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Review on Vesicular Drug Delivery System - Ethosome

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ABSTRACT

This work is the structure of the ethosome, advantages and disadvantages of the ethosome, components, preparation and characterization of the ethosome, as well as a description of their applications in drug delivery systems. It provides information on a new drug delivery system in the vast field of the pharmaceutical industry. The new vesicular carrier is more beneficial in recent years [7,16]. Suitable carriers protect the drug from rapid degradation and increase the concentration of the drug in the target area. Drug targeting is the process of delivering a drug in such a way that the drug is associated with the target tissue to achieve the desired therapeutic response. The most commonly used targeted drug delivery are ethosome, liposome, niosome, which are alternative vesicular systems [5,24]

INTRODUCTION

Ethosomes are an interesting and widely accepted vesicular system that has emerged in the field of the pharmaceutical industry. Ethosomes are soft malleable vesicles modified for better delivery of the active substance [1,3]. The higher concentration of ethanol makes the ethosome unique [4,23]. Ethosomes were first developed by Touitou et al in 1997 [21]. Ethosomes can vary in size from 10 nanometers to very few microns and can contain a high concentration of ethanol (20-40%) and a very low concentration of water. The main ingredients in the ethosomal formulation are phospholipid (phosphatidic acid, phosphatidylcholine) 0.5-10% and higher concentrations of alcohol (ethanol, isopropyl alcohol), glycol such as propylene glycol enhances permeation or acts as edge activators. Cholesterol is used in the range of 0. 1-1% [15,8].

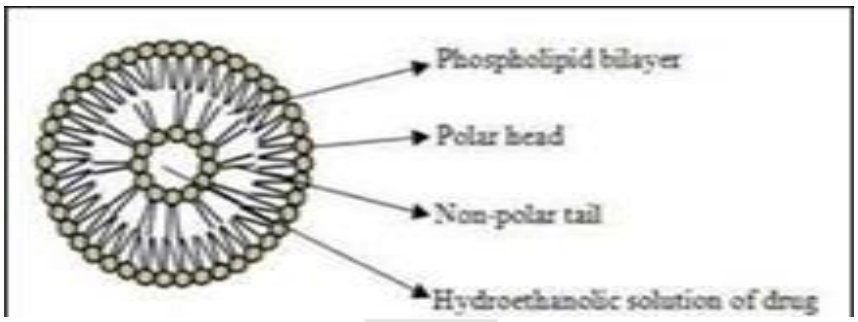

Figure 1. Structure of ethosome 3

Table 1. Advantages and disadvantages of ethosomes

ADVANTAGES	DISADVANTAGES
1.Enhanced permeation of drug through the deeper layer of skin [7].	1.Product loss occur during transfer from organic to water media [12,7].
2.Simple method for drug delivery	2.Molecular size of the drug depend the skin permeability [3,16]
3.Ethosomal system is passive, non-invasive drug delivery	3.Poor yield
4.Better patient compliance as compared to other formulations	4.Sometime causes skin irritation
5.Delivery of large molecular components are possible such as protein and peptide [3].	5.May not be economical

Different additives employed in formulation of ethosomes [23].

Table 2 Different components of ethosomes

Class	Examples	Uses
Phospholipid	Soya phosphatidyl choline, Egg phosphatidyl choline, Dipalmityl phosphatidyl choline, Distearyl phosphatidyl choline [4,20]	Vesicles forming components
Polyglycol	Propylene glycol	As a skin penetration enhancer.
Alcohol	Ethanol, Isopropyl alcohol	To provide softness to the vesicles and act as skin penetration enhancer.
Cholesterol	Cholesterol	To provide the stability to the vesicular membrane.
Dye	Rhodamine -123, rhodamine red	For characterization study
Vehicle	Carbopol934, HPMC, Pectin	As a gel former.

DIFFERENT TYPES OF ETHOSOMES

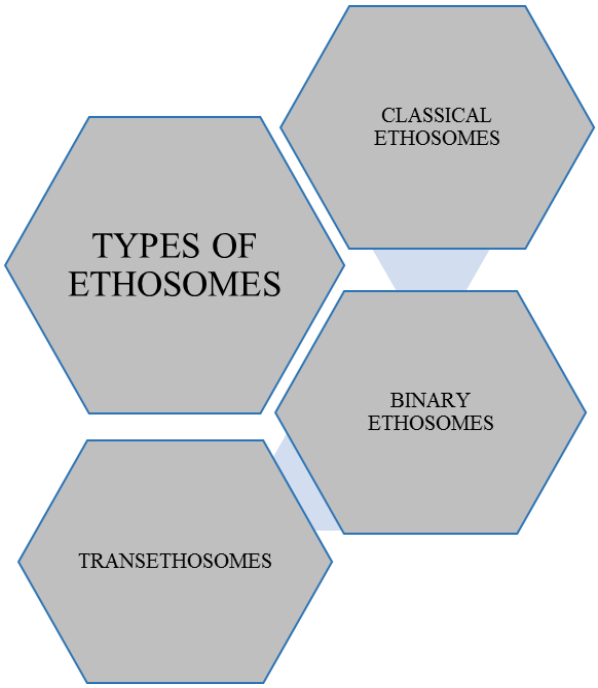

Figure 2 Types of ethosomes

Table 3 Difference between various ethosomes [5,19]

CLASSICAL ETHOSOMES	BINARY ETHOSOMES	TRANSETHOSOMES
Slightly modified and smaller than the classical liposomes	These are simple, equal or smaller than classical ethosomes	New generation of vesicular ethosomal systems and the size depend on edge activator/permeation enhancer
Skin permeation higher than classical liposome	Skin permeation higher than classical ethosomes	Skin permeation higher than classical ethosome
Entrapment efficiency higher than classical liposome	Entrapment efficiency higher than classical ethosome	Entrapment efficiency higher than classical ethosomes
Zeta potential negatively charged	Zeta potential is negatively charged	Zeta potential positively or negatively charged

MECHANISM OF ETHOSOME

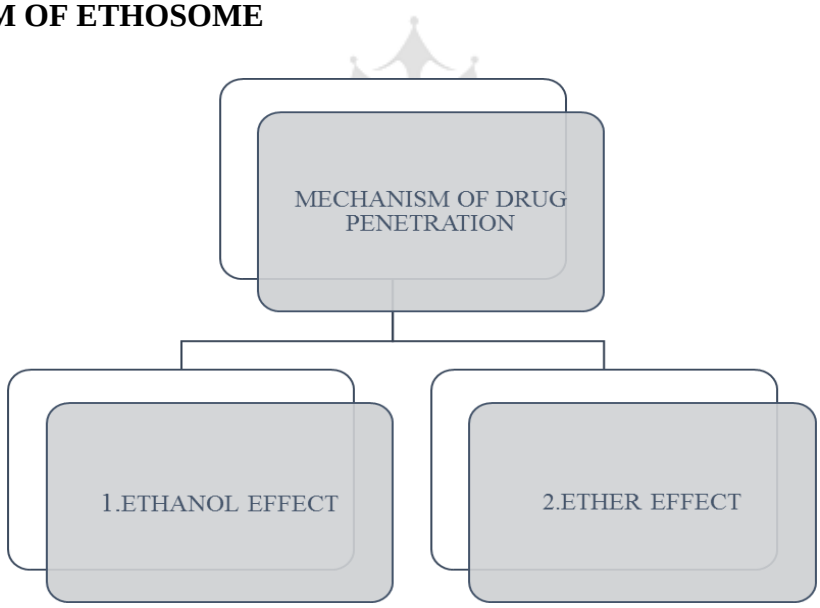

Figure 3 Mechanism of drug penetration

1. Ethanol effect

In this ethosomal formulation, Ethanol acts as a skin penetration enhancer. where ethanol penetrates the intracellular lipid membrane and increases the fluidity and decreases the density of the lipid multilayer [10,23].

2. Ether effect

Increased fluidity of the lipid membrane caused by the ethanol effect of the ethosome dispersion. Thus, these ethosomes vesicles easily penetrate into the deeper layer of the skin and drug is released into it [10,23].

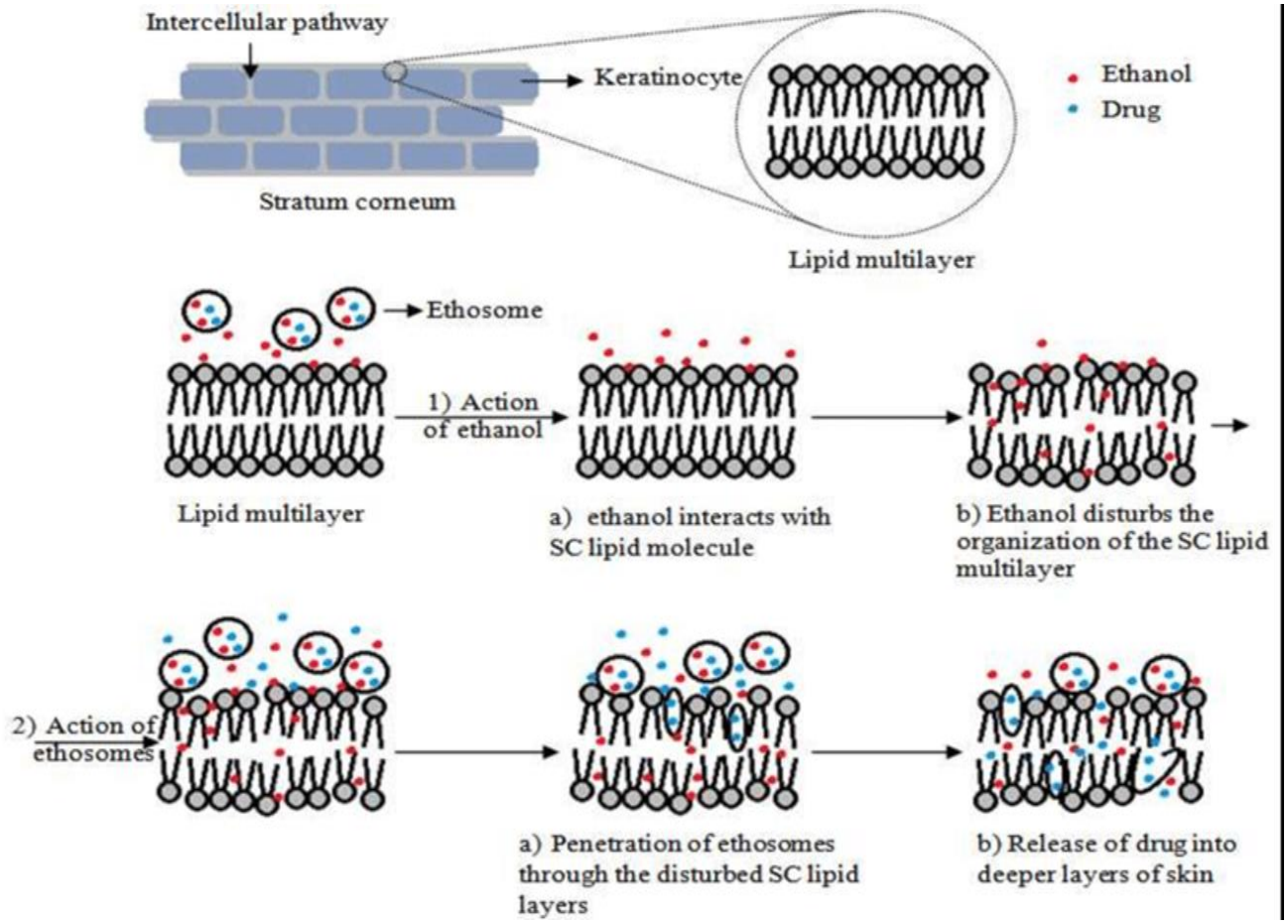

Figure 4 shows mechanism of ethosomes [15]

METHOD OF PREPARATION

Ethosomes can be prepared by very simple and convenient methods [12].

- Cold method
- Hot method
- Ethanol injection method
- Reverse phase evaporation method

1. Cold method

In this method dissolve phospholipids, drug and other lipid materials in ethanol in a covered beaker at room temperature with vigorous stirring using magnetic stirrer. Add slowly propylene glycol or other polyglycol during stirring. Heat the mixture up to 30°C in a water bath. Heat the water up to 30°C in a separate vessel and add to the mixture and form fine stream dispersion. This ethosome dispersion stirring it for 5 min in a covered vessel. The size of the ethosomal vesicle can be reduced by using sonication or extrusion method.

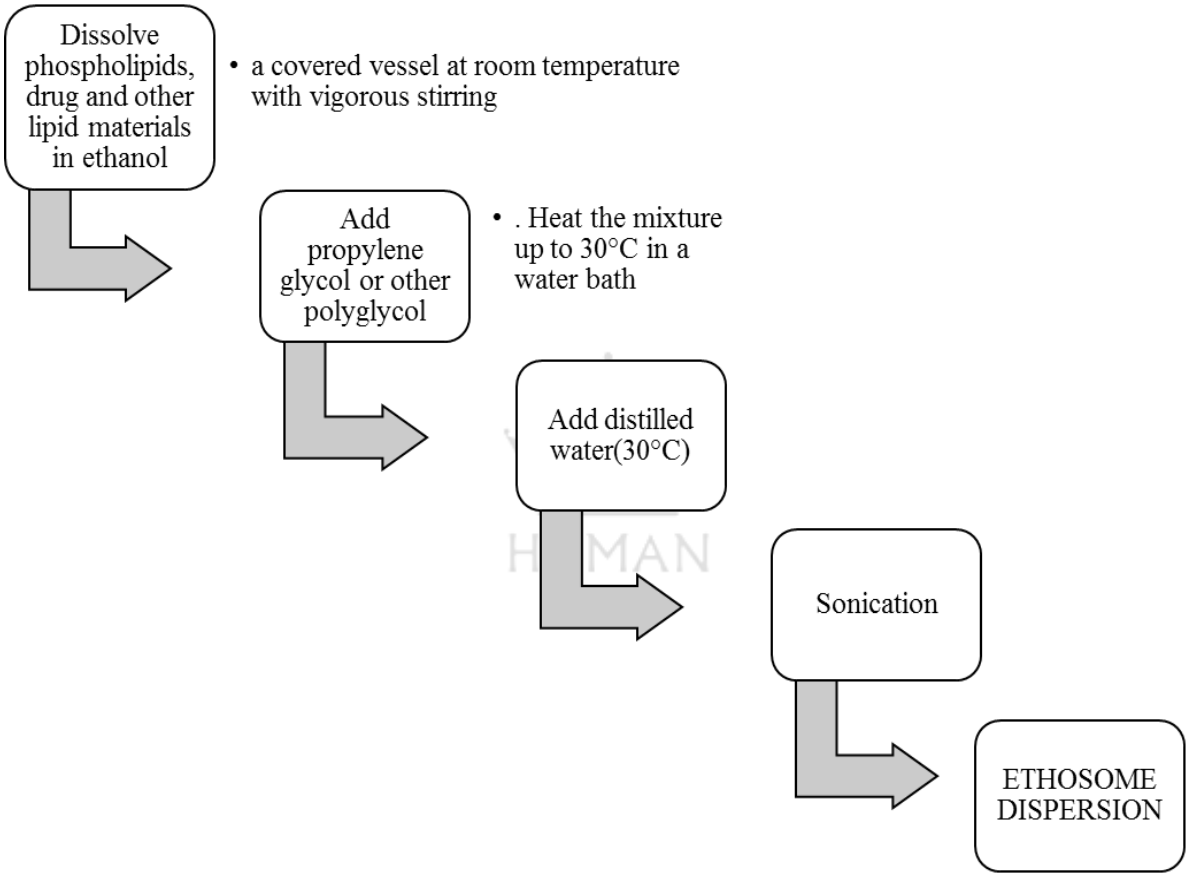

Figure 5 Ethosome prepared by cold method [23]

2. Ethanol injection method:

In this method lipid are dissolved in ethanol in a glass bottle and drug dissolved in another beaker, it is filled into the syringe. This syringe is attached to flask and added aqueous phase to the organic phase to form a fine stream solution with constant stirring.

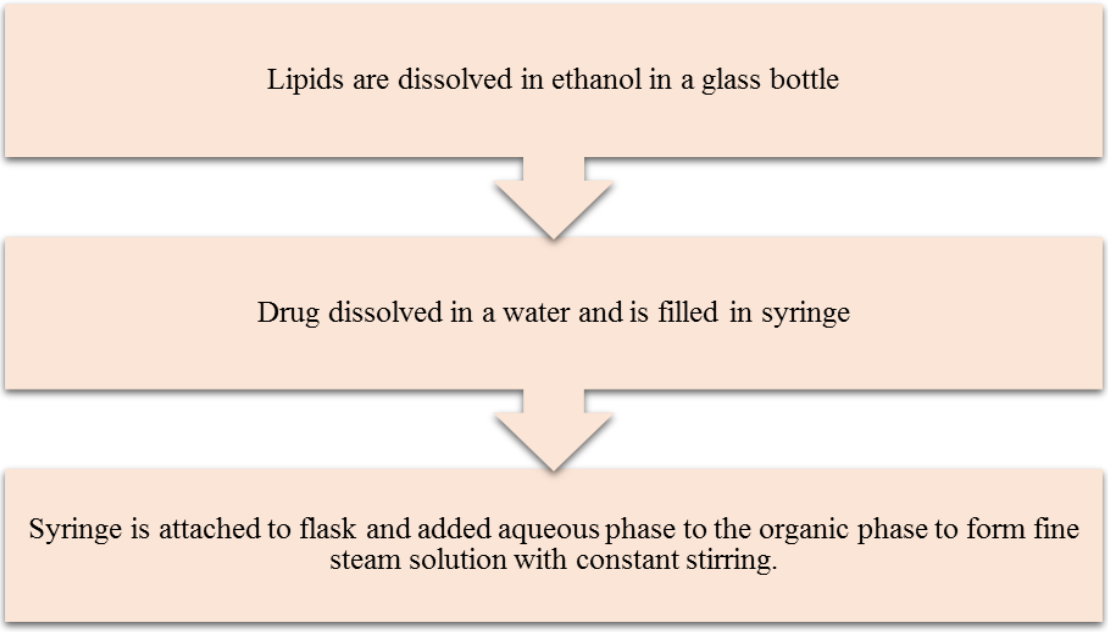

Figure 6 ethanol injection method of ethosome [17]

3. Hot method:

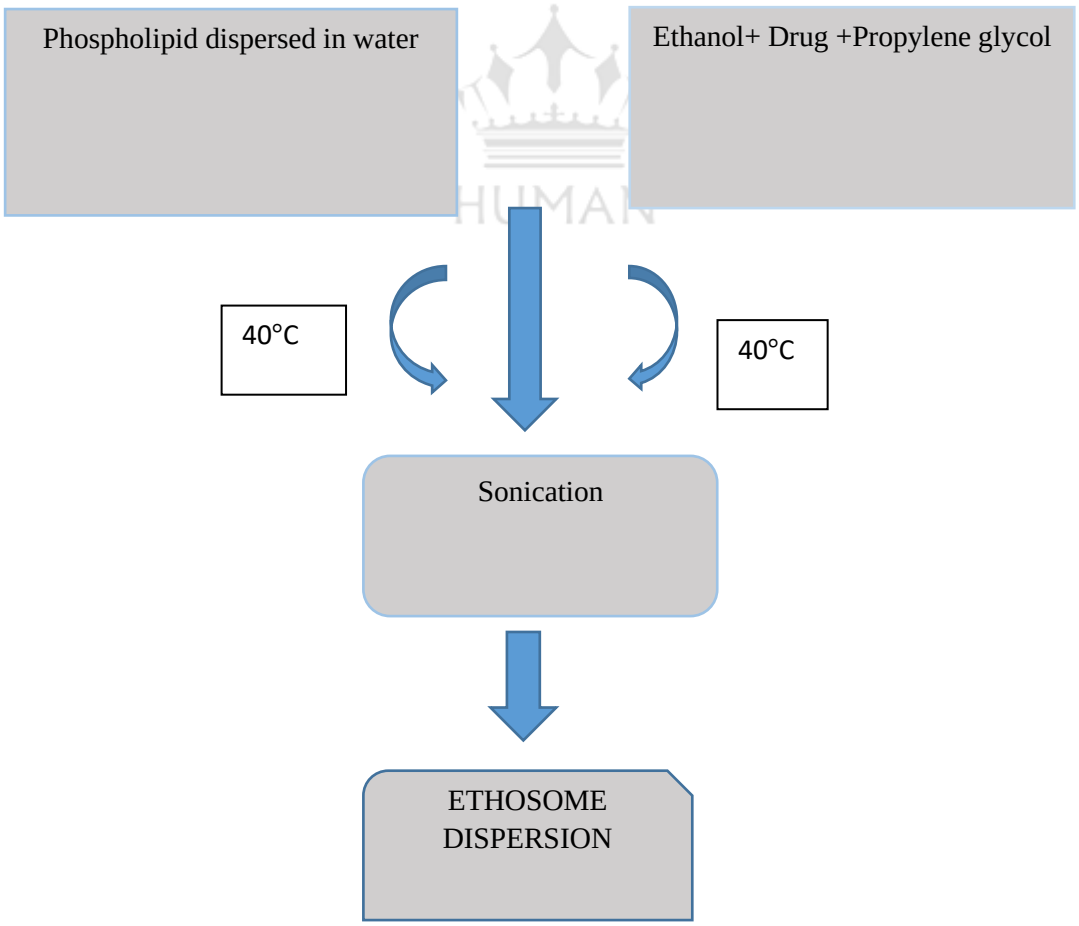

Figure 7 Preparation of ethosome by hot method [17]

4. Reverse phase evaporation method:

In particular, this method produced large Unilamellar vesicles. The phospholipid is dissolved in diethyl ether to form the organic phase and mixed with the aqueous phase in a 3:1 v/v ratio. and sonicated for 5 minutes in an ultrasonic bath. To form a water-in-oil emulsion. The organic solvent is removed under reduced pressure to form a gel, which turns into an ethosomal dispersion under vigorous mechanical stirring [9,18].

CHARACTERIZATION AND EVALUATION OF ETHOSOME [18]

1. Visual examination

The ethosome dispersion were visually examined for one week after the preparation such as

- Colour
- Odour
- appearance

2. Optical microscopic examination:

One drop of ethosome dispersion was placed on the slide before sonication. The formation of vesicles examined under 10x and 40x magnification.

3. Particle size analysis

Particle size of ethosome dispersion determined by dynamic light scattering technique (DLS) by using nano plus zeta/ Nano particle analyzer [7,19].

4. Zeta potential:

Zeta potential is determined by dynamic light scattering technique using Malvern instrument. The analysis was performed under a temperature of 25°C with double distilled water as dispersion medium. Zeta potential is an essential parameter for identify the vesicular stability of ethosomal carrier molecules.

Stability behaviour at colloidal dispersion

Table 4 shows stability behaviour at colloidal dispersion [7,19]

Zeta potential (mv)	**Stability behavior**
From 0 to ± 5	Rapid coagulation or flocculation
From ± 10 to ± 30	Incipient instability
From ± 30 to ± 40	Moderate stability
From ± 40 to ± 60	Good stability
More than ± 61	Excellent stability

5. Polydispersity index (PDI)[7,19]

The vesicle size was determined by DLS techniques, for vesicle size measurement, ethosome dispersion was diluted with distilled water and put into the cuvettes of zetasizer.

Solubility range of PDI

Table1.5 solubility range of poly dispersity index [14,23]

Poly dispersity index	**Stability range**
<0.05	Monodisperse particles
<0.08	Nearly monodisperse
0.08 to 0.7	Particle distribution algorithms is best
>0.7	Very broad distribution

6. Vesicle shape determination [11,7]

Surface morphology of Ethosome dispersion can be visualized by using Transmission electron microscopy (TEM), Scanning electron microscopy (SEM).

7. Entrapment efficiency

The entrapment efficiency of ethosome dispersion can be determined by the ultracentrifugation method. To take 10 ml of the ethosomal dispersion in cooling

centrifugation at 12000 rpm for 1hr at 4°C. After centrifugation the supernatant and the sediment are separated. Where supernatant analysed by UV spectroscopic method at specific wave length. The percentage entrapment efficiency was calculated by using following equation [5,13].

$$\% \text{ Entrapment efficiency} = \frac{\text{Total amount of drug} - \text{amount of drug in supernatant}}{\text{Total amount of drug}} \times 100$$

8. *In vitro* drug release study

An in vitro drug release study of the ethosome was performed using a Franz diffusion cell. The formulation was collected in the donor compartment and the phosphate buffer was collected in the receptor compartment. a cellophane membrane, pre-soaked overnight in the diffusion medium, was placed between the donor and receptor compartments, the ethosomes dispersion was placed on the dialysis membrane. which is contact with the receptor medium. The temperature of the medium was maintained at 37±0.5 °C. At specific intervals, a 1 ml sample was taken from the receptor compartment and placed in the receptor compartment with the same fresh medium. After appropriate dilution, the absorbance at specific nm was determined using a UV-visible spectrometer [17,8].

9. Stability study

A stability study was performed, the formulation was sealed in a vial at 40°C for 1, 2 and 3 months. Zeta potential, particle size, drug entrapment and release efficiency were measured at the time period [21,14].

APPLICATION OF ETHOSOME IN PHARMACEUTICAL INDUSTRY

Table 5 Applications of ethosomes [3,17]

Formulation	Activity
❖ Ketoprofen suspension (2011) used in the treatment of arthritis related to pain	To enhanced transdermal delivery.
❖ Ibuprofen ethosomal gel (2010), treatment of rheumatoid arthritis	Improved transdermal flux.
❖ Benzocaine ethosomal gel (2009) act as topical anesthesia	To improved skin penetration and therapeutic activity.
❖ Finasteride ethosome suspension (2008), treatment of androgenetic alopecia.	To enhanced skin penetration and accumulation.
❖ Melatonin ethosome suspension (2007) used in the treatment of delayed sleep phase syndrome	Improved transdermal flux, reduced lag time and skin irritation
❖ Zidovudine ethosome suspension (2004) used in the treatment of AIDS	Improved transdermal flux
❖ Acyclovir suspension (1999), treatment of herpes labialis	Improved clinical efficacy.

FUTURE ASPECTS

Ethosome drug delivery system is a promising future in the pharmaceutical field for drug development. Advanced research in this novel drug delivery will allow better control over drug delivery in *in vivo*. ethosome have more advantages as compared to transdermal and topical delivery, ethosome are soft malleable vesicular system that reaches the deeper layer of the skin and delivering drug into the systemic circulation. Will allow large molecules like protein and peptide. Hence it concluded that ethosomal formulation possess promising future in the drug delivery system.

CONCLUSION

New vesicular carriers would also allow the rate of drug release to be controlled over a longer period. Ethosomal vesicles are preferred when compared to other formulations. Ethosome composed of phospholipid, higher concentration of alcohol and water. The concentration of

phospholipids and alcohol make ethosomes unique. The ethosome is more similar to the liposome, but the ethosome contains a higher concentration of ethanol, which makes them malleable vesicles it is easily penetrated through the SC, leading to successful drug delivery to the deeper layer of the skin. Ethosomal drug delivery opens up new challenges and opportunities for pharmaceutical technologies.

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