A Review on Ethosomes: A Novel Approach to Enhancing Transdermal Drug Delivery

Abstract

The skin plays a dual role in topical and transdermal drug delivery, serving as both a key Focus and a significant barrier. Despite its advantages, the system is hindered by the low absorption rate of drugs through the skin barrier corneum, a important barrier in effective delivery. Ethosomes in novel Vesicles play a crucial role in transdermal drug delivery by encapsulating medications and facilitating their absorption transdermally. show Notable impact Pertaining to Medicine penetration through the biological membrane. Ethosomes are phospholipid-based elastic nanovesicles containing a high content of ethanol (20-45%). Ethosomal systems have shown superior efficacy During delivery substances to the skin, outperforming Traditional liposomes and Alocohal based solutions regarding of both quantity and depth of penetration. Ethosomes carriers facilitate enhanced delivery bioactive molecules across skin plus cellular barriers presenting opportunities and challenges for developing innovative therapies.

Keyword: Ethosomes, Transdermal, Ethanol, Phospholipid.

Introduction [1]

As the largest and most accessible organ, the skin offers an attractive route for drug delivery, providing benefits such similarty reduced fluctuations in plasma medicine concentrations. Avoidance of Digestive system disturbances and first-pass Biochemical processes of the drugs, and large number of individuals compliance. The skin's low permeability poses a significant challenge to transdermal drug delivery, limiting the number of drugs that can be effectively administered. The skin's stratum corneum layer poses a substantial challenge to molecular transport, effectively blocking the passage of many drugs and limiting their absorption. However, lipophilic and low-molecular-weight drugs are exceptions to this rule. For transdermal and topical drug delivery systems to be effective, the drug must be able to penetrate the skin barrier and ultimately reaching the target site. In the past few decades, researchers have explored various methods to compromise or disrupt the skin barrier, enabling drug delivery through intact skin. Techniques such as permeation coefficient enhancers, iontophoresis, sonophoresis, electroporation, and microneedles have been investigated to enhance transdermal transport, but their limited efficacy, skin irritation, complexity, and high cost have hindered widespread adoption. Lipid-based suspensions like liposomes and niosomes have limited value in transdermal drug delivery due to their shallow skin penetration, prompting the development of novel elastic lipid vesicular systems that able to deeply also easily penetrate the skin. Phospholipids, ethanol, digestive fluid salts, and wetting agent used to create elastic liposomes with adaptable membranes, allowing them to pass across the tiny openings in the stratum corneum. In 1992, Cevc al successfully developed Ultra-deformable liposomes, a novel elastic lipid vesicular carrier, consisting of lipid molecules and border activators, which efficiently penetrated intact skin and delivered drugs across the skin under non-occlusive conditions.

Skin:-

Human shin is the body's largest organ. Dermatological layer a normal grown-up Physical form around 20 square feet and it got around one third of the total blood supply. Physique covering is diverse tissue made beyond of the given three histological membranes the furthest layer of skin, cuticle is which gives moisture proof hindrance and makes our complexion. Dermis, underneath epidermis, contains intense supporting tissue, hair follicles, and sweat organs and more profound The layer of tissue beneath the skin composed formed from binding tissue and fat.

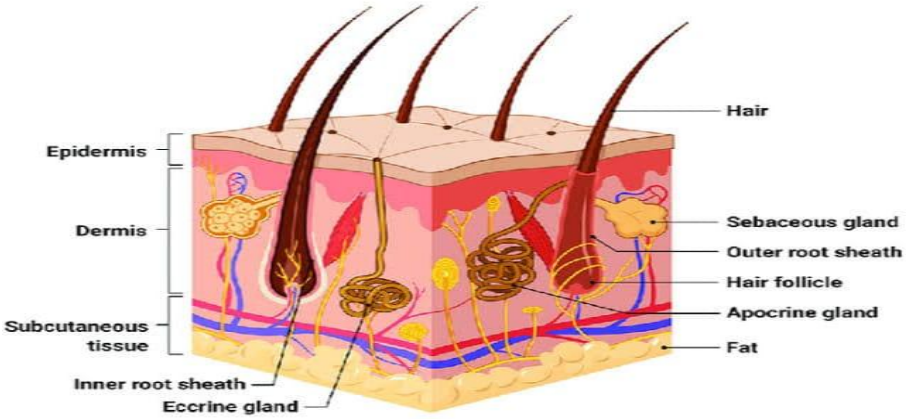

Figure1:-Skin's structure

The skin's structure includes a multi-layered epidermis and a dermis of connective tissue.

1. Epidermis
2. Dermis

Epidermis: The epidermis is composed of four layers

1. Stratum Basale (Basal Layer)
2. Skin layer Spinosum (Spinous Layer)
3. Tissue layer Granulosum (Granular Layer)
4. Surface layer of the epidermis

- The superficial layers comprise of separated Squama cells. The principal squamous cell is known as keratinocytes, which combination the protein keratin. Furthermore, a clear layer of skin cells is a slim layer of clear cells visible in thick epidermis.

Dermis: The skin's connective tissue layer changes in thickness, starting from 0.6mm on the back, vololar surfaces to 3 mm on the eyelids. It is tracked down beneath the epidermis and is made out of a extreme, steady cell framework.

The dermis is composed of two layers

1. A slight papillary dermis.

2. A thicker dermal reticular layer.

Function of skin [2]

They Gives a defensive obstruction against mechanical, warm furthermore, actual injury and nonoxious specialists.

1. Protective barrier

2. Moisture retention

3. UV radiation protection

4. Sensory perception

5. Thermoregulation

6. Immunological defense

7. Vitamin D3 production

Ethosomes [3]

Touitou et al. 1996 was the year when ethosomes were first discovered and developed. Ethosomes are essentially ethanol-based liposomal system. Ethosomes can be described as innovative, non-invasive system that facilitate targeted delivery of medications to deep skin tissues and/or the systemic circulation. These flexible, gentle vesicles are designed to enhance the delivery of active ingredients. The elevated ethanol and lipid levels in ethosomes necessitate investigation into their effects on skin, showing that ethanol boosts drug solubilization and generates flexible lipid structures for improved skin permeation. These vesicles have a spanning from 30mm to micrometer scale and are characterized by their flexible and supple nature. It has been observed that ethosomes, even without undergoing size reduction, are reduced compared to liposomes prepared using the same method. The scale is reduced because of the high alcohol level, as ethanol concentration increases to 20-45%, the ethosomes' size decreases. Ethanol contributes to their net negative charge, which in turn minimizes their size. Notably, adding 30% ethanol reverses the vesicles' charge from positive to negative. Consequently, the zeta potential, an indicator of surface charge, also undergoes a significant transformation influence their interaction with the skin. Although a high negative charge could suggest repulsion, the skin's lipid environment and the ethosomes' deformability facilitate their penetration. The high level of ethanol in ethosomes makes them more flexible and deformable, facilitating their passage through the stratum corneum's narrow intercellular spaces. The flexibility of ethosomes plays a critical role in ensuring efficient skin infiltration while preventing drug leakage.

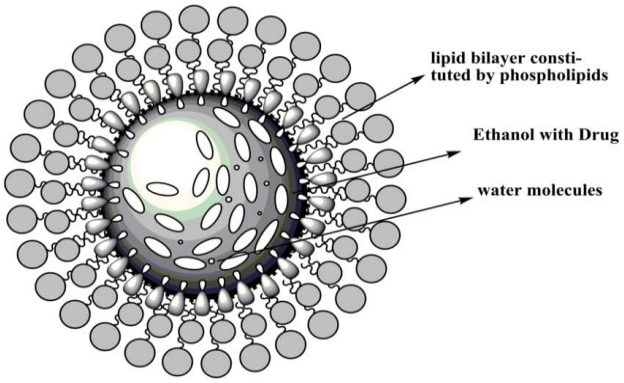

Figure 2:- Provides a visual representation the ethosomes structure

Advantage of Ethosomes drug System:[4]

1. Effective delivery of large molecules

2. The formulation comprises non-toxic raw materials, ensuring safety.

3. Increased drug absorption through skin for transdermal drug delivery.

4. Multidisciplinary applications

5. Improved Patient compliance

6. Simplified drug delivery method

7. Commercially viable and non-invasive solution**.**

Disadvantage of ethosomes drug delivery System [5]

1) Poor yield.

2) Adequate solubility of the drug in both lipophilic and aqueous environments to penetration dermal blood vessels and gain access to the systemic circulation.

3) A reasonable molecular size ensures that the drug can navigate the skin's barrier function and enter the bloodstream circulation.

4) Adhesive may not provide consistent adhesion across various skin types.

5) Can be expensive.

6) Dermatitis or skin inflammation may occur due to the use of certain excipients or penetration enhancers.

Type of Ethosomes system [6]

1. Classical Ethosomes

The composition of classical ethosomes includes phospholipids, ethanol concentrations as high as 45% w/w, and water, distinguishing them from traditional liposomes. The smaller size and negative surface charge of classical ethosomes make them more effective than traditional liposomes for transdermal drug delivery, allowing for greater efficiency and reduced risk of clogging. Compared to traditional liposomes, conventional ethosomes demonstrated enhanced skin penetration and durability profiles and were capable of encapsulating drugs with molecular weights molecular weights spanning 130.077 Da to 24,000 Da highlighting their versatility in drug delivery applications.

2. Binary ethosomes

Incorporation a secondary alcohol similar as propylene glycol into the formulation of binary ethosomes enhanced their durability enhances drug solubility and facilitates increased skin penetration, making them a more effective delivery system.

3. Transethosomes

Transethosomes are the latest generation of ethosomal systems and were first recorded in 2012 by Song et al. the composition of this ethosomal system comprises the basic elements of classical ethosomes by incorporating a penetration enhancer or surfactant, the formulation's transdermal drug delivery capabilities are significantly augmented these novel vesicles were formed Studies have consistently shown that transethosomes exhibit superior properties compared to traditional ethosomes, driving research into optimizing their formulation using various surface active agent and penetration enhancers.

Mechanism of action ethosomes [7,8]

The Ethosomes Mechanism is designed to optimize transdermal drug delivery by utilizing ethosomal vesicles to enhance skin penetration, reduce systemic side effects and provide targeted sustained therapeutic release. Two – phase Drug absorption process

1. Ethanol effect

2. Ethosomes effect

1. Ethanol effect:

The addition of ethanol helps to improved the transdermal diffusion of drugs allowing for more efficient delivery the penetration-enhancing effect of ethanol is attributed to its ability to penetrate the intercellular lipids reduce the lipid membrane density and increase the flexibility of the cell membrane lipids.

2. Ethosomes effect

Ethosomes capacity to increase phospholipids fluidity via ethanol results in improved skin permeabilit enabling them to effortlessly infiltrate the skin's deeper structures lipids and deliver drugs to the target site.

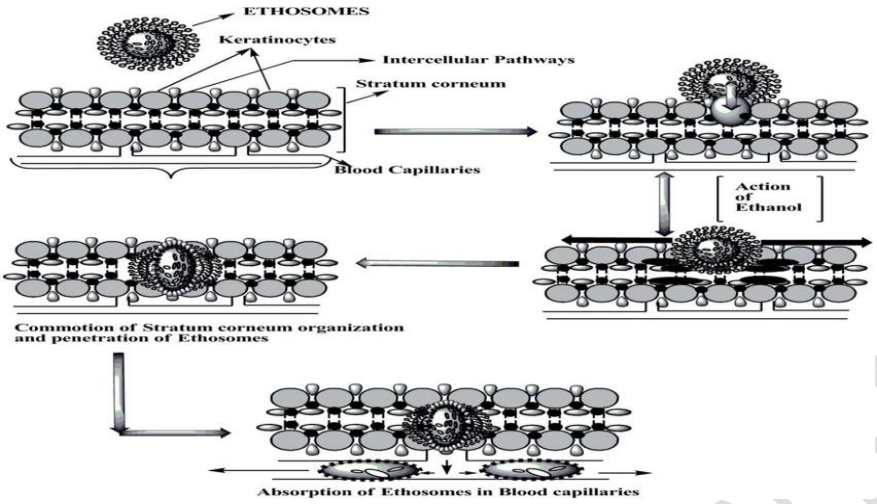

Figure3: Mechanish of action of ethosomes

Composition of Ethosomes [9]

Table No 1: Composition of Ethosomal

Class	Example	Uses
Phospholipid	Soya phosphatidyl choline, Egg phosphatidyl choline, Dipalmitoyl phosphatidyl choline, Distearoyl phosphatidyl choline	Vesicles forming component
Polyglycol	Propylene glycol	As a skin penetration Enhancer
Alcohal	Ethanol, Isopropyl alcohol	For providing the softness for vesicle membrane As a penetration enhance
Cholesterol	Cholesterol	For providing the stability to vesicle membrane
Dye	Rhodamin -123 Rhodamine red Fluorescence Isothiocyanate (FITC)	For characterization study
Vehicle	Carbopol934	As a gel former

Method of preparation of Ethosomes [10,11]

The preparation of ethosomes can be achieved throught multiple methods as mentioned earlier.

Cold method:

The most widely used method for preparing ethosomes involves dissolving phospholipids drugs and lipid materials in ethanol in a covered vessel at room temperature with vigorous stirring. The mixture is then heated to 30°C using a water bath followed by the addition of preheated water

from a separate vessel, and stirred for five minutes in a covered vessel. The vesicle size of the ethosomal formulation can be optimized by applying sonication or extrusion techniques and subsequent refrigerated storage is required.

Hot method

A mixture of ethanol and propylene glycol is used to dissolve the drug, which is then added to a phospholipid dispersion in water maintained at 40°C a five-minute mixing period is followed by sonication at 4°C using a Probe Sonicator, consisting of three cycles each five minutes long with five-minute intervals between cycles. The formulation is further processed using a high-pressure homogenizer where it is subjected to a pressure of 15,000 psi for three cycles resulting in the formation of nano-sized ethosomes.

Classic Mechanical Dispersion Method

Soya phosphatidylcholine is dissolved in a solvent mixture of chloroform and methanol (1:1 EP) within a round-bottom flask. A rotary evaporator under vacuum is utilized is employed to remove the organic solvents causing the lipids to transition into a thin film adhering to the flask's walls, above the lipid transition temperature. To ensure complete removal of the solvent mixture, the deposited lipid film is left under vacuum overnight, allowing any residual solvents to evaporate. Hydration of the lipid film is achieved by adding a hydroethanolic mixture containing the drug and rotating the flask at an optimal temperature.

Classic method

Lipid molecule and drug dissolved in ethanol and then heated to a temperature of 40°C ± 1°C using a water bath. Double-distilled water is introduced into the lipid mixture in a controlled thin stream accompanied by constant stirring at 1000 rpm within a closed system. The resulting vesicle suspension is then uniformized through a polycarbonate membrane using a hand extruder with the process being repeated for three cycles to achieve optimal uniformity.

Ethosomes Characterization and Evaluation [12,13,14,15,16]

1. Vesical Size and Zeta-Potential

To analyze ethosomes, photon correlation spectroscopy (PCS) and dynamic light scattering (DLS) are employed for particle size determination and zeta potential is assessed using a zeta meter.

2. Vesicle Shape

The morphology of ethosomes can be easily observed through scanning electron microscopy (SEM) and transmission electron microscopy (TEM) analyses.

3. Stability Studies

Tests performed to determine the shelf-life of a formulation by assessing its stability under various storage conditions.

4. Drug Content Studies

The amount of drug uptake can be accurately determined using high-performance liquid chromatography (HPLC) method in drug content studies.

5. Drug Entrapment

To evaluate the Encapsulation rate of ethosomes the ultracentrifugation method is commonly utilized.

6. Transition Temperature

To evaluate the thermal properties of vesicular lipid systems, differential scanning calorimetry (DSC) is used to determine their transition temperature.

7. Surface Tension Measurement

The surface tension activity of drugs in aqueous solutions can be quantified using the ring method with a Du Nouy tensiometer.

8. Skin Permeation Studies

Confocal laser scanning microscopy (CLSM) enables the measurement of the ethosomal preparation's ability to penetrate skin layers.

Application of ethosomes [17,18]

1. Transdermal delivery

As ethosomes increase the drug permeation through the skin barrier barrier, they can be used to administer drugs that Experience skin problems permeation. Despite having low oral bioavailability and undergoing extensive first-pass metabolism they can effectively target skin infections.

2. Anti-Inflammatory and Anti – Arthritis ethosomes

Ammonium glycyrrhizinate (AG) ethosomes were prepared and tested for anti-inflammatory effects on human volunteers with methyl-nicotinate induced erythema (Paolino et al. The anti-inflammatory effects of ammonium glycyrrhizinate ethosomes on inflammation treatment were compared with aqueous or hydroethanolic drug solutions. The results evaluated the skin inflammtion using a reflectance visible spectrophotometer. AG ethosomes increased a significant Decrease in the intensityand duration Inflammation in comparison to hydroethanolic drug solutions that showed the presence of erythema. Cannabidiol (CBD) a highly lipophilic drug is used For therapy of rheumatic arthritis. The drug has Limited bioavailability because of Comprehensive first-pass Degradation instabilityin gastric ph and low solubility in water.

3. Transdermal delivery of hormones:

When hormones are taken orally, it can lead to issues like low oral bioavailability, high first pass metabolism However this treatment approach is frequently hampered by dose-dependent side effects. Confocal laser scanning microscopy (CLSM) enables the measurement of the ethosomal preparation's ability to penetrate skin layers the results showed that the ethosomal formulation significantly enhanced skin permeation by approximately 30-fold.

4. Delivery of antibiotics

Applying antibiotics directly to the skin is a more efficient method to increase their healing potentia conventional oral therapy often results in allergic reactions and several side effects a study has revealed that ethosomal formulations of antibiotics offer a highly effective solution addressing the shortcomings of conventional therapies.

5. Delivery of antifungal drugs

Ethosomes have emerged as a promising tool for Percutaneous drug delivery offering a unique combination of rapid drug release, reduced side effects, and preservation of skin integrity.

6. Cosmeceutical Applications of Ethosomes

Ethosomes in cosmeceuticals offer multiple benefits including increased stability of key ingredients, reduced skin irritation, and improved transdermal delivery, especially in flexible formulations.

7. Delivery of problematic drug molecules

Ethosomes present a groundbreaking solution for overcoming the hurdles of transdermal delivery of biogenic molecules, enabling more efficacious and efficient therapeutic outcomes.

Recent work:[19-25]

[1].Preeti Gupta et al. (2024). The ethosomes gel's antifungal efficacy surpassed that of other formulation against C. albicans, demonstrating its potential as a treatment for fungal infections. This study highlights the benefits of using EBZ –loaded ethosomes gel, including improved patient compliance and cost –effective treatment outcomes.

[2].Fahad Sami Alfehaid et al. (2024). The in vivo results showed that apremilast ethosomal gel administered throught the skin had a significant higher bioavaility (225% relative biovailability) than the oral suspension while achieving a steady peak exposure. In summary the formulation ethosomal gel offers greater promise for potential transdermal treatment making it suitable for once daily use.

[3]. Hassanien Sagban Taghi et al. (2024). The SM- ETO was successfully development and optimized to create nano-sized vesicles with hogh entrapment efficiency. The optimized into a carbopol 934p gel for transdermal delivery. Drug diffusion studies demonstrated the ability of the SM-ETO-based gel to sustain the release of SM for 7.5 hrs. This finding has implications for in vivo pharmacokinetic release studies.

[4].Mehavarshini S et al. (2023). A novel ethosomal formulation loaded with Beta-sitosterol was prepared and characterized arthritis. The optimized formulation F3 demonstrated exceptional entrapment efficiency (91.62%) and in-vitro drug release (96%) surpassing other formulation with variable concentrations. Stability studies were undertaken with evaluation scheduled after 3 months. The study concludes that the developed ethosomes formulation is a viable and efficient for beta-sitosterol in the treatment of Rheumatoid arthritis.

[5].Kampanart Huanbutta et al. (2022). In this research, Z. zerumbet (L.) rhizome extract was effectively incorporated into an ethosome system. TEM and light scattering analysis revealed that the ethosome size was below 200 nm, maling it an ideal candidate as a permeation enhancer for drug or active ingredients. Size distribution and zeta potential analysis indicated that the ethosome production method and formulation were stable and consistent.

Conclusion:

Ethosomes a novel approach have introduced a new direction in the field of topical medication. Their unique properties such as flexibility deformability and capacity to entrap both Hydrophobic and lipophilic drugs have made them an attractive option for delivering a wide range of therapeutic agents. The advantages of ethosomes, including enhanced permeation enhanced bioavailability and minimizing adverse reactions have made them a encouraging tool for treating multiple conditions and disorders. Future studies should focus on exploring the potential of ethosomes for delivering biologics and other complex healing agents. Furthermore the advancement of ethosomes for use in mixture with other delivery systems such as micro needles and iontophoresis may offer further opportunities for enhancing skin permeation.

REFERENCES:

1. Nandure Hiraman P, Puranik, Dr. Prashant, "Ethosome :A Novel Drug Carrier" International Journal of Pharmaceutical Research & Allied Science, Volume 2, Issue 3(2013), 18-30
2. Prajapati Vishakh, Shah Dr. Chainesh, Upadhyay Dr. Umesh, "A Review on Ethosomes" International Journal of All Research Education and Scientific Method, ISSN: 2455-6211, Volume 12, Issue 5, My -2024.
3. Shetty Bhuvankumar Manjunath, Miranda Fmith Celvia, "Ethosomes: The Upgraded Liposomes –A Review" Journal of Advanced Pharmacy Research , Sec C 2024, 8 (4), 205-217
4. Mohanty Dibyalochan, Mounika A, Bakshi Vasudha, "Ethosomal: A Noval Approach For Transdermal Drug Delivery" International Journal of Chem Tech Research, ISSN:0974 – 4290, Vol.11 No.08, (2018) pp219-226,
5. Tiwari Pallavi, Yadev Pankaj , "Modernize Devising Method of Ethosomes" Internation Journal of Science and Research, ISSN: 2319-7064 , Volume 10 Issue 7,july 2020,pp56-60.
6. Jadhav K Pratiksh , Kapadnis A Kundan, Shinkar M Dattatraya, "Ethosomal as Noval Drug Delivery System : A Review" International Journal of Pharmaceutical Review and Research, ISSN 0976-044X 62(1), May –June 2020 Article No. 29, pg 173-182.
7. T. Mohite Mukesh, N. Ahire Saurabh, "an overview on ethosomes: need of future" Internation Journal of Creative Research Thoughts, Volume 9, Issue 8 August 2021 pp 796-811
8. Aute Pravin P, Kamble Meghane s, "a comprehensive review on ethosomes" International Journal of Research and Development in pharmacy amd Life sciences, December – January 2012-2013, Vol.2, No, 1 pp 2018 -224.

9. Patrekar Prasad V, “Inamdar Suhel J, Ethosomes as novel drug delivery system : A review” The pharma Innovation, 2015,4(9),pp10-21.
10. Sanka V, Wilson V, “topicaldelivery of drug using ethosomes : a review” indian drug 56(08) septermber 2019, PP 7- 20
11. Varma Poonam, Pathak k, “Therapeutic and cosmeceutical potential of ethosomal : An overview” Journal of advanced pharmaceutical Technology & Research, Jul sep2010,Vol 1, Issue 3, pp274-282.
12. Mazhar Khizra , Khan Aleesha Azhar, “A Review on Ethosomes As Nanocarrier For Skin Delivery of Drug “ Journal of contemporary pharma Volume 8 : Issue 2 : 2024pp 120-131.
13. Rada Santosh kumar , Yadav Sbubham , “Ethosomes : A Novel Approach in Vesicular Drug Delivery System ”Journal of Pharmaceutical Research International ,34928B) : PP, 62-71, 2022.
14. Gupta N.B, Loona S, “ETHOSOMES AS ELASTIC VESICLES IN TRANSDERMAL DRUG DELIVERY: AN OVERVIEW” International Journal Pharmaceutical Sciences And Research,2012 Vol.3(3):682-687.
15. Anitha P, K.S. Ramkanth, “ Ethosomes - A noninvasive vesicular carrier for transdermal drug delivery”Int,j,Rev, Life, Sci., 1(1),2011,pp.17-24.
16. Stayam Gangwar, Shivani Singh, “Ethosomes : A novel tool drug delivery throught the skin”Journal of pharmacy Research, Vol , 3.Issue 4 April 2010 pp688-691
17. Mandlik –Yogita Chunchuwar, Kasliwal Dr. Rahul h, “An updated Review on Nanovesicles-Ethosomes, As A Novel Drug Delivery System” World Journal Of Pharmaceutical Research, (2024) Volume 13,Issue 13, pp 1689-1702.
18. Nainwal Nidhi, Jawla Sunil, “Transdermal application of ethosomes – a detailed review” Journal of liposomes research, 2018,pp: 1-11.
19. Gupta Preeti, Kushwaha, Hafeez Abudul, “Development and Characterization of Topic ethosomal gel for improved antifungal therapeutics” Journal of Molecular Liquids405 (2024) 125111.
20. Alfehaid Fahad Sami, Nair Anroop B, Shah Hiral, “Enhanced transdermal delivery of apremilast loaded ethosomes: Optimization, characterization and in vivo evaluation” Journal of Drug Delivery Sciences and Technology 91(2024) 105211
21. Taghi Hassanien Sagaban, Issa A Anmar, “Formulation and Development of Ethosomal Drug Delivery Sysetem of Silymarin For Transdermal Application” Journal of Pharmaceutical Sciences P- ISSN: 1683-3597.
22. S Mehavarshini, James Sanjana Emily, “Product Development of Beta-Sitosterol Ethosomes for the Treatment for of Rheumatoid Arthiritis” A Journal for New Zealand Herpetology, Vol 12 Issue (2023) pp 2140 -2150
23. Huanbutta Kampanart, Rattanachittawat Napapat, “Development and Evaluation of Ethosomes Loaded with Zinigiber zerumbet Linn Rhizome Extract for Antifungal Skin Infection in Deep layer Skin”Pharmaceutical (2022),14,276