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Formulation And Evaluation of Nanovesicle Gel of Antifungal Drug

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Abstract

This paper describes the use of ultra-deformable nanovesicles for targeted delivery systems, which will increase the usage of nanovesicles in the present because of their exceptional capacity to penetrate the skin and increase the bioavailability of medications that are poorly soluble in water. The study includes a list of several vesicle kinds along with preparation and evaluation techniques. Transdermal Conveyance Framework (TDDS) has traditionally used ethersomes because they increase drug saturation via the skin. The planning of nanovesicles can be done using a variety of methods, including the hot, cold, transmembrane pH slope, ethanol infusion, and minimal film hydration strategies. By transdermal route, the UDV can be utilized to deliver many classes of pharmaceuticals, such as anti-toxin, anti-cancer, antiviral, anti-tumor, and pain-relieving drugs. This model incorporates a manufactured or homegrown pharmaceutical atom into vesicles that can penetrate the skin further for targeted drug delivery. And highly effective on subcutaneous layer.

Key word: Nanovesicle and its types, ethosomes, mechanism of action of ethosomes, Methods of preparation of ethosomes, list of materials, evaluation parameters of ethosomes.

Introduction

Ethosomes are vesicular nanoparticles made of phospholipid lipids that have a high ethanol and water content. These elements have special characteristics and benefits. These are **high deformable,** and high Drug entrapment efficiency, and **improve drug permeation rate** in the skin, make a suitable skin administration of different therapeutic agent.[1]**.** Ethosomes These are **soft, floppy** and flexible nanovesicles revised for better-quality drug delivery of active agents. **Ethanol as an important solvent enhance** corneal permeability and brings about relaxing of ethosomal lipid nanovesicle.[4]Ethosomes might be a possibly powerful conveyance framework to increment anthralin viability against psoriasis and cutoff its unfavorable effects.in this study worried by create and assess an ethosomal gel readiness of anthralin and contrast it and a liposomal gel planning. The review reports, interestingly, a relative clinical assessment of anthralin-stacked ethosomes and liposomes in psoriatic patient.[5] Nanotechnology has been utilizing generally in beauty care products as lotions and particularly in likely enemy of maturing items. The utilization of nanotechnology and the quantity of items from driving organizations in the market are expanding. The utilization of cell reinforcement intensifies in enemy of maturing items is essential to decrease or forestall oxidative harms, to make more youthful looking skin.[2]Docetaxel (DTX) is a first-line anticancer specialist use to fix and analyzed different disease, for example, ovarian malignant growth, bosom disease and so on. Its profoundly lipophilic nature and extremely unfortunate H_2O solvency drive the producers to utilize an exceptionally high measure of manufactured surfactant polyoxy ethylene monooleate alongside got dried out liquor as solubilizer to make it reasonable for venous (I.V.) organization. Utilization of enormous measure of tween 80 caused hemolytic harmfulness and touchiness response. Various teachers educated the change regarding nanoparticles, nanoemulsions, micelles , liposomes, ethosomes and so forth.[3] Ethosomes development of a fruitful drug dose structure is subject to a few elements, for example, its capacity to keep up with the adequate medication focus in higher sum than the base inhibitory fixation in the salivary liquid, for a delayed timeframe, as well as decreasing the recurrence of measurements organization and improve the transdermal penetrability properties and request to the fast therapeutics viability of Ciclopirox olamine.[6] Griseofulvin-loaded nanovesicle ethosomes are very effective transdermal delivery of antifungal agent. ethosomes may be deformable and across the skin pores without any significant loos of entrapped entities. Griseofulvin is a very effective antifungal agent. Griseofulvin drug are not suitable for oral route because they are poor water solubility and poor oral bioavailability. Griseofulvin are show large numerous side effect on oral route.[7] Ethosomal preparation of

simvastatin, may be permeate in transdermal delivery into systemic circulation directly and avoid the 1st pass metabolism in the liver Thusly, the transdermal organization of simvastatin ethosome

could be likely to tackle the issue of liver and a lesser measurements of simvastatin ethosome.[8]Contrasted with other existing medication conveyance courses, transdermal conveyance is a harmless method portrayed by the evasion of first pass digestion, the capacity of drawn out drug discharge designs overstretched timeframes and minimization of potentially related torment and inconvenience, in this way really further developing patient compliance.to improve drug saturation across the skin, utilizing of entrance enhancers, like unsaturated fats and natural solvents.[9]ethosomes take a compelling method for drug conveyance through transdermal way of organization. The traditional vesicular transporters like liposomes and biosomes neglect to ensnare drug into center. Methoxsalenis is a famous medication suggested for PUVA treatment. It incites melanin creation on openness of the skin tissue to UV light. Vitiligo [PUVA] required greatest remedial impact of methosalen in photochemotherapy. [10] Because of their flexible structure, manufacture, and nanosize, which allow them to be delivered through skin cells, ethersomes exhibit a preferred limit over enter the skin even more excellently.[11]. Ethosomal drug conveyance framework is painless and conveys the medication to the profound skin layers to fundamental dissemination. Ethosomes are delicate, pliable vesicles made basically out of phospholipids, ethanol and water having a size range from several nanometers to microns. size of ethosomes relies on the strategy for readiness and utilization of methods like sonication.[12] Ethosomes are a creative vesicular conveyance framework, with benefits that incorporate thermodynamic strength, little molecule size, high stacking productivity, and high embodiment proficiency. can really invade the skin, and even into additional significant layers of the skin. [13] Deformable liposomes and ethosomes could further develop skin conveyance of the model hydrophilic medication, ketotifen fumarate (KT), under non-occlusive conditions.[14]metformin-stacked ethosomal arrangements and to choose the greatest ideal recipe to test its effective anticancer action against tentatively actuated skin disease in mice. This concentrate similarly expected to pass metformin on to the skin layers for the treatment of skin dangerous development. [15] ethosomes in conveying ketoprofen through the skin. We estimate that like ketotifen, ethosomes might be a reasonable vehicle to ketoprofen too. Ketoprofen is a nonsteroidal mitigating drug and is a decent possibility for transdermal conveyance attributable to issues in conveyance by different courses. Endeavors have been made to foster reasonable framework for worked on transdermal conveyance of ketoprofen regardless of a few

effective gels/fixes currently accessible in the market.[16]Ethamomes nanoparticles were shaped and stacked into several ocular in situ gel (ISG) and hydrogel game-plans to further promote the ketoconazole antifungal effect and reduce the drug's sometimes delayed effects during oral therapy. The antifungal effect, ocular irritation, and visual aid were taken into account when examining the

abundance and safety of the plant arrangement. Better skin testimony and porosity of psoralen were provided by 17 ethosomes than by traditional conveyance techniques, which may help achieve more appropriate psoralen treatment in the future. They were then employed as means of updating the psoralen vehicle and skin announcement following skin relationships to various rodent skin grievances, such as the scapular region, chest, and mid-area. Using micro dialysis, the psoralen center was screened in vivo.18 The lipid vesicles that include liquor and phospholipids are called ethosomes. Etosomas can be created by combining medications that are both hydrophilic and lipophilic and range in size from ten nanometers to microns.[19] ethosomes including phospholipids and Carbopol 934P as a vesicle describing an expert nearby TH to observe its impact at the designated spot for a generally longer period of time with a zero-solicitation release profile.

Skin:

ectosomes containing Carbopol 934P and phospholipids as vesicle framing master nearby TH to see its impact at relegated site for a generally longer time frame with a zero-requesting discharge profile.[20]

The outermost layer of the epidermis is called the layer corneum. It consists of a network of phospholipid bilayers enclosing 10 to 25 layers of fully keratinized, enlarged, dead corneocytes. Studies have indicated that the stratum corneum serves as the main barrier to penetration through the skin. When applied properly, it fully resists water and keeps most pathogens, diseases, and other objects out of the body. In the stratum corneum, dead squamous cells that have finished replicating are known as keratinocytes.

The dermis is more impermeable than the epidermis and is primarily composed of thick, erratic connective tissue. The derma is at risk for the skin's ability to adapt. Its primary functions are controlling body temperature and delivering blood that has been soaked with supplement to the skin. Large amounts of the body's water supply are restricted to the dermis.

he hypodermic layer, commonly known as the subcutaneous layer, is located beneath the dermis. Fat and connective tissue make up the majority of the inner layer. In order to protect the body, it

serves as a defensive pad that regulates temperature growth and in Ttensity tragedy. This layer undoubtedly affects how the skin looks, even if not all manufacturers see it as a component of the skin.[21]

Various techniques of nanovesicles

1.Ethosome

Ethosomes (lipid vesicular carriers) were made as unique lipid carriers, made from phospholipids, ethanol, and water (Figure 1). Ethosomes are second time of liposomes, depicted by more noticeable flexibility, adequacy and ability to trap hydrophilic and hydrophobic molecules.[22]

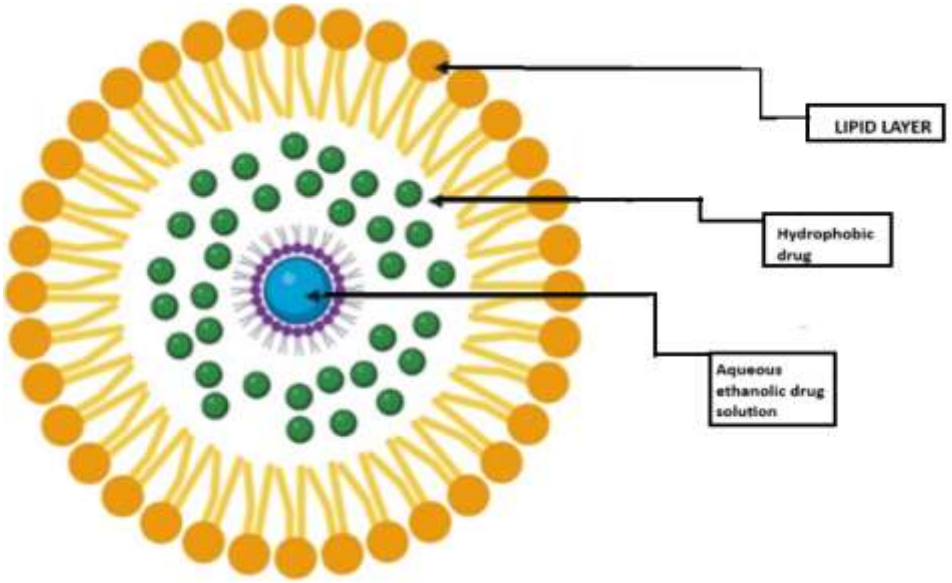


Figure:1 Ethosomes

Mechanism of drug penetration:

The object of ethosome preparation ended liposome preparation is the enhanced drug permeation on transdermal delivery.the mechanism of ethosomes drug delivery system are not identify. The mechanism are follow two step:

1. Ethanol{C_2H_5OH} effect

2. Ethosomes {nanovesicles} effect

C_2H_5OH Effect: $CH3OH$ goes about as a dissemination enhancer over the transdermal medication conveyance framework. Ethanol infiltrates into profound layer of skin and expands the ease of the corneal film of skin and reduction the thickness of lipid multi-facet of skin

Ethosomes effect: Ethanol are improving fluidity on cell membrane, These ethosomal ethosomes are enhance the skin permeability. Then the ethosomes diffused easily subcutaneous layer.

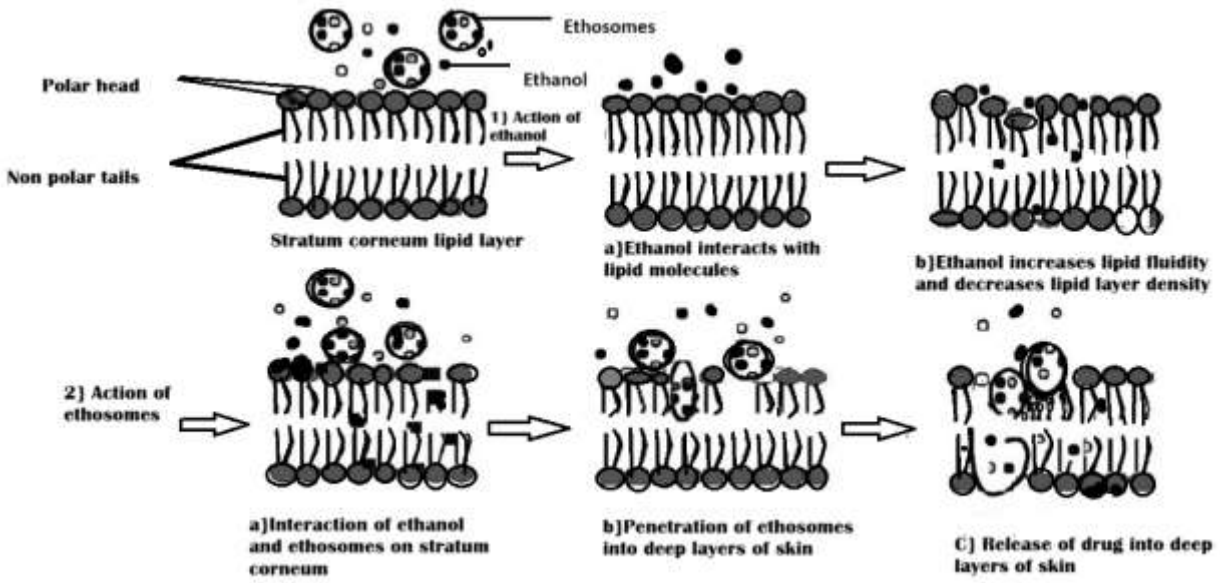


Figure:2 Mechanism of drug pernetratin

2.Proniosomes or Noisome: Both are Amphiphilic structure loaded hydrophilic and lipophilic drug. These are enhance the bioavailability of poorly soluble drugs. Having a Non-ionic surfactant {mostly use}.These are multilamellar and unicellular nanoparticle structure similar to liposomes.[23]

Figure:3 Niosomes

3.Transferosomes: The 1990s saw the first mention of transferosomes. Ultra-deformable, flexible vesicles called transferosomes penetrate the epidermis via the stratum corneum, reaching the corium and underlying tissue. Maintain a fluid center with a bilayer of lecithin, phospholipids

(which are amphipathic in nature), or other lipid combinations. Additionally, other appearances include modest concentrations of alcohol, surfactant, edge activator, ranges, and sodium cholates. They contain 10–25% bilayer-loosening agents, surfactants, or edge activators such as Tweens, Degrees, and sodium cholates, despite having a very low alcohol content.[24]

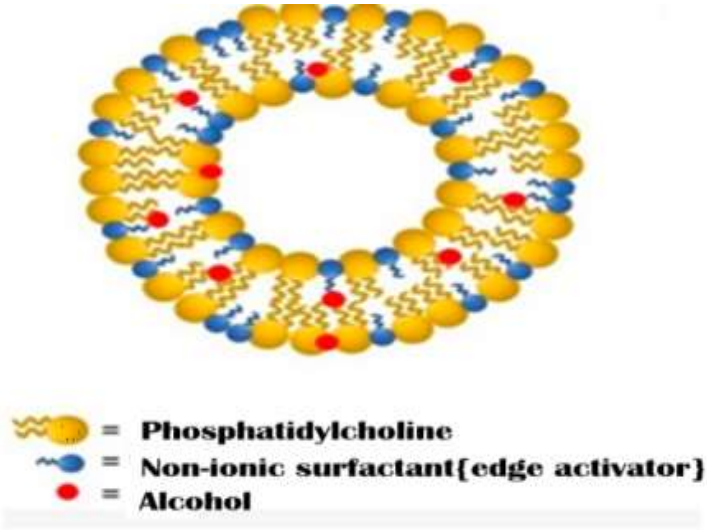


Figure:4 Transferosomes

4.Pharmacisomes. The pharmacosomes are nanovesicle advantage over the noisome, transferosomes and liposomes. Unlike those indicated by the existence of an amino or hydroxyl group, dynamic particles with an open carboxylic party can be esterified without a piece being secured.[25]

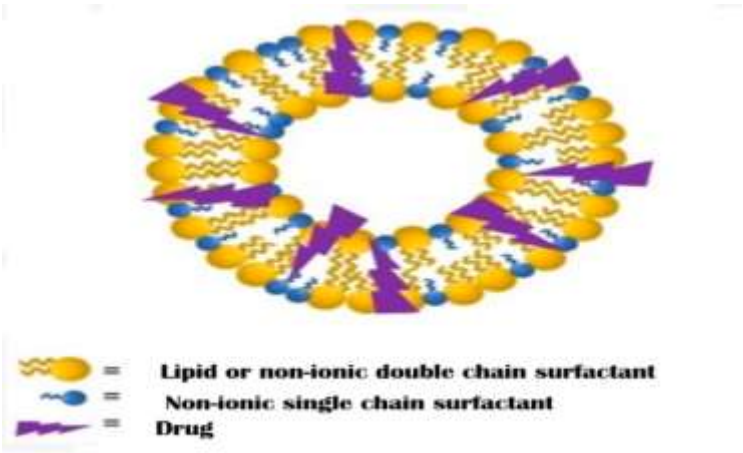


Figure:5 Pharmacisomes

5.Ufasomes: Gebicki and Hicks are first interduced ufasomes. Ufasomes are called as, Unsaturated fatty acid nanovesicle preparation. its PH 7-9.it is a suspension closed lipid bilayered.[26]

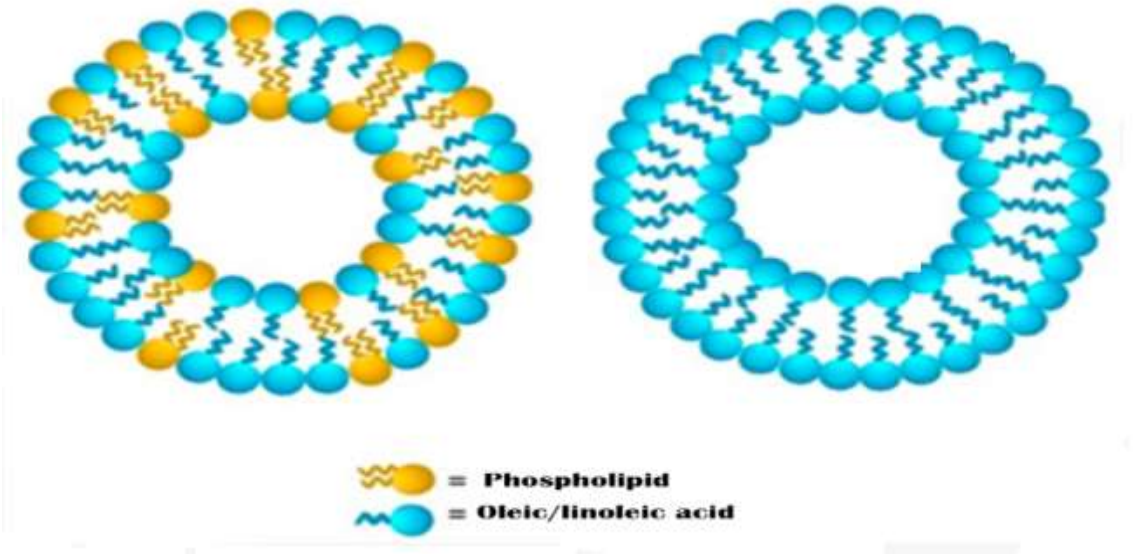


fIgure:6 Ufasomes

6.Phytosomes: Phytosomes nanoparticles, which are based on Phyto-Phospholipid Complex, have been developed as an effective way to increase the bioavailability of common prescription drugs. Phytosomes nanovesicles commencing by Phyto-Phospholipid Complex begins by the phospholipids water soluble head and dynamic ingredients' interchanges. When resuspended in water, the two long unsaturated fat chains can exchange, reflecting the polar location of designs and beginning a lipophilic side. They do not participate in the confusion. [27]

Figure:7 Phytosomes

7.Catanionic Vesicles: A revolutionary class of recyclable and biocompatible materials. The ability of catanionic {+} vesicles to consider the fidelity and cell uptake of different strong particles is addressed to phospholipidic nanoparticles [215]. Dispersed in H2O, these half-and-half nanovesicles unexpectedly form when uneven concentrations of {+ }and {-} single-followed wetting agent are present. Thermodynamically, they are stable.[28]

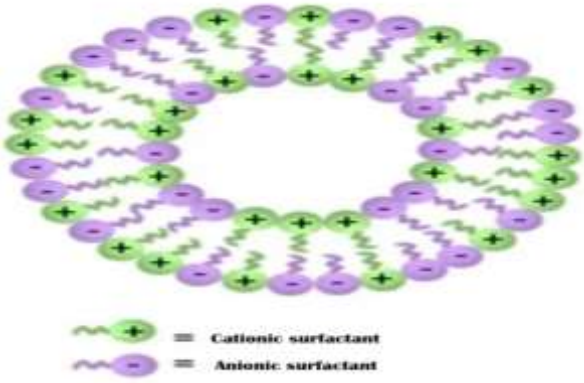


Figure:8 Catanionic vesicles

METHOD AND MATERIALS

List of materials used in the preparation of ethosomes:[29]

CLASS	EXAMPLE	USES
Phospholipid	Soyaphosphatidyl choline, Eggphosphatidylcholine, Dipalmitylphostidylcholine, Distearylphosphatidyl choline.	Vesicles forming component.
Alcohol	C_2H_5OH, Isopropyl alcohol.	For providing the softness for vesicle membrane. As a penetration enhancer.
Polyglycol	Transcutol RTM	As a skin penetration enhancer.
Cholesterol	Cholesterol	For a provide the stability to vesicle membrane..
Dye	Rhodamine-123, Rhodamine red fluorescence Isothiocynate{FITC} 6-carboxy fluorescence.	For characterization study.
Vehicle	Carbopol934	As a gel former.

MEHODS OF PREPARATION OF ETHOSOMES:

1.Hot method: After substance {API} is isolated, it is mixed with PG[C3H8O2] and CH30H at 40°C. Phospholipid scattering is then added to the mixture. Following a five-minute mixing period, the mixture is subjected to three five-minute sonications at 4 degrees Celsius, separated by a five-minute interval, utilizing the Test Sonicator. The mixture is then homogenized in three cycles at a pressure of 15,000 psi using a high strain homogenizer to produce nano-sized ethosomes.[30]

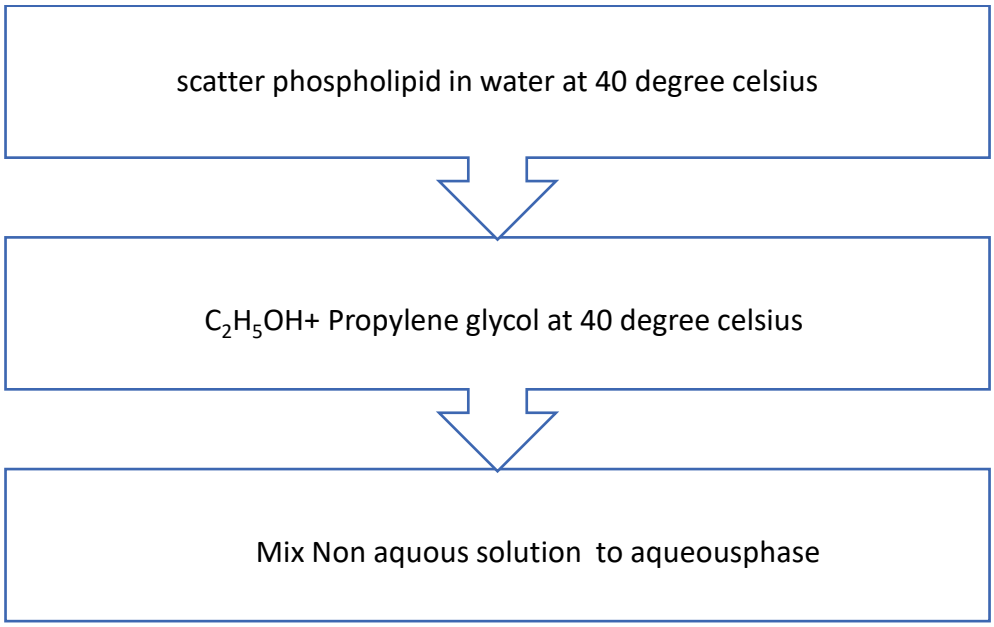
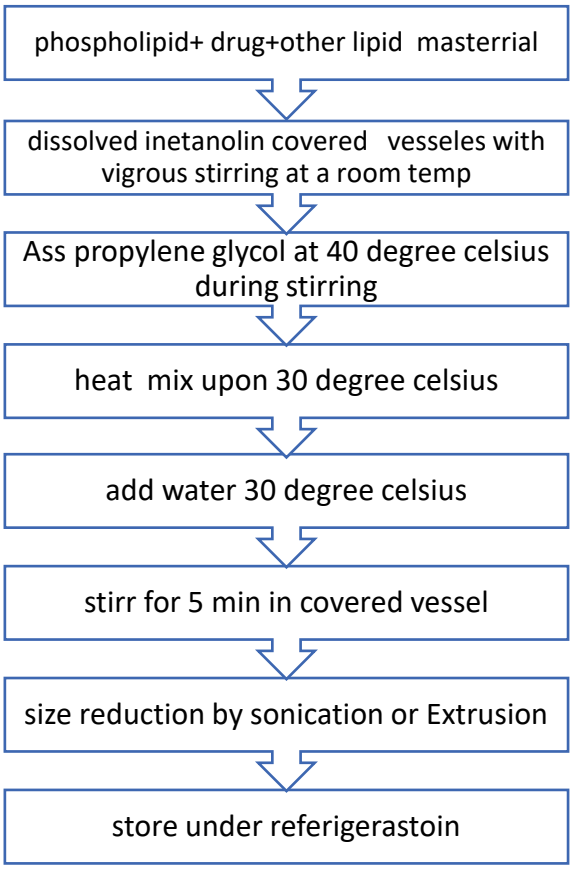


Figure:9 Hot method

2.Cold method

This is the most well-known and efficient way to prepare ethosomal material. The medicine, phospholipids, and other lipid components are dissolved with vigorous mixing in CH3OH in a covered container kept at room temperature. The mixture is brought to room temperature under a water spray. The water is added to the mixture above and stirred for five minutes in a covered vessel after heated to 30°C in a separate vessel. The vesicle size of the ethosomal definition can be decreased at any time to grow by sonication or expulsion. Lastly, the detailing must be kept ina refrigerated environment.[31]

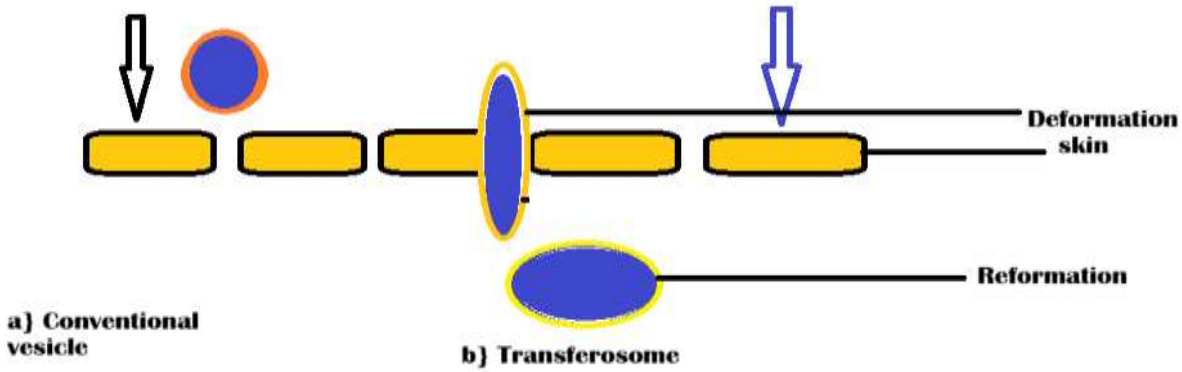


3.Classic method

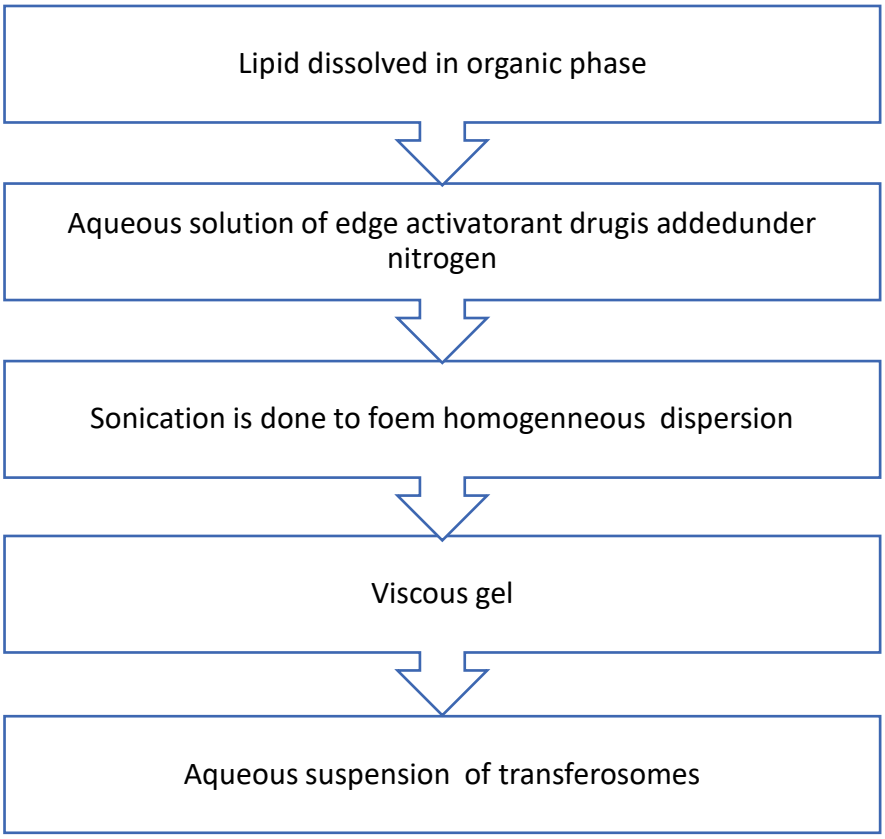
The prescription and phospholipid are heated to 30°C±1°C under a water shower after being separated in ethanol. Double-refined water is introduced to the lipid mixture in a closed vessel in a fine stream while mixing continuously at 700 rpm. The vesicle solution is then homogenized by using a hand extruder to run it through three cycles of a polycarbonate layer.[31]

4.The Hand Shaking Method { thin-film hydration method}:

Medication and phospholipids broke down in chloroform: methanol in 3:1 proportion and kept in round base jar and afterward dissipated in turning evaporator above lipid change temperature for example above 600C to dissipate total methanol and chloroform to shape a flimsy film in RBF. Then, at that point, it is hydrated with phosphate cushions saline with pH 7.4 containing ethanol. Then, at that point, the definition is sonicated for 5 minutes to diminish the molecule size to give ethosomes. Then stored in refrigerator. This method is similar to that of Phytosomes but here only slight change in buffer with ethanol.[32]



5.Reverse Phase Evaporation Method: In this strategy, lipids disintegrated in natural solvents are taken in a round base jar. Fluid media containing edge activators is added under nitrogen cleansing. The medication can be added to the lipid or fluid medium in view of its solvency characters. The framed framework is then sonicated until it become a homogeneous scattering and shouldn't separate for something like 30 minutes after sonication. The natural dissolvable is then eliminated under decreased pressure. Right now, the situation will change over completely to a thick gel followed by the development of vesicles. The non-epitomized material and lingering solvents can be taken out utilizing dialysis or centrifugation.[33]



Evaluation

through the application of transmission electron microscopy (TEM), sifting electron microscopy (SEM), and atomic power microscopy (AFM). To view the FES under the SEM, a drop of the necessary 10 ml was evenly spread out on a glass slide and allowed to dry at room temperature. After being gold coated with a Polaron E5100 gold powder coater (Polaron Parts Ltd., Watford, UK), the models were examined under a Philips 505 looking at electron amplification equipment (Present day Closeout Eindhoven BV, Eindhoven, Netherlands) at an accelerating voltage of 20 Kv.[34]

1.Vesicle Size, Size determination and Zeta potential:

The ethosomal framework's vesicles' continuous size transport was assessed using the dynamic light dissipating (DLS) approach, and the zeta-expected assessment was conducted using laser doppler velocimetry (LDV). Zetasizer Nano ZS (Malvern equipment, U.K.) with clearing cuvette for size and cuvette DTS-1060 for zeta-potential was the equipment used for these assessments. The assessments were carried out at a set dissipation point of 173°C and a temperature of 25±0.5°C.[35]

2.Drug Entrapment Efficiency {DEE}:

Drug ensnaring proficiency is not completely resolved by using the ultracentrifugation technique. Using centrisort tubes, every detail was subjected to ultracentrifugation at 20,000 rpm for three hours (Remi Electrotechnics Restricted, Mumbai, India) [16]. After centrifugation, the supernatant fluid was diluted using a 1:1 water-ethanol ratio. The amount of TH in the definition was examined using the above-mentioned HPLC technique[36]

Entrapment Efficiency = Amount of drug entrapped

Total amount of drug loaded 100

$$\mathbf{DEE = [\langle Qt - Qs \rangle \div Qt] \times 100}$$

3.Viscosity:

Thickness assume a significant part in spread ability of ethosomes on skin, their application and expulsion. It very well may be estimated by Ostwald viscometer, Brookfield viscometer and cup or bounce viscometer.[37]

4.In Vetro diffusion study:

In vitro drug dissemination review did to choose the plan for ex vivo discharge concentrates by utilizing a Franz dispersion cell with Cellophane dialysis film of grade '110'.[38]

5.Transition Temperature:

Can be determine by utilizing Differential Checking Calorimetry. [39]

6. **Drug Content:**

A UV spectrophotometer can be used to determine the drug content of the ethosomes. Similar to that, this can be evaluated by modifying the primary liquid chromatographic execution approach.[40]

7.Surface Tension Measurement:

The ring approach in a Du Nouy ring tensiometer can be used to assess the surface strain action of medication in a watery environment.[41]

8. Phospholipid-ethanol interaction:

concentrated utilizing Differential Sifting Calorimetry and Proton Decoupled 31P-NMR.[42]

9.Stability Study:

Ethomes are kept at three different temperatures (25 ± 2°C, 37 ± 2°C, and 45 ± 2°C) over variable periods of time. Changes in the size and state of the vesicles can be evaluated using DLS and

TEM to determine the ability of ethosomes to support the medicine over an extended period of time and under various situations.[43]

10.PH Measurements:

The pH of ethosomal definitions was assessed by using the pH meter. The cathode was dunked into the vesicles a s long as covered by the vesicles.[44]

11.**In Vitro skin permeation study:**

A segment of newly extracted rodent skin was submerged in isotonic arrangement (0.9g NaCl disintegrated in 100mL of R.O H_2O). Ethosomal vesicles and gel were on rodent skin and put on top of the benefactor compartment of Franz dissemination cell. The dermal side of the skin should simply contact the receptor fluid surface for saturation. Any remaining examination conditions were like the in vitro discharge study.And skin maintenance of dug was dissected by HPLC strategy.[45]

12.Degree of deformability and turbidity:

A nephelometer can be used to assess the blueprint's turbidity, and the expulsion method can be used to gauge how malleable the ethosomal preparation is.Thirteen.[46]

APP LICATION OF ETHOSOMES:

1.Treatment of microbial and viral skin infections:

Antimicrobial drugs found in ethosomal structures have been studied in the treatment of several skin diseases. The ethosomal structures of bacitracin and erythromycin were identified and investigated for their feasibility in animal models of serious skin disorders.[47]

2.Used as Anti-inflammatory ethosomal systems:

Paolino and associates attempted to remedy provocative set-up skin defilements involving human workers using methyl-nicotinate erroneously influenced erythema with ammonium glycyrrhizinate ethosome.[48]

3.Analgesic and Antipyretic Ethosomal Systems:

Another investigation examined the in vivo torment mitigating and antipyretic obliging impacts of transdermal ethosomal ibuprofen in two creature models, the Brewer's yeast induced fever rat and tail flick nociception mice.24 The application of ibuprofen gel on the skin of fevered rats resulted in a progressive reduction in body temperature, as anticipated. The influence of ethosomal ibuprofen gel on exacerbation was compared to oral treatment in mice using the tail flick test. The

ethosomal ibuprofen structure showed a statistically significant greater influence 120 and 360 minutes after delivery. The impact was roughly six meters long h.[49]

4.Management of Erectile Dysfunction:

Another study examined the effects of transdermal ethosomal ibuprofen in two creature models for the purpose of minimizing in vivo torture and reducing fever. Out of 15 men, 12 patients showed improved penile unbending nature, a single effective use of PGE1, and further developed top systolic speed. After using the empty ethosomal vehicle, there was no observed erectile reaction or alteration in the penile blood stream. The duration of the erection varied from 10 to 60 minutes.[50]

5.Ethosomal systems for menopausal syndromes:

The capacity of ethosomal attachments to address androgen requirement associated with menopause and menopausal problems in women has made them desirable. Testosome, a testosterone ethosomal fix structure, was developed to treat androgen-dependent men.[51]

Conclusion:

Transdermal course has turned into a most positive courses for the conveyance of medications from most recent couple of years. It vanquished many detriments happened with the oral course of medication conveyance framework, for example, significant downsides is first pass digestion. To beat this impediment transdermic conveyance framework has been grown however the medication which is conveyed through transdermal course is as yet a test as hardly any medication particles doesn't handily go through the layer corneum and empower to proficiently infiltrate. To beat this challenge our researcher and specialists have fostered another framework known as ultra deformable vesicle framework (UDV). In this framework the medication particle either manufactured or home grown is integrated into vesicles which can without much of a stretch enter further into skin for designated drug conveyance. Among Transferosomes and Ethosomes Transethosomes is an original possibility for improved transdermal medication conveyance through skin. The successful vulnerability of Nanotransethosomes is because of ethanol, edge activator and phospholipids

References:

1. **Ahmed TA, Khalid M, Aljaeid BM, Fahmy UA, Abd-Allah FI**. Transdermal glimepiride delivery system based on optimized ethosomal nano-vesicles: Preparation, characterization,

in vitro, ex vivo and clinical evaluation. International journal of pharmaceutics. 2016 Mar 16;500(1-2):245-54.

2. **Yücel Ç, Şeker Karatoprak G, Değim İT**. Anti-aging formulation of rosmarinic acid-loaded ethosomes and liposomes. Journal of microencapsulation. 2019 Feb 17;36(2):180-91.
3. **Singh A, Thakur S, Singh H, Singh H, Kaur S, Kaur S, Dudi R, Mondhe DM, Jain SK.** Novel Vitamin E TPGS based docetaxel nanovesicle formulation for its safe and effective parenteral delivery: Toxicological, pharmacokinetic and pharmacodynamic evaluation. Journal of liposome research. 2021 Oct 2;31(4):365-80.
4. **Paliwal S, Tilak A, Sharma J, Dave V, Sharma S, Yadav R, Patel S, Verma K, Tak K.** Flurbiprofen loaded ethosomes-transdermal delivery of anti-inflammatory effect in rat model. Lipids in health and disease. 2019 Dec;18:1-5..
5. **Fathalla D, Youssef EM, Soliman GM**. Liposomal and ethosomal gels for the topical delivery of anthralin: preparation, comparative evaluation and clinical assessment in psoriatic patients. Pharmaceutics. 2020 May;12(5):446.
6. **AbouSamra MM, Salama AH, Awad GE, Mansy SS**. Formulation and evaluation of novel hybridized nanovesicles for enhancing buccal delivery of ciclopirox olamine. AAPS PharmSciTech. 2020 Oct;21:1-2.
7. A**ggarwal N, Goindi S**. Dermatopharmacokinetic and pharmacodynamic evaluation of ethosomes of griseofulvin designed for dermal delivery. Journal of nanoparticle research. 2013 Oct;15:1-5.
8. **An K, Sun Y, Xu L, Cui X**. Preparation and in vitro evaluation of simvastatin ethosome. Artificial Cells, Blood Substitutes, and Biotechnology. 2011 Dec 1;39(6):347-50.
9. **Abd El-Alim SH, Kassem AA, Basha M, Salama A**. Comparative study of liposomes, ethosomes and transfersomes as carriers for enhancing the transdermal delivery of diflunisal: in vitro and in vivo evaluation. International journal of pharmaceutics. 2019 May 30;563:293-303.
10. **Garg BJ, Garg NK, Beg S, Singh B, Katare OP.** Nanosized ethosomes-based hydrogel formulations of methoxsalen for enhanced topical delivery against vitiligo: formulation optimization, in vitro evaluation and preclinical assessment. Journal of drug targeting. 2016 Mar 15;24(3):233-46."
11. **Alfehaid FS, Nair AB, Shah H, Aldhubiab B, Shah J, Mewada V, Jacob S, Attimarad M**. Enhanced transdermal delivery of apremilast loaded ethosomes: Optimization,

12. characterization and in vivo evaluation. Journal of drug delivery science and technology. 2024 Jan 1;91:105211.

13. **Yadav KK, Verma NK.** Formulation and evaluation of ethosome of mefenamic acid using hot method. Journal of chemical and pharmaceutical research. 2018;10(5):4-15.

14. Z**hu X, Li F, Peng X, Zeng K**. Formulation and evaluation of lidocaine base ethosomes for transdermal delivery. Anesthesia & analgesia. 2013 Aug 1;117(2):352-7.

15. **Elsayed MM, Abdallah OY, Naggar VF, Khalafallah NM**. Deformable liposomes and ethosomes: mechanism of enhanced skin delivery. International journal of pharmaceutics. 2006 Sep 28;322(1-2):60-6.

16. M**ousa IA, Hammady TM, Gad S, Zaitone SA, El-Sherbiny M, Sayed OM.** Formulation and characterization of metformin-loaded ethosomes for topical application to experimentally induced skin cancer in mice. Pharmaceuticals. 2022 May 25;15(6):657.

17. **Chourasia MK, Kang L, Chan S**Y. Nanosized ethosomes bearing ketoprofen for improved transdermal delivery. Results in pharma sciences. 2011 May 1;1(1):60-7.

18. **Ahmed TA, Alzahrani MM, Sirwi A, Alhakamy NA.** Study the antifungal and ocular permeation of ketoconazole from ophthalmic formulations containing trans-ethosomes nanoparticles. Pharmaceutics. 2021 Jan 24;13(2):151.

19. **Zhang YT, Shen LN, Zhao JH, Feng NP.** Evaluation of psoralen ethosomes for topical delivery in rats by using in vivo microdialysis. International journal of nanomedicine. 2014 Jan 23:669-78."

20. **Kumar JR.** Development and Antifugal Activity of Itraconazole Loaded Ethosomal Gel in Rat Animal Model. Journal of Pharmaceutical Sciences and Research. 2019 Jul 1;11(7):2728-33.

21. **Iizhar SA, Syed IA, Satar R, Ansari SA.** In vitro assessment of pharmaceutical potential of ethosomes entrapped with terbinafine hydrochloride. Journal of advanced research. 2016 May 1;7(3):453-61.

22. **Razavi H, Janfaza S**. Ethosome: a nanocarrier for transdermal drug delivery. Archives of advances in biosciences. 2015 May 6;6(2):38-43.

23. **Abdulbaqi IM, Darwis Y, Khan NA, Assi RA, Khan AA**. Ethosomal nanocarriers: the impact of constituents and formulation techniques on ethosomal properties, in vivo studies, and clinical trials. International journal of nanomedicine. 2016 May 25:2279-304.

24. **Verma P, Pathak K**. Therapeutic and cosmeceutical potential of ethosomes: An overview. Journal of advanced pharmaceutical technology & research. 2010 Jul 1;1(3):274-82.
25. **Satyam G, Shivani S, Garima G.** Ethosomes: A novel tool for drug delivery through the skin. J Pharm Res. 2010 Apr;3(4):688-91.

26. **Limongi T, Susa F, Marini M, Allione M, Torre B, Pisano R, di Fabrizio E.** Lipid-based nanovesicular drug delivery systems. Nanomaterials. 2021 Dec 14;11(12):3391."
27. **Yücel Ç, Şeker Karatoprak G, Değim İT.** Anti-aging formulation of rosmarinic acid-loaded ethosomes and liposomes. Journal of microencapsulation. 2019 Feb 17;36(2):180-91.
28. Garg BJ, Garg NK, Beg S, Singh B, Katare OP. Nanosized ethosomes-based hydrogel formulations of methoxsalen for enhanced topical delivery against vitiligo: formulation optimization, in vitro evaluation and preclinical assessment. Journal of drug targeting. 2016 Mar 15;24(3):233-46.
29. Singh A, Thakur S, Singh H, Singh H, Kaur S, Kaur S, Dudi R, Mondhe DM, Jain SK. Novel Vitamin E TPGS based docetaxel nanovesicle formulation for its safe and effective parenteral delivery: Toxicological, pharmacokinetic and pharmacodynamic evaluation. Journal of liposome research. 2021 Oct 2;31(4):365-80.
30. Paliwal S, Tilak A, Sharma J, Dave V, Sharma S, Yadav R, Patel S, Verma K, Tak K. Flurbiprofen loaded ethosomes-transdermal delivery of anti-inflammatory effect in rat model. Lipids in health and disease. 2019 Dec;18:1-5."

31. Fathalla D, Youssef EM, Soliman GM. Liposomal and ethosomal gels for the topical delivery of anthralin: preparation, comparative evaluation and clinical assessment in psoriatic patients. Pharmaceutics. 2020 May;12(5):446.
32. Aggarwal N, Goindi S. Dermatopharmacokinetic and pharmacodynamic evaluation of ethosomes of griseofulvin designed for dermal delivery. Journal of nanoparticle research. 2013 Oct;15:1-5.
33. AbouSamra MM, Salama AH, Awad GE, Mansy SS. Formulation and evaluation of novel hybridized nanovesicles for enhancing buccal delivery of ciclopirox olamine. AAPS PharmSciTech. 2020 Oct;21:1-2.
34. Ahmed TA, Khalid M, Aljaeid BM, Fahmy UA, Abd-Allah FI. Transdermal glimepiride delivery system based on optimized ethosomal nano-vesicles: Preparation, characterization,

35. in vitro, ex vivo and clinical evaluation. International journal of pharmaceutics. 2016 Mar 16;500(1-2):245-54.

36. **Abd El-Alim SH, Kassem AA, Basha M, Salama A.** Comparative study of liposomes, ethosomes and transfersomes as carriers for enhancing the transdermal delivery of diflunisal: in vitro and in vivo evaluation. International journal of pharmaceutics. 2019 May 30;563:293-303.

37. **Iizhar SA, Syed IA, Satar R, Ansari SA**. In vitro assessment of pharmaceutical potential of ethosomes entrapped with terbinafine hydrochloride. Journal of advanced research. 2016 May 1;7(3):453-61.

38. **Thadanki M, Babu AK. Review on Ethosomes:** A novel approach of Liposomes. International Journal of Pharmacy & Life Sciences. 2015 Jan 1;6(1).

39. **Thadanki M, Babu AK**. Review on Ethosomes: A novel approach of Liposomes. International Journal of Pharmacy & Life Sciences. 2015 Jan 1;6(1).

40. **Mohite Mukesh T, Ahire Saurabh N, Shinde Supriya S, Revan K, Shubham K**. An overview on ethosomes: need of future.

41. **Garg V, Singh H, Bimbrawh S, Kumar Singh S, Gulati M, Vaidya Y, Kaur P.** Ethosomes and transfersomes: Principles, perspectives and practices. Current drug delivery. 2017 Aug 1;14(5):613-33.

42. **Wilson V, Siram K, Rajendran S, Sankar V.** Development and evaluation of finasteride loaded ethosomes for targeting to the pilosebaceous unit. Artificial cells, nanomedicine, and biotechnology. 2018 Nov 17;46(8):1892-901.

43. **Mahmood S, Mandal UK, Chatterjee B.** Transdermal delivery of raloxifene HCl via ethosomal system: Formulation, advanced characterizations and pharmacokinetic evaluation. International journal of pharmaceutics. 2018 May 5;542(1-2):36-46.

44. **Iizhar SA, Syed IA, Satar R, Ansari SA.** In vitro assessment of pharmaceutical potential of ethosomes entrapped with terbinafine hydrochloride. Journal of advanced research. 2016 May 1;7(3):453-61.

45. **Garg V, Singh H, Bimbrawh S, Kumar Singh S, Gulati M, Vaidya Y, Kaur P.** Ethosomes and transfersomes: Principles, perspectives and practices. Current drug delivery. 2017 Aug 1;14(5):613-33.

46. **Iizhar SA, Syed IA, Satar R, Ansari SA**. In vitro assessment of pharmaceutical potential of ethosomes entrapped with terbinafine hydrochloride. Journal of advanced research. 2016 May 1;7(3):453-61.

47. **Aute PP, Kamble MS, Chaudhari PD, Bhosale AV.** A comprehensive review on ethosomes. International journal of research and development in pharmacy & life sciences. 2012 Jan 15;2(1):218-24.

48. **Satyam G, Shivani S, Garima G. Ethosomes**: A novel tool for drug delivery through the skin. J Pharm Res. 2010 Apr;3(4):688-91."

49. **Anitha P, Ramkanth S, Sankari KU, Alagusundaram M, Gnanapraksah K, Devi PD, Prasanna RI.** Ethosomes-A noninvasive vesicular carrier for transdermal drug delivery. Int J Rev Life Sci. 2011;1(1):17-24.

50. **Abu-Huwaij R, Zidan AN.** Unlocking the potential of cosmetic dermal delivery with ethosomes: A comprehensive review. Journal of cosmetic dermatology. 2024 Jan;23(1):17-26.

51. **David SR, Hui MS, Pin CF, Ci FY, Rajabalaya R**. Formulation and in vitro evaluation of ethosomes as vesicular carrier for enhanced topical delivery of isotretinoin. International Journal of drug delivery. 2013 Jan 1;5(1):28.

52. **Ramakrishna.A.et.al**" Ethosomes: Carrier for Enhanced Transdermal Drug Delivery.system. journal of advance pharmacy Education and Research.2008"

53. **Mohanty D, Mounika A, Bakshi V, Haque MA, Sahoo CK.** Ethosomes: a novel approach for transdermal drug delivery. Int. J. ChemTech Res. 2018;11(8):219-26.

54. **Ainbinder D, Godin B, Touitou E. Ethosomes**: Enhanced delivery of drugs to and across the skin. Percutaneous penetration enhancers chemical methods in penetration enhancement: nanocarriers. 2016:61-75.