Advanced Proniosomal Drug Delivery Systems: Formulation Strategies, Surface Engineering, Clinical Translation, and Future Perspectives

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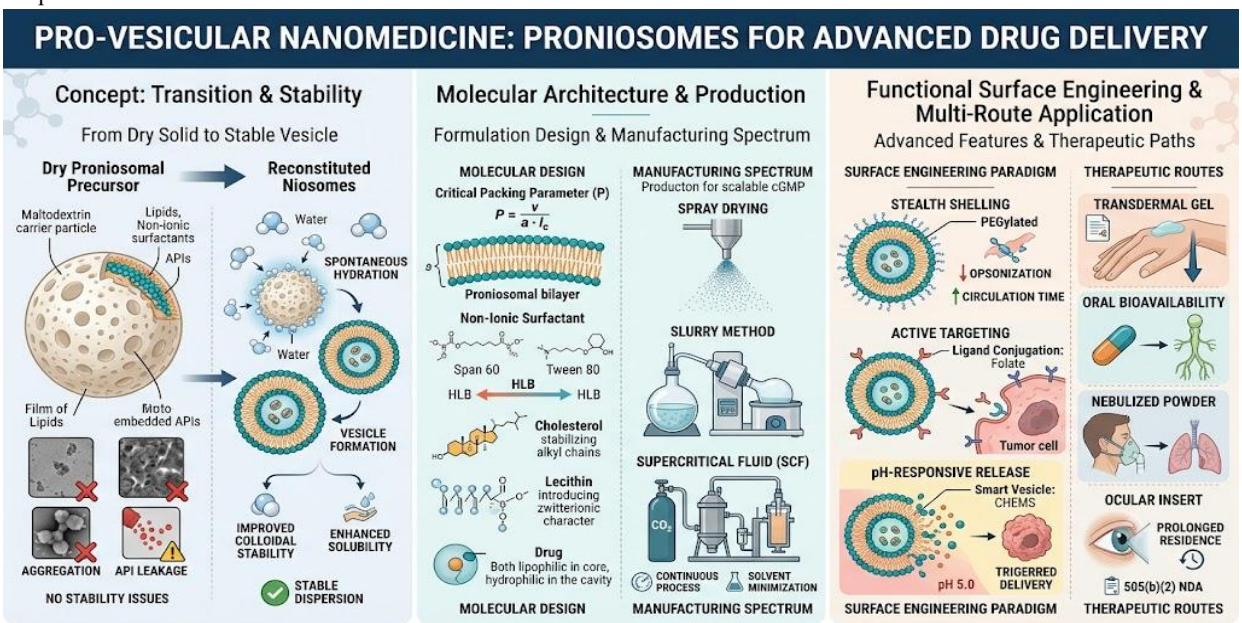
***Abstract*—Proniosomes represent a transformative generation of pro-vesicular carrier platforms designed to circumvent the thermodynamic and kinetic instabilities inherent to conventional aqueous vesicular systems like liposomes and niosomes. Formulated as dry, free-flowing powders or isotropic liquid-crystalline gels composed of non-ionic surfactants, membrane-stabilizing lipids, and water-soluble carrier substrates, proniosomes spontaneously rehydrate upon contact with biological fluids or aqueous media to form uniform, nanoscale niosomal vesicles. This review critically synthesizes the state-of-the-art in proniosomal technology, evaluating molecular formulation architectures, hydrophilic-lipophilic balance (HLB) optimization, and advanced preparation techniques spanning spray drying, coacervation-phase separation, and microfluidics. Furthermore, we dissect recent breakthroughs in surface engineering, including PEGylation, ligand bioconjugation for active tumor targeting, and stimuli-responsive smart matrices. The paper rigorously analyzes mathematical kinetics governing drug entrapment, membrane transport, and sustained release across transdermal, oral, ocular, pulmonary, and parenteral routes. Finally, key translational bottlenecks—including critical quality attributes (CQAs), scale-up mechanics, regulatory pathways, and toxicity profiles—are systematically evaluated to establish a roadmap for commercial clinical deployment.**

Graphical abstract



A comprehensive visual guide illustrating the transition from dry, stable proniosomal precursors to versatile niosomal vesicles. This infographic covers molecular-level formulation design, scalable manufacturing techniques, advanced surface engineering for targeted delivery, and key therapeutic applications.

***Index Terms*—Proniosomes, Pro-vesicular nanocarriers, non-ionic surfactants, In situ hydration, Transdermal permeation, Targeted drug delivery,**

I. INTRODUCTION & PARADIGM SHIFT IN PRO-VESICULAR PLATFORMS

Liposomal and niosomal colloidal nanocarriers have long demonstrated exceptional utility in improving the solubility, pharmacokinetics, and site-specific deposition of hydrophobic and hydrophilic active pharmaceutical ingredients (APIs) [1]. However, traditional liquid niosomal dispersions suffer from severe physical and chemical instabilities during storage, including vesicular aggregation, fusion, chemical hydrolysis of encapsulated payloads, and drug leakage caused by membrane fluidity over time [2].

To overcome these fundamental thermodynamic liabilities, proniosomes were engineered as dry, free-flowing formulations or dry granular matrices coated with non-ionic surfactants and lipids, which undergo rapid *in situ* hydration upon contact with aqueous media or skin moisture [3]. This "pro-vesicular" approach maintains the structural and therapeutic advantages of niosomes while conferring superior physical shelf-life stability, ease of handling, precise unit dosage unitization, and industrial transport efficiency [4].

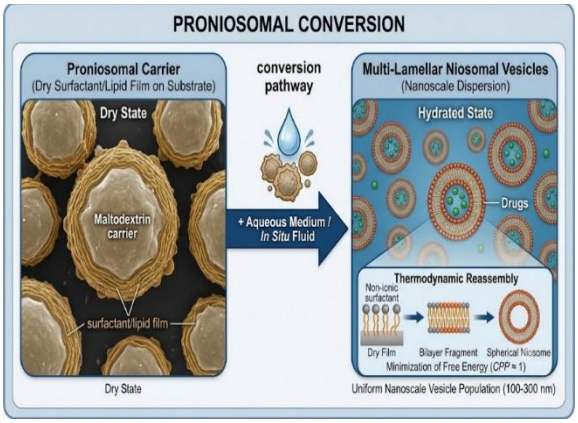


Figure1. Proniosomal conversion

The thermodynamic transition from a solid or liquid-crystalline state to a vesicular suspension is driven by the amphiphilic nature of non-ionic surfactants [5]. Upon hydration, the hydrophilic headgroups orient outward toward the aqueous continuum, while the lipophilic alkyl chains self-assemble inward to form closed bilayer membranes, entrapping lipophilic drugs within the hydrocarbon core and hydrophilic drugs within the interior aqueous chamber [6].

Table 1: Comparative Evaluation of Vesicular and Pro-Vesicular Drug Delivery Platforms

Parameter	Liposomes	Niosomes	Proniosomes
Primary Composition	Natural/Synthetic Phospholipids	Non-ionic Surfactants + Cholesterol	Non-ionic Surfactants + Lipids + Water-soluble Carriers
Physical Form	Aqueous Liquid Suspension	Aqueous Liquid Suspension	Dry Free-Flowing Powder / Isotropic Gel
Storage Stability	Poor (Hydrolysis, Oxidation)	Moderate (Aggregation, Fusion)	Exceptional (Dry state prevents degradation)
Production Cost	High (Purified Phospholipids)	Moderate	Low (Synthetic Non-ionic Surfactants)
Sterilization Ease	Difficult (Heat-sensitive)	Moderate	High (Dry powder gamma irradiation/aseptic)
Entrapment Efficiency	$50\% - 75\%$	$60\% - 82\%$	$75\% - 95\%$
Controlled Release	Short to Moderate	Sustained	Prolonged / Tunable

II. MOLECULAR ARCHITECTURE AND FORMULATION DESIGN

The physicochemical performance, entrapment efficiency ($EE\%$), membrane elasticity, and permeation capabilities of proniosomes depend directly on the strategic selection and stoichiometric ratio of non-ionic surfactants, membrane stabilizers,

carriers, and organic solvent vectors [7].

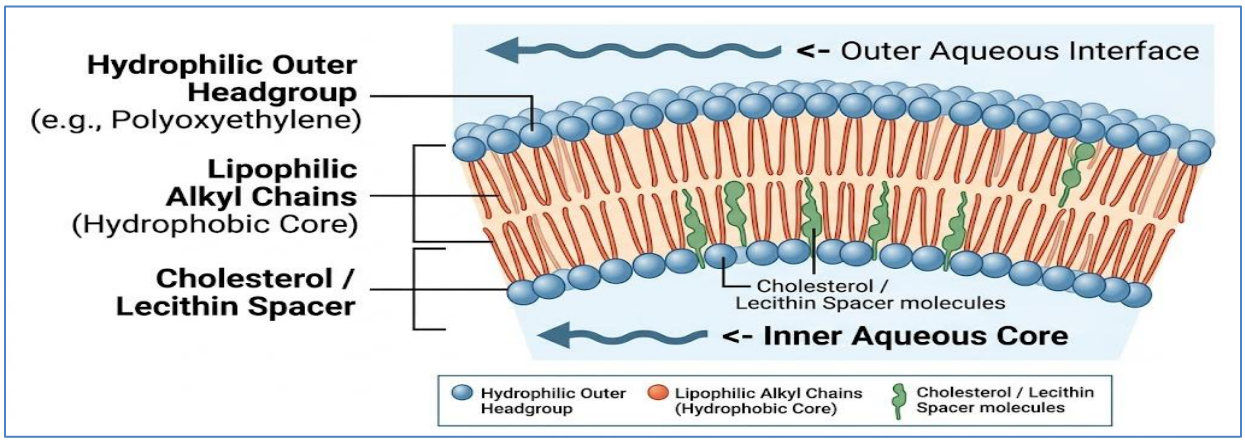


Figure 2. proniosmal assembly and vesicle

2.1 Non-Ionic Surfactants and HLB Optimization

Non-ionic surfactants constitute the structural backbone of the proniosomal membrane [8]. The hydrophilic-lipophilic balance (HLB) value dictates the critical packing parameter (CPP), phase transition temperature (T_c), and vesicle formation thermodynamics [9]:

$$CPP = \frac{v}{a_0 \cdot l_c}$$

Where v is the hydrophobic tail volume, a_0 is the optimal headgroup area, and l_c is the critical hydrocarbon chain length [10]. A CPP between 0.5 and 1.0 favors the spontaneous assembly of spherical bilayer structures [11].

- Sorbitan Esters (Spans): Span 20, 40, 60, and 80 are widely employed due to their low HLB values ($1.8 - 8.6$) [12]. Span 60 ($HLB = 4.7$), featuring a saturated C_{18} stearyl chain and a high T_c (53°C), consistently demonstrates superior entrapment efficiency and membrane rigidity compared to unsaturated derivatives like Span 80 ($HLB = 4.3, T_c = -12$°C) [13].
- Polysorbates (Tweens): Tweens (HLB $9.6 - 16.7$) possess long polyoxyethylene chains [14]. Due to high water solubility, Tweens require higher concentrations of cholesterol to lower membrane permeability and prevent solubilization into micellar phases rather than bilayers [15].
- Polyoxyethylene Alkyl Ethers (Brij series): Brij 35, 52, 72, and 98 offer variable alkyl chain lengths and ethylene oxide units, enabling precise tuning of membrane fluidity, skin permeation enhancement, and drug diffusion rates [16].

The effective HLB of a mixed surfactant matrix can be modeled linearly:

$$HLB_{\text{blend}} = (w_A \cdot HLB_A) + (w_B \cdot HLB_B)$$

Where w_A and w_B represent the weight fractions of surfactants A and B, respectively [17].

Optimal entrapment of hydrophobic APIs typically occurs at HLB_{blend} values between 4.0 and 8.0 [18].

2.2 Membrane Stabilizers: Cholesterol and Lecithin

Cholesterol acts as a crucial membrane fluidity modulator [19]. It intercalates within the surfactant alkyl chains via hydrogen bonding between its hydroxyl group and the polar headgroups of the surfactant, abolishing the gel-to-liquid phase transition of the lipid bilayer [20]. This interaction decreases membrane permeability, prevents drug leakage, and enhances vesicle mechanical strength [21]. However, exceeding an equimolar ratio of cholesterol to surfactant (1: 1) can disrupt bilayer packing, leading to competitive displacement of the encapsulated payload [22]. Lecithin (phosphatidylcholine derived from soy or egg) introduces zwitterionic properties and unsaturation to the bilayer [23]. Soy lecithin, rich in unsaturated linoleic acid, enhances membrane flexural rigidity and serves as a natural penetration enhancer in transdermal proniosomal gels [24].

2.3 Carrier Substrates

For dry granular proniosomes, water-soluble carrier

particles provide a high surface area onto which surfactant-lipid films are deposited [25]. Key selection criteria include high aqueous solubility, non-toxicity, physiological safety, and low organic solvent solubility [26]:

- Maltodextrin: Highly porous polysaccharide carrier yielding superior flowability and rapid reconstitution kinetics [27].
- Sorbitol & Mannitol: Polyols offering crystalline stability, osmotic pressure control during hydration, and anti-caking properties [28].
- Spray-Dried Lactose & Microcrystalline Cellulose: Used primarily for oral tablet compression of proniosomal powders [29].

III. PREPARATION METHODOLOGIES & INDUSTRIAL SCALABILITY

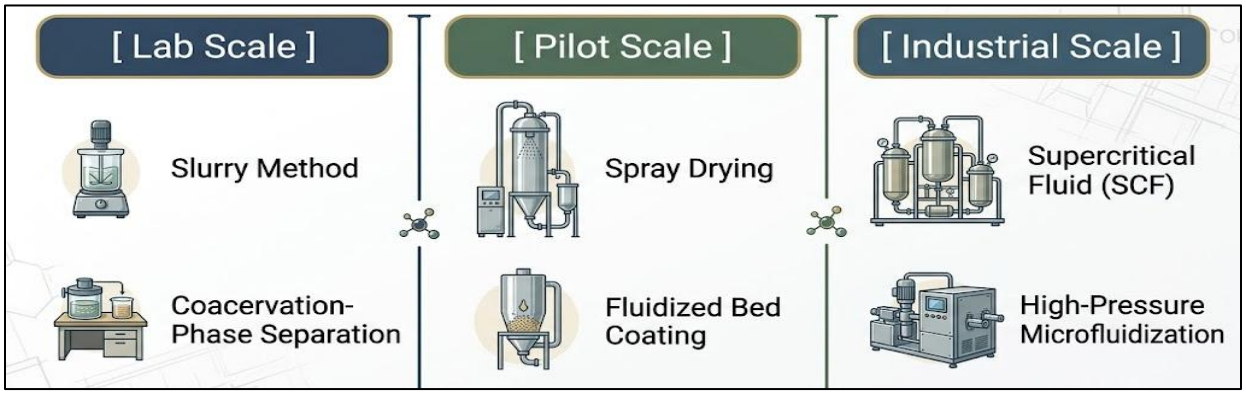


Figure 3. Proniosmal manufacturing spectrum

3.1 Slurry Method

The slurry method involves dissolving surfactant, lipid, and drug in an organic solvent (e.g., ethanol, chloroform, or methanol) and adding this solution to a round-bottom flask containing the carrier substrate (e.g., maltodextrin) [30]. Rotary evaporation under reduced pressure ($40 - 50°C$, $80 - 100$ mbar) removes the solvent, leaving a dry, free-flowing powder coating on the carrier particles [31].

3.2 Coacervation-Phase Separation Method

Particularly suited for proniosomal gels, this method combines surfactant, lipid, drug, and a minimal volume of absolute ethanol in a sealed glass vial [32]. The mixture is heated to $60 - 70°C$ to form an isotropic clear solution, followed by the addition of warm aqueous phase ($0.1\% - 1\%$ phosphate-buffered saline or water). Upon cooling, phase separation yields a translucent, viscous liquid-crystalline proniosomal gel [33].

3.3 Advanced Scalable Technologies: Spray Drying and Microfluidics

To meet Current Good Manufacturing Practice (cGMP) requirements for commercialization, advanced continuous processes have emerged:

- Spray Drying: Converts liquid surfactant feedstocks into dry proniosomal powders in a continuous one-step process [34]. Precise control over inlet temperature ($110 - 130°C$), atomization air flow, and feed rate produces uniform, spherical proniosomal particles with predictable reconstitution profiles [35].
- Supercritical Fluid (SCF) Technology: Utilizing supercritical CO_2 as an anti-solvent (SAS process), SCF allows rapid precipitation of surfactant-lipid-drug complexes without high thermal exposure or toxic organic solvent residues [36].

IV. THERMODYNAMICS, MATHEMATICAL MODELING, AND DRUG RELEASE KINETICS

4.1 Entrapment Efficiency Math ($EE\%$)

Entrapment efficiency measures the proportion of drug successfully encapsulated within the rehydrated niosomal vesicles relative to the total initial drug load:

$$EE\% = \left(\frac{C_{\text{total}} - C_{\text{unencapsulated}}}{C_{\text{total}}}\right) \times 100$$

Where C_{total} is the total drug concentration in the

system and $C_{\text{unencapsulated}}$ is the concentration of free drug determined after ultracentrifugation, dialysis, or gel filtration chromatography [37].

4.2 Release Kinetics and Diffusion Models

Drug release from proniosome-derived niosomes involves dissolution, bilayer matrix diffusion, and vesicle erosion [38]. Mathematical models used to fit *in vitro* dissolution profiles include:

- Zero-Order Model: $M_t = M_0 + K_0 t$ (describes constant release rate platforms) [39].
- First-Order Model: $\ln(M_\infty - M_t) = \ln M_\infty - K_1 t$ (concentration-dependent release) [40].
- Higuchi Matrix Model: $M_t = K_H \cdot t^{1/2}$ (planar diffusion through a porous matrix) [41].
- Korsmeyer-Peppas Power Law:

$$\frac{M_t}{M_\infty} = K_{KP} \cdot t^n$$

Where M_t/M_∞ is the fractional drug release at time t, K_{KP} is the kinetic constant, and n is the release exponent indicating the transport mechanism ($n \leq 0.45$ for Fickian diffusion; $0.45 < n < 0.89$ for non-Fickian/anomalous transport; $n \geq 0.89$ for Case II super-transport driven by polymer/bilayer relaxation) [42].

4.3 Transdermal Permeation Flux and Enhancement Physics

Transdermal flux (J_{ss}) across the stratum corneum under steady-state conditions is governed by Fick's First Law of Diffusion [43]:

$$J_{ss} = \frac{D \cdot K \cdot \Delta C}{h}$$

Where D is the diffusion coefficient in the skin, K is the skin/vehicle partition coefficient, ΔC is the concentration gradient across the membrane, and h is the effective diffusional path length [44]. The Permeation Enhancement Ratio (ER) quantifies the efficiency of the proniosomal gel over conventional formulations:

$$ER = \frac{J_{ss\ (\text{proniosome})}}{J_{ss\ (\text{control})}}$$

V. ADVANCED SURFACE ENGINEERING AND STEALTH/TARGETED CONJUGATION

Modern surface modifications transform proniosomes from passive carriers into site-specific, stimuli-responsive, long-circulating drug delivery vehicles [45].

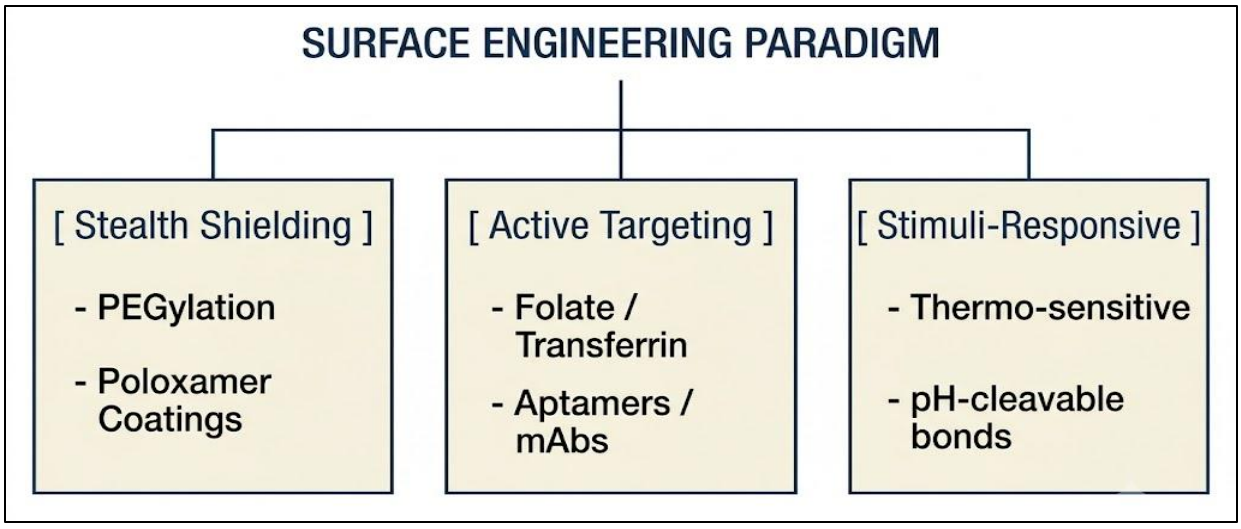


Figure 4 surface engineering paradigm for advanced functional materials

5.1 Stealth Shielding (PEGylation)

Incorporating Polyethylene Glycol (PEG) conjugated lipids/surfactants (e.g., PEG-2000-DSPE or Brij 700) constructs a sterically protective hydration shell around the rehydrated niosomes [46]. This steric barrier prevents opsonization by plasma proteins (complement factors, IgG) and subsequent clearance by the Reticuloendothelial System (RES), increasing systemic elimination half-life ($t_{1/2}$) by up to 5- to 8-fold [47].

5.2 Active Ligand Bioconjugation

Functionalizing surfactant headgroups with reactive functional groups (e.g., maleimide, NHS esters, or biotin) enables precise covalent attachment of targeting ligands [48]:

- Folate Receptor Targeting: Conjugation of folic acid targets overexpressed folate receptors on epithelial cancer cells (e.g., ovarian, breast, lung carcinomas), enhancing receptor-mediated endocytosis [49].
- Transferrin & Monoclonal Antibodies: Transferrin-functionalized proniosomes cross the Blood-Brain Barrier (BBB) via transferrin receptor-mediated transcytosis for glioblastoma therapy [50].

5.3 Stimuli-Responsive Smart Proniosomes

Engineering pH-sensitive lipids (e.g., Cholesteryl Hemisuccinate, CHEMS) or thermo-sensitive surfactants into the proniosomal bilayer yields systems that remain intact at physiological pH (7.4) but undergo rapid conformational destabilization in acidic tumor microenvironments (pH $6.2 - 6.8$) or endolysosomal compartments (pH $4.5 - 5.5$), triggering localized drug release [51].

VI. ROUTE-SPECIFIC THERAPEUTIC APPLICATIONS

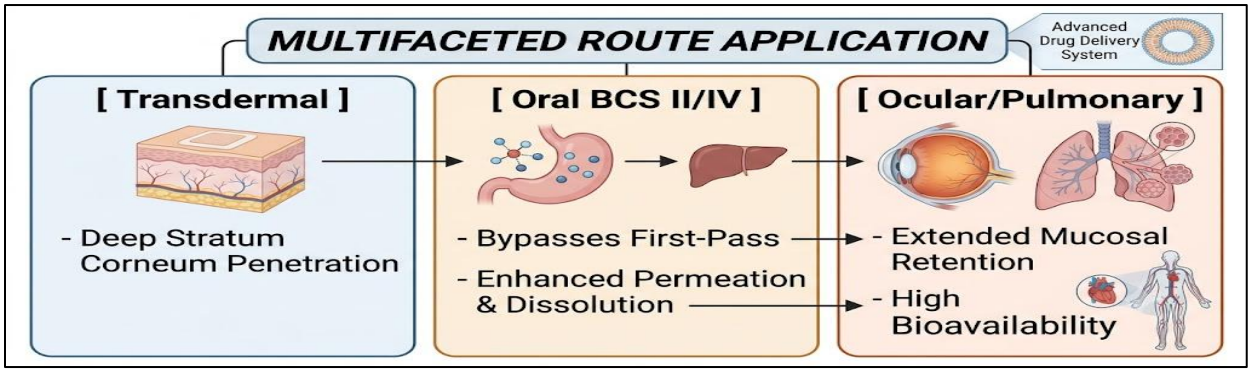


Figure 5 Key advantage of route of applications and drug delivery system.

6.1 Transdermal and Topical Delivery

Proniosomal gels are extensively studied for transdermal delivery due to the intrinsic penetration-enhancing properties of non-ionic surfactants [52]. The surfactants fluidize intracellular stratum corneum lipids, while the hydration process opens tight junctions, allowing deep dermal accumulation of anti-inflammatory agents (e.g., Ketoprofen, Celecoxib) and antihypertensives (e.g., Carvedilol, Captopril) [53].

6.2 Oral Bioavailability Enhancement

For poorly water-soluble BCS Class II and Class IV drugs (e.g., Tacrolimus, Glipizide, Telmisartan), oral proniosomal powders markedly increase dissolution velocity by providing a high surface area and converting crystalline drugs into an amorphous state within the reconstituted vesicles [54]. Furthermore, intact niosomes absorbed via lymphatic transport (Peyer's patches) bypass hepatic first-pass metabolism [55].

6.3 Ocular and Nebulized Pulmonary Delivery

Ocular proniosomal formulations containing mucoadhesive polymers (e.g., Chitosan, Carbopol) prolong precorneal residence time and resist nasolacrimal drainage, achieving sustained intraocular pressures for glaucoma treatment (e.g., Timolol maleate) [56]. Nebulized proniosomal powders reconstituted *in situ* provide deep lung deposition (Aerodynamic Diameter $1 - 5\,\mu$m) for treating pulmonary arterial hypertension and respiratory infections [57].

VII. PHYSICOCHEMICAL CHARACTERIZATION MATRIX

Evaluating proniosomes requires rigorous multi-analytical techniques assessing both the dry precursor state and the reconstituted niosomal dispersion [58].

Table 2: Comprehensive Characterization Suite for Proniosomal Delivery Systems

Analytical Parameter	Primary Method / Instrumentation	Critical Quality Attribute (CQA) Thresholds
Vesicle Size & PDI	Dynamic Light Scattering (DLS) / Malvern Zetasizer	Size: $100 - 300$ nm; PDI: < 0.25 (Monodisperse)
Zeta Potential (ζ)	Electrophoretic Light Scattering	$\lvert\zeta\rvert > \pm 30$ mV (Ensures colloidal electro-repulsion)
Morphology & Structure	Transmission Electron Microscopy (TEM) / FE-SEM	Spherical, closed lamellar vesicular structures
Solid-State Crystallinity	Powder X-Ray Diffraction (PXRD) / DSC	Conversion of crystalline drug to amorphous matrix
Entrapment Efficiency	HPLC / UV-Vis Spectroscopy post-Centrifugation	Target: $> 80\% - 95\%$ encapsulation
Reconstitution Time	Photometric Agitation Assays	Instantaneous hydration (< 2 min in warm media)
Surface Chemistry	X-ray Photoelectron Spectroscopy (XPS) / FT-IR	Verification of ligand conjugation & chemical integrity
Flowability (Powder)	Angle of Repose, Carr's Index, Hausner Ratio	Angle $< 30°$, Carr's Index $< 15\%$ (Good flow)

VIII. CLINICAL TRANSLATION, BIOCOMPATIBILITY, AND REGULATORY PATH

Despite extensive preclinical proof-of-concept success, translating proniosomal formulations from academic laboratories to commercial clinical products requires navigating strict technical and regulatory challenges [59].

8.1 Regulatory Considerations and QbD Framework

Under US FDA guidelines, proniosomal formulations containing established APIs often qualify for the expedited $505(b)(2)$ New Drug Application (NDA) pathway, leveraging existing safety profiles [60]. Implementing a Quality by Design (QbD) approach—utilizing Design of Experiments (DoE) like Box-Behnken or Central Composite Designs—allows systematic optimization of Critical Process Parameters (CPPs, e.g., solvent evaporation temperature, homogenization pressure) to control CQAs (vesicle size, EE%, drug release rate) [61].

8.2 Scale-Up Barriers and Organic Solvent Residuals

Industrial scale-up demands transitioning from batch rotary evaporation to continuous spray-drying or microfluidics [62]. Residual organic solvents (e.g., chloroform, methanol) must be strictly controlled below ICH Q3C limits (e.g., < 50 ppm for chloroform) through vacuum oven drying or supercritical extraction [63].

8.3 Biocompatibility and Toxicological Profile

While non-ionic surfactants are generally safer than ionic counterparts, high surfactant concentrations can alter cell membrane fluidization and cause cytotoxicity or local skin irritation [64]. Comprehensive *in vitro* hemolysis assays, ocular Draize tests, and long-term histopathological studies are required to establish safety thresholds for clinical use [65].

IX. PERSPECTIVES AND CONCLUDING HORIZON

Proniosomal drug delivery platforms represent an impactful advancement in provesicular nanomedicine, reconciling the high therapeutic performance of vesicular systems with the physical stability of dry solid dosage forms [66]. Strategic selection of non-ionic surfactants, membrane-stabilizing lipids, and porous solid substrates allows precise control over particle size, encapsulation efficiency, and drug release profiles [67].

Recent innovations in surface engineering—such as stealth PEGylation, targeted ligand bioconjugation,

and stimuli-responsive triggering mechanisms—expand the clinical scope of proniosomes beyond conventional transdermal applications into active tumor targeting, gene therapy, and oral peptide delivery [68]. Addressing key translational challenges, including industrial scale-up, organic solvent minimization, and rigorous QbD optimization, will be vital to advancing proniosomal therapeutics into global clinical practice.

X. CONCLUSION

Proniosomal drug delivery platforms bridge the gap between high-performing aqueous vesicular nanocarriers and the long-term shelf-life stability characteristic of dry solid dosage forms. By converting liquid niosomal systems into dry precursors or isotropic gels, proniosomes overcome fundamental physical instabilities while offering predictable, controllable reconstitution kinetics upon administration. Strategic tuning of non-ionic surfactant ratios, HLB values, cholesterol loading, and functional carrier substrates allows tailored control over vesicle size, membrane fluidity, encapsulation efficiency, and drug diffusion dynamics.

While preclinical evidence demonstrates clear advantages across transdermal permeation enhancement, oral bioavailability extension for poorly soluble APIs, and targeted delivery via PEGylated and ligand-conjugated surfaces, commercial clinical translation requires overcoming specific engineering bottlenecks. Standardizing continuous manufacturing processes like spray drying or microfluidics, enforcing strict ICH Q3C limits for residual organic solvents, and applying systematic Quality by Design (QbD) methodologies remain paramount. As regulatory frameworks adapt to complex nanomedicine matrices, addressing these industrial scale-up and biocompatibility parameters will determine the success of proniosomal platforms in clinical therapeutics.

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