



Ethosomal Gel: A Comprehensive Review of Formulation, Evaluation, and Recent Patents

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ABSTRACT:

Ethosomes, which are soft, flexible phospholipid vesicles with a relatively high ethanol concentration, have better skin-penetration properties and more deformability than conventional liposomes [1,12]. When incorporated into a gel matrix, the resulting ethosomal gel combines the deep-penetrating, dual (hydrophilic and lipophilic) drug-loading capability of the vesicular core with the beneficial spreadability, retention time, and patient acceptance of a semisolid dosage form [3,32]. This paper summarises ten years of ethosomal gel technology research. The main ethosome fabrication techniques (cold method, hot method, ethanol/classic injection, mechanical dispersion/probe sonication, and thin-film hydration) [14], gelling techniques for converting ethosomal dispersions into topical/transdermal gels, and the complete set of physicochemical, in vitro, ex vivo, and in vivo evaluation parameters used to characterise these systems are all covered [3,7]. The shift in industrial interest from simple high-ethanol vesicle compositions to low-irritation, low-ethanol platforms, ceramide-modified vesicles, and extension of the ethosome concept to non-dermal routes like the eye is demonstrated by a dedicated section that examines patents granted or published over the past ten years [21,22,23,24]. NSAIDs, antiviral and antifungal medications, anticancer medications, hormonal In addition to the ongoing issues of ethanol-related irritation, physical stability, and scale-up, agents, peptides, and cosmeceutical actives are summarised [7,20,28,33,34]. The next generation of ethosomal gel products is being shaped by emerging directions (transethosomes, nanoethosomes, binary ethosomes, and hybrid nanocarrier–gel systems) [16].

Keywords: vesicular carriers, penetration enhancers, ethosomes, ethosomal gel, transdermal medication administration, nanotechnology, and patents.

1. Introduction

Transdermal/topical administration is an appealing, non-invasive method that avoids gastrointestinal degradation, avoids hepatic first-pass metabolism, and increases patient compliance in comparison to oral dosing [10,17]. The skin is the largest and most accessible organ in the human body. The stratum corneum (SC), the epidermis's topmost, densely packed layer of keratin and lipids, is the main barrier to this pathway since it is purposefully designed to keep out exogenous chemicals. Only medications with a limited range of physicochemical characteristics (low molecular weight, moderate log P, low melting point) passively penetrate the SC in amounts that are therapeutically significant [13].

By utilising the lipid architecture of the skin, vesicular carriers were created to get past this obstacle. The first of these carriers, liposomes, are mainly restricted to the top layers of the SC and offer very little transdermal or deep-skin flux [13]. This restriction led to the creation of transfersomes, which are elastic and ultra-deformable vesicles (surfactant edge-activator).

based) and ethosomes (based on ethanol), which can fit through intercellular channels that are much smaller than their own diameter [13,16]. Phospholipids, a relatively high concentration of ethanol (usually 20–45% w/w), and water make up ethosomes, which were first described by Touitou and colleagues in the mid-1990s [1,2,12]. Since then, it has been demonstrated that ethosomes significantly outperform conventional liposomes and hydro-alcoholic drug solutions in both skin deposition and transdermal flux for a variety of small and macromolecular drugs [9,18,19].

Due to their poor retention at the application site, possible run-off, and difficult dosing, plain ethosomal dispersions—which are low-viscosity colloidal suspensions—are not recommended for direct topical application [17]. An ethosomal gel, a semisolid formulation that maintains the improved permeation behaviour of the vesicles while offering controlled application, extended skin contact time, and aesthetically acceptable rheology, is produced by incorporating ethosomes into a gel base (most frequently Carbopol/carbomer, hydroxypropyl methylcellulose, or Poloxamer 407) [3,8,32]. Analgesics and NSAIDs, antifungals, antivirals, anticancer agents, cardiovascular and antidiabetic medications, peptides/proteins, and cosmeceutical actives are just a few of the therapeutic categories for which ethosomal gels have been studied over the past ten years [4,7,20,28,30,34]. At the same time, ethosomal gels have drawn increasing patent activity aimed at enabling industrial-scale manufacturing [21,35].

The objective of this review is to offer a single, organised reference on the following topics: (i) ethosome composition, classification, and mechanism of action; (ii) ethosome fabrication and gel formulation techniques; (iii) the standard panel of evaluation parameters applied to ethosomal gels; (iv)

representative therapeutic applications reported in the last ten years; and (v) an analysis of patents filed or granted over the last ten years (2016–2026), concluding with the main obstacles and future directions for this delivery platform.

2. The Skin Barrier and Rationale for Vesicular Carriers

Corneocytes embedded in a highly organised, multilamellar lipid matrix made primarily of ceramides, cholesterol, and free fatty acids make up the stratum corneum [13]. This "brick-and-mortar" configuration is the rate-limiting stage for percutaneous absorption and is in charge of the skin's barrier function. To get over this obstacle, physical techniques (iontophoresis, microneedling, sonophoresis), chemical penetration enhancers, and carrier-based strategies (liposomes, niosomes, transfersomes, ethosomes, solid lipid nanoparticles, and nanostructured lipid carriers) have all been investigated [13,16]. Because the ethanol inside the vesicle simultaneously (a) fluidizes the vesicle's own phospholipid bilayer, providing softness and deformability, and (b) disrupts the packing of SC intercellular lipids, temporarily increasing their fluidity, ethosomes occupy a unique niche among carrier-based strategies [9,17]. The main reason ethosomes perform better than ordinary liposomes in terms of both the depth and the amount of skin penetration is thought to be the "ethosomal effect," which works in tandem with the traditional "ethanol effect" [15,19].

3. Ethosomes: Structure, Composition, and Classification

3.1 Structural Features

Ethosomes are soft, unilamellar or multilamellar vesicles with an aqueous-ethanolic core surrounded by a phospholipid bilayer [12]. Differential scanning calorimetry (DSC), electron microscopy (TEM/SEM/cryo-TEM), and ³¹P-NMR have all been used to demonstrate their general vesicular architecture [12]. Depending on the phospholipid and ethanol concentration as well as the manufacturing technique used, vesicle size can vary from tens of nanometres to the low micron scale [11,12].

3.2 Composition

The principal constituents of an ethosomal system are [10,11]:

- Phospholipids, such as hydrogenated soy lecithin, dipalmitoyl phosphatidylcholine, or soy or egg phosphatidylcholine, are commonly utilised at 0.5–4% w/v; they create the vesicular bilayer and are the main factor influencing the entrapment efficiency for lipophilic medicines [7,14]
- Ethanol—used at 20–45% w/w as the signature penetration enhancer and fluidiser of the SC lipids and vesicle membrane; ethosome size typically decreases as ethanol concentration rises, but too much ethanol can also result in vesicle leakiness and decreased entrapment of hydrophilic drugs [11,17].
- Water: the continuous watery phase that disperses the vesicles [12]

To create binary ethosomes with even higher flux and better vesicle stability, co-solvents/penetration enhancers as propylene glycol or isopropyl myristate are commonly added (5–20%) [11,14].

- Charge-inducing chemicals are utilised to modify zeta potential and physical stability, such as dicetyl phosphate (which imparts negative charge), stearylamine (which gives positive charge but can increase vesicle size and minimise entrapment), and cholesterol (which stabilises membranes) [11].

- Edge activators/surfactants: Tween 80, Span 80, sodium cholate, or comparable surfactants combine the elasticity processes of transfersomes and ethosomes to transform conventional ethosomes into transethosomes [14,16].

3.3 Types of Ethosomal Systems

- Classical ethosomes — phospholipid, ethanol, and water only [1,12].
- Binary ethosomes, which combine the traditional ethosome composition with an additional alcohol or glycol (often isopropyl alcohol or propylene glycol) to enhance stability and flux [11,14].
- Transethosomes—which combine ethanol with an edge activator/surfactant or penetration enhancer—are said to exhibit better skin penetration and deformability than traditional ethosomes [14,16].
- Nanoethosomes: ethosomal systems designed to have a smaller, more consistent nanometric size range (usually through high-pressure homogenisation or sonication), which is frequently linked to better skin retention and flow [9,16].

4. Advantages and Limitations

4.1 Advantages of Ethosomes over Conventional Liposomes

- Higher transdermal flux and significantly deeper skin penetration as a result of the combined actions of ethanol and vesicle fusion [9,19].
- The capacity to capture peptides and other macromolecules, as well as hydrophilic and lipophilic medications, in a single carrier [3,20].
- Easy, repeatable, low-energy (cold/hot) preparation techniques that are easily scalable in comparison to some other nanocarrier systems [3,14].
- Better chemical and physical stability than simple liposomes, which are vulnerable to hydrolytic and oxidative destruction [16].
- Compared to injectable or oral alternatives for the same medicine, non-invasive administration has the potential for both localised cutaneous and systemic (transdermal) therapeutic effects, as well as increased patient compliance [10,17]

4.2 Limitations

- Chronic or high-dose application of a high ethanol concentration might result in skin irritation, dryness, or disruption of the barrier, especially in sensitive skin [15,16].
- One justification for adding ethosomes to a gel matrix is that ethanol volatility can jeopardise the dispersion's long-term physical stability (vesicle aggregation, fusion, or drug leakage) [8,16].

Some hydrophilic medicines have a comparatively lower entrapment efficiency than some stiff vesicular systems, necessitating formulation optimisation (e.g., factorial design) [4].

- Recent patent activity has focused on the difficult task of scaling up laboratory thin-film hydration techniques to industrial manufacturing [21].

5. Methods of Preparation of Ethosomes

5.1 Cold Method

The most straightforward and popular method for preparing ethosomes on a laboratory scale is the cold method [14]. To limit ethanol evaporation, the phospholipid (and, if applicable, surfactant/penetration enhancer for transethosomes or binary ethosomes) is dissolved in ethanol (or an ethanol/propylene glycol mixture) at room temperature while being constantly stirred in a covered vessel [14]. The organic phase is then mixed with the aqueous phase (water, buffer, or regular saline, which may contain the medicine if it is hydrophilic) in a fine stream, dropwise, or with a syringe pump at a regulated rate while being continuously stirred at 700–2000 rpm [14]. In order to minimise vesicle size and restrict the size distribution, the resultant dispersion is usually further homogenised by probing sonication or extrusion before being refrigerated [3,6].

5.2 Hot Method

The hot approach involves first dispersing the phospholipid in water and heating it (usually to about 40 °C) while stirring until a transparent, colloidal dispersion is produced [3,5]. The aqueous phospholipid dispersion is mixed with ethanol (and propylene glycol, if needed) after each is heated to the same temperature [5]. Before mixing, the medication is dissolved in the ethanol if it is lipophilic and in the water phase if it is hydrophilic. After stirring the liquid until a uniform ethosomal dispersion forms, it is cooled to room temperature [3,5].

5.3 Classic (Ethanol Injection) Method

A variation that is closely related to the cold method but emphasises the injection/addition rate as a crucial process parameter for controlling vesicle size [14] involves injecting the ethanolic phospholipid solution directly into the aqueous phase under continuous, high-speed stirring, allowing spontaneous vesicle self-assembly.

5.4 Mechanical Dispersion and Probe Sonication

To decrease vesicle size, narrow the polydispersity index, and enhance dispersion homogeneity, mechanical dispersion techniques such as vortexing, high-speed homogenisation, or probing sonication are used to pre-formed lipid films or coarse ethosomal dispersions [34]. Because too much sonication can cause vesicle rupture and drug leakage, sonication timing and amplitude are optimised [7].

5.5 Thin-Film Hydration Method

A thin lipid film is deposited on the flask wall by dissolving the phospholipid (and cholesterol, if applicable) in an organic solvent and then evaporating it under low pressure (rotary evaporation). This film is then hydrated with the drug-containing hydro-ethanolic phase while being stirred to create

ethosomal vesicles, which can later be sonicated or extruded to the required size. For instance, repaglinide and loxoprofen ethosomes have been made using this technique [4,7].

5.6 Formulation Optimisation

Design of Experiments techniques, such as 3^2 factorial designs, Box–Behnken designs, and response surface methodology, are frequently used to determine the ideal formulation from a small number of experimental runs, minimising trial-and-error and enabling statistically defensible process/formulation understanding because vesicle size, entrapment efficiency, and drug release are simultaneously influenced by phospholipid concentration, ethanol concentration, and (where applicable) surfactant or penetration-enhancer concentration [4,7,20].

6. Formulation of Ethosomal Gel

By dispersing or mixing it with a pre-made hydrogel foundation, the optimised ethosomal dispersion is transformed into a gel [3,8,32]. Carbopol 934/940/974 (carbomer), hydroxypropyl methylcellulose (HPMC), sodium carboxymethyl cellulose, and Poloxamer 407 are frequently used gelling agents [29, 34]. Carbopol 940 is frequently chosen over Carbopol 934 when a transparent, aesthetically pleasing gel is desired, whereas Carbopol 934 typically yields a more opaque, milky-white gel [8]. Carbopol gels are normally made by dispersing the polymer in water with constant stirring, letting it hydrate/swell, and then neutralising with triethanolamine to achieve the target viscosity and clarity. Following purification, the ethosomal dispersion (or isolated ethosomes) is added to the gel basis under Add any additional humectants, preservatives, or permeation enhancers needed for the final product, and mix gently to prevent vesicle disruption [34]. Compared to a low-viscosity vesicular suspension applied directly to the skin, the resulting semisolid offers greater retention at the site of application, ease of dosing, and better patient acceptability while maintaining the improved permeation profile of the parent ethosomal dispersion [8,32].

7. Evaluation of Ethosomal Gel

7.1 Evaluation of the Ethosomal Dispersion (Pre-Gel)

- Dynamic light scattering (DLS/Zetasizer) measures vesicle size, size distribution, and polydispersity index (PDI); smaller, more homogeneous vesicles are typically linked to better skin penetration [7, 8].
- Zeta potential: This measures colloidal stability and surface charge; a sufficiently high positive or negative zeta potential (usually greater than ± 20 –30 mV) denotes a decreased propensity for vesicle aggregation [4,7].
- Entrapment/encapsulation efficiency: measured by UV spectrophotometry or HPLC after the untrapped medication has been separated (by ultracentrifugation, dialysis, or minicolumn centrifugation) [4,30].
- Vesicle morphology is determined using transmission electron microscopy (TEM), scanning electron microscopy (SEM), field-emission SEM (FESEM), or cryo-TEM; ethosomes are usually spherical, nanometric, unilamellar or multilamellar vesicles [4,5,7].
- Drug content/percent drug loading: measures the amount of drug present per dispersion weight or volume [4].
- Differential scanning calorimetry (DSC) and Fourier-transform infrared spectroscopy (FTIR) are employed to verify drug-exipient compatibility and identify any drug-lipid interactions or changes in the drug's crystalline or amorphous state within the vesicle [28, 34].

7.2 Evaluation of the Finished Ethosomal Gel

- Physical appearance and homogeneity: colour, clarity/opacity, and lack of phase separation or grittiness are evaluated visually [8,34].
- pH: tested using a calibrated pH meter; to reduce the risk of irritation, formulations are usually aimed at a pH that is near to skin-compatible (around 5.5–7) [5,34].
- Viscosity and rheological behaviour: tested at various shear rates using a Brookfield or cone-and-plate rheometer, the majority of ethosomal gels show pseudoplastic (shear-thinning) activity, which is ideal for application and spreading [8].
- Spreadability—measured using parallel-plate techniques to determine application ease or by measuring the diameter of gel spread under a fixed weight/time [34].
- Extrudability: assesses how easily the gel can be released from its tube or container [3].
- Uniformity of drug content: ensures uniform dosage throughout the batch [4].
- In vitro drug release is usually carried out using Franz diffusion cells with a synthetic membrane (such as dialysis or cellulose acetate). Release data are fitted to kinetic models (zero-order, first-order, Higuchi, Korsmeyer-Peppas, or Weibull) to clarify the release mechanism; it has been demonstrated that many ethosomal gels follow first-order or diffusion-controlled (Higuchi/Weibull) kinetics [4,8,20].

- Ex vivo permeation tests, which produce steady-state flux, permeability coefficient, enhancement ratio, and lag-time data in comparison to a plain drug solution or traditional gel, are carried out over excised animal (often rat, mouse, or pig) or human skin mounted on Franz diffusion cells [7,29].
- Skin retention/deposition studies: these are especially important for dermatological indications since they measure the amount of drug retained within skin layers (usually through tape-stripping or skin homogenisation) as an indicator of localised depot development [7].
- Skin irritation studies: Given the ethanol content of ethosomes, it is particularly crucial to demonstrate formulation safety using Draize-type scoring in animal models or rebuilt human epidermis experiments [29, 30].
- Stability studies: carried out under ICH-type settings (e.g., 4 °C, 25 °C/60% RH, and 40 °C/75% RH) over predetermined intervals, tracking vesicle size, entrapment efficiency, pH, viscosity, and drug content for indications of drug leakage, degradation, or aggregation [14].
- In vivo pharmacodynamic/pharmacokinetic studies: carried out in suitable animal models to verify therapeutic efficacy (such as anti-inflammatory, antifungal, or anticancer activities) and/or to produce a systemic pharmacokinetic profile in comparison to oral or other reference routes [20,30,33].

8. Therapeutic Applications Reported in the Last Decade

- Over the past ten years, a variety of drug classes have been developed as ethosomal gels in the literature, demonstrating the platform's versatility:
 - NSAIDs and analgesics: piroxicam and loxoprofen ethosomal gels have demonstrated enhanced ex vivo penetration and in vitro release in comparison to free drug; loxoprofen ethosomes have achieved an augmentation ratio in apparent permeability that is many times greater than a hydro-alcoholic solution [5,7].
 - Antidiabetic agents: Repaglinide ethosomal gel, which was improved by factorial design, produced vesicle sizes of about 199 nm, entrapment effectiveness of more than 92%, and prolonged transdermal drug release, providing an alternative to oral dosage for long-term glycaemic management [4].
 - Miconazole nitrate and ketoconazole ethosomal systems, which have been expanded to an ocular trans-ethosomal formulation, are antifungal drugs that have shown improved penetration and, in the case of the eye, platform adaptability beyond skin [5,22].
 - Antiviral applications: Using nano-vesicular phosphatidylcholine-based gel delivery for a repurposed small molecule, an ethosomal gel of dimethyl fumarate was studied for topical therapy of herpes simplex virus type-1 (HSV-1) lesions [28].
 - Oncology: studies in chemically induced skin cancer animal models have examined the topical and localised anticancer effects of ethosomal gels loaded with mitoxantrone, metformin, and brucine; metformin ethosomal gel demonstrated notable topical anti-tumor activity in mice [6,30,33].
 - Antihypertensive/cardiovascular medications: ethosomal/nanoethosomal transdermal systems for losartan and valsartan have demonstrated good in vitro release and high entrapment efficiency, with the goal of improving pharmacokinetic profiles in comparison to oral delivery [9].
- Peptide/protein delivery: Using an orthogonal-design-optimized ethanol infusion approach, an ethosomal gel of thymosin β -4, a macromolecular wound-repair peptide, was created to overcome the typical poor membrane permeability of big peptides [20].
- The platform's wide application in both prescription dermatology and cosmetic science is demonstrated by dermatological/cosmeceutical actives, such as cryptotanshinone (anti-acne), retinyl palmitate (acne vulgaris), epigallocatechin-3-gallate/EGCG (antioxidant/anti-aging), and SabiWhite-loaded ethosomal gels (anti-inflammatory, active against multidrug-resistant pathogens) [24,29,31,34].
 - Hair-loss treatment: One of the first patented applications aimed at enhancing transdermal distribution for androgenetic alopecia was an ethosomal gel containing finasteride [26].

9. Recent Patents on Ethosomal Gel Technology (Last 10 Years)

Three general trends can be seen in the patent activity surrounding ethosomes over the past ten years: (i) attempts to lower the ethanol concentration needed for effective vesicle formation, thereby reducing irritation potential while maintaining transdermal performance [21]; (ii) expansion of the platform to new administration routes (e.g., ophthalmic) and new categories of actives (peptides, ceramide-based actives) [22,23,27]; and (iii) ongoing filings of ethosomal gel compositions specific to specific therapeutic or cosmetic indications [26,35]. Table 1 summarises representative patents and patent families [24, 35].

Table 1: Typical ethosome and ethosomal gel technology patents (about from 2016 to 2026)

Patent / Publication No. (Inventor(s), Year)	Title	Key Disclosure / Significance
US 11,452,679 B2 / US 2021/0030640 A1 (Kim & Jang, 2022)	Method of preparing bioactive substance-encapsulated ethosome; ethosome and cosmetic composition	Discloses a low-ethanol-content (0.1–20 wt%) ethosome manufacturing process addressing high skin irritation and low encapsulation efficiency of conventional high-ethanol ethosomes; includes wrinkle-improving peptide (palmitoyl pentapeptide/ acetyl hexapeptide) nanoethosome examples
WO 2019/004563 A1 (2019)	Method of preparing bioactive substance-encapsulated ethosome, ethosome composition, and cosmetic composition	International (PCT) filing corresponding to the above technology; broadens claims to varied bioactive/cosmetic actives encapsulated in low-ethanol ethosomes
US 11,285,148 B1 (Ahmed, Alzahrani, Alhakamy & Felimban, 2022)	Ketoconazole ophthalmic preparations containing trans-ethosomal drug nanoparticles	Extends the trans-ethosome concept beyond skin to ophthalmic delivery of an antifungal agent, illustrating platform versatility
CN 115919680 A (2023)	Preparation technology and application of composite ceramide liposomes/ethosomes	Covers ceramide-modified lipid vesicles (including ethosomal variants) aimed at improving skin-barrier compatibility and moisturization
US 11,660,268 B2 / US 11,219,601 B2 / US 11,246,830 B2 (2019 PCT family)	Emulsified gel composition	A transdermal emulsified-gel platform (claiming priority to a 2018 Japanese application) relevant to gel-based vesicular carriers, addressing flow/spreading limitations of low-viscosity lotions versus gels
CN 1555804 A	Finasteride ethosome gel preparation	Early Chinese patent describing an ethosomal gel of finasteride (vesicle size 50–800 nm) using soybean phospholipid/lecithin and ethanol–propylene glycol as the alcohol phase, intended to enhance transdermal delivery for androgenetic alopecia
US 2024/0279275 A1 (2024)	Hexapeptide derivative and cosmetic/pharmaceutical composition	Lists ethosomes among approved carrier/sustained-release systems for a novel peptide active, reflecting continued patent-level recognition of ethosomes as a standard delivery vehicle in cosmetic patents
Korean Patent Publication 10-2014-0101570 (cited prior art in later filings)	Ethosome composition containing <i>Persicaria hydropiper</i> L. extract	Representative of numerous herbal-extract ethosome patents filed in the decade under review; frequently cited as prior art establishing high-ethanol (>20%) baseline ethosome formulations

The explicit identification of high ethanol content (20–40%) in earlier art, including foundational compositions such as US 5,540,934 and Korean Publication 10-2014-0101570, as a source of skin irritation and manufacturing limitation (unsuitability of thin-film hydration for mass production), is a recurrent theme throughout the 2019–2022 Korean-origin patent family (WO2021/0030640A1 and US11,452,679B2) [21]. An industry-wide shift toward gentler, more scalable ethosome chemistries is indicated by these later filings, which claim ethosome formulations with significantly lower ethanol content (as low as 0.1–20 wt%, preferably 2–8 wt%) while maintaining nanometric vesicle size and sufficient transdermal absorption [21]. Additionally, the patent family for emulsified gel composition (US11,660,268B2, US11,219,601B2, US11,246,830B2), It is an example of the wider industrial interest in gel-based transdermal platforms that handle the practical problem of low-viscosity vesicular dispersions running off the skin after application, even though it is not just an ethosome patent [25]. The trans-ethosome concept was extended to ocular delivery (US11,285,148B1) [22], and "ethosome" is still an acknowledged carrier choice in general cosmetic/pharmaceutical composition patents

(eg.-US2024/0279275A1) [27] further show that, 10 years later, ethosomes are no longer considered a merely experimental technology but rather an established, patent-referenced delivery platform [24,35].

10. Challenges and Future Prospects

- A number of recent low-ethanol patent applications specifically address the formulation difficulty of balancing ethanol content to ensure sufficient vesicle deformability and transdermal flux while minimising skin irritation and barrier disruption [15,21].
- Strong stabilisation techniques, suitable packing, and, frequently, integration into a gel matrix particularly to address these problems are necessary for long-term physical stability (vesicle aggregation, fusion, or ethanol evaporation during storage) [8,16].
- Patent interest in alternate, more scalable preparation procedures is driven by the difficulty of scaling up from bench-scale cold/hot techniques or thin-film hydration to repeatable, GMP-compliant industrial manufacturing [21].
- Clinical translation of many academically published ethosomal gels is still restricted in comparison to the volume of preclinical publications, and regulatory procedures for nanocarrier-based topical/transdermal medicines require comprehensive characterisation and toxicity assessment [14,18].
- Hybrid systems (transethosomes, nanoethosomes, ceramide-modified ethosomes), combination with physical enhancement methods like microneedling, and application of ethosomal gels to macromolecular peptide/protein therapeutics and non-dermal routes (ophthalmic, and possibly mucosal) delivery are examples of emerging directions [16,20,22,23].

11. Conclusion

For improved transdermal and topical drug administration, ethosomal gels are an established, thoroughly studied, and increasingly patent-protected vesicular platform [3,9,32]. Over the past ten years, this technology has consistently improved skin penetration, drug entrapment, and controlled release across a wide range of therapeutic classes by combining the ethanol-driven deformability of the ethosome with the advantageous handling and retention properties of a semisolid gel base [4,7,20,28,30]. Ethosomal gels are positioned as a promising and commercially relevant delivery system for future dermatological, systemic transdermal, and cosmeceutical products due to ongoing improvements in preparation techniques, formulation optimisation through statistical design, and the recent patent-driven shift toward lower-ethanol, more scalable, and more versatile ethosomal compositions [21,24,35].

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