Binary Ethosomal Nanovesicles for Enhanced Topical and Dermal Delivery of Therapeutics in Atopic Dermatitis

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ABSTRACT

Atopic dermatitis (AD) is a chronic inflammatory skin disorder characterized by impaired skin barrier function and persistent flare-ups that hinder the efficiency of traditional topical medications. Conventional formulations for the treatment of skin disorders may suffer from inadequate skin permeability, limited skin retention, and the need for frequent application, which may compromise therapeutic effectiveness. Within the past several years, binary ethosomal nanovesicles have been considered as an innovative nanovesicular platform for increasing skin permeation. Ethosomes consisting of phospholipids, ethanol, and a cosolvent are flexible and can enhance skin permeation through interaction with the skin barrier. Binary ethosomes have numerous advantages in their physicochemical properties, such as favorable particle size distribution, low polydispersity index, suitable zeta potential for stability, and high entrapment efficiency, depending on their formulation and preparation conditions. Moreover, in vitro drug release and skin permeability studies have reported sustained drug release, enhanced drug permeation, and increased skin deposition with selected binary ethosomal formulations. Finally, stability testing of selected binary ethosomal formulations has demonstrated their ability to retain physicochemical characteristics and drug content over a defined period under different storage conditions. Therefore, the benefits of binary ethosomes make them a promising platform for delivering corticosteroids, immunomodulatory drugs, and non-steroidal substances. The purpose of this review is to discuss the aspects related to formulation, assessment, and therapeutic potential of binary ethosomes, particularly their potential application in the topical management of AD.

Keywords: Atopic dermatitis; Binary ethosomes; Topical drug delivery; Nanovesicular carriers; Controlled drug release.

INTRODUCTION

Atopic dermatitis (AD) is a chronic, relapsing, inflammatory skin disorder that involves impaired epidermal barrier function and immune dysregulation (Figure 1). The condition is characterised by recurrent flares influenced by genetic, environmental, and immunologic factors [Pinto LM et al.,2022]. As disease is increasingly recognised as a nonuniform entity, there is clinical heterogeneity in morphology, age-related presentation, and anatomic distribution that complicates diagnosis and treatment selection [Girolomoni G et al., 2021]. Manifestations include xerosis; eczematous lesions; lichenification, which shows chronic scratching; intense, often intractable pruritus; and continuing inflammation associated with barrier damage [Pinto LM *et al*.,2022].

AD is one of the most common chronic inflammatory skin diseases found worldwide in children and adults, with long-term management posing a challenge in dermatology [Rohayem R *et al*.,2025]. Beyond the clinical importance of visible skin lesions, they are associated with ongoing itch, sleep disruption, and significant psychosocial distress, leading to a reduced quality of life and a substantial patient burden [Pinto LM *et al*., 2022]. Furthermore, the recurrent nature of the disease and the resulting need for prolonged therapy significantly

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contribute to healthcare utilisation and related treatment burden, resulting in a substantial socioeconomic impact and public health relevance [Kang Y *et al*. 2024].

Figure 1: Atopic Dermatitis on Skin

Need for Improved Topical/Transdermal Delivery Systems

Topical drugs such as corticosteroids, calcineurin inhibitors and newer anti-inflammatory agents are important in atopic dermatitis (AD) treatment but often suffer from poor skin penetration, associated irritation and a relatively short residence time in the skin with low compliance during chronic treatment. Considering the stratum corneum as the main obstacle for cutaneous drug delivery, the development of topical and transdermal formulations should respect the normal skin physiology as well as its pathological alterations when diseased [Brito S *et al*.,2024]. Advances in topical and transdermal drug delivery highlight the potential of nanocarrier-based formulations to increase the local bioavailability of drugs while enhancing their deposition in dermal layers and minimizing their unwanted systemic absorption, being of great interest in the treatment of chronic inflammatory dermatoses such as AD [Bakhrushina EO *et al*.,2025]. In this setting, ethosomal and binary ethosomal nanovesicles emerge as very appealing carriers due to their deformation ability and membrane penetration-enhancing composition, which allow for higher drug permeation and retention into the skin compared to conventional formulations [Al-Ameri AAF *et al*.,2024].

Ethosomes, usually phospholipid-based vesicular nanosystems rich in ethanol, aim at improving dermal and transdermal drug delivery by inducing vesicle flexibility and enabling their passage through the main cutaneous barrier, the stratum corneum [Bakhrushina EO *et al*.,2025]. Recent nanocarrier research emphasizes their application to increase the skin hydration degree, disrupt its lipids and promote a controlled drug localization, which are important features of potential interest in AD-directed topical therapy [Kang Y *et al*.,2024]. In particular, binary ethosomes, namely those incorporating in their composition a second solvent (like propylene glycol), besides ethanol, have shown in recent years higher levels of drug entrapment, permeation flux and topical efficacy compared to classical ethosomes, so emerging as a topical formulation platform deserving consideration in the future [Al-Ameri AAF *et al*.,2024].

Pathophysiology of Atopic Dermatitis

Atopic dermatitis (AD) is a chronic, relapsing, inflammatory dermatosis, characterised by bidirectional interaction between epidermal barrier impairment, type 2-skewed immune activation, microbial dysbiosis and pruritus pathways. [Furue M. *et al*.,2020; Tsuji G *et al*.,2023], barrier failure has emerged as a consequence of inflammation, epidermal abnormalities allowing allergen penetration, microbial colonization and immune dysregulation contributing to disease chronicity [Kim HB *et al*.,2025]. This integrated view of how modern

targeted therapies work by restoring the barrier and suppressing cytokine signalling and itch-related inflammatory cascades [Biliński K *et al*.,2025].

In AD skin, lipid organization within the Stratum corneum (SC) is severely impaired, and the ceramide profile is altered, affecting the lipid bilayer structure and leading to increased epidermal permeability [Kondo A *et al*., 2024]. In line with these data, recent clinical and biophysical studies have provided strong evidence for barrier disruption in lesional AD skin, with significantly increased transepidermal water loss (TEWL) and reduced SC hydration compared with non-lesional skin and healthy controls, as well as objective evidence for epidermal barrier disruption [Montero-Vilchez T *et al*., 2021]. It has also been reported that disturbed lipid metabolism is closely correlated with disease activity and that type 2 inflammatory signals were associated with disturbed ceramide profiles, showing that inflammation itself may also play a role in reducing barrier quality [Kondo A *et al*., 2024] [Furue M *et al*., 2020].

In particular, IL-13 has been shown to induce epidermal barrier failure by downregulating the expression of differentiation-related genes, such as profilaggrin and OVOL1, leading to defective SC formation and impaired skin barrier maturation [Furue M *et al*., 2020]. More recently, a link has been reported between the IL-13-dominant cutaneous environment and OVOL1 dysregulation, thus confirming the interplay between cytokine excess and barrier-related pathways [Ratnarajah K *et al*., 2021]. This hypothesis is clinically relevant, as treatments able to downregulate IL-4/IL-13 signalling and/or restore barrier-related pathways, such as SIRT6, can reduce inflammation and improve skin barrier integrity [Biliński K *et al*., 2025].

Barrier disruption in AD skin promotes skin microbiota imbalance, characterized by reduced microbial diversity and increased Staphylococcus aureus colonization in lesional skin. [Kim HB *et al*.,2025]. Microbial imbalance further exacerbates lipid disruption and immune activation, creating a self-reinforcing cycle in which impaired barrier function and inflammation perpetuate one another [Kim J *et al.,* 2023]. Thus, skin barrier dysfunction in AD should be understood as a dynamic biological defect involving lipids, structural proteins, hydration status, and host–microbiome interactions rather than as a simple mechanical weakness alone.

Skin barrier dysfunction and Immune dysregulation

In atopic dermatitis, the stratum corneum exhibits altered lipid architecture, especially abnormalities in ceramide composition, which weaken barrier integrity and increase transepidermal water loss [Kondo A *et al*.,2024]. Objective studies confirm that lesional skin has higher TEWL and lower stratum corneum hydration than nonlesional skin, reflecting measurable barrier impairment [Montero-Vilchez T *et al.*,2021]. Type 2 cytokines, particularly IL-13, further aggravate this defect by suppressing epidermal differentiation and barrier-related pathways, thereby linking inflammation directly to barrier failure [Ratnarajah K *et al*.,2023].

Atopic dermatitis is predominantly driven by a type 2 immune response in which IL-4 and IL-13 act as central effectors of allergic cutaneous inflammation [Ratnarajah K *et al*.,2023] [Tsuji G *et al*.,2023]. However, chronic and severe disease demonstrates endotypic heterogeneity, with contributions from Th1, Th17, and Th22 axes in addition to type 2 inflammation [Choi J *et al*.,2021] [Biliński]. Keratinocyte-derived innate signals and JAK–STAT-mediated cytokine pathways further amplify immune activation, illustrating the close interplay between barrier dysfunction and immune dysregulation [Chieosilapatham P et al.,2021] [Crowley EL et al.,2020]

Role of inflammatory mediators and cytokines

IL-4/13 and Th2 cytokines are considered the main inflammatory cytokines involved in AD since they sustain type-2 inflammation, inhibit barrier-related epidermal pathways, and trigger chronic and persistent pruritic eczema [Dubin C et al.,2021] [Pappa G et al.,2022]. Such cytokines also induce microbiome disturbance and enable the inflammatory milieu that favours disease flares and chronicity [Napolitano MN et al.,2023] [Kabashima K et al.,2022]. The excellent clinical performance of IL-4 and IL-13-targeted agents confirms these mediators are not exclusively associated with AD but play a central driving role in disease activity [Upadhyay PR et al.,2023].

Epithelial alarmins and early proinflammatory mediators, including thymic stromal lymphopoietin (TSLP), IL-33, IL-1-13, and TNF-11a, play a crucial role in triggering and propagating local cutaneous immune responses by promoting recruitment and activation of inflammation, boosting cytokine production, and contributing to the development and prolonged nature of eczema flares [Kim HJ et al.,2025] [Liu Q et al.,2020]. These mediators' role highlights the relevance of keratinocyte-derived signals in connecting barrier disruption to downstream immune activation.

Itch, the hallmark feature of AD is closely associated with IL-31 signalling, and recent therapeutic studies have demonstrated IL-31 pathway inhibition to alleviate itch and improve disease severity. IL-23 receptor expression on keratinocytes, inflammatory cells, and peripheral nerve supports its role as a bridge between cutaneous inflammation and neuroimmune itch signalling. Consistently, IL-31 has shown to play a role as a biomarker-relevant cytokine and a promising therapeutic target for moderate-to-severe AD [Orfali RL et al.,2023]

Additional and important proteins like chemerin, elafin and nicotinamide phosphoribosyltransferase/ visfatin (NAMPT) have gained recent attention as modulators of epidermal barrier biology and skin inflammation in AD. Such mediators may exert pro-inflammatory, anti-inflammatory, or context-dependent effects, adding to the complexity of cytokine networks and protein interplay that shape AD pathophysiology. Their importance highlights the potential need for biomarker-guided therapy in AD for not classic Th2 cytokines, but an expanded panel of inflammatory and barrier-associated mediators [Matwiejuk M et al.,2025]

Current Therapeutic Approaches for Atopic Dermatitis

Topical corticosteroids are the gold standard for first-line management of atopic dermatitis flares since they rapidly induce anti-inflammatory effects; however, prolonged or inappropriate use can cause cutaneous adverse effects, including skin atrophy, but also cause steroid aversion in clinical practice of atopic dermatitis routine [Mudaliyar VR et al.,2020] [Ghosalkar et al.,2022]. Topical calcineurin inhibitors, especially tacrolimus and pimecrolimus, are key steroid-sparing agents at sensitive sites such as the face, eyelids, neck and flexures, but they are also useful for intermittent maintenance or pre-emptive therapy just because they avoid steroid-induced skin atrophy [Luger T et al.,2021].

Novel non-steroidal topical drugs have opened new avenues in treatment options with phosphodiesterase-4 inhibitors such as crisaborole and roflumilast, topical Janus kinase inhibitors such as ruxolitinib and delgocitinib, aryl hydrocarbon receptor modulators such as tapinarof, reflecting a shift towards more mechanism-guided topical management approaches [Farkouh C et al., 2023] [Ghosalkar et al., 2022]. However, conventional topical therapies still present important limitations that include local irritation, variable penetration through inflamed or lichenified skin, adherence problems, and uncertainty on long-term safety for some newer agents, and poor disease control on persistent or refractive disease have inspired interest in improved formulations and targeted alternatives [Murai H et al., 2025]

Challenges in Transdermal Drug Delivery for AD

The stratum corneum remains the major impediment to achieving transdermal drug delivery in atopic dermatitis, as its compact lipid–protein organisation obstructs the transdermal passage of most therapeutic molecules and significantly diminishes skin permeation [Shabbir M et al.,2020].

Exacerbating this difficulty, poor penetration of drugs is further affected by physicochemical properties of the drug, carrier system, and diseased skin microenvironment, such that conventional topical formulations frequently fail to ensure adequate dermal deposition or to provide sustained therapeutic blood concentrations [Cheng T et al., 2023].

Additionally, drug stability and sub-optimal bioavailability in topical vehicles can jeopardize treatment efficacy that drives the interest in using newer nanocarrier-based systems to protect the drug better, improve penetration and increase local drug bioavailability in inflammatory skin disorders, with examples in AD. [Kang Y, et al., 2024]

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Nanocarrier-Based Drug Delivery Systems in Dermatology

Lipid-based nanocarriers such as liposomes, ethosomes, transfersomes, and solid lipid nanoparticles (SLNs), or nanostructured lipid carriers (NLCs), as well as polymeric platforms including polymeric nanoparticles, nanogels, micelles, dendrimer-like systems and nanofibrous matrices have emerged as versatile dermologic delivery systems because their nanoscale size, tunability of surface properties, and in some instances deformability enable interaction with the stratum corneum and improved drug localized epidermally and dermally [Souto EB et al., 2021]. Compared to conventional creams and ointments, these carriers may optimize incorporation of poorly soluble or labile drug, improving protection from degradation, enhancing penetration and skin retention, allowing sustained or controlled release behavior, possibility of minimizing dosing frequency and systemic exposure, and possibly show reduced local irritation while bettering therapeutic efficacy and patient adherence in topical dermatology [Yuniarsih N, et al.,2024] [Yan Z, et al.,2026]

Overview of Ethosomal Systems

Ethosomal systems are soft, ethanol-rich phospholipid vesicles intended for dermal and transdermal delivery commonly and typically containing phospholipids, a relatively high percentage of ethanol, water and sometimes polyols or penetration-modifying additives, which altogether generate highly fluid and deformable bilayers capable of entrap both hydrophilic and lipophilic drugs [Abdulbaqi I et al.,2016].

Their high skin transportability is primarily attributable to the synergism of the two essential components, ethanol and vesicle flexibility, since ethanol enhances drug solubility and also fluidizes the stratum corneum lipids [Garg V, et al., 2017] while the vesicles themselves could have the ability to follow inter and follicular pathways and release the payload in deeper skin layers [Yang L, 2017]. This renders ethosomes more appealing for their use in topical therapy, where increased permeation and greater skin deposition, accompanied by improved local retention and better therapeutic response, have been ascribed to ethosomal compared to conventional preparations [Kaur M et al.,2020]. Employing ethosomes in dermatologic use also has shown the potential to boost efficacy by reducing adverse events and bettering tolerability [Salem HF et al., 2021].

Besides their advantages, these carriers could also protect encapsulated actives against degradation and induce sustained release behavior that may counterbalance and reduce dosing frequency [Natsheh H et al.,2019]. Summing up, ethosomes have emerged as a promising topical nanocarrier platform because they offer enhanced penetration as well as improved bioavailability, along with formulation versatility and better patient-friendly delivery performance.

[Goindi S, et al., 2014] Binary ethosomal nanovesicles are an advanced ethosomal system where the conventional phospholipid–ethanol vesicle (Figure 2) has been redefined by the incorporation of a second water-miscible alcohol or polyol, such as propylene glycol, alongside ethanol, to form a softer, more deformable and stable carrier for dermal or transdermal application routes. While this modification aims to reduce some constraints of the classical ethosomes, especially the above-mentioned ethanol-related volatility, leakage, and instability, it retains the core mechanism of enhanced skin penetration by bilayer fluidisation and stratum corneum lipid disturbance of ethosomes [Lu J *et al*., 2021].

Recently reported formulation studies show that binary systems can improve vesicle stability, encapsulation efficiency, skin permeation, and show improved therapeutic performance. Binary ethosomal hydrogels have demonstrated sustained release, better bioadhesion and lower irritation potential compared to other ethosomal variants [Apolinário AC et al.,2022] optimized binary ethosomes have also shown higher ex vivo flux and improved in vivo anti-inflammatory efficacy compared to classical ethosomes in topical delivery models.

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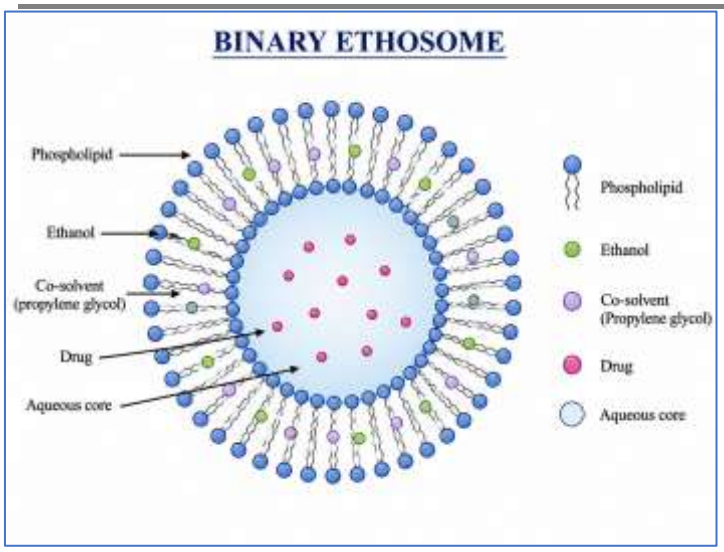

Figure 2: Structure of Binary Ethosomes

Advantages of Binary Ethosomes

- Enhanced skin permeation due to the synergistic effect of ethanol and secondary alcohol, which increases the fluidity of the stratum corneum. [Hameed et al., 2024]
- Higher drug entrapment efficiency compared to conventional liposomes and classical ethosomes. [Patil & Kawale, 2025]
- Improved vesicle flexibility and deformability, which may facilitate penetration through the intercellular pathways of the stratum corneum.
- Suitable for both hydrophilic and lipophilic drugs, allowing versatile drug encapsulation. [Abu-Huwaij & Zidan, 2024]
- Provides controlled and sustained drug release, improving therapeutic efficacy. [Mahajan et al., 2024]
- May enhance local drug deposition and improve cutaneous drug delivery while potentially limiting unnecessary systemic exposure. [Zhan et al., 2024]
- May improve physical stability by reducing some limitations associated with high ethanol content through incorporation of a second alcohol or polyol. [Patil & Kawale, 2025]

Disadvantages of Binary Ethosomes

- Limited long-term stability due to ethanol volatility and possible vesicle aggregation during storage. [Musielak & Krajka-Kuźniak, 2024]
- High ethanol concentration may cause skin irritation or erythema in sensitive individuals. [Abu-Huwaij & Zidan, 2024]
- Preparation requires precise optimization of phospholipid, ethanol, and secondary alcohol concentrations. [Mahajan et al., 2024]
- Scale-up and industrial manufacturing remain challenging because of formulation complexity. [Mahajan et al., 2024]
- Sensitive to storage conditions, requiring appropriate temperature and humidity control. [Abu-Huwaij & Zidan, 2024]

Applications of Binary Ethosomes

- Potential application in atopic dermatitis by enhancing skin penetration and local drug retention. [Patil & Kawale, 2025]

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- Potential application in psoriasis through improved topical delivery of anti-inflammatory drugs. [Hameed et al., 2024]
- Treatment of fungal skin infections by improving dermal delivery of antifungal agents. [Mahajan et al., 2024]
- Acne therapy by enhancing topical delivery of antimicrobial and anti-inflammatory drugs. [Abu-Huwaij & Zidan, 2024]
- Transdermal delivery of analgesics and anti-inflammatory drugs with improved bioavailability. [Zhan et al., 2024]
- Delivery of peptides, proteins, and other poorly permeable drugs across the skin barrier. [Hameed et al., 2024]

Components of Binary Ethosomes

1. Phospholipids

Phospholipids are the key structural components that make up the bilayer membrane of the binary ethosomes. Phosphotidylcholine, soya lecithin, egg, and hydrogenated phospholipids are the most commonly used phospholipids for the preparation of ethosomes. They provide vesicle stability, biocompatibility, and effective drug encapsulation in the surfactants. The choice of phospholipid is based on drug properties, desired entrapment efficiency, and rigidity of the membrane. Soya lecithin and phosphotidylcholine are the most widely used phospholipids in binary ethosomal formulations because these have excellent vesicle forming ability as well as safety (Al-Ameri AAF et al., 2024).

2. Ethanol (Primary Alcohol)

Ethanol is the characteristic component of binary ethosomes that functions as a penetration enhancer. Ethanol plays a variety of roles, that includes increasing the fluidity of both the phospholipid bilayer and the stratum corneum lipids, thereby enhancing deeper skin penetration. Ethanol can also increase the solubility of both hydrophilic and lipophilic drugs, and the vesicles show improved flexibility. However, excessive ethanol concentration might lead to vesicle instability and also increased drug leakage. (Lu J et al., 2021).

3. Secondary Alcohol / Co-solvent

The secondary alcohol is used as a co-solvent and also further enhances the vesicle flexibility and stability, as well as drug permeation. Propylene glycol is the most commonly used secondary alcohol in binary ethosomes as it works in a synergetic manner with ethanol to increase skin penetration and drug retention. Other co-solvents such as glycerol and polyethylene glycol (PEG) may also be used to modify vesicle properties and to enhance the formulation stability. (Lu J et al., 2021).

4. Aqueous Phase

The aqueous phase is usually purified or distilled water that hydrates the lipid film and provides the formation of vesicular structures. It also serves as a dispersion medium of ethosomal suspension and helps to maintain the vesicle integrity and stability.

5. Drug

The therapeutic agent may be incorporated into the binary ethosomes depending upon its physicochemical properties. Drugs of hydrophilic nature are mainly entrapped in the aqueous core, while for the lipophilic drugs, the phosphatidylcholine bilayer incorporates the drug. Binary ethosomes are capable of efficiently delivering both types of drugs over the skin.

6. Optimized Ethanol–Propylene Glycol Ratio

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Ethanol–propylene glycol ratio is an important formulation parameter, and it influences the vesicle size, entrapment efficiency, stability and skin permeation. Although an appropriate ratio depends upon drug and formulation, Wang et al. (2024) reported that an ethanol: propylene glycol ratio of 5:5 (w/w) produced favorable formulation characteristics in their studied system with the smallest particle size, higher entrapment efficiency, improved stability and better skin penetration

Preparation methods of Binary Ethosomes

1) Cold or classic method

In the cold method, lipid and drug are dissolved along with the second alcohol/ co-solvent, such as PG, in ethanol, and then the aqueous phase is added gradually under continuous stirring at room temperature or below. The vesicles form spontaneously as the hydroalcoholic medium provides fluidisation of the lipid bilayer, which assembles without heat stressing (Figure 3). This method is suitable for the use of thermolabile drugs, and it is the most popular and common choice when preparing binary ethosomes with ethanol and PG in practical use due to its simplicity, reproducibility, and fitness in case of further size reduction by means of sonication or extrusion, if required [Wang H et al., 2024].

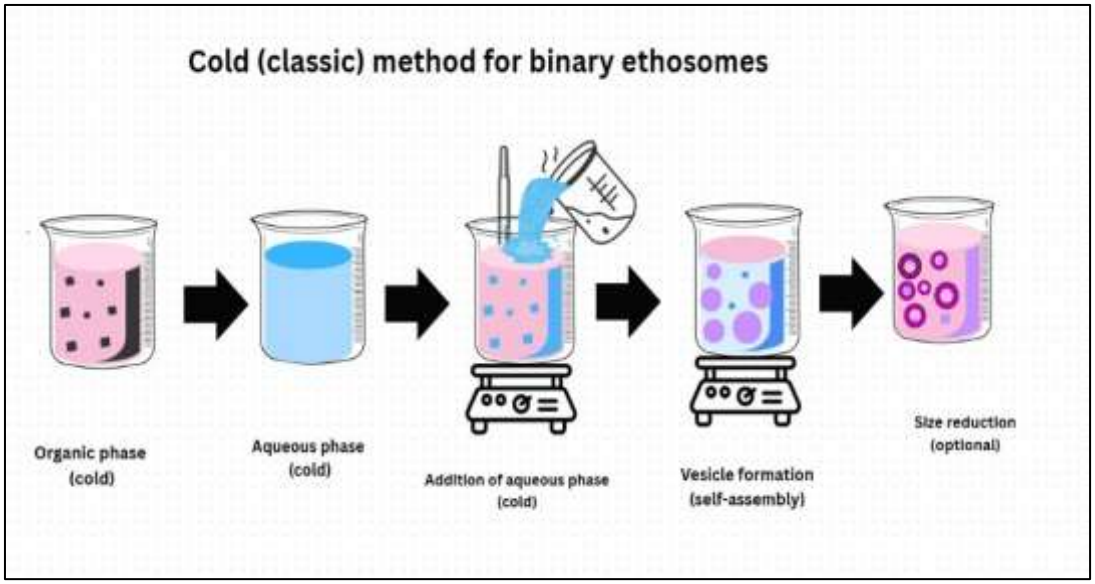

Figure 3: Cold method for Binary Ethosomes

2) Hot method

In the hot method, the lipid and aqueous phases are heated, typically above the phospholipid transition temperature, prior to controlled mixing of the alcohol-containing phase. After homogenization, the system is cooled to facilitate vesicle stabilization. For binary ethosomes, the second alcohol, such as PG, is added with ethanol during the hot processing step. The method is useful when improved lipid solubilization and consistent batch uniformity are needed, but less suitable for heat-sensitive actives. A recent example of a binary ethosome is the meloxicam system, where the product was explicitly prepared by the hot method and yielded nanosized vesicles with good encapsulation efficiency, performance, and good topical [Al-Ameri et al.,2024].

3) Thin-film hydration method

In the thin-film hydration method, phospholipids are dissolved first in a volatile organic solvent, with subsequent evaporation of the solvent, thus producing a thin lipid film on the wall of the flask (Figure 4). Subsequently, the film is hydrated with a hydroalcoholic phase comprising ethanol and a second alcohol or enhancer for binary ethosomes. This method is very useful when precise control of lipid composition is needed and is widely used in laboratory-scale formulation studies due to its ability to generate well-defined vesicles, which are later downsized by sonication or extrusion. While recent papers usually report this method for ethosomes in general,

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it is still one of the established preparation platforms applicable to binary ethosomal systems as well [Lin B et al.,2022]

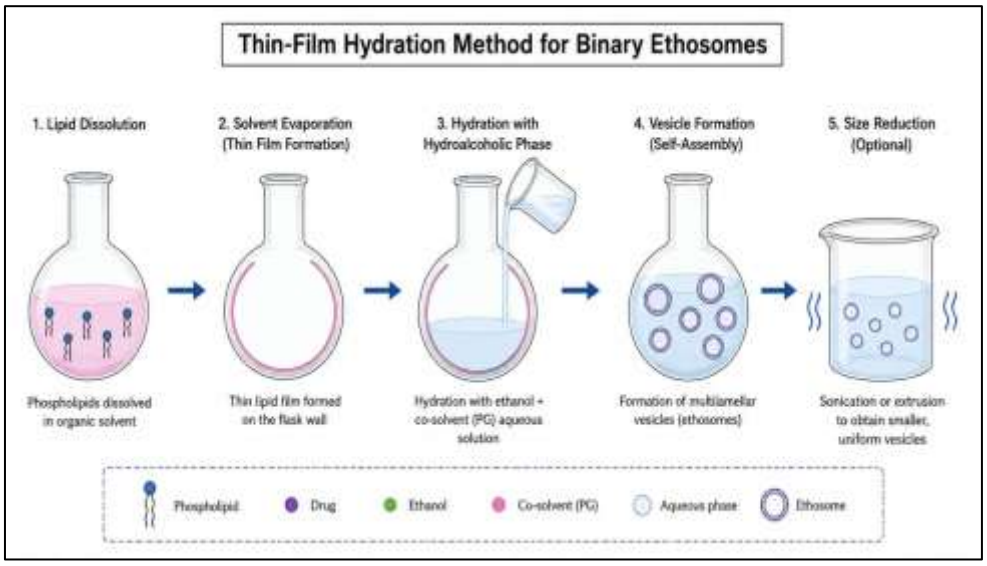

Figure 4: Thin film Hydration method

4) Alcohol/ethanol injection method

The alcohol injection method involves the injection into an aqueous phase while stirring of a lipid solution prepared in ethanol or in an ethanol-containing binary solvent system, and the fast diffusion of the solvent in water causes the spontaneous formation of the vesicles. In the case of binary ethosomal systems, they can be loaded with both ethanol and a second alcohol, or the latter can be arranged between the phases according to the given formulation strategy. This method is attractive as it is simple, scalable and can produce relatively small-sized vesicles. For a recent binary ethosomal hydrogel study, the vesicles that had been produced by an alcohol injection–sonication strategy confirmed that injection-based manufacture is a current effective strategy for binary ethosomes [Xiong Z et al.,2025]

5) Water-dropping method

In the water-dropping method, the aqueous phase is fed dropwise into the lipid–ethanol system under controlled stirring such that vesicles can form gradually as the system is hydrated. In principle, this corresponds to a controlled modification of spontaneous ethosome generation, and is particularly valuable for controlling vesicle size and avoiding rapid aggregation during hydration. While reported recently for ethosomes generally, the principle also pertains to binary ethosomes by replacing the single alcoholic phase with a mixed alcoholic phase, such as a preparation with ethanol plus PG or another compatible cosolvent. The method has currently been acknowledged as a relevant modern approach for producing ethosomal vesicles [Andrade JFM et al.,2025]

Post-formation processing methods used in binary ethosomes

Method	Category	Principle / key step	The main purpose of binary ethosomes	Reference
Sonication	Post-formation processing step	Ultrasonic energy from a probe or bath is applied to preformed vesicles to break larger vesicles into smaller ones and reduce polydispersity.	Rapid nanosizing and improvement of size uniformity, though overheating or oxidative degradation can occur if overused.	[Muslim RK et al.,2022]
Extrusion	Post-formation processing step	The preformed vesicle dispersion is forced through membranes of	Produces a more homogeneous vesicle	[Ong SGM et al.,2016]

		defined pore size, often for multiple passes.	population with controlled size distribution.	
High-pressure homogenization / microfluidization	Post-formation processing step	Very high pressure, shear, turbulence, and cavitation are used to reduce vesicle size and narrow the distribution, including scalable continuous processing	Useful for scalable nanosizing and batch reproducibility in pilot/industrial manufacturing.	Fukuta Tet al.,2023]
Freeze–thaw cycling	Post-formation processing step	Repeated freezing and thawing of a preformed vesicle suspension reorganizes bilayers and can alter lamellarity.	Used to modify bilayer structure, sometimes improve entrapment of hydrophilic cargo, and restructure vesicles.	[Arsiccio A et al.,2020]

Mechanism of Skin Penetration of Binary Ethosomes

Microscopic mechanism of binary ethosomes in skin penetration Binary ethosomes are thought to interact with the skin by two-level mechanism, involving on one hand the lipid barrier where the ethanol content directly interact with the highly ordered SC lipid lamellae, which disrupts their packing hence decreasing the rigid structural barrier, while on the other hand, the phospholipid-based vesicles, as small and deformable structures, can then partition into the loose intercellular spaces and could mediate the transfer of the drug more deeply into the skin. Recent reviews consistently depicted this as an additive to the effects induced by lipid disruption, vesicle flexibility and increased partitioning under skin, rather than a simple consequence of passive diffusion [Balakrishnan P et al.,2024] [Anchan R et al.,2025]. For binary ethosomes, the co-solvent component, which is commonly propylene glycol, is assumed to play a supporting role in this mechanism by contributing to improved stability and flexibility of the vesicles, which, in addition, are implicated in ethanol-associated solvent interactions with SC lipids. There is support for this opinion, which was found in the case of nicotine-loaded binary ethosomes, in which reported that the combination of ethanol/propylene glycol has resulted in the smallest vesicles with the maximal penetration depth and fluorescence intensity inside the skin, reflecting the stronger vesicle-skin interaction and deeper migration across the SC [Wang H et al.,2024].

The second important mechanism of skin penetration is the ethanol-induced fluidization, which has direct impact on the transdermal drug transport. Ethanol can cause the disorganization of the ceramide/cholesterol/fatty-acid arrangement in the SC, to temporary increase the lipids mobility, and to decrease the diffusional resistance, while the flexible binary ethosomal vesicles serve as drug carriers, which plays the role of depositing the drug inside the viable epidermis and dermis or continue the transport across the skin [Almuqbil RM, et al.,2025] There is concrete experimental evidence found in recent binary ethosome studies: they recorded chloramphenicol filled binary ethosomes having attenuated total reflection Fourier transform infrared (ATR-FTIR) spectroscopy and confocal laser scanning microscopy (CLSM) finding that the formulation permits of the passage of the drug through the SC, together with increased flux, permeability coefficient, and skin deposition [Liu RJ,et al., 2025] similarly, meloxicam binary ethosomes lead to significantly higher ex vivo flux than the classical ethosomal type, demonstrating that the binary composition contributes to improved transport efficiency across skin [Al-Ameri et al.,2024]. Collectively, the present available literature supports the view that binary ethosomes contribute to skin delivery improvement by disorganization of the SC lipids, improvement of the vesicles' deformability, and widening or softening of intercellular transport pathways to thereby increase intradermal retention and the transdermal flux.

Therapeutic Applications of Binary Ethosomes in Atopic Dermatitis

Binary Ethosomes as a Targeted Delivery System for Topical Therapy for AD Binary ethosomes are well suited to AD because their ethanol–phospholipid–co-solvent combination tends to at least momentarily loosen up the stratum corneum lipids, while the small sized, deformable vesicles, rather than being dependent on the passive diffusion, favor to deposit more drug in the epidermis and superficial dermis [Balakrishnan P et al.,2024]. In

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AD, this is very beneficial from a therapeutic perspective due to the fact that the disease is based on barrier dysfunction and chronic inflammation, while the currently available topical agents still have drawbacks associated with insufficient penetration, local irritation, and chronic safety concerns [Pinto LM et al,2022]. Regarding corticosteroids, the use of binary ethosomes would lead to a more effective local anti-inflammatory performance at a reduced dose applied by increasing the cutaneous retention and the sustained release at the inflamed sites, which is corroborated by ethosomal studies for anti-inflammatory drugs which demonstrated a superior performance in terms of permeation and retention in skin and an increased pharmacodynamic activity compared to conventional topical vehicles [Sharma G, et al.,2016]. In the case of calcineurin inhibitors such as pimecrolimus and tacrolimus, targeted epidermal drug delivery is the main advantage: a binary ethosomal carrier may lead to an increased drug localization into the diseased skin, while avoiding unnecessary systemic passage, which is useful for steroid-sparing maintenance treatment on sensitive sites such as the face and flexures. [Cheng T et al.,2023].

The same platform is also very promising to non-steroidal approaches like the optimization of crisaborole in future, as binary ethosomes can lead to an improvement of the solubilization of lipophilic drugs, increased intradermal uptake and increased residence time inside the skin tissue. There is evidence from binary ethosomal anti-inflammatory systems that supports this translational potential: a chloramphenicol-filled binary ethosomal hydrogel has shown ATR-FTIR/CLSM findings of the easier passage of the drug through the stratum corneum, in addition to the increased deposition and a substantial in vivo anti-inflammatory benefit, which contributes to the view that binary ethosomes can improve localized cutaneous therapy, which relies on a deeper and more controlled skin penetration [Liu RJ et al.,2025]. Thus, for AD binary ethosomes are best interpreted as a targeted dermal delivery platform: they may allow corticosteroids to act at a lower exposure, improve the local performance of a pimecrolimus or tacrolimus, and potentially enhance the skin-selective delivery of non-steroidal agents such as crisaborole and increase their local skin retention while potentially limiting unnecessary systemic exposure.

Evaluation and Characterization of Binary Ethosomes

Particle Size and Polydispersity Index (PDI)

For a binary ethosomes aimed to be used for dermal or transdermal delivery, an ideal size range of 80–250 nm is preferred, as smaller vesicles tend to increase the skin interaction as well as the homogeneity of the distribution, while a lower PDI generally indicates a more homogeneous particle-size distribution. The recent systems are within this size range, such as meloxicam binary ethosomes (169 nm, PDI 0. 2), and chloramphenicol ethosomes (~98 nm) [Al-Ameri AAF et al.,2024], [Liu RJ, 2025]. Usually, measurements are performed using dynamic light scattering (DLS), after adequate dilution and equilibrium at about 25 °C. Values exceeding 300 nm or PDI higher than 0.4 suggest of an aggregation or poor homogeneity of the formula [El-Shenawy AA et al.,2020], [Andleeb M et al.,2021]

Zeta Potential

The zeta-potential represents the vesicles' stability. It is assumed that values around -25 to -45 mV are optimal, yet values around of ±20 mV could also be accepted as a result of the ethanol mediated stabilization. The presented values of the reported paper are -42.76 mV for the meloxicam systems and -23.5 mV for the chloramphenicol systems [Al-Ameri AAF2024], [Liu RJ, 2025]. The measurements are conducted using the electrophoretic light scattering technique, after dilution with purified or conductivity adjusted mediums. Enhancing the absolute values is in correlation with an enhancement of the electrostatic repulsion and the decrease in the aggregation [El-Shenawy AA,2020], [Ibrahim TM et al.,2019]

Entrapment Efficiency

Entrapment efficiency (EE%) is the value that represents the part of the drug that is encapsulated inside the vesicles. Values above 70% are commonly desired, while from 50–70% may be acceptable depending upon the drug properties. The binary ethosomes showed EE% values of 83. 1% for the meloxicam and ~60. 36% for the chloramphenicol-filled ethosomal [Al-Ameri AAF,2024], [Liu RJ, 2025]. Corresponding systems gave values

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ranging from 48–86% [3]. EE% is calculated by the free drug separation (centrifugation/dialysis), by the vesicles disruption, and drug quantification through HPLC or UV analysis. The triplicate measurements are advised to increase the accuracy [Mousa IA, et al.,2022] [Abdallah MH et al.,2021]

Drug Content

The drug content guarantees the homogeneity and the correct drug filling. The range of the values is commonly between 95–105% of the labelled amount. It is usually expressed as % assay or mg/g formulation, which should display minor fluctuations between batches [Ibrahim et al.,2019] [Al-Ameri AAF et. al.,2024]. The methodology incorporates the vesicle disruption using appropriate solvents, followed by the analysis by HPLC or UV, after the validation of the process. The consistent drug contents are used for the formulation reliability assessment [Andleebe et al.,2021]

Vesicle Morphology (TEM/SEM)

The morphological characterization supplies knowledge about vesicle form and the structure's integrity. The general appearance of the binary ethosomes is spherical, well-defined, and not fused. TEM visualisation of the intact vesicles is a common practice, as the SEM characterization is useful for surface analysis. These techniques support effective vesicle formation and drug encapsulation [Ibrahim et al.,2019] [Parekh K et al.,2021]

***In-Vitro* Drug Release Studies**

The *in-vitro* release studies determine the rate and the intensity of the drug release from the binary ethosomes. Ideal specification of the formulation is represented by controlled and sustained release, and it may achieve from 60–90% of the drug release over a certain time. These experiments are commonly conducted based on the Franz diffusion cell system or dialysis, and with controlled temperature values. The release kinetics is further analyzed according to mathematical models to determine the mechanism of drug release. [Al-Ameri, 2024] [Abd Alhur S J et al.,2025]

***In-vitro* Skin Permeation Studies**

The permeation studies assess the propensity of the binary ethosomal delivery system to release drugs through the skin barrier. Important parameters are the cumulative drug permeation, the flux, the permeability coefficient and the time lag. They are usually implemented in a system containing a Franz diffusion cell based on the dissected animal or human skin. Binary ethosomes generally exhibit better permeation than common formulations due to their flexibility and their ethanol content [El-Shenawy et al., 2020] [Vishwakarma et al., 2025]

Skin Deposition/Retention Studies

The deposition studies are conducted to determine the quantity of drug retained in different layers of the skin, which is very important for targeted treatment of the Ad patients. After permeation studies, the skin is processed for the extraction of the drug content in the stratum corneum and the deeper layers. Higher deposition reflects more effective targeting and effectiveness of the therapeutic effects of the formulation [Ibrahim T M et al, 2019] [Mahajan A et al, 2015].

Stability Studies (Physical and Chemical)

Stability studies aim to determine the ability of the binary ethosomes to maintain their physicochemical properties over time. Important such values are: size of the particles, PDI, zeta potential, drug content, and visual appearance. The formula contain are usually stored under different conditions, such as refrigerated and room temperature, and are periodically evaluated for stability. This examination of these parameters reveals whether the physical and chemical stability is acceptable.

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Comparative table: binary ethosomes vs other vesicular and conventional systems

System	Penetration	Drug loading	Therapeutic efficacy	Reference
Binary ethosomes	Very high; dual-solvent composition increases stratum corneum fluidization, vesicle flexibility, and deeper skin partitioning	High co-solvent helps solubilize drug and improve entrapment	High; better local delivery, sustained action, and lower irritation/systemic exposure potential than simpler systems	Apolinário AC,2022
Classical ethosomes	High; ethanol-rich vesicles penetrate better than liposomes and many conventional topical forms	Good; better solubilization and dermal loading than rigid vesicles	Good; improved skin accumulation and local effect, though usually below optimized binary systems	Lu J, 2021
Transfersomes /elastic vesicles	Very high; ultra-deformable vesicles enable penetration through narrow intercellular pathways, sometimes exceeding ethosomes	Moderate to good; depends on drug and surfactant type	Good to very high; effective skin targeting, though performance is formulation- and drug-dependent	Pena-Rodríguez E et al.,2020
Conventional liposomes	Limited to moderate; often remain near the skin surface compared with ethanol-based vesicles	Moderate; can encapsulate drugs, but skin-directed loading is usually less efficient than ethosomal systems	Moderate to low for deep dermal targeting	Abdulbaqi I, 2016
Conventional creams/gels/solutions	Lowest; relies on passive diffusion with minimal barrier disruption	Lowest effective skin loading; no vesicular carrier to enhance transport/retention	Lowest; often need higher dose/frequency and show less targeted local action	Sharma G, 2016

Limitations and Challenges

The binary ethosomes lead to better topical delivery, yet they have an inherent risk of stability as a consequence of their ethanol and phospholipid-heavy content. The high amount of ethanol in the formula can volatilize during storage, which may affect the vesicle size, membrane fluidity and drug entrapment. At the same time, vesicle fusion, aggregation and release of the drug from the carriers may tend to a reduction of the shelf term and consistency of the batches. An analysis of the existing review of the ethosomes showed the system instability, and drug leakage, the possible irritation of the skin related to the high level of ethanol as a limitation of the formulations, for products that are chronic application for dermatological disease [Lu J, 2021]. The concern of stability is corroborated by studies related to formulation, which showed the strong dependence of the stability on the composition of the formula and the storage conditions. For example, ethosomal dispersions can retain a reasonable stability only with an appropriate balance between the solvent-lipid components, while the encapsulation is often needed to protect the poorly stable active components for a long time [Hallan S S et al.,2020]. The second main difficulty becomes the application on an industrial scale of the preparations that were developed at a laboratory scale. These binary ethosomes are highly sensitive to the variability of formulation variables and process, including the ethanol/co-solvent ratio, lipid concentration, hydration conditions, mixing rate, sonication or homogenization intensity, and temperature. The slight variation in these variables can alter the critical quality characteristics, such as particle size, polydispersity, zeta potential, and entrapment efficiency, leading to problems with the reproducibility of the formulations on a large scale. The recent works based on the framework of Quality by Design (QbD) for the ethosomal products demonstrated the important role of system risk evaluation, and the process optimization for defining a robust design space, to keep the product quality during the developments, and large-scale up [Mohapatra S et al.,2023]. From a more general point of view, the

nanovesicular delivery system still suffer of restrains for scalability, low robustness of loading, and relatively high production cost, which contribute to reducing the commercialization [Jacob S et al., 2025].

From a regulatory point of view, the most important challenges for binary ethosomes become more general for topical nanomedicines: it is expected of the regulator a precise definition of the critical quality characteristic, and the most important evidence of their analytical characterization, long term of the physical and chemical stability, and convincing safety evidence for repeated skin application. For chronic use in the dermatological field, this is one of the key parameters, because the modifications to the formulation during storage can lead to an alteration of the efficacy, or a local irritating effect. In practice, the development must adapt to the consolidated expectation of the pharmaceutical stability, in terms of ICH-oriented long-term, intermediate, and accelerated study, while reflecting the repeatable batches, and the excipients safety for the nanovesicular systems [Gonzalez-Gonzalez O et al.,2022]

Future Perspectives

The binary ethosomes have chances to move to more application in clinical dermatology, as more versatile vesicular systems for to improve the local drug deposition for the disease, such as for acne, psoriasis, hyperpigmentation, fungal disease, and even cutaneous malignancy, especially, when the conventional topical treatments suffer of an insufficient penetration, or the necessity of frequent doses in therapy [Abdulbaqi I, 2016]. The future will reinforce the role of the binary ethosomes with combination therapy, not only with the co-loading of different pharmacologically complementary agents in a single carrier, but also with the introduction of the vesicles in multifunctional gels, which can deliver synergic composition with drugs more effectively to the diseased skin [Lin H M et al, 2020]. This potential translation is also underpinned by the emerging clinically oriented topical application, such as a vesicular delivery system that has been evaluated for melasma use, with improved retention of the drugs and a therapeutic response, pointing to a realistic pathway for treatment of the lesions focused on dermatological applications [Kandil S M et al., 2022]. In long term, the use of the binary ethosomes is particularly alleging for a more personalized dermatologic therapy, due to the ratio of solvents, the composition of lipids, the size of the vesicles, charge and the final dosage of the product, they can perform in relationship to the thickness of the lesions, anatomic positioned, and sensitivity of the skin, make them as in a modular system, that can be used for the patient specific management, rather than one system for all, topical carriers. [Natsheh H et al., 2019]

CONCLUSION

In summary, the binary ethosomal represented an interesting and flexible platform for topical drug delivery with increased skin penetration, enhanced local retention, and possibilities of decreasing the systemic side effects in various dermatologic applications. The versatility of the composition allowed them to optimise in connection with different drugs and skin diseases, thus making it extremely interesting for the development of a new generation of these kinds of dermal delivery systems. However, the successful translation of these systems, in common utilizations, depends upon overcoming their persistence problems, related to the physicochemical stability, the reproducibility on a large scale, the regulatory acceptance and the generation of convincing clinical evidence. Overall, the binary ethosomes locate themselves at the cross of the innovations and the relevant applications, with a potential to turn from an experimental carrier to a safe, effective and customised system for modern dermal delivery.

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