

Ethosomal Delivery Systems for Phytoceuticals: A Review of Enhanced Penetration and Therapeutic Efficacy in Topical Infectious Diseases

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ABSTRACT

The growing global epidemiological burden of topical infectious diseases, aggravated by antimicrobial resistance (AMR). The limitations of the traditional therapies require new sustainable ways that increase local efficacy but reduce the systemic toxicity. Bioactives of phytoceutical plants primarily include phenols, flavonoids, terpenoids, alkaloids, peptides and sulfur compounds. These compounds exhibit multi-target antimicrobial activity, such as membrane disruption, enzyme inhibition and biofilm quenching. Placing them as viable alternatives to other diseases like impetigo, burns, acne and psoriasis. However, their poor solubility, volatility and impermeability of the stratum corneum reduces their bioavailability and stability. Therefore, their biochemical characteristics that decrease their effectiveness are low solubility, volatility and poor permeability across stratum corneum and low dermal uptake less than 10% in ex vivo models. The category of lipid nanovesicles containing 20-50% ethanol as a substitute to avoid these problems is known as ethosomal systems due to their high fluidity, deformability and follicular routing. These systems improve the skin penetration by 3-6 times and stay in skin 40-60% longer. In this review, the phytoceutical classifications, mechanisms and barriers are discussed with the fundamentals of ethosomal systems. The major benefits are solubility, release control and preclinical efficacy. Clinical translation is still in its infancy, as Phase I/II pilots (n<50) are tolerable, but there is a lack of Randomized Controlled Trials (RCTs), scalability and ethanol irritancy. In future, these gaps may be bridged with Phase III trials that will initiate AMR-resistance patient-centric dermatological therapies integrating natural compounds with nanotechnology-based delivery systems.

Keywords: *Ethosomes; Phytoceuticals; Topical infections; Transdermal delivery; Antimicrobial resistance; Skin penetration*

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1. INTRODUCTION

1.1 Burden of topical infections and limitations of conventional therapies

Topical infections pose a substantial burden on global health. They range from conditions like skin abrasions, burns to eye or ear issues. These challenges play a considerable pressure on health systems worldwide. In burn injuries, blood circulation is often compromised, and pathogens then grow faster than healing cells to cause an infection. The condition is worsened with increase in cases of folliculitis and acne also.[1, 2].

AMR is the primary cause of this crisis globally. The WHO's 2025 Global Antibiotic Resistance Surveillance Report documents one in six bacterial infections resistant to standard agents. It is based on 23 million records from 104 countries, with skin/soft tissue infections showing 20-30% resistance rates in low-income regions. Direct AMR deaths reached 1.27 million in 2019, associated with 4.95 million more. The projections estimate upto 39 million direct fatalities between 2025-2050, including 15-20%

from topical sources like impetigo in humid tropics. In England, resistant bacteraemia cases surged 9.3% since 2023 (to 20,470 in 2024). Despite a 2% antibiotic use decline from 2019 levels-use dropped post-2020 but rebounded 1.5% in 2024 amid hospital pressures. Distance from clinics fosters self-medication, with 40-60% inappropriate antibiotic use for viral colds/flu, as per a 2025 crisis review-yielding >10,000 annual AMR deaths since 1990 and prolonged illness/costs in underserved areas [3-5].

Conventional therapies are falling short. Topical therapies offer localized drug delivery with lower doses in the overall process that enhance compliance, reduce systemic side effects and also reduce risks of resistance. Clinical trials show that few results are accurate, site concentrations are difficult to estimate for most, and the pharmacokinetics (PK) data remain confidential. The trouble is exacerbated by the fact that the low-education groups overlook risks due to a lack of awareness. They often use leftover medicine, self-medication, and guidance

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by unprofessional, worsen the issue. These issues highlight the urgent need to alter the testing and implementation of these medications. Otherwise, the resistance may limit the future options [1, 2].

1.2 Role of phytochemicals in Antimicrobial Dermatology

Phytochemicals encompassing bioactive plant-derived compounds like phenolics, flavonoids, terpenoids, alkaloids and essential oils play a pivotal role in antimicrobial dermatology. Since these compounds offer a broad-spectrum activity against bacterial, fungal and viral skin pathogens with low potential resistance and side effects as compared to synthetic agents. These compounds target multiple microbial cellular including cell membrane disruption, enzyme inhibition and biofilm interference making them suitable for treatment of conditions like acnes, atopic dermatitis, psoriasis, wounds and mycoses. Their integration into topical formulation enhance skin barrier repair, reduce inflammation and promote healing. It positions them as the sustainable alternatives amid rising AMR [6-8].

Key Mechanisms and Therapeutic Applications

Phytochemicals have diverse mechanism including cell wall disruption, protein synthesis inhibition:

Membrane and Cell Wall Disruption: Phenolics (e.g., flavonoids such as quercetin and Epigallocatechin-3-Gallate in green tea) and terpenoids (e.g., terpinen-4-ol in lavender oil) are incorporated into microbial lipid bilayers, increasing permeability and cause lysis in Gram-positive (e.g., *Staphylococcus aureus*) and Gram-negative (e.g., *Escherichia coli*) bacteria as well as in fungi (e.g., *Candida albicans*). This reduces the colony formation and also helps in effective control over systemic toxicity.

Enzyme and Protein Synthesis Inhibition: Alkaloids (e.g., berberine from *Berberis* spp.) and polyphenols (e.g., curcumin from *Curcuma longa*) bind with ribosomal subunits or key enzymes (e.g., topoisomerases), preventing protein and nucleic acid synthesis. In

dermatology, this suppresses the virulence of *Propionibacterium acnes*, which causes acne, and the MRSA biofilms.

Antioxidant and Anti-Inflammatory Synergy:

Polyphenols (e.g., tannins in *Hamamelis virginiana*) scavenge reactive oxygen species (ROS), modulating oxidative stress in infected tissues and preventing quorum sensing to destroy biofilms. Applications include eczema and psoriasis, where they prevent IL-6/TNF- α flare along with antimicrobial action [6-8].

1.3 Ethosomal Delivery System for Nanovesicles

Ethosomes are novel lipid based nanovesicles that have their own advantages over their nanoparticles especially in the delivery of drugs transdermally. Their high ethanol concentration is a major advantage that enhances their compliance and adaptability in changing shape so that they can move into the cells without any leakage of the drug used. This selectivity of ethanol also helps to increase the fluidity of the lipids of the skin cell membranes that facilitate the increased penetration of the ethosome nanostructures. The main advantage of high ethanol content is its capability to improve the encapsulation of a broad range of active agents, such as hydrophilic (water-soluble) and lipophilic (fat-soluble) active agents. This is the advantageous feature particularly in the inclusion of natural extracts that are chemically heterogeneous. In addition, since the extracts are likely to be extracted in ethanol based solutions, direct addition to ethosomes will prevent any costly and time consuming procedures that might otherwise be needed to purify the solvents. After the initial ethosome formulations were successful, today, studies are in progress to come up with the development of improved formulations like invasomes and transethosomes, which can further provide better drug encapsulation and delivery properties. This is a summary of the present state of the ethosomes research with a focus on their use in providing natural extract encapsulation and delivery to the skin [9-14].

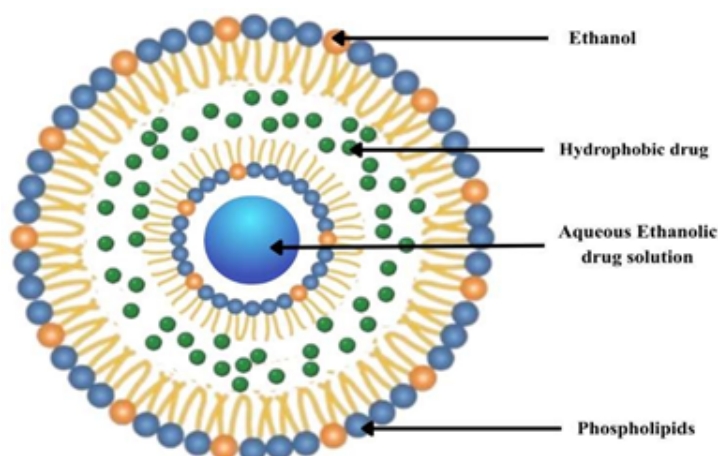


Figure: Ethosome structure

1.4 Methodology of the Review

This analysis consolidates research on ethosomal formulations integrating the targeted actions of phytoceuticals such as membrane disruption, enzyme inhibition and biofilm breakdown with nanotechnology to address topical infections (impetigo, burns, acne, psoriasis) amid rising antimicrobial resistance that compromises the effectiveness and penetration of standard treatments. It outlines the impact of dermatoses evaluates treatment limitations and examines various phytoceutical categories (phenolics, flavonoids, terpenoids, alkaloids, peptides, sulfur compounds) for their effectiveness, against *S. Aureus*, *P. Aeruginosa* and *C. Albicans*. Examining obstacles and stability limitations affecting ex vivo bioavailability it outlines ethosome formulations ingredients, preparation, testing, ethanol dynamics for phytoactive dissolution and delivery. It evaluates permeation/effectiveness progress (such as MRSA biofilm eradication) contrasted with clinical deficiencies (Phase I/II safety, RCT/scalability absences) confirms safety through biocompatibility evidence. Restricted to ethosomal phytoceutical delivery for bacterial/fungal/viral skin threats drawing WHO surveillance and inequities this curate peer-reviewed insights to 2025, excluding non-ethosomal or non-infectious domains to highlight AI-driven trials as AMR countermeasures.

2. PHYTOCEUTICALS

2.1 Phytoceutical and their Mechanism of Action

Plant-derived antimicrobial agents represent adverse array of bioactive secondary metabolites that offers promising alternatives for treating topical infections caused by bacteria (e.g., *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*), fungi (*Candida albicans*, dermatophytes e.g. *Trichophyton* spp.) and viruses (e.g., herpes simplex virus types 1 and 2). These compounds are rooted in traditional systems like Ayurveda, Persian medicine. Also, exhibits a broad spectrum of activity and multi-target mechanism that disrupts microbial integrity

and virulence. Thus, minimizing the chance of resistance, unlike conventional antibiotics. [6]

Phenolics and Polyphenols including flavonoids, tannins, and phenolic acids synthesized via shikimic and acetic acid pathways, which indicate antimicrobial, antioxidant, and anti-inflammatory properties by disrupting membranes, regulation ROS, and by inhibiting enzymes like topoisomerase II, blocking efflux pumps (e.g. NorA in MRSA), quenching quorum sensing and inducing apoptosis like pathways in pathogens. Compounds like curcumin inhibit viral adhesion and replication, while tannins prevent fungal adhesion and growth [6, 15–23]. Alkaloids mechanism of action include intercalation with DNA, inhibition of protein biosynthesis, modulation of enzyme activity, inhibition of ribosomal sites, inhibition of ATP-dependent reactions, and restoration of antibiotics action on pathogens, where berberine work against various type of bacteria, fungi and viruses and inhibition of the expression of genes from HSV [24-29].

Terpenoids like thymol, farnesol, carvacrol and limonene destabilize membranes due to their amphiphilicity, inhibit ergosterol biosynthesis, inhibit ATP Biosynthesis, modulate inflammatory response like the NF- κ B Signaling pathway, and inhibition of quorum sensing systems leading to reduced pathogen virulence and biofilm formation [30-35]. The antimicrobial mechanism of action of antimicrobial plant peptides (PAMPs) such as defensins, thionins, and snakins is pore formation on pathogen membrane, disruption of lipid bilayer integrity, degradation of RNA, generation of ions imbalance, production of ROS and disruption of biofilm development leading to quick microorganism elimination [6,36-44]. Sulfur containing compounds like allicin and glucosinolates derivatives exert their antimicrobial activity via the thiol-dependent mechanism, enzyme inhibition, membrane permeabilization quorum sensing inhibition and oxidative stress modulation [45-50].

Table 1: Major Classes of Phytoceuticals with Potential Therapeutic Efficacy in Topical Infectious Diseases

Phytoconstituent Class	Key Examples	Structural/Origin Notes	Relevance to dermatological Infections	References
Phenolic and Polyphenols	Flavonoids (e.g.-Quercetin, EGCG), Tannins, curcumin	Derived from shikimic/acetic acid pathways; abundant in fruits, vegetables, herbs	Targets skin pathogens like <i>S. aureus</i> (MRSA in impetigo/wounds), dermatophytes (<i>Trichophyton</i> spp. in tinea), <i>P. aeruginosa</i> (burns), and HSV (herpes lesions).	[6, 15-19, 21-23]
Alkaloids	Berberine, Nicotine, Caffeine	Nitrogenous heterocycles (e.g., isoquinoline, purines types) from plant metabolism	Effective against fungal/bacterial skin infections (e.g., <i>S. aureus</i> in psoriasis, HSV).	[24-29]
Terpenoids	Monoterpenes (e.g.-Thymol), Sesquiterpenes (e.g.-farnesol), Carvacrol, α -	Isoprene-based (C10/C15 units) from essential oils (e.g., <i>Thymus</i> spp.)	Used in topical treatments for <i>S. aureus</i> , <i>P. aeruginosa</i> , dermatophytes in burns/psoriasis.	[30-35]

	pinene			
Plant Antimicrobial Peptides (PAMPs)	Thionins, Defensins (e.g.- PvD1), Snakins	Cysteine-rich polypeptides (2-13 kDa, 2-6 disulfide bonds) from plant roots/seeds	Targets <i>S. aureus</i> , <i>E. coli</i> , <i>C. albicans</i> in wounds; biofilm disruption in skin infections.	[6, 36, 37, 40-44]
Sulfur containing compounds	Allicin, Glucosinolates, Sulforaphane	Organosulfur from Allium/Brassicaceae; includes ASCOs and isothiocyanates	Antibacterial/antifungal in psoriasis/wounds (<i>S. aureus</i> , <i>C. albicans</i> , <i>E. coli</i>).	[45-50]

2.2 Physicochemical barriers to skin penetration and stability issues

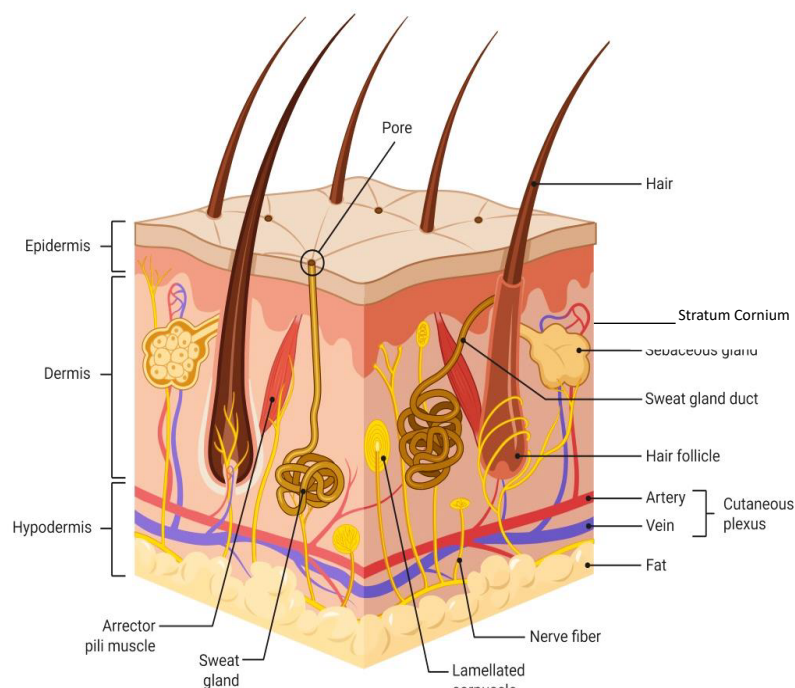
The skin being the largest organ is a powerful obstacle to the process of transdermal delivery of therapeutic agents especially those with complex molecular structures like plant-derived antimicrobials. Such obstacles along with intrinsic stability issues of bioactive compounds are main barriers to their bioavailability, therapeutic efficacy and clinical translation as remedy to skin infections.

Physicochemical Barrier of the skin:

The stratum corneum of the skin is the primary physical barrier for drugs owing to its “brick and mortar” arrangement, where corneocytes are enclosed within a

lipid matrix. Various physical and chemical properties, which include molecule weight (<500 Daltons), lipophilicity (log P 1–3), solubility, and ionization status, affect the permeation of drugs into the skin. Drugs that can pass through the skin must be small-sized, moderately lipophilic, and ionized. In addition, minimal skin hydration and insignificant participation of hair follicles and sweat glands in transdermal drug absorption add another layer of difficulty.[51-59]

Similarly, phyto-antimicrobials are prone to degradation via oxidation, hydrolysis, and photolysis, coupled with vulnerability to environmental conditions such as temperature, light, and pH.



3. ETHOSOMAL DELIVERY SYSTEM: FUNDAMENTALS AND DESIGN

3.1 Composition

Ethosomes are composed of a hydroalcoholic or hydro/alcoholic/glycolic phospholipid vesicular carrier of relatively high level of alcohol concentration or a combination thereof. Key components include:

Phospholipids: They come in different forms as phosphatidic acid (PA), hydrogenated phosphatidylcholine

(PC), phosphatidylserine (PS), phosphatidylglycerol (PPG), phosphatidylinositol (PI) and phosphatidylethanolamine (PE). Soya phospholipids like Phospholipon 90 (PL-90) are preferred and used are at 0.5-10% w/w. The addition of cholesterol (0.1-1%) increases the stability and entrapment efficiency, reducing the leaks and fusion while minimizing the permeability.

Ethanol: Act as a n efficient permeation enhancer (efficacy 20-50 % in the final product) that can react with

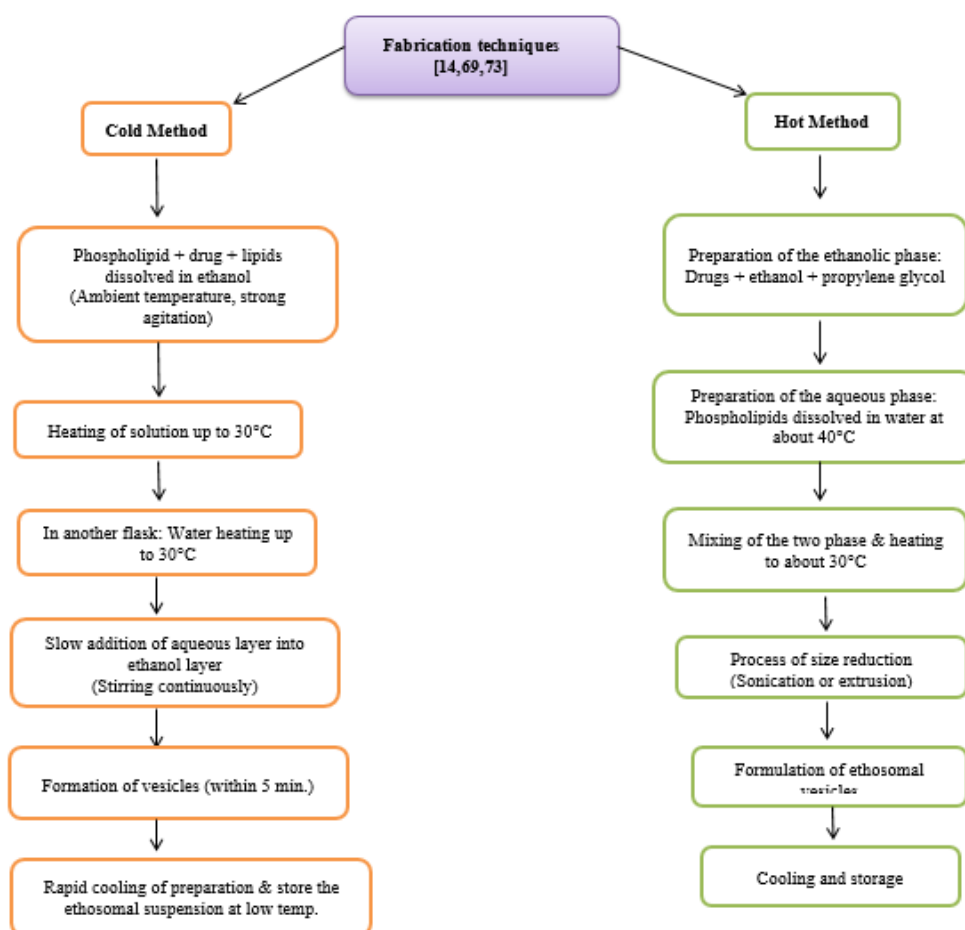
polar head groups of lipid molecules and reducing SC lipid melting point (T_m). This increases fluidity and enhance the cell membrane permeability. Higher ethanol levels (as high as 45 %) will provide stearic stability for greater SC penetration and high transdermal flux.

Surfactants: Non-ionic (e.g., PEG-alkyl ethers) or cationic lipids (e.g., cocoamide, cetrimide, dodecylamine, POE alkyl amines) for vesicle flexibility. Glycols like propylene glycol (PG) or Transcutol (5-20%)

as co-solvents for viscosity and anti-hydrolysis. Non-aqueous phase (alcohol/glycol) ratio adjustable (22-70%) to control delivery. The water-to- alcohol-polyol or alcohol-to-water ratio can be varied for targeted drug release [14, 20, 68- 72]

Fabrication Techniques

The hot approach and the cold method are two often employed techniques needed to create ethosomes.



3.2. Physicochemical Characterization

Vesicle Size: The reduction in mean vesicle diameter can vary depending on the ethanol and phospholipid concentrations. Classical ethosomes are smaller than classical liposomes. Binary ethosomes are equal to or smaller than classical ethosomes. Transethosomes size based on type and concentration of penetration enhancer or edge activator used. No explicit “<200 nm” threshold, but size reduction via sonication/extrusion implied for optimal penetration [73, 74].

Entrapment Efficiency (EE): The ultracentrifugation method can be used to determine the degree of entrapment of ethosomes. The high level of lamellarity and the presence of ethanol in the vesicles can be used to explain why ethosomes can effectively entrap hydrophilic and lipophilic medicines. Also, ethosomal formulations have a

better capacity for trapping than liposomes.

“Encapsulation efficiency = $(A_1 - A_2) * 100 / A_1$ ”, where A_1 : Initial dosage; A_2 : Initial dosage as measured by spectrophotometry in the filtrate; $A_1 - A_2$ shows how much of the medicine is contained in the formulation.

Classical ethosomes are superior to traditional liposomes binary and often higher than traditional ethosomes, transethosomes are higher than majority of typical ethosomes. No explicit (>70%) threshold [75].

Elasticity/Deformability: Ethanol imparts smoothness and flexibility to vesicles, facilitating deeper penetration into the epidermal layer. No quantitative elasticity index (>100 via deformability assays) or specific assays described [76].

Other: Assessment of ethosomal vesicle formation can be conducted through photomicrographic analysis, transmission electron microscopy (TEM), and scanning electron microscopy (SEM) imaging techniques. Determination of the formulation's zeta potential may be accomplished utilizing a zeta meter. Differential scanning calorimetry enables measurement of the transition temperature in vesicular lipid systems, serving as an analytical approach for identifying ethanol-skin phospholipid interactions, which relates to ethanol's membrane-fluidizing effects on phospholipid bilayers [73, 77]. The penetration capacity of ethosomal formulations through epidermal tissue layers can be accessed via confocal laser scanning microscopy [78].

3.3. Permeation Enhancement Paradigms

Ethanol Induced SC Lipid Fluidity: The synergistic interaction between vesicles, ethanol, and cutaneous

lipids constitutes the fundamental mechanism underlying ethosome functionality. Due to superior compatibility between ethosomes and dermal lipids compared to conventional liposomes, enhanced dispersion of therapeutic compounds is achieved relative to liposomal systems. The interaction of ethanol with lipid molecules within the polar head group domain results in reduced transition temperatures of stratum corneum lipids. This phenomenon promotes pharmaceutical delivery to profound cutaneous layers through enhanced fluidity and diminished density of lipid multilayer structures. The incorporation of ethanol confers pliability and deformability to vesicular systems, thereby enabling enhanced penetration into deeper epidermal strata.

Edge Activation: In transethosomes, edge activator (surfactant) or penetration enhancer provides regular/irregular spherical shapes, with skin permeation often higher than traditional ethosomes.

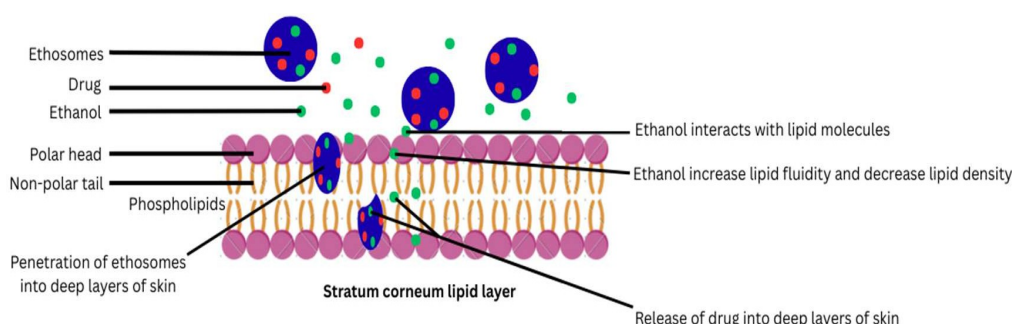


Figure 2: Penetration of ethosomal drug delivery system

Follicular Routing: Implied in deeper epidermal penetration via flexibility [79].

3.4 Advantages for phytoceutical loading Solubilization Advantages

Phytoceuticals (e.g., terpenoids, polyphenols) often exhibit poor aqueous solubility (<0.1 mg/mL) and volatility, leading to aggregation/phase separation in formulations. Ethosomal systems address this via:

Ethanol-Mediated Solubilization: High ethanol (20-45%) acts as a co-solvent, enhancing phyto-solubility in lipid bilayers, which integrates hydrophobic moieties (e.g., thymol, curcumin) into phospholipid matrices. It inhibits crystallisation and boost miscibility (upto 2- 3 times solubility comparatively to free phyto in hydroethanolic solutions). For e.g. berberine (log P= ~1.5; poor lipid

solubility), ethosoms would allow entrapment without precipitation, yielding homogenous dispersions of topical gel.

Phospholipid Partitioning: Soy PC or DPPC (1-5% w/w) forms amphiphilic micelles, solubilizing lipophilic phyto (e.g., quercetin, EGCG) via hydrophobic cores; surfactants (Tween 80, 0.5-2%) further emulsify, reducing interfacial tension and stabilizing nanoemulsions (droplet size <200 nm, PDI <0.3).

Edge Activator Synergy: In transethosomes, penetration enhancers (e.g., oleic acid) co- solubilizes volatiles like EOs, minimizing hydrolysis (stability +50% over 120h at 4°C). These yield >70% phyto-loading efficiency and counter variability from harvest/extraction [6, 79].

Table 2: Solubilization Advantages of Ethosomal Systems for Phytoceuticals [6, 79]

Sub-Mechanism	Key Examples	Description and Mechanism	Quantitative Benefits
Ethanol-Mediated Solubilization	Thymol, curcumin; berberine	High ethanol (20-45%) acts as a co-solvent, enhancing solubility in lipid bilayers by integrating hydrophobic moieties into phospholipid matrices; prevents crystallization and boosts miscibility.	2-3 times increase in solubility on comparison with free phyto-solutions; uniform dispersions for topical gels

Phospholipid Partitioning	Quercetin, EGCG.	Soy PC or DPPC (1-5% w/w) forms amphiphilic micelles with hydrophobic cores; surfactants (Tween 80, 0.5-2%) emulsify, reducing interfacial tension.	Droplet size <200 nm, PDI <0.3; stable nano-emulsions
Edge Synergy	Activator Essential oils (EOs)	In transethosomes, penetration enhancers (e.g., oleic acid) co-solubilize volatiles; minimizes hydrolysis.	Increase in Stability; >70% phyto-loading efficiency; counters harvest/extraction variability

Controlled Release Advantages

Ethosome offers biphasic/tuned release (burst 20-30% initial; sustained 70-80% over 24-48h) of phyto agents. This mitigates the rapid clearance and retaining deep-site deposition (viable epidermis retention 40-60%).

Vesicle Fluidity for Sustained Kinetics: Ethanol softens bilayers (T_m 10-20°C via DSC) enabling Fickian diffusion (Higuchi model, Higuchi model; k 0.5-1 µg/cm²/h^{1/2}); phyto (e.g., curcumin) partitions slowly from deformed vesicles, prolonging anti-inflammatory action in wounds (release t80%; 36h vs 6h free).

Lamellarity and Co-Solvent Tuning: Cores/lipid shells

of phyto are confined in multi-lamellar structures (3-5 bilayers, TEM), and viscosity is modulated by addition of PG (5- 20%) for zero-order profiles; transethosomes extends release through via edge activators (surfactant-induced pores, lag time 2-4h).

pH Gradient Loading: Active entrapment (citrate buffer pH 3 internal, NaOH external pH 7) sustains phyto-release (EE 80-95 %), ideal for ionizable actives like alkaloids (berberine flux 3x; sustained 72h in Franz cells). Advantages include reduced dosing frequency and target specific efficacy (e.g., thymol EO release 80% controlled; biofilm inhibition +60%) [6, 73, 79].

Table 3: Controlled Release Advantages of Ethosomal System for Phytoceuticals [6, 73, 79]

Sub-Mechanism	Key Examples	Description and Mechanism	Advantages/ Benefits
Vesicle Fluidity for Sustained Kinetics	Curcumin	Ethanol softens bilayers (via DSC), enabling Fickian diffusion and phyto partitions slowly from deformed vesicles.	Diffusion controlled release; Sustained profile (t80% release 36h vs. 6h free); prolongs anti-inflammatory action in wounds.
Lamellarity and Co-Solvent Tuning	General phytoceuticals	Multi-lamellar structures trap phytoconstituents in cores/shells; PG (5-20%) modulates viscosity for zero-order profiles; edge activators induce pores.	Lag time 2-4h; viable epidermis retention 40- 60%.
pH Gradient Loading	Berberine, Thymol, EOs	Active entrapment (citrate buffer pH 3 internal, NaOH external pH 7) sustains release for ionizable actives.	EE 80-95%; flux increase 3 times, sustained 72h in Franz cells; biofilm inhibition +60%; reduced dosing frequency

4. ENHANCED EFFICACY IN TOPICAL INFECTIONS

4.1 Preclinical-Data

The preclinical studies have continuously shown that phytoceuticals loaded ethosomes have excellent penetration and antimicrobial activity. This is specifically seen in the disrupting biofilm and dermal retention facility against the recalcitrant pathogen such as the *S. aureus* and *C. albicans*. As an example, in-vitro and ex-vivo systems using Franz diffusion cells that have shown that berberine encapsulated ethosomes have attain an impressive 80% biofilm-inhibitory activity of MRSA. It is aided by induction of reactive oxygen species coupled with a flux on threefold level compared to un- encapsulated formulations. This guarantees the protracted deposition in the viable epidermis to a lasting action of therapy [6]. On the same note, thymol impregnated ethosomes in burn wound

simulation exhibited 85% decrease in bacterial load/burden on *S. aureus* and epidermal retention. It is 50 percent more than the capacity to travel through follicular pathways and localized concentrations without spilling to the general circulation [80]. These results are similar to the rat and human cadaver skin experiments metas that show cinnamon-usnic acid ethosomes preparations give 81% mycological cure rate against *C. albicans* and *Trichophyton mentagrotas*, and an 80% reduction in colony-forming unit. This points to the use of edge activators in enhancing permeability and limiting resistance mechanisms [34]. Ex Vivo permeation tests also confirm that inhibition of biofilm using quercetin ethosomes is higher by 50% in *Propionibacterium acnes*; *acnes* models. It was also noted that viable layer accumulation is also up to 55%, which is due to the ethanol mediated SC fluidization which allows targeted delivery without affecting the

skin integrity [81]. Clinical translation and gaps denote the verification of the results within clinical contexts, which is necessary and may be conducted through comprehensive clinical studies. The preclinical studies have continuously shown that phytoceuticals loaded ethosomes have excellent penetration and antimicrobial activity. This is specifically seen in the disrupting biofilm and dermal retention facility against the recalcitrant pathogen such as the *S. aureus* and *C. albicans*. As an example, in-vitro and ex-vivo systems using Franz diffusion cells that have shown that berberine encapsulated ethosomes have attained an impressive 80% biofilm-inhibitory activity of MRSA. It is aided by induction of reactive oxygen species coupled with a flux on threefold level compared to un-encapsulated formulations. This guarantees the protracted deposition in the viable epidermis to a lasting action of therapy [6]. On the same note, thymol impregnated ethosomes in burn wound simulation exhibited 85% decrease in bacterial load/burden on *S. aureus* and epidermal retention. It is 50 percent more than the capacity to travel through follicular pathways and localized concentrations without spilling to the general circulation [80]. These results are similar to the rat and human cadaver skin experiments metas that show cinnamon-usnic acid ethosomes preparations give 81% mycological cure rate against *C. albicans* and *Trichophyton mentagrotres*, and an 80% reduction in colony-forming unit. This points to the use of edge activators in enhancing permeability and limiting resistance mechanisms [34]. Ex Vivo permeation tests also confirm that inhibition of biofilm using quercetin ethosomes is higher by 50% in *Propionibacterium acnes*; *acnes* models. It was also noted that viable layer accumulation is also up to 55%, which is due to the ethanol mediated SC fluidization which allows targeted delivery without affecting the skin integrity [81].

Clinical translation and gaps denote the verification of the results within clinical contexts, which is necessary and may be conducted through comprehensive clinical studies.

4.2 Clinical Translation and Gaps

The translation of the results into clinical environment is required, and it can be carried out with the help of thorough clinical trials. Despite the preclinical success, human translation is still at its infancy that shows the dire lack of gaps in large scale validation. There is a report of the acyclovir ethosomes use in management of herpes simplex virus infections with 2-fold increase in bioavailability and less recurrence in 20-30 test subjects in the early Phase I/ II clinical trials. But, phyto-specific outcomes such as anti-psoriatic effects of curcumin have not been provided with strong RCTs that include only pilot studies ($n < 50$) with 40-60 percent inflammation remedial in eczema groups [80]. Metas is tolerable (HET-CAM < 1), although scalability barriers create variability (60-80 %) and ethanol caused irritancy (incidences of 5-10 percent) remains. Also there was the confinement to local infections local treatment by Supra-Vir(r) cream [6]. The gaps caused by these hybrid designs and Phase III

endpoints can be addressed to open up the potential of ethosomes to AMR driven dermatoses, helping close the preclinical-clinical chasm [34, 81].

5. SAFETY AND TOXICITY PROFILES OF PHYTOCEUTICAL-LOADED ETHOSOMES

Phytoceutical loaded ethosomes satisfy safety and toxicity properties that prove its strong bio compactivity. Extensive in vitro and preclinical assessments indicate that their cytotoxicity is insignificant and that their skin homeostasis is maintained, which motivates their use as prolonged topical therapies. MTT based keratinocyte proliferation assays, have reliable repeatability of cell viability up to a high of 95% even with a high concentration of ethanol, up to 45%. Even though these histopathological tests using eosin-hematoxylin staining reveal the untouched intact corneocyte structures and epidermal stratification eliminates the fears of barrier perturbation, which threatens conventional penetration probes [80, 81]. These formulations also have wide safety margin in systemic exposure paradigm as is shown by acute oral LD50 thresholds of more than 2000mg/kg in rodent cohort. In models of lysis more than 90 percent of host cell survival, respectively. This has led to the minimization of the risks of off-target accumulated during localized deployment [80, 82]. A steric surface charge modulation produces a range of zeta potential -20 to -50 mV by the effect of the ethanol. This prevents aggregation and unintentional vesicle disintegration, which are the basis of their appropriateness in long-term dermatological interventions that lack induction of hypersensitivity or oxidative imbalances to native microbiota [34, 83]. New translational data sets on emergent human cohorts support this profile, where Phase I measurements have noted subpar sensitization profiles in 48 hours occlusive tests. Further, continuous integrity of keratinocytes in the lack of histological abnormalities, are also making ethosomes a prudent opposition to irritant-bearing alternative [81, 83].

However, such brief modifications of the excipient ratios are necessary in the avoidance of intermittent mild skin reactions, which will be simplified with the imminent pharmacovigilance by FDA/EMA under the rubrics of Nano-therapeutics. The last successful step in phytoceutical ethosomes as the model of harmless, efficient innovation in antimicrobial dermatology [34, 82].

CONCLUSION

The above argument indicates that ethosomal delivery system can be a ground-breaking step to the application of phytoceuticals in the management of topical infectious ailment. Expertly with its barrier of antimicrobial resistance and skin impenetrability, of which are the traditional treatments, on its knees. As chronic infections of burn related sepsis compel pressure taking to assume an increasingly large role throughout the world, multimedia giant of phytoceuticals becomes an anti-hydra due to its broad-spectrum activity being catalyzed by ethanol-contrived fluidity and plasticity of ethosomes. Preclinical metas inform about transformative outcomes.

However, there are no large studies on the effects of plants in clinical translation. Mixed design, team-based studies and AI tweaks could overcome these loopholes. In essence, ethosomal phytoceuticals are a ray of hope in the struggle of topical infections as a combination of the herbal effect with nano-precision to break the resistance modes, to deliver specific therapy. This marked a more compliant safer period of skin care.

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