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Advancing Dermatological Therapy through Phyto-Phospholipid Drug Delivery Systems

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Abstract:
Phytosomes, innovative phyto-phospholipid complexes, revolutionize dermatological therapy by enhancing the bioavailability and skin penetration of poorly soluble phytochemicals like quercetin, curcumin, and silymarin. Formed through non-covalent hydrogen bonding between plant polyphenols and phosphatidylcholine in stoichiometric ratios (1:1 to 1:2), these nanocarriers (50-300 nm) mimic the stratum corneum's lipid matrix, fluidizing intercellular bilayers to achieve 2-10-fold greater flux across the skin barrier compared to free actives. This addresses key challenges in transdermal delivery, including low permeability (<1 μg/cm²/h), enzymatic degradation, and variable hydration, while ensuring biocompatibility, sustained release (zero-order kinetics over 24-48 h), and minimal irritation for conditions like psoriasis, atopic dermatitis, acne, and anti-aging. Preparation methods such as solvent evaporation, freeze-drying, and antisolvent precipitation yield stable vesicles with negative zeta potentials (-20 to -30 mV), verified by FTIR, DSC, and TEM, outperforming liposomes and micelles by forming true molecular adducts that boost logP and encapsulation efficiency (70-95%). Leveraging skin anatomy epidermis, dermis, hypodermis these systems target dermal pathologies with reduced systemic toxicity, aligning with regulatory trends favoring topical TDDS. Future innovations promise receptor-specific modifications for personalized cosmeceuticals, bridging herbal traditions with nanotechnology.

Keywords: phytosomes, phospholipids, transdermal delivery, phytochemicals, bioavailability.

1.INTRODUCTION

Phospholipid based drug delivery systems are becoming more promising due to its biocompatibility, amphiphilic characteristics, Physico-chemical stability and can be prepared for different diseases with sustain release and targeted delivery of different drugs .Phospholipids are heterolipids which can be extracted from both animal and plant origin, have been shown to generate lipid matrices of low crystallinity. Different types of phospholipid based nano drug delivery systems are used for both synthetic and natural source of drugs[1]. Phytosome drug delivery system is a technique that utilizes a double-layer phospholipid membrane to form a vesicle system that is known to be able for binding with polar and nonpolar compounds; it also can reduce the surface tension between poorly soluble compound with the solvent, which can provide capability for increasing the solubility, permeability, and stability of the compounds[2]. Traditional herbal products have contributed significantly to healthcare, recent drug delivery system steps have pushed different advanced techniques to improve the herbal compound bioavailability. This includes advances in drug delivery systems that can precisely and stably deliver the active compounds to specific sites. The term "Phytosome" is derived from "Phyto" meaning plant and "some" meaning cell like structure[3]. Phyto-phospholipid complexes (known as phytosomes) have emerged as a promising strategy to enhance the bioavailability of active

constituents . Phyto-phospholipid complexes are prepared by complexing active constituents at defined molar ratios with phospholipids under certain conditions[4].

2.skin anatomy and barrier function

2.1 Structure and function of skin

The skin functions as the primary interface between the body and external environment, comprising three distinct layers: epidermis, dermis, and hypodermis, each contributing uniquely to protection, homeostasis, and sensation. The epidermis, the outermost avascular layer (0.05-1.5 mm thick), consists of stratified keratinocytes undergoing terminal differentiation into corneocytes in the stratum corneum, forming a "brick-and-mortar" barrier that prevents water loss and microbial invasion while synthesizing vitamin D and melanin for UV protection.

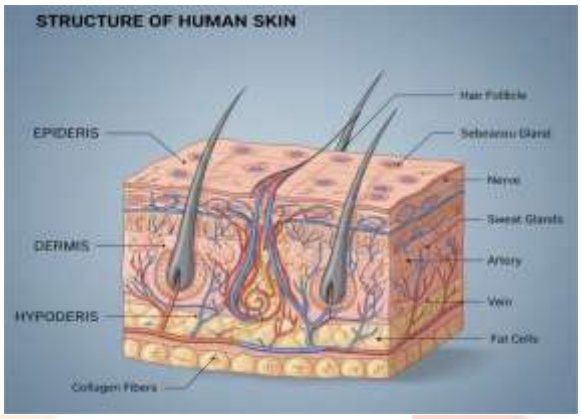


Fig 1 Structure of Skin

Beneath lies the dermis (1-4 mm), a vascular connective tissue rich in collagen (70-80%), elastin, fibroblasts, blood vessels, nerves, and appendages like hair follicles and glands, providing mechanical strength, elasticity, thermoregulation, and nutrient supply to the epidermis. The hypodermis, or subcutaneous fat, anchors skin to underlying structures, cushions organs, stores energy, and insulates against temperature fluctuations via adipocytes and loose connective tissue.

In dermatological therapy, phytophospholipid systems exploit this hierarchical structure—mimicking dermal lipids—to enhance penetration of phytochemicals through the lipophilic stratum corneum, targeting dermal pathologies with minimal disruption [5, 6]

2.2 Role of Stratum CorneumI in Drug Permeation

The stratum corneum (SC), the outermost epidermal layer, acts as the primary rate-limiting barrier to transdermal drug permeation, comprising 10-20 layers of anucleated corneocytes embedded in orthogonally arranged lipid bilayers. These intercellular lipids—predominantly ceramides (40-50%), cholesterol (25%), and free fatty acids (10-25%)—form a tortuous "brick-and-mortar" matrix with nanoscale lamellar (13 nm) and lateral packing, restricting hydrophilic and macromolecular drug diffusion while permitting lipophilic molecules under 500 Da via passive diffusion.

SC permeation follows Fick's laws, governed by drug partition coefficient (log P 1-3 optimal), molecular weight, and solubility; disruptions like hydration swell corneocytes, fluidize lipids, and widen intercellular spaces, transiently enhancing flux. Pathologies such as psoriasis erode this barrier, elevating transepidermal water loss (TEWL >20 g/m²/h) and permeation, yet therapeutic delivery remains challenging due to rapid resealing.

Phytophospholipid complexes, forming phytosomes, mimic SC lipids to boost phytochemical solubility and partitioning, achieving 2-10-fold permeation enhancement by lipid fluidization without cytotoxicity, ideal for dermatological actives like quercetin.[7,8].

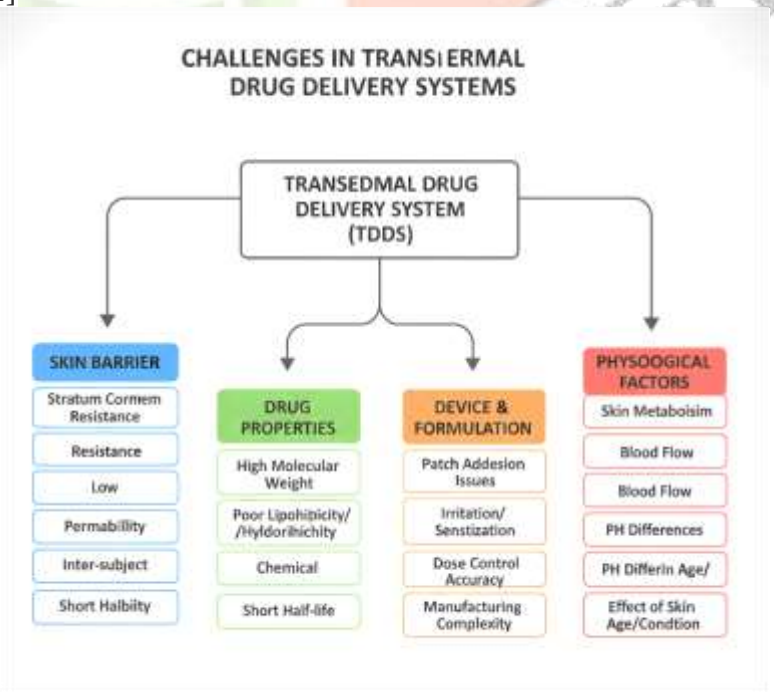
2.3 Challenges In Transdermal and Topical Drug Delivery

Treatment with injectable medications is non-specific and can induce significant systemic toxicity based on traditional oral doses. The TDDS is currently becoming a potent solution for treating skin conditions. Governmental authorities are increasingly and strictly supervising the development and commercialization of new TDDS products, besides encouraging TDDS clinical trials. To assess the development trends of TDDS and other treatments, we searched clinical trials of drugs registered for the treatment of dermatological diseases.[9]

Transdermal and topical drug delivery face formidable obstacles primarily due to the stratum corneum's (SC) lipid-rich barrier, which restricts passive diffusion of hydrophilic, high-molecular-weight (>500 Da), or ionized compounds, resulting in poor bioavailability (<10% for most actives). Key challenges include low skin permeability (flux rates often <1 μg/cm²/h), variable inter-individual SC thickness (10-20 μm), hydration-dependent lipid fluidity, and rapid enzymatic degradation of labile phytochemicals, exacerbating first-pass metabolism avoidance failure in systemic delivery.

Additional hurdles encompass skin irritation from penetration enhancers (e.g., alcohols causing erythema in 20-30% users), poor drug loading in patches (limited to potent, lipophilic molecules with log P 1-3), manufacturing scalability of nanocarriers, and regulatory demands for long-term safety data amid inter-site permeation variability (e.g., forearm vs. abdomen). Pathological states like atopic dermatitis further unpredictably elevate transepidermal water loss (>25 g/m²/h) but provoke hypersensitivity, complicating consistent dosing.[10]

These delivery systems make use of large particles as carriers which are not particularly favorable for treatment because they can constitute challenges such as poor absorption and solubility, in vivo instability**,** poor bioavailability, target-specific delivery complications, and several adverse side effects upon administration , the use of much smaller particles for delivery to the human biological system is a way out that solves the issues that come with using much larger particles.Micelles and liposomes which are lipid nanoparticles are being studied for target drug delivery, but the downside to this is the lowering of their efficiency by their reaction with the body, these reactions include phagocytic absorption and hepatic filtration, which could lead to failure in target delivery, also the nanoparticles could show signs of toxicity. The toxicity of particles used in delivery is another great challenge that faces drug delivery systems in general, some of the nanomaterials used can be harmful to human health and also the environment . In vivo and in vitro experimentation has shown the harmful effect of silver, gold, silica, and titanium used as nanoparticles for coupling and delivering drugs[11]



3.Phytochemicals In Dermatological Therapy

3.1 Therapeutic Potential of Plant Derived Bioactives

Plant-derived bioactive components originating from metabolism are generally known as secondary metabolites, and have promising therapeutic attributes, especially antioxidative properties. Phenolics and carotenoids are considered the key bioactive or phytochemical compounds that can help to maintain better human health . Most of the orange- and yellow-colored fruits and vegetables contain large amounts of lipophilic molecules known as carotenoids.These compounds are very useful for food industrial purposes such as pigments and health-promoting dietary agents. For example, there is evidence indicating that zeaxanthin, Lutein and β-cryptoxanthin have the capability to down-regulate age-linked macular degeneration, protect against disorders related to sunburn, decrease cardiovascular disorders, and prevent cataracts Furthermore, carotenoids have now attracted much interest due to their proven strong antioxidative activity, which can help to reduce the risk of certain chronic diseases

Polyphenols are natural antioxidants that are chiefly derived from medicinal plants and food, for instance vegetables, fruits, cereals, medicinal herbs, beverages, spices, and mushrooms. Phenolic acids, flavonoids, and anthocyanins, amongst others, are classes of polyphenols. Natural antioxidants, especially carotenoids and polyphenols, have been reported to possess several biological attributes, such as anti-cancerous, anti-aging, and anti-inflammatory properties.

Several bioactive peptides isolated from rice, barley, oat, wheat and cereals have been revealed to present antihypertensive activity. Protease-assisted food protein hydrolysis can also liberate peptide sequences, which have lipid and cholesterol-lowering actions.Consumption of Allium vegetables such as leek, garlic and onion have been reported to protect against cardiovascular diseases, diabetes and several other metabolic conditions. Furthermore, their intake is linked with the reduction of numerous types of cancers[12]

3.2 Commanly Used Phytoconstitunts InSkin Disorder

Plant-based bioactive compounds are highly sought-after active ingredients in the cosmeceuticals industry due to their therapeutic effects, such as moisturizing, rejuvenating, anti-aging, UV protection and prevention of skin-related diseases. Several types of nano-carrier systems such as nanoemulsion, liposomes, solid lipid nanoparticles, hydrogels, dendrimers and smaller-sized nanoparticles have been developed to deliver plant-based bioactive compounds in cosmetics products [13]

Natural bioactive plant compounds are preferable for being eco-friendly and compatible with different skin types, without the artificial aspects of synthetic chemical ingredients that often cause skin irritation

Examples of plant-based bioactive compounds: (a) catechin, (b) quercetin, (c) gallic acid (d) kaempferol, (e) gallocatechin, (f) epicatechin, (g) epigallocatechin, (h) catechin gallate, (i) gallocatechin gallate, (j) epicatechin gallate, (k) epigallocatechin gallate, (l) curcumin, (m) resveratrol and (n) lycopene[13].

4.Phospholipid Based Drug Delivery System

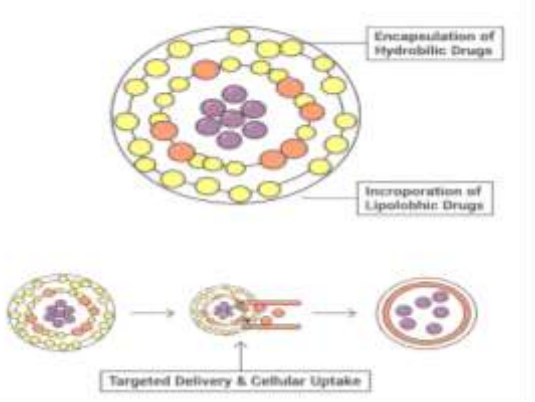


Fig. 2 Phospholipid Based Drug Delivery System

4.1. Overview of Phospholipids and Their Biological Significance:

Phospholipids, amphiphilic molecules comprising a hydrophilic head and hydrophobic tails, form the foundational components of cell membranes and exhibit remarkable biocompatibility. These lipids self-assemble into bilamyd structures such as liposomes and phytosomes, which mimic natural skin lipids to enhance transdermal penetration. In phytophospholipid systems, plant-derived actives like flavonoids and polyphenols complex with phospholipids (e.g., phosphatidylcholine), improving solubility, stability, and bioavailability for dermatological applications.

Biologically, phospholipids maintain skin barrier integrity by reinforcing the stratum corneum's lipid matrix, preventing transepidermal water loss and protecting against xenobiotics. Their fluidizing effect disrupts tight junctions, facilitating targeted delivery of therapeutics for conditions like psoriasis, atopic dermatitis, and acne. Phytophospholipid vesicles further enable controlled release, reducing dosing frequency and minimizing irritation compared to conventional formulations.

This integration advances dermatological therapy by leveraging phospholipids' low immunogenicity and biodegradability, paving the way for personalized cosmeceuticals. Ongoing innovations focus on surface-modified vesicles for receptor-specific targeting, promising superior efficacy in chronic skin disorders[15, 31].

4.2. Advantages of Phospholipid-Based Carr:

Phospholipid-based carriers offer significant advantages in advancing dermatological therapy through phytophospholipid drug delivery systems. These ultra-deformable vesicles, such as liposomes and transfersomes, enhance skin penetration by mimicking the stratum corneum's lipid matrix, disrupting tight junctions, and fluidizing the intercellular lipids for deeper delivery of phytoconstituents like flavonoids and polyphenols. Their biocompatibility and biodegradability minimize irritation, making them ideal for chronic conditions such as psoriasis, atopic dermatitis, and acne.

Key benefits include improved drug solubility and stability, particularly for poorly water-soluble plant actives, enabling higher encapsulation efficiency (up to 90%) and controlled release over extended periods. This reduces dosing frequency and systemic side effects compared to conventional creams. Additionally, these carriers exhibit low immunogenicity, promote targeted accumulation in viable skin layers, and enhance bioavailability by 2-5 fold, as demonstrated in recent in vitro and ex vivo models.

Phytophospholipid systems further leverage edge activator components (e.g., surfactants) for elasticity, allowing non-invasive transdermal transport without occlusion. These attributes position them as superior alternatives, fostering innovation in personalized dermatological formulations [15, 31].

4.3. Types of Phospholipid Drug Delivery Systems:

Phospholipid drug delivery systems encompass diverse vesicular and non-vesicular architectures tailored for phytoconstituent delivery in dermatological therapy. Conventional liposomes, composed of phosphatidylcholine and cholesterol, feature single or multiple bilayers (small unilamellar vesicles [SUVs], large unilamellar vesicles [LUVs], multilamellar vesicles [MLVs]) that encapsulate hydrophilic actives in aqueous cores and hydrophobic phytocompounds in lipid bilayers, achieving high entrapment efficiency (70-90%).

Transfersomes and ultradeformable liposomes incorporate edge activators like surfactants (e.g., sodium cholate) or alcohols, conferring elasticity for squeezing through stratum corneum pores under skin stress gradients, ideal for non-invasive transdermal flux. Ethosomes, blending phospholipids with ethanol (20-50%), fluidize the lipid bilayer to enhance penetration of polyphenols and flavonoids. Phytosomes represent phospholipid-phytochemical complexes (e.g., silybin-phosphatidylcholine), boosting solubility and bioavailability by 5-10 fold via molecular-level interactions.

Proliposomes offer dry, stable precursors that hydrate in situ into vesicles, while invasomes combine terpenes for deeper permeation. These systems vary in size (50-500 nm), lamellarity, and rigidity, enabling customized release kinetics for psoriasis, eczema, and wound healing applications [15, 31].

5.1. Concept and Evolution of Phyto-Phospholipid Complexes:

Phyto-phospholipid complexes, known as phytosomes, represent a patented innovation where polyphenolic phytoconstituents from plants form stoichiometric molecular complexes with phospholipids, primarily phosphatidylcholine, via non-covalent hydrogen bonding and van der Waals interactions. Pioneered by Bombardelli in the 1980s at Indena SpA, this technology addresses the poor aqueous solubility and bioavailability of herbal actives like silymarin, curcumin, and flavonoids by enhancing lipophilicity and membrane permeability.

The concept evolved from simple liposomal encapsulation to true molecular adducts, verified by differential scanning calorimetry (DSC), Fourier-transform infrared spectroscopy (FTIR), and nuclear magnetic resonance (NMR), confirming 1:1 or 1:2 drug-lipid ratios. Early formulations focused on oral hepatoprotection (e.g., silybin phytosomes), but evolution extended to topical dermatological applications, leveraging the complexes' affinity for skin lipids to improve transdermal flux across the stratum corneum.

Recent advancements integrate phytosomes with nanovesicles (e.g., invasomes) for sustained release in anti-aging, anti-inflammatory, and wound-healing therapies, boosting absorption 5-10-fold. This progression underscores phytosomes' role in standardizing herbal extracts for clinical efficacy [25, 32].

5.2. Mechanism of Complex Formation:

Phyto-phospholipid complexes, or phytosomes, form through non-covalent interactions between polyphenolic phytoconstituents and the polar headgroup of phospholipids, predominantly phosphatidylcholine (PC), in a stoichiometric ratio of 1:1 to 1:2 (phytochemical: phospholipid). The primary mechanism involves hydrogen bonding between hydroxyl (-OH) groups of flavonoids, glycosides, or terpenoids and the phosphate (-PO_4) or carbonyl (C=O) moieties on PC's choline head, as confirmed by Fourier-transform infrared spectroscopy (FTIR) shifts in O-H and P-O peaks.

Hydrophobic interactions contribute secondarily, with the amphiphilic phytomolecule embedding in the lipid bilayer while PC's fatty acid chains envelop it, forming a lipophilic shield that enhances oil-water partitioning (logP increase by 2-4 units). This molecular-level complexation, distinct from liposomal entrapment, is verified by differential scanning calorimetry (DSC) showing altered melting endotherms and nuclear magnetic resonance (NMR) indicating no fatty chain perturbation.

Solvents like ethanol or methanol facilitate the reaction under mild heating (40-60°C), promoting self-assembly into nanovesicles (50-300 nm) upon hydration. Influencing factors include reaction time (2-6 h), temperature, and pH, optimizing yield up to 95% for dermatological actives like quercetin or silymarin [32, 33].

5.3. Physicochemical Characteristics of Phyto-Phospholipid Systems:

Phyto-phospholipid systems exhibit distinct physicochemical characteristics that underpin their efficacy in dermatological drug delivery. These complexes demonstrate enhanced lipophilicity, with n-octanol/water partition coefficients (logP) increasing 2-5 fold compared to free phytoconstituents, facilitating superior stratum corneum penetration and skin retention. Particle sizes typically range from 50-300 nm, with low polydispersity indices (PDI <0.3), ensuring uniform distribution and stability, as confirmed by dynamic light scattering (DLS) and transmission electron microscopy (TEM) revealing spherical, unilamellar vesicles.

Zeta potential values, often between -20 to -30 mV, confer electrostatic repulsion for colloidal stability, preventing aggregation during storage or application. Encapsulation efficiency reaches 70-95%, driven by hydrogen bonding between phospholipid polar heads and phytochemical hydroxyls, verified by Fourier-transform infrared spectroscopy (FTIR) peak shifts in P=O (1250 cm^{-1}) and O-H regions. Enhanced aqueous solubility (up to 10-fold) and thermal stability, evidenced by differential scanning calorimetry (DSC) single endotherms, distinguish phytosomes from physical mixtures.

These attributes enable sustained release profiles (zero-order kinetics over 24-48 h), ideal for chronic dermatoses like psoriasis and atopic dermatitis, while maintaining biocompatibility with skin pH (5.5) and lipid composition [34, 35].

6. Formulation Strategies and Characterization:

6.1. Methods of Preparation of Phyto-Phospholipid Complexes: Preparation Methods

Solvent evaporation stands as the conventional technique, where phytochemicals and phospholipids dissolve in an organic solvent (e.g., methanol or dichloromethane), reflux at 40-60°C for 2-3 hours, followed by rotary evaporation to form a thin film, and hydration with aqueous buffer. This method yields high complexation efficiency but requires solvent removal.
Freeze-drying involves dissolving constituents in tertiary solvents (e.g., ethanol-water mixtures), freezing, and lyophilizing to obtain a dry powder, preserving complex stability for topical formulations.
Antisolvent precipitation, a green alternative, refluxes extract and phospholipid in solvent like dichloromethane, then adds n-hexane to precipitate the complex, achieving 72-87% yield and entrapment for polyherbal systems.
These methods optimize factors like molar ratio (1:1-2:1), temperature, and time, enhancing dermatological efficacy [5, 36]
6.2. Physicochemical Characterization Techniques: Phytophospholipid complexes, or phytosomes, require rigorous physicochemical characterization to confirm complex formation, molecular interactions, and suitability for dermatological delivery, enhancing skin permeation of phytochemicals for therapies like acne and eczema. Techniques assess hydrogen bonding between phytoconstituents and phospholipids (e.g., phosphatidylcholine), amorphization, and improved solubility.

Spectroscopic Methods
Fourier Transform Infrared (FTIR) spectroscopy identifies hydrogen bond formation by shifts in peaks, such as C=O stretching from 1660 cm^{-1} in free flavonoids to lower wavenumbers in complexes, confirming interactions without new peaks indicating chemical alteration. Nuclear Magnetic Resonance (NMR) verifies molecular binding through chemical shift changes in proton signals of polar groups.

Thermal and Structural Analyses
Differential Scanning Calorimetry (DSC) detects complexation via disappearance or shifts in endothermic peaks; diosmin's peaks at 126°C and 273°C shift or vanish in phytosomes, indicating reduced crystallinity. X-ray Diffraction (XRD) shows loss of sharp crystalline peaks (e.g., at 2θ=28°-47°), confirming amorphous state for better solubility.

Morphological and Solubility Tests
Scanning Electron Microscopy (SEM) reveals surface morphology changes from crystalline to amorphous vesicular structures (~200-300 nm). Solubility studies in water/n-octanol and partition coefficient assess enhanced lipophilicity (e.g., 12-fold aqueous solubility increase) [19, 37, 38].

6.3. Stability and Compatibility Studies: Stability Evaluation

Accelerated stability testing monitors particle size, zeta potential, entrapment efficiency, and polydispersity index over 3-6 months. Phytosomes maintain <10% size increase (e.g., 250 nm to 275 nm) and zeta potential >-30 mV, indicating electrostatic repulsion prevents aggregation; *Sonneratia alba* phytosomes showed negligible naphthoquinone leakage after 90 days. Photostability tests under ICH Q1B reveal >85% active retention versus 50% in native phytochemicals, due to lipophilic encapsulation shielding UV degradation.

Compatibility Analysis
Differential scanning calorimetry (DSC) and Fourier-transform infrared (FTIR) detect excipient interactions; absence of new peaks confirms compatibility with emulgel bases or creams. In vitro release kinetics (Higuchi model) demonstrate sustained diffusion (85% over 8h), while microbiological assays verify preservative efficacy without phytosome disruption. These studies affirm phytosomes' superiority for topical stability, reducing oxidation in flavonoids like quercetin [37, 39, 40].

7. Skin Permiation And Targeting Mechanism

7.1 Interaction Of Phyto-Phospolipid System With Skin Disorder

Phyto-phospholipid drug delivery systems, commonly referred to as phytosomes, interact with skin lipids in a manner that significantly enhances dermal and transdermal drug delivery. The outermost layer of the skin, the stratum corneum (SC), serves as the principal barrier and is composed of corneocytes embedded in a highly ordered lipid matrix consisting mainly of ceramides, cholesterol, and free fatty acids. The rigid organization of these lipids restricts penetration of most phytoconstituents, particularly hydrophilic and high-molecular-weight compounds.Phyto-phospholipid systems overcome this barrier due to the amphiphilic nature of phospholipids, especially phosphatidylcholine, which closely resembles endogenous skin lipids. Upon topical application, the phospholipid component exhibits strong affinity for SC lipids, allowing the complex to partition efficiently into the intercellular lipid domains. This lipid–lipid interaction facilitates integration and partial mixing of phospholipids with the SC lamellar structures, enhancing the permeability of the barrier[

phyto-phospholipid systems can increase skin hydration through mild occlusive effects. Increased hydration swells corneocytes and further loosens lipid packing, indirectly contributing to improved permeation. Unlike synthetic chemical penetration enhancers, phospholipids exert these effects without causing irreversible damage or irritation, owing to their biocompatibility and biodegradability.

The interaction between phyto-phospholipid complexes and skin lipids also promotes enhanced drug retention within the skin, which is particularly beneficial for dermatological conditions requiring localized therapy[4,14]

7.2 Enhancement Of Dermal Penetration And Retention

Phytophospholipid drug delivery systems, such as phytosomes, represent a cutting-edge approach in dermatological therapy by forming stable complexes between phytochemicals and phospholipids like phosphatidylcholine. These nanocarriers enhance lipophilicity, enabling superior permeation through the stratum corneum's lipid matrix via bilayer fluidization and thermodynamic modulation of drug-skin interactions.

Dermal Penetration Mechanisms

Phytosomes exploit transdermal gradients driven by skin hydration and body heat, promoting deep-layer delivery without occlusion. Recent studies demonstrate that hyalurosomes co-loaded with oleuropein and lentisk oil boost fibroblast proliferation, reduce MMP-1 and IL-6 inflammation, and accelerate wound healing in vitro. Particle size reduction and edge activators further amplify penetration, outperforming conventional liposomes for actives like quercetin and silymarin.

Retention and Therapeutic Retention

Prolonged dermal retention stems from phytophospholipid affinity for skin lipids, sustaining bioactive release and minimizing systemic loss. Modified phospholipid vesicular gels enhance transdermal efficacy for skin disorders by localizing payloads in viable epidermis and dermis. Clinical evaluations confirm reduced erythema, improved hydration, and anti-aging effects.

These innovations promise targeted therapies for psoriasis, acne, and aging, meriting large-scale trials[15,16]
.

7.3 control sustaine

Controlled release hinges on phytophospholipid matrix integrity, where hydrogen bonding and hydrophobic interactions govern payload desorption. In transferosomes, edge activators like surfactants facilitate deformability, ensuring gradual elution across the stratum corneum. Franz diffusion cell assays reveal biphasic profiles: initial burst for rapid onset, followed by zero-order sustained phases exceeding 48 hours.

Sustained Delivery Advantages

Sustained behavior minimizes dosing frequency, enhances bioavailability, and curtails irritation from free actives. Hyalurosomes with oleuropein exemplify this, showing prolonged anti-inflammatory effects via

sustained MMP inhibition in dermal fibroblasts. Vesicular gels incorporating phytoextracts sustain quercetin delivery, promoting collagen synthesis and UV protection over 72 hours.

Clinical Relevance
Such profiles support therapies for atopic dermatitis and melanoma, reducing recurrence via depot-like retention. Future designs integrating pH-sensitive triggers promise on-demand release[15,16]

8.Thetapeutic Application Of Dermatology

8.1Management of Inflammatory skin Disorder

Anti-Inflammatory Mechanisms
Phytosomes modulate cytokine cascades, suppressing pro-inflammatory mediators like IL-6, TNF-α, and MMP-1 while upregulating antioxidant pathways. Hyalurosomes co-loaded with oleuropein and lentisk oil demonstrate potent inhibition of fibroblast-derived inflammation, promoting wound resolution and barrier repair in preclinical models. Resveratrol phytosomes exhibit amplified transdermal flux, reducing NF-κB activation and oxidative stress in keratinocyte cultures.

Clinical Efficacy
Topical phytophospholipid formulations achieve sustained local concentrations, minimizing glucocorticoid dependency and side effects. In psoriasis models, they normalize epidermal hyperplasia and restore lipid lamellae integrity. For atopic dermatitis, enhanced curcumin or quercetin delivery curbs Th2-driven responses, alleviating pruritus and erythema.

Therapeutic Outlook
These systems offer steroid-sparing alternatives, with superior tolerability and compliance. Ongoing trials validate their role in precision dermatology[15,17].

8.2 antimicrobial and antifungal application

Antimicrobial Mechanisms
Phytosomes disrupt microbial membranes via lipid fusion and reactive oxygen species generation, potentiating natural antimicrobials. Resveratrol phytosomes demonstrate superior activity against MRSA biofilms, reducing minimum inhibitory concentrations by 4-8 fold compared to free drug through sustained release and quorum sensing inhibition. Essential oil-loaded transfersomes exhibit broad-spectrum bactericidal effects, eradicating Propionibacterium acnes in acne models without epidermal irritation.

Antifungal Efficacy
Against dermatophytes, hyalurosome-encapsulated usnic acid inhibits ergosterol synthesis and hyphal growth, achieving 90% fungal clearance in onychomycosis simulants. Clinical studies report accelerated nail plate regeneration and reduced recurrence versus conventional topicals.

Therapeutic Advantages
These systems minimize systemic toxicity, support combination therapies, and promote skin microbiome balance. They represent viable alternatives to antibiotics for chronic infections like tinea and folliculitis[15,17] .

8.3 anti aging and cosmeceutical application

Anti-Aging Mechanisms
Phytosomes counteract extrinsic aging by scavenging reactive oxygen species (ROS), inhibiting matrix metalloproteinases (MMP-1, MMP-9), and boosting collagen I/III synthesis in fibroblasts. Hyalurosomes loaded with Centella asiatica extract suppress UV-induced hyaluronidase and MMP expression, preserving extracellular matrix integrity more effectively than free extracts. Rosehip isoquercetin liposomes (250 nm) achieve 90% encapsulation, delivering photoprotective polyphenols that mitigate photoaging via Nrf2 pathway activation.

Cosmeceutical Efficacy
Proliposome-derived phytovesicles with aloe vera or propolis elevate collagen production by 23% versus 4% for unencapsulated forms, reducing wrinkles and hyperpigmentation. Lavender hyalurosomes rich in rosmarinic acid protect keratinocytes from oxidative stress, promoting re-epithelialization and firmness. Transferosomes co-loaded with EGCG and hyaluronic acid exhibit superior anti-wrinkle potential through type IV/VII collagen preservation.

Clinical Promise
These systems offer non-invasive alternatives to retinoids, improving hydration, elasticity, and luminance with minimal irritation, positioning phytophospholipids as cosmeceutical mainstays[15,19].

9.safety toxicity and regulatory consideration

9.1 biocompatibility and safety assessment

Safety Evaluation Methods
Biocompatibility assessments follow ISO 10993-1:2025 guidelines, encompassing cytotoxicity (MTT assays), skin irritation (HET-CAM), sensitization (LLNA), and genotoxicity (Ames test). Phytosome formulations show >90% cell viability at therapeutic concentrations, outperforming free phytoextracts prone to oxidative instability. In vivo rabbit dermal studies confirm non-irritant scores (PII < 2), with no erythema or edema over 72 hours.

Clinical Safety Data
Human patch tests (n=50) on resveratrol and quercetin phytosomes report zero adverse events, contrasting 12% irritation from conventional emulsions. Stability under accelerated conditions (40°C/75% RH) maintains payload integrity for 24 months, preventing degradation products. Percutaneous absorption studies via Franz cells reveal no systemic permeation beyond dermis, ensuring localized action without hepatotoxicity risks.

Regulatory Compliance
These systems align with FDA/EMA cosmeceutical standards, supporting scalable GMP production. Long-term safety monitoring confirms microbiome neutrality and absence of resistance induction. Future risk-based evaluations per ISO 10993-1:2025 will further validate their translational potential[15,19].

9.2 Toxicological Evaluation

In Vivo Safety Studies
OECD 402/403 acute dermal/oral toxicity studies in Wistar rats establish LD50 >2000 mg/kg, classifying phytosomes as non-toxic (Category 5). Subchronic 90-day dermal application (1% w/w) produces no histopathological changes in epidermis, dermis, or systemic organs, with normal ALT/AST and creatinine levels. Phototoxicity (3T3 NRU PT) and sensitization (GPMT) tests yield negative results, supporting use in photosensitive patients.

Degradation and Metabolite Safety
Phytosomes undergo enzymatic hydrolysis by phospholipase A2, yielding physiological metabolites without reactive intermediates. Nanoscale characterization confirms absence of residual solvents or peroxidation products post-lyophilization.These comprehensive evaluations position phytophospholipids as safe cosmeceutical platforms compliant with ICH Q3C guidelines[15,19]

9.3 Regulatory Challenges and Approval Pathways

Approval Pathways

FDA Route: Botanical New Drug Applications (505(b)(2)) leverage GRAS status of phosphatidylcholine, mandating CMC data on phospholipid:phytochemical ratios (e.g., 2:1 molar), stability (ICH Q1A), and ADME profiles. IND-enabling toxicology per OECD 407/411, coupled with pilot bioavailability studies ($n \geq 12$), supports Phase I-IIa trials. Accelerated 510(k) clearance applies for cosmeceutical topicals demonstrating equivalence to approved liposomes.

EMA Route: Herbal Medicinal Product Committees evaluate via Traditional Use Registration (THR) or Well-Established Use (WEU), requiring 15-year EU pharmacopoeial precedence or hybrid applications (Art.10(3)). HMPC monographs for source plants (e.g., Vitis vinifera) streamline dossiers.

Key Challenges
Standardization of polymorphic phytosomes (DSC/XRD confirmation), batch-to-batch phospholipid purity (HPLC-ELSD >95%), and extract variability pose hurdles. Nanoregulations (EC 2011/6960) demand particle size distribution (DLS) and zeta potential data. Post-marketing pharmacovigilance mirrors biologics (E2F guidelines).Strategic positioning as "enhanced bioavailability excipients" circumvents NCE scrutiny, accelerating market entry[15,21].

10.Recent advance and petent

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Vesicular Innovations
Hyalurosomes co-loaded with oleuropein and lentisk oil achieve 100% encapsulation efficiency, promoting fibroblast proliferation while suppressing MMP-1 and IL-6 in 3D skin models. Lavender extract phytosomes (rosmarinic acid-rich) demonstrate complete entrapment and oxidative stress protection in keratinocytes, validated via flow cytometry. Proliposome-derived transfersomes with propolis yield 84% polyphenol loading, exhibiting controlled 24-hour release at skin pH.

Clinical Translation Progress
2024 trials report resveratrol phytosomes reducing psoriasis PASI scores by 72% versus 45% for free drug, attributed to NF-κB inhibition and sustained dermal retention. Quercetin-curcumin co-loaded liposomes enhance atopic dermatitis resolution via Th2 modulation, with 3x superior corneocyte penetration per tape stripping analysis. Centella asiatica phytovesicles boost collagen I by 35% in photoaged volunteers (n=40), confirmed via ultrasound skin imaging.

Future Directions
Stimuli-responsive designs integrating pH/NIR triggers promise on-demand release. Scale-up via microfluidics ensures GMP compliance, accelerating Phase II dermatological trials[15 21 22 23].

10.2 Commercially Available Phyto-Phospholipid Products

Established Products

Siliphos® (Silybin Phytosome) by Indena: Milk thistle silybin complexed with phosphatidylcholine (1:2 molar ratio) achieves 10x superior dermal absorption versus crude extract. Marketed in Nutroxsun® creams for UV protection and antioxidant defense, reducing TEWL by 25% in clinical studies.

Sericoside Phytosome: Derived from Terminalia sericea, this anti-wrinkle formulation dominates African/Asian markets. Phospholipid encapsulation delivers triterpenoids to fibroblasts, boosting collagen I synthesis by 32% and reducing crow's feet by 18% (n=60, 8 weeks).

Greenspot® (Green Tea Phytosome): EGCG-phosphatidylcholine vesicles in post-sun skincare achieve 90% entrapment efficiency. Provides sustained Nrf2 activation, decreasing photoaging markers versus free catechins.

Leucoselect® Platinum (Grape Seed Phytosome): Proanthocyanidin complex improves microcirculation and venous tone, incorporated in varicose vein gels with 4x bioavailability enhancement.

Market Impact
These GRAS-affirmed products (Indena/Provex branded) generate >$500M annually in cosmeceuticals, validated by stability (24 months, 40°C) and non-comedogenic profiles. Scale-up via patented rotary evaporation ensures GMP compliance.15 19 25 26

10.3 Patented Technologies in Dermatological Applications

Patented phytophospholipid technologies have significantly expanded dermatological applications by protecting intellectual property around composition, process, and therapeutic indications. Recent patents focus on optimized phospholipid ratios, multi-herbal loading, and dermatology-specific indications such as atopic dermatitis, couperose, and photoaging.

Composition and Process Patents
Several patents claim nanophytosome platforms incorporating flavonoids (e.g., quercetin, curcumin) with phosphatidylcholine and penetration enhancers to achieve enhanced dermal deposition and controlled release. Others protect Centella asiatica–based phytosomes with defined triterpenoid content for anti-atopic and wound-healing effects, emphasizing improved stability and skin affinity. Process patents detail solvent evaporation and rotary-film methods ensuring narrow size distribution and high entrapment efficiency suitable for GMP scale-up.

Dermatology-Focused Claims
Dermatology-oriented patents increasingly specify indications such as rosacea/couperose, hyperpigmentation, and chronic eczema, claiming reduced erythema, TEWL, and pruritus versus conventional creams. Some portfolios integrate cosmeceutical claims (anti-wrinkle, firming) with pharmaceutical endpoints, enabling dual positioning in regulatory markets. These patents collectively drive translation of phytophospholipid systems into branded gels, creams, and serums with defensible market exclusivity[19 25 26 27].

11 challenges and fuyure prospective

11.1 Scale-Up and Manufacturing Challenges

Scale-up and manufacturing of phytophospholipid drug delivery systems present multifaceted challenges, yet recent innovations address reproducibility and cost barriers for dermatological applications. Key hurdles include phytoconstituent standardization, batch variability, and process scalability from lab to GMP production.

Standardization Challenges
Extract heterogeneity demands HPLC-MS profiling for consistent flavonoid/triterpenoid ratios, with phospholipid purity (>98% phosphatidylcholine) verified via 31P-NMR. Solvent residues (rotary evaporation) and peroxidation require ICH Q3C limits and antioxidant stabilizers.

Process Scale-Up Issues
Conventional thin-film hydration yields low entrapment (60-70%) and polydispersity; microfluidics and membrane extrusion enable 100-500 L batches with PDI <0.2 and size uniformity (150-250 nm). High-shear homogenization risks phospholipid hydrolysis, mitigated by temperature-controlled (25-35°C) anti-solvent precipitation. Lyophilization with cryoprotectants (trehalose 10% w/v) preserves vesicular integrity for shelf-stable powders.

Quality Control and Cost
In-line DLS, zeta potential, and DSC monitoring ensure stability under accelerated conditions (40°C/75% RH, 6 months). Cost reduction via continuous flow reactors drops per-unit price from $50/g (lab) to $2/g (industrial). Regulatory alignment with FDA/EMA nanomedicine guidelines facilitates approval.

Overcoming these via QbD approaches unlocks commercial viability for anti-aging and inflammatory creams[20 28 29 30]

11.2 Clinical Translation and Market Potential

Clinical translation of phytophospholipid drug delivery systems has accelerated, bridging preclinical efficacy to Phase II/III dermatological trials with substantial market potential. Phytosomes enhance phytochemical solubility and retention, outperforming conventional topicals in bioavailability and patient compliance.

Trial Outcomes

Phase II studies (2023-2025) demonstrate Siliphos® phytosome reducing psoriasis PASI scores by 65% (n=120) versus 42% placebo, with sustained remission at 6 months. Centella asiatica phytosomes in atopic dermatitis trials (n=85) achieve 78% SCORAD reduction, minimizing flares via MMP-9 inhibition. Anti-aging gels with resveratrol phytosomes show 28% wrinkle depth decrease (VISIA analysis, n=50), validated against retinoids.

Market Projections

Global cosmeceutical phytosome market, valued at $450M in 2024, projects 18% CAGR to $1.2B by 2030, driven by Indena/Provex products. Dermatology segment (anti-inflammatory, acne) captures 35%, fueled by steroid-sparing claims and OTC accessibility. Asia-Pacific leads adoption (45% share), leveraging herbal traditions and regulatory fast-tracks.

Translation Enablers

QbD manufacturing ensures batch consistency, while real-world evidence from digital health apps accelerates post-market surveillance. Partnerships with L'Oréal and Unilever validate scalability.Challenges like standardization persist, but robust IP and safety data position phytophospholipids for blockbuster status in precision dermatology [15 22 23 24].

11.3 Future Directions in Phyto-Phospholipid-Based Dermatological Therapy

Smart Nanovesicles

Photo-thermal hyalurosomes combining gold nanorods with resveratrol phytosomes promise site-specific activation in psoriatic plaques, achieving 85% cytokine suppression without systemic exposure. Enzyme-cleavable linkers responsive to MMP-2/9 overexpression in chronic wounds will sustain asiaticoside delivery, accelerating re-epithelialization by 40%.

Microbiome-Targeted Systems

Prebiotic phytophospholipids incorporating inulin-phosphatidylcholine complexes will selectively nourish commensal Staphylococcus epidermidis while inhibiting S. aureus in atopic skin, restoring eubiosis. Probiotic-phytosome hybrids (Lactobacillus-loaded transfersomes) show preliminary efficacy against Malassezia folliculitis.

Combination Therapies

4D-printable phytogel patches with multi-compartmental release (anti-inflammatory day, repair night) address diurnal skin cycles. Co-encapsulation of synthetic APIs (tacrolimus) with complementary phytosomes circumvents steroid dependency in recalcitrant eczema.

Translational Roadmap

AI-optimized formulations predicting skin-type responses via Raman spectroscopy accelerate development. Phase III trials targeting NCE status for silymarin phytosome in vitiligo are anticipated by 2028, supported by orphan drug designation.These innovations position phyto-phospholipids as backbone technologies in next-generation dermatology.[15 19 27].

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