



ETHOSOMES IN COSMECEUTICALS: A REVOLUTIONARY APPROACH TO SKIN CARE DELIVERY

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ABSTRACT

Ethosomes, advanced lipid-based vesicular carriers, have emerged as a promising transdermal drug delivery system. Their unique structure, consisting of phospholipids, ethanol, and water, enhances the penetration of active compounds through the stratum corneum, making them highly effective for topical applications. Ethosomal formulations have found extensive use in cosmeceuticals, pharmaceuticals, and veterinary science. Several studies demonstrate their ability to improve the bioavailability of both hydrophilic and lipophilic drugs, with applications ranging from anti-aging skincare to the treatment of hyperpigmentation, acne, and skin infections. Ethosomal systems are also being explored for transdermal delivery of more complex molecules, including proteins and peptides. Despite the various benefits, including high patient compliance and simple formulation techniques, ethosomes face challenges such as low yield and high production costs. Continuous advancements and commercialization efforts are contributing to their growing relevance in therapeutic and cosmetic markets.

Keywords: Ethosomes, cosmeceuticals, transdermal drug delivery, phospholipid vesicles, skin penetration

INTRODUCTION:

For the longest period, different drug delivery methods have been used in the cosmeceuticals industry to treat a variety of skin-related illnesses. Numerous studies have been conducted to help with the local treatment of a variety of skin conditions including skin cancer, burns, wounds, acne, and aberrant pigmentation. Targeting the location of action, reducing the need for various dose regimens, and improving patient compliance are just a few benefits of topical medication delivery via the dermal route. That being said, it is shown that the majority of molecules cannot effectively pass through the stratum corneum (SC) in cases of anomalies or illnesses that do not impact the SC [1, 2].

The most flexible way to administer medication topically and systemically is through the skin. Drugs cannot penetrate since it is made up of keratinised cells the stratum corneum the skin's outermost layer that have undergone nucleation. Therefore, when given topically, it prevents the medicine from being bio accessible [2, 3].

Penetration enhancers, such as DMSO, urea, solvents, polysaccharides, etc., have been developed to make it easier for active compounds to enter the skin. These compounds typically work in conjunction with lipid bilayers in the stratum corneum (SC) to facilitate the drug's penetration into this tissue. Over the past forty years, the

notion of nanocarriers—lipid, polymeric, and nanovesicular carriers, among others—has been developed to transport drugs via the dermal route for the cure of several illnesses. As a result, "ethosome," a novel skin penetration-enhancing delivery vehicle made of phospholipid soft vesicles, was developed [4, 5].

ETHOSOME

Ethosomes, are considered as the developed and modified versions of the initial phospholipid soft vesicles, namely, liposomes and transferosomes. By Tuitou, first presented in 1997, Ethosomal systems refer to defined as the Cholesterol vesicular carriers that are assessed by their fluid lipid bilayers, comprising of molecules such as 20–50% w/w ethanol, phospholipid, water, and an active pharmacological molecule, either with or without glycols [2, 3]. Upon topical administration, the carriers present in these undergo fluidization, following which, the lipid bilayers between the stratum corneum undergo disruption. This brings about facilitation of the entrance of ethosomes deep into the skin layer, followed by the release of the active drug molecule. Based on the contents like ethanol, ethosomes are again divided into different types like binary, transethosomes and classical [4, 5]. **Figure 1** represent the structure of ethosomes.

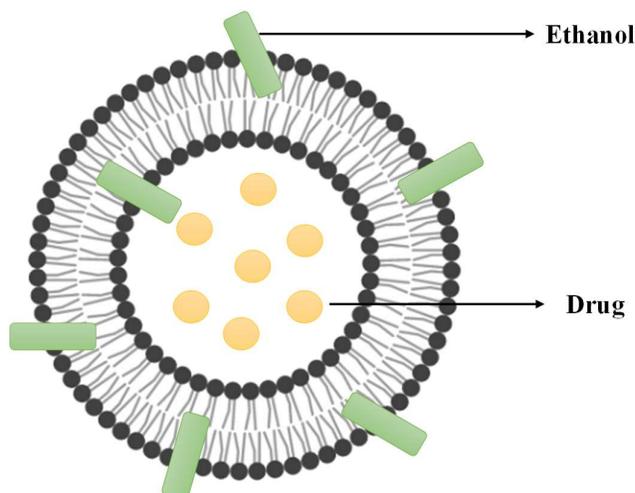


Figure 1: Structure of ethosomes

ADVANTAGES OF ETHOSOME [1, 5]

- i. Supply of peptides and proteins can be enhanced.
- ii. The raw materials easily diffuse through the skin.
- iii. Not only in pharmaceuticals, it is also used in cosmetic formulation and veterinary sciences.
- iv. Patients have high compliance with ethosomes because of the design of the dosage form as gel or cream in semisolid administration.
- v. A straightforward drug delivery strategy that can be distinguished from more intricate techniques like phonophoresis and iontophoresis.
- vi. Commercialisation can be immediate as the ethosome system is a non-invasive and passive therapeutic approach.

LIMITATIONS [1, 5]

- i. Low yield
- ii. Expensive method of formulation

- iii. Not all skin variations cohere well
- iv. Exact molecular size of drug is required for transcutaneous absorption.
- v. Increased levels of drug/dosage are required. Only high powered compounds with a day to day intake of 0.01g or less are permitted.
- vi. It is seen as a means of achieving rapid medication input of the bolus variety.
- vii. Solubility of drug in both lipophilic and hydrophilic conditions is maintained for penetration through cutaneous route and enter systemic circulation.

TYPES OF ETHOSOMES [4, 5]

Based on their compositions, ethosomes are divided as follows:

1. Classical ethosomes
2. Binary ethosomes
3. Transethosomes

Table 1: Composition of ethosomes

Categories of Ethosomes			
Composition of Ethosomes	Conventional Ethosomes	Ethosomes in Binary Form	Transethosome
	Phospholipids	Phospholipids	Phospholipids
	Ethanol	Ethanol	Ethanol
	Stabilizer	Propylene glycol/ other alcohol	Edge activator (surfactant) or penetration enhancer
	Source of charge	Source of charge	Source of charge
	H ₂ O	H ₂ O	H ₂ O

METHOD OF PREPARATION

1. Hot Method
2. Cold Method
3. Method for Injecting Ethanol
4. Mechanical Dispersion Method

HOT METHOD

This approach involves dissolving the drug in an ethanol and propylene glycol blend (or any other polyol), which is then added to a 40°C water-based phospholipid dispersion. Based on the nature of the drug (hydrophilic/lipophilic), it is accordingly added to ethanol or water in the respective steps. The final mixture is then mixed for 5 mins, followed by utilising a Probe Sonicator to sonicate at 4°C, for three cycles of five minutes each, resting by five-minutes between each cycle. A high-pressure homogenizer is then used for homogenisation of the formulation, at a pressure of 15,000 psi in three cycles to obtain nanosized ethosomes [1, 4].

COLD METHOD

The cold approach is the most often used and well-liked technique for ethosomal preparation. The drug, phospholipids, and other lipid components are dissolved in

ethanol vigorously stirred in a sealed vessel at room temperature. This mixture is heated in a water bath continuously until it reaches a temperature of 30°C. It is then added to the combination mentioned above and swirled for five minutes in a covered vessel. If required, the ethosomal formulation's vesicle size can be reduced by utilizing extrusion or sonication. Lastly, the mixture needs to be refrigerated and stored correctly [1, 4].

METHOD FOR INJECTING ETHANOL

Another preferred method for ethosome preparation is ethanol injection method, due to its advantages of rapid, safe, and reproducible therapeutic actions. This method involves injecting an ethanol-phospholipid solution into an agitated aqueous solution. This permits phospholipids that have been dissolved to precipitate and create a bilayer of phospholipid fragments by diffusing ethanol into the aqueous solution. These fragments further fuse to form closed liposomal and ethosomal structures. The ethosomes can be

finally obtained after evaporation of ethanol [6, 7].

MECHANICAL DISPERSION METHOD

A solution of 3:1 chloroform: methanol is used to dissolve soya phosphatidylcholine in a round-bottom flask method. Using a within a rotating vacuum evaporator, the organic solvents are extracted above the lipid transition temperature to form a thin lipid coating on the flask wall. Finally, by vacuuming contents for a whole night, any remaining solvent combination is eliminated from the lipid film that has been deposited. By revolving the flask at an appropriate temperature, hydration is accomplished with varying concentrations of the drug-containing hydroethanolic mixture⁴.

MECHANISM OF ACTION OF ETHOSOMES

In the functioning of an ethosome system, the vesicles, ethanol, and skin lipids mutually stimulate and working together. An improved distribution of active drug is observed due to the contact between the ethosomes and skin lipids. Reaction between ethanol and bilayer fat molecules in the area of the polar head group lowers/reduces that critical temperature of the stratum corneum's lipids. This leads to diffusion of medication into the skin's deeper layers by a ascend in its the lipid's fluidity and loss of density multilayer. Ethanol even relays evenness and pliability to vesicles,

thereby easing intense perforation into epidermal layer [1, 4, 5, 6].

ROLE OF ETHOSOMES IN SKIN INFECTIONS

Utilising nanotechnology to develop effective drug delivery methods for transdermal and topical treatments have been widely studied. Because ethanol improves skin penetration, it improves the composition of ethosomes, which in turn helps deliver therapeutic agents more effectively than traditional liposomes for a variety of pathologies, such as acne, skin infections, hormone deficiencies, abnormal pigmentation, etc. [7-11].

SKIN BIOLOGY [12]

The largest organ is the skin, which covers the whole exterior of the body. Three layers make up the skin, namely, each of the three layers—the epidermis, dermis, and hypodermis—has a distinct anatomical structure and function. The epidermis, the outermost layer of skin, is composed of several layers and distinct cell types that are vital to its function. The layers of the epidermis are the Layers: base layer, middle layer, and upper layer, stratum lucidum, and stratum corneum, arranged from deepest to shallowest. Keratinocytes, melanocytes, Langerhans and Merkel cells are among the epidermal cells. The basement membrane binds the dermis, the skin's middle layer, to the epidermis. Two layers of connective tissue make up the dermis: the reticular

(deeper) layer and the papillary (higher) layer. This layer also includes blood arteries, sweat glands, hair follicles, muscles, sensory neurons, and strong connective tissue made of bundles of collagen fibres.

- The dermis lies above the hypodermis, also referred to as the subcutaneous fascia. This layer, which is the deepest layer of the skin, is home to blood arteries, adipose lobules, sensory neurons, and sparse skin appendages like hair follicles.

SKIN DISORDERS: HYPERPIGMENTATION AND MELASMA

The most common ailments produced by the cells of the skin, melanocytes, are the skin pigmentation disorders.

- Melasma, originally known as chloasma, is a hyperpigmentary condition that is acquired and typically affects the face. Middle-aged patients are impacted, notably those with darker textures. It usually affects the skin of the face and neck region and is evident in photo-exposed areas. It ranges in color from brown to bluish-gray. This illness is more common in women and people with darker skin tones. UV light exposure is the main cause of melasma growth and progression. Other variables that might have a

role include excessive makeup use, photosensitizing medications, hormonal therapy, and irregular melanocyte stimulating hormone synthesis [13].

- Primarily a dermatological condition affecting the face, *hyperpigmentation* emerges as symmetrically distributed, dark brown, hyperpigmented patches with uneven, serrated borders. It is a very psychosocially significant condition. The primary cause of hyperpigmentation is an increase in melanin that comes from melanocytes secreting excess amounts of the pigment, which then accumulates in the dermis [14].
- Melanogenesis, is the term coined to describe the process by which melanocytes produce melanin. By absorbing UVA and UVB rays, melanin pigment serves as the skin's primary defense against ultraviolet radiation. Hyperpigmentation results from the overproduction of melanin brought on by UV light exposure [13, 14].
- The enzyme tyrosinase is a vital enzyme that is a part of the manufacture of the pigment melanin. It facilitates the multi-step process that turns the amino acid tyrosine

into melanin. Therefore, preventing an excessive production of melanin is the key to preventing skin hyperpigmentation [14].

- Pigmentation can appear as dots, confetti, continuous or linear lines. Three fundamental patterns of pigmentation distribution have been identified:
 - i. The forehead, cheeks, nose, and upper lip are all impacted by the central facial pattern.
 - ii. Malar pattern in, which specifically relates to the nose as well as the cheeks.
 - iii. Mandibular pattern, distinctively affects mandibular region [13, 14].
- Abnormal pigmentation and Skin discoloration on the facial part of the body because of both internal and external substances or acquired or congenital factors causes mental and emotional disorders that have a psychosocial impact on sufferers [13, 14].

TREATMENT OF LIPID-BASED NANOCARRIERS REQUIRED FOR HYPERPIGMENTATION:

Treatment methods for melasma and hyperpigmentation based on nanotechnology show promise in extending the therapeutic range of anti-hyper

pigmenting medications. Topical hypo pigmenting medications have recently been enclosed within nanocarrier-based delivery mechanisms for the efficient therapy for melasma. In order to cure hyperpigmentation, the ethosomes represent contemporary methods for encasing hypo pigmenting molecules to improve their ability to penetrate skin layers and their physicochemical strength. Among the numerous benefits of these nanocarrier approaches are, improved drug penetration, drug targeting, increased therapeutic potential, stability against rapid and protracted degradation, and rapid and sustained administration. One possible initial treatment strategy could involve the topical use of nanotechnology-based hypo pigmenting drugs in conjunction with oral administration of additional treatments [15].

- i. The commonly used agents for treatment of hyperpigmentation include skin brighteners, skin whiteners, chemical peels, etc. The ingredients in topical hypo-pigmentating agents include azelaic acid, kojic acid, tretinoin (RA), and hydroquinone (HQ) [14, 15, 16].
- ii. Skin-whitening treatments come in two varieties: synthetic and natural. The restriction is the limited stability of whitening chemicals. As a result, encapsulating these whitening agents can improve their concentration and

physicochemical stability at the desired locations [16, 17].

iii. Under physical therapies for this condition, chemical peels

(trichloroacetic acid [TCA], glycolic acid [GA]) are typical treatments [18].

Table 2: Skin conditions managed with active compounds integrated into phospholipid soft vesicles-containing carriers [3]

S. No.	Disordered behaviour	Looked at vesicular carriers
1.	Acne vulgaris	Azelaic acidic ethosomal system, Karanjin Ethosomal system, Clindamycin along with the salicylic acid ethosomal system, Cryptotanshinone Ethosomal system.
2.	Skin pigmentation disorders	Methoxsalen The mechanism of ethosomal Linoleic acid.
3.	Skin aging	Curcumin Ethosomal system, Rosmarinic acidic ethosomal system, Vitamin E Etomal system

LITERATURE STUDIES OF ETHOSOMES

With the goal of treating melasma, Celia *et al.* improved the way linoleic acid was applied topically using ethosomes. In order to accomplish this, the compound's in vitro percutaneous penetration through human skin was evaluated in relation to a hydroethanolic solution when it was loaded into both vesicular systems. The results indicate that when ethosomes were used, about 80% of the Linoleic acid had by the conclusion of the 24-hour trial, penetrated. Between the ethosomal formulations with 40 and 45% ethanol, respectively, there was 237.75 and 195.15 ug/cm² of linoleic acid percutaneous penetration. In contrast, the hydroethanolic solution with the same molecular content yielded a result of 39.61 ug/cm². These findings demonstrate that ethosomes can considerably ($p < 0.05$) increase linoleic acid's percutaneous penetration. The results of this work indicate

that ethosomes may be useful as medication carriers for the topical treatment of illnesses related to skin hyperpigmentation [19]. Magnesium ascorbylphosphate (MAP) ethosomal gel demonstrated statistical and clinically notable drop in melanin levels after a month, whereas MAP nucleosomal gel demonstrated statistical and six-month decline in clinically significant melanin levels later, according to research by Soha M. Kandil *et al.* Niosomes and MAP ethosomes together may be a crucial component of a cosmetics solution six-month decline in clinically significant melanin levels and hyperpigmentation [20]. Charoo NA *et al.* described how hydroquinone is used to treat hyperpigmentation by whitening the skin. It functions by stopping the production of the pigment known as melanin, which gives skin its colour. Quinine hydroquinone, which has been approved by the FDA to treat hyperpigmentation (dark spots), is

typically applied topically and is sold under a variety of brand names, including Melamin®, Nuquin®, and many more. By directly delivering the medication to the melanocytes through ethosomes, hydroquinone has been shown to have improved efficacy and fewer adverse effects. Hydroquinone ethosomes are not yet medicines on the market, despite their intriguing potential as skin whiteners; further study is needed to determine their efficacy and safety [21]. In addition, Phasha V *et al.* reported Kojic acid's application as a nature derived skin-brightening agent that is widely used to manage hyperpigmentation. Sold under different brand names, Kojic acid has been formulated as different dosage forms such as, serum, cream and others. The source of kojic acid is a fungal strain, *Aspergillus oryzae*, for commercial production [22]. As mentioned by Tanveer N *et al.*, though studies have looked into the potential Using kojic acid ethosomes as a treatment for hyperpigmentation and skin lightening, additional to be eligible for FDA approval, Kojic acid ethosomes must undergo study to prove their efficacy and security [23]. A novel cellulite lightweight cream called lipoduction was disclosed by Osmotics Inc. of the USA. Its components were delivered directly into the fat cells by permeating the skin lipid barrier through the use of the ethosome system. In fewer than sixty days,

constituents in lipoduction decreased the visibility of cellulite through up to 80% [24]. In addition, Haji Muhammad Shoaib Khan *et al.* study findings suggested such ethosomes laden with alpha arbutin be regarded as viable treatment Regarding skin aging and hyperpigmentation, as demonstrated by *in vivo* experiments. Since The alpha arbutin is used as a cosmetics component that whitens skin, the goal the goal of this study was to develop the best possible nanostructured ethosomal gel that contained the chemical to cure skin pigmentation [25]. The purpose of the study by Valentina Sallustio *et al.* was to investigate the use of an environmentally friendly anti-aging gel using *Rosa canina* L. extract as a botanical ingredient. After being evaluated for antioxidant activity, rosehip extract was put into ethosomal vesicles containing varying amounts of ethanol. The rosehip extract ethosomal gel turned out to be a cutting-edge, environmentally friendly skincare solution that reduced hyperpigmentation and wrinkles [26]. *Arctostaphylosuva-ursi* (AUU), which is high in arbutin and polyphenols, has been shown to have interesting biological activity and may be a good option for a cosmetic, in line with research done by Nayla Javed *et al.* The purpose of this work was to develop an optimised formulation of nanostructured ethosomal gel loaded with AUU extract. for skin depigmentation and rejuvenation [27].

Table 3: Nanotechnology based ethosomes formulation

Formulations	Active Ingredients	Techniques used	Particle size, PDI	Results/ Special comments	References
Ethosomes	phenylethyl resorcinol	Cold method/Thin film hydration	389 nm, 0.266	Good stability on storage at 4 and 30°C at 75% RH for 4 months	[20]
Ethosomes/Niosomes	Magnesium ascorbyl phosphate	Thin film Hydration	340nm, 0.244	he optimized ethosomal and niosomal gels showed comparable controlled permeation and higher skin retention over their ethosomes and niosomes formulations	[22]
Ethosomes	Kojic acid dipalmitate	cold method.	148 nm, 0.344	Ethosomal gel gives significant decrease in skin melanin, erythema, and sebum level while it causes improvement in skin hydration level and elasticity during non-invasive <i>in vivo</i> studies.	[24]
Ethosomes	Alpha arbutin	Cold method	196.87 nm, 0.217	Alpha arbutin causes significant improvement in skin melanin, moisture content and elasticity.	[25]
Ethosomes	Rosehip extract	Cold method	254 nm, 0.26	Good spreadability, and stability over 60 days at 4 °C. Considering sustainable ingredients and eco-friendly manufacturing technology	[26]
Ethosomes	Arctostaphylosuvarurs	Cold method	114.7nm, 0.492	It significantly reduced skin erythema, melanin as well as sebum level and improved skin hydration and elasticity.	[27]
Ethosomes	Aceclofenac,	Thin film Hydration	112nm, 0.472	Stability profile of prepared system was assessed for 45 days and the results revealed that very less degradation of drug was observed during storage condition.	[28]
Ethosomes	Melatonin	Thin film Hydration	250 nm, 0.27	An ethosomal gel of optimized formulation was prepared by using carbopol 934 and compared with plain gel formulation showed pseudoplastic rheological behavior, optimum pH, spreadability	[29]
Ethosomes	Stavudine	Thin film Hydration	142nm, 0.27	It was concluded from the study that, ethosomes can increase the transdermal flux, prolong the release and present an attractive route for sustained delivery of stavudine.	[30]

Table 4: Recent studies of ethosomes

S. No.	Title	Source	Year	Statement	Conclusion
1.	An evaluation of a multimodality pigment-correcting serum using lotus sprout extract in comparison to hydroquinone in a randomly assigned, regulated, split-face, a double-blind study treating melasma and other moderate to severe cases of face hyperpigmentation in a multicultural setting.	Elsevier	June 2024	With no HQ (hydroquinone), the Advanced Brightening Treatment (ABT) is a multimodal, groundbreaking pigment-correcting serum that targets biological pathways related to hyperpigmentation.	For the long-term management of melasma and other persistent, difficult-to-treat face hyperpigmentation, ABT is an effective choice.
2.	Ethosomes: A Novel Approach to Vesicular Drug Administration	AJPR	January 2024	. Ethosomes are stretchable nanovesicles that have a phospholipid base and 20–45% ethanol within them. Vesicular structures known as etherosomes have significant advantages. The aqueous and lipid bilayer composition of hydrophilic and lipophilic medications is thought to contribute to their greater absorption.	The discovery of ethosomes has created a whole new field of study for transdermal medication administration. Etosomas possess a bright future in increasing transdermal administration's safety for a range of medications, as demonstrated by a multitude of studies.
3.	Depigmenting agent alpha arbutin encased in nanoscale ethosomes: in vitro and in vivo research with humans	PubMed	August 2023	Alpha arbutin is a common skin-whitening component in cosmetic formulations.	The stable ethosomal formulation containing arbutin may be a better option than traditional formulations for cosmeceutical objectives like moisturizing and depigmentation.
4.	A thorough analysis of the prospective advantages of ethosomes for cosmetic dermal delivery	PubMed	July 2023	A fascinating development in the delivery of cosmetic drugs is the emergence of ethers.	Provides a thorough description examines the ethosomal system and assesses if it may be used as a nanocarrier to transport active ingredients to the skin. Investigating their uses in different pathologies—especially skin conditions including acne, hair loss, and skin pigmentation—is the main aim.
5.	Creation and Evaluation of a Rosehip Extract-Encapsulating Ethosomal Gel	PubMed	April 2023	To use an environmentally sustainable method to provide Rosa canina L. extract (in terms of its antioxidant activity) as a botanical component in an anti-aging gel.	Strong antioxidant activity was shown by the ethosomal gel derived from rosehip (1 mg/mL), which was effectively packed in ethosomes with 30% ethanol; this may be a cutting-edge, environmentally responsible skincare product.
6.	Production ethanol injection approach for the production of liposomes.	PubMed	February 2023	One technique for preparing liposomes is the injectable technique using ethanol, which has the advantages of being quick, safe, and repeatable.	Using this technique, phospholipid solution of ethanol is injected into an agitated aqueous solution. It is among the most favored techniques for producing ethosomes.
7.	Kojic acid dipalmitate-loaded nanosized ethosomal gel's whitening impact in curing hyperpigmentation	PubMed	December 2022	One important enzyme involved in hyperpigmentation is tyrosinase. An ester derivative of kojic acid, kojic acid dipalmitate (KAD) has good tyrosinase-inhibiting action on human skin, which helps treat melasma and	Skin-whitening and moisturizing properties are provided by the Etomal formulation with KAD added, which is stable and allows for deep skin penetration of KAD.

				hyperpigmentation.	
8.	Analyzing the Prospects of Cutting-Edge Nanotechnology-Based Techniques for the Therapy of Hyperpigmentation Disorder	PubMed	December 2022	This review's goals center on the application of nanotechnology-based tactics, like lipid-based nanocarriers, in the treatment of hyperpigmentation.	This article highlighted how sophisticated equipment can be used to cure excessive pigmentation by incorporating hypopigmenting molecules in skin layers and increasing their physical strength and permeability. Examples of these techniques include the topical application of nanotechnology-based lipid- and inorganic-based nanocarriers to efficiently cure hyperpigmentation. Hypopigmenting medications could be utilized as a first line of treatment in addition to oral therapy.
9.	Factorial optimization, in vivo and in vitro evaluation, preparation, clinical assessment in melasma patients, and vesicular carriers of magnesium ascorbyl phosphate for topical administration	PubMed	December 2022	As ethosomes and niosomes, vesicular carriers, magnesium ascorbyl phosphate (MAP), an ascorbic acid stabilised derivative, was developed. The goal was to administer MAP for a long enough period of time with improved penetration to the skin, the desired site of action, to elicit a useful response.	One month later, the magnesium ascorbyl phosphate ethosomal gel demonstrated a clinically significant statistically significant decrease in melanin levels, and after six months, the MAP niosomal gel demonstrated a similar decrease in melanin levels. Niosomes and MAP ethosomes together may offer melasma and hyperpigmentation sufferers effective short- and long-term skincare solutions.
10.	Ethosomes: An innovative method of drug delivery	Elsevier	October 2022	Since its introduction twenty years ago, ethosomal systems have seen tremendous growth in popularity as a transdermal drug delivery method.	For more than 20 years, ethosomes have been demonstrated to be a viable and developing carrier system. Over time, their capacity to deliver potent systemic and topical medicinal effects through the skin has elevated them to the status of an innovative and enticing carrier system. Additionally, extensive research has prompted the creation of Transethosomes, a new class of ethosomal systems. These metasomes have improved systemic circulation and cutaneous penetration over standard ethosomes.
11.	Innovative nanotechnological methods for aging and skin care	Elsevier	August 2022	The subject of cosmeceutical nanomaterials is developing quickly, and we anticipate that a range of cutting-edge cosmetic solutions based on nanotechnology will revolutionize the multibillion dollar anti-aging cosmetics market.	Solid lipid nanoparticles, carbon nanotubes, liposomes, niosomes, transfersomes, ethosomes, and nanostructured lipid carriers are a few of the cutting-edge nanotechnological strategies being employed to prevent skin aging.

					Novel nanocarriers have replaced conventional delivery methods with a number of benefits, including enhanced skin penetration and permeation. Examples of these include liposomes, niosomes, nanoemulsions, SLNs, NLCs, and nanospheres.
12.	Arctostaphylosuva-ursi Extract-Loaded Nanostructured Ethosomal Gel: In-Vitro/In-Vivo Assessment as a Cosmeceutical Formulation for Skin Revival.	PubMed	January 2022	For skin renewal and depigmentation, a stable ethosomal gel formulation based on AUUs may be a more effective delivery system for phytoextracts.	It is abundant in Arctostaphylosuva-ursi (AUU) arbutin (for depigmentation) and polyphenols, making it a promising candidate for cosmetic use. To produce an optimal AUU extract-loaded nanostructured ethosomal gel formulation.
13.	External Delivery of Medications Integrated in Phospholipid Soft Vesicles Carriers for the Management and Treatment of Skin Diseases	PubMed	December 2021	Reports on some medical skin conditions that have been successfully treated topically disorders using medication supplied via phospholipid soft vesicles are given. Topical drug delivery is superior to other methods of administration in several aspects, such as better patient compliance, prevention of the first-pass impact after oral drug administration, and avoidance of the need for repeated dose administration.	Numerous in vitro, in vivo, and clinical investigations have demonstrated that the inclusion of drugs into ethosomes has improved the management of skin conditions such as skin cancer, psoriasis, acne vulgaris, skin infections, skin inflammation, hair loss, skin damage, and skin aging. Glycerosomes and transethosomes were able to increase the integrated active compounds' in vitro penetration.
14.	Using Ethosomes as Nanotechnology-based carriers to Develop Skin Delivery Products	PubMed	May 2021	There are reports on the effective topical therapy of certain medical skin problems using drug delivered via phospholipid soft vesicles. Topical medication distribution is better than other delivery modalities in a number of ways, including increased patient compliance, avoiding the need for repeated dose administration, and preventing the first-pass impact that happens after taking a medication orally.	The topical distribution of active compounds through ethosomal-based formulations shows a lot of potential and is becoming more and more recognized as a competitive option to oral administration.
15.	Development and assessment of melatonin's topical ethosomal gel for UV protection	PubMed	August 2020	Melatonin's (MLT) oral route is less preferred because to its wide first-pass action and unpredictable oral absorption. The extreme deformability of human skin allows ethosomes to pass through it unharmed.	According to this study, MLT loaded ethosomes may one day be employed as a topical medication delivery mechanism.
16.	Inflammatory Skin Diseases: focusing the Hyaluronic Acid-Mediated Drug Delivery System	PubMed	July 2020	More biocompatibility, permeability, and effective release are demonstrated by HA-based TDDS.	Hyaluronic acid based ethosomes shows enhanced skin maintenance and deals with psoriasis related skin inflammation.
17.	Recent advancements in the use of phospholipid vesicular medication delivery using nanocarriers to the skin	Elsevier	July 2020	The first elastic and malleable phospholipid vesicles were developed, and this has brought attention to the critical function that vesicle	Research has shown for over 50 years that liposomes have a major part in improving the percutaneous delivery of both big and tiny

				composition plays in facilitating the diffusion of vesicle content via the skin and into it.	compounds that are unable to passively diffuse across the skin barrier. Since their introduction into therapy, these safe and biocompatible carriers have proven to have several benefits.
18.	Vesicular delivery systems such as liposomes, invasomes and transfersomes, that contain phenylethyl resorcinol for topical administration	Elsevier	September 2018	Phenylethyl resorcinol (PR), when used topically, has garnered significant interest as a high anti-tyrosinase properties in a skin-lightening agent properties.	Compared to typical liposomes, elastic vesicle carriers are more effective in providing PR into the deep more effective in providing of both amount as well as effectiveness, making them suitable for use in skin-lightening products.
19.	Phenylethyl Resorcinol Ethosomes as Vesicular Delivery Networks for Skin Lightening Purposes	PubMed	July 2017	Ethosomes showed lower melanin content and higher tyrosinase inhibitory efficacy when compared to other formulations.	Phenylethyl resorcinol (PR) can be effectively delivered to the skin by ethosomes, which may be useful for the topical use of skin-lightening treatments.
20.	Melasma: A Current, Thorough Review	PubMed	July 2017	Individuals with darker skin tones and women are more likely to develop symmetric hyperpigmentation, a common acquired condition known as melasma. Usually, the face is affected.	New studies keep adding to our knowledge about melasma and the most effective ways to treat it. In the last ten years, new oral, topical, procedural, and combination medicines has developed.
21.	A review of ethosomes	IJPMR	August 2016	Ethosomes are noninvasive delivery systems made of phospholipids, water, and a high ethanol content that make it possible for medications to permeate deeply either permeate the layers of skin or go into the bloodstream.	It is simple to determine that ethosomes have superior skin penetration vs liposomes. Comparing ethosomes to transdermal and dermal distribution, there are more benefits.
22.	Modern use of phytocompound-based nanocosmeceuticals for skin care and beauty	PubMed	May 2016	The toxicity of some delivery methods, such carbon nanotubes, needs to be investigated.	Phytocompounds can be made nanoscale to overcome low penetration and high compound instability while maintaining sustained delivery and skin-protecting properties in a variety of cosmetic products. Using a variety of delivery technologies, it was possible to successfully nanosize Green tea catechins, genistein, Vitamins C and E, aloe vera, curcumin, and quercetin. These nanoparticles were then incorporated into different lotions and gels, and creams for hair care, lip and skin as carbon nanotubes, fullerenes, transfersomes, ethosomes, solid lipid nanoparticles and lipid carriers with nanostructures.
23.	Development of the procedure for improved and evolved ethanol injection toward liposomes	PubMed	October 2012	To create liposomes, the MDEI technique, or modified and derived ethanol injection was created. The current study set out to manage the	When it comes to the ethanol injection process, MDEI is a suitable substitute for preparing liposomes.

				vesicle width more effectively than it could have with the traditional ethanol injection technique.	
24.	Linoleic acid-containing ethosomes and transfersomes: chemical, physical, and technological aspects of topical medication delivery vehicles for the possible management of disorders related to melasma	PubMed	February 2012	Regarding the current administration of linoleic acid, a medicament used in the healing management of excessive pigmentation disorders like Melasma, a skin condition that involves marked by an increase in the skin's synthesis of melanin, two colloidal vesicles carriers, transfersomes® and ethosomes®, were developed.	The lecithin component, phospholipon 100 G®, and the salt cholate and ethanol as edge activators, were used to make ethosomes® and transfersomes®, respectively. Colloidal vesicles include between 0.05% and 0.1% (w/v) of linoleic acid were employed as the active component.
25.	Ethosome production and description for topical aceclofenac administration	IJPR	October 2010	The current work set out to create and characterize ethosomes of aceclofenac that could more effectively deliver the medication to the intended place than commercial gel preparations while also resolving issues associated with oral drug delivery.	These pliable vesicles possess the capacity to serve as a useful vehicle for aceclofenac transdermal administration. It aids in lowering the dosage of medication given topically, raising the prospect of using local therapy instead of systemic therapy for rheumatoid arthritis and osteoarthritis. This could lead to a reduction in gastrointestinal adverse effects and an increase in patient compliance.
26.	Ethosomes medicinal and commercial potential	PubMed	September 2010	Highlights the function of ethosomes as permeation enhancers in cutaneous as well as transdermal medication administration scenarios and provides an overview of the techniques and therapeutic uses of ethosomes.	Because ethanol is an effective permeation enhancer, ethosomes outperform tdds, which have limited penetration. Some of the clinical uses for ethosomes include: antioxidant Ethosomes in Topical Administration Azelaic acid liposomes and ethosomes, an anti-keratinizing agent used to treat acne, were prepared as a topical vehicle (gel) by making use of the complementary qualities of vitamin C, vitamin E, and vitamin A palmitate. Lipoduction, a novel cellulite lotion, uses ethosomes, was introduced by a USA company supplied components straight into fat cells.
27.	Development of Stavudine's Ethosome Formulation and Assessment	IJPER	March 2010	Ethosomes, a novel penetration enhancer, were effectively created using the mechanical-dispersion method to Permit the controlled and prolonged Permit the controlled and prolonged release. stavudine throughout SC.	The investigation revealed that ethosomes can extend the release, boost transdermal flux, and offer a desirable delivery method for stavudine over time.
28.	Creation and Evaluation of a Rosehip Extract-Encapsulating Ethosomal Gel	PubMed	April 2023	To use an environmentally sustainable method to deliver Rosa canina L. extract as a botanical	The ethosomal gel rosehip extract (1 mg/mL) demonstrated a strong protective activity when it was effectively enveloped in ethosomes

				ingredient in an anti-aging gel (in terms of its antioxidant activity).	with 30% ethanol; this might constitute a novel and environmentally friendly rejuvenating skincare product.
29.	Kojic acid dipalmitate-loaded nanosized ethosomal gel's whitening impact in curing hyperpigmentation	PubMed	December 2022	One important enzyme involved in hyperpigmentation is tyrosinase. An ester derivative of kojic acid, kojic acid dipalmitate (KAD) has good tyrosinase-inhibiting action on human skin, which helps treat melasma and excessive pigmentation.	The KAD-loaded ethosomal formulation is a therapeutic strategy for treating skin hyperpigmentation, lightening and hydrating the skin while offering deep penetration of KAD into the skin.
30.	Arctostaphylosuva-ursi Extract-Loaded Nanostructured Ethosomal Gel: In-Vitro/In-Vivo Assessment as a Cosmeceutical Formulation for Skin Revival	PubMed	January 2022	For skin renewal and depigmentation, a stable ethosomal gel formulation based on AUUs may be a more effective delivery system for phytoextracts.	Arctostaphylosuva-ursi (AUU) is rich in arbutin (for depigmentation) and polyphenols, making it a promising candidate for cosmetic use. To produce an optimal AUU extract-loaded nanostructured ethosomal gel formulation.
31.	Inflammatory Skin Diseases: focusing the Hyaluronic Acid-Mediated Drug Delivery System	PubMed	July 2020	More biocompatibility, permeability, and effective release are demonstrated by HA-based TDDS.	Hyaluronic acid-based ethosomes improve skin maintenance and reduce skin inflammation associated with psoriasis.
32.	Modern use of phytocompound-based nano cosmeceuticals for skin care and beauty	PubMed	May 2016	The toxicity of some delivery methods, such carbon nanotubes, needs to be investigated.	Phytocompounds can be made nanoscale to overcome low penetration and high compound instability while maintaining sustained delivery and skin-protecting properties in a variety of cosmetic products. Using a variety of delivery technologies, it was possible to successfully nanosize Green tea catechins, genistein, vitamins C and E, aloe vera, curcumin, and quercetin. These nanoparticles were then incorporated into different lotions and gels, and creams for hair care, lip and skin as carbon nanotubes, fullerenes, transfersomes, ethosomes, solid lipid nanoparticles and lipid carriers with nanostructures.

CHARACTERIZATION OF ETHOSOMES VESICULAR SHAPE

Equipment such as scanning electron microscopy (SEM) and as transmission electron microscopy (TEM) are used to visualize ethosomes. Based on these approaches, research show that an ethosomal formulation has a vesicular shape with a diameter of roughly 300–400 nm. The imprecise circular shape of the vesicles indicates that they are flexible [28, 29, 30].

ZETA POTENTIAL AND SHAPE OF VESICLE

The equipment that allows for the identification of the zeta potential and the ethosomes' particle size are dynamic dispersion of light (DLS) along with the use of a photon correlation spectroscopy (PCS) and computerized inspection system [28, 29].

DRUG ENTRAPMENT

The ethosomes entrapment efficiency may be determined using the ultracentrifugation technique. The percentage EE was calculated using the ultracentrifugation method. of the ethosomal solution. In a cold centrifuge, the optimized ethosomal formulation was centrifuged for two hours at 4C at 11,000 rpm. The supernatant layer was also subjected to UV-Vis spectrophotometer analysis after being separated and diluted with PBS (pH 7.4). By dividing The quantity of unentrapped substance in the supernatant liquid by the entire quantity of medication in

the formulation, the percentage EE was indirectly determined. The provided equation accustomed to determine the medication entrapment percentage:

$$EE (\%) = \frac{T - C}{T} \times 100$$

where T is the total medication quantity, C is the amount of drug obtained in the supernatant [28, 29].

TRANSITION TEMPERATURE

Using differential scanning calorimetry (DSC) find the vesicular lipid systems' temperature of transition [28, 19].

DRUG CONTENT

The drug content of the ethosomes can be evaluated with a UV measuring device. A high-performance liquid chromatographic modified method may additionally be employed to quantify this. One gram of gel and fifty milliliters of methanol were dissolved in a 50-milliliter volumetric flask. The mixture was subjected to sonication within a bath until it reached a clear state. The mixture was then suitably diluted with methanol and filtered through a 0.45micron filter. By measuring absorbance at a certain wavelength with methanol serving as the reference solution, the drug concentration was ascertained [28, 29].

Drug content

$$= \frac{\text{Actual drug content in vesicles}}{\text{Theoretical drug content in vesicles}} \times 100$$

APPLICATIONS OF ETHOSOMES [1, 4, 5, 6, 7]

1. The use of ethosomes in the management of various microbial epidermis infection and viral infections. Efficacy of bacitracin and erythromycin were also studied on animal models of deep skin infections.
2. Anti-inflammatory effect on the skin was shown by ammonium glycyrrhizinate ethosomes in human subjects.
3. Experimentation on rabbits in vivo through ethosomal patches have efficiently demonstrated better results which lead to the treatment of menopausal symptoms in women and androgen deficiency in men.

4. According to research, ethosomes may also have anti-fever, analgesic, and pain-relieving properties when used to treat erectile dysfunction.

ETHOSOMAL PATENTS AND MARKETED FORMULATION [31]

Ethosomal systems, known for their enhanced delivery of active pharmaceutical ingredients through the skin, have gained significant attention in drug delivery research. Several patents have been filed for ethosomal formulations to improve the therapeutic efficacy of various drugs, especially for transdermal applications (**Table 5**). Several ethosomal formulations have been successfully commercialized, capitalizing on their superior ability to deliver drugs and active ingredients through the skin (**Table 6**).

Table 5: List of patents of ethosomes

Patent Number	Year	Subject	Outcomes
CN104983675A	2015	Ethosome Gel Containing Tretinoin as well as Its Manufacturing Process	The ethosomes gel that is generated is a transdermal distribution getting ready intended for external usage.
CN103536700(A)	2014	Herbal Gel Patch for Ethosomes the Treatment of Zooster Herpes	It is simple to take, easy to utilise, offers a potent medicinal impact, and responds quickly.
CN103893394(A)	2014	The Multimodal Wound Ethosome Gel Coating Agent Healing and Its Preparation Process	The layer of film material enclosed in a phagosome aids in wound healing and tissue nutrient delivery.
CN103006562(A)	2013	Formulation of Daptomycin in Ethosomes	The drug release, slow-release impact, and transdermal performance of this product are all excellent. manufacturing process is easy to use, affordable, and stable.
CN102406605(A)	2012	Preparation Based on Ethosomes of Male Hormone	To enhance male hormone transdermal transfer
CN102579323(A)	2012	Paclitaxel Ethosome Gel and How It Is Made	There is a good percutaneous penetration impact and a reduction in the stimulation of the skin's surface.
CN102133183(A)	2011	Acyclovir Ethosome additionally Its Production Process	High stability and a restricted dispersion of particle sizes characterize acyclovir ethosome.
CN102144972(A)	2011	Podophyllotoxin Ethosome Formulations and Methods of Production	There are two methods for preparing the ethosomes of podophyllotoxin. are disclosed in the invention.
WO2010086723A1	2010	Terbinafine-Based Formulations for Treating Onychomycosis	Novel topical terbinafine formulations for the management of onychomycosis of the nails.

Table 6: List of marketed products of ethosomes.

Name of product	Uses	Manufacturer
Cellutight EF	A strong combination of ingredients included in topical cellulite cream combine to increase metabolism and burn fat.	Hampden Health, USA
Decorin cream	Treatment for visible signs of aging on the skin, such as wrinkles, sagging, age spots, lack of elasticity, and hyperpigmentation, using anti-aging cream.	Genome Cosmetics, Pennsylvania, US
Nanominox	The first ethosome-using product that contains minoxidil. contains 4% minoxidil, a well-known stimulant for hair growth that needs to be sulfated in order to be converted into the active component.	Sinere, Germany
Noicellex	Anti-cellulite topical cream	Novel Therapeutic Technologies, Israel
Skin genuity	Strong cellulite-busting agent minimizes orange peel	Physonics Nottingham, UK
Supravir cream	In order to treat the herpes virus	Trima, Israel
Body Shape	Gel stretches the skin to carry out solidification.	Maccabi CARE
Osmotics Lipoduction Cellulite Cream	When used topically, ethosomal cream helps burn fat and minimize cellulite.	(Osmotics, Israel)

CONCLUSION

Over the past two decades, Ethosomes have been discovered demonstrated as a developing, reliable and efficient carrier infrastructure. Their incredible capacity to deliver significant healing effects both on topical and systemic application through the skin has made them a attractive and innovative carrier system over time. Ongoing research about ethosomal systems states that these carriers, especially when dealt in combination Using penetration enhancers, might furthermore therapeutically efficient for the medication delivery in various dosage forms such as gels, patches, and creams. With the developed elastic vesicular formulation of ethosomes, formulation of Dermal and transdermal delivery techniques that are secure and efficient need to be much more popular. However, more detailed research studies are required to further investigate

and analyse the stability of ethosomal systems.

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