circulation. It delivers large molecules such as peptides, protein molecules. Ethosomes are characterized by simplicity in their preparation, safety and efficacy and can be tailored for enhanced skin permeation of active drugs. Continuous research in ethosomal technology has led to the introduction of a new generation of the ethosomal system called transethosomes which are the updated version of classical ethosomes in terms of vesicle properties and skin permeation abilities.

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