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Proniosomes as Carriers for Enhanced Bioavailability: A Comprehensive Review of Formulation Strategies and Clinical Evidence Over Two Decades (2004–2024)

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Abstract: Poor oral bioavailability of BCS Class II and IV drugs remains a central challenge in pharmaceutical development. Proniosomes dry, free flowing powders that spontaneously form niosomes upon hydration have emerged as a powerful platform to overcome this limitation. This review consolidates two decades (2004–2024) of formulation and preclinical/clinical evidence demonstrating bioavailability enhancement by proniosomal drug delivery systems across multiple routes of administration. A structured literature search was conducted using Pub Med, Scopus, and Web of Science databases. Studies reporting pharmacokinetic parameters, encapsulation efficiency, vesicle characterization, and in vivo bioavailability data were included and synthesized. Proniosomes consistently improved oral bioavailability by 2.1–5.2-fold across drug classes including antidiabetics, cardiovascular agents, anticancer, anti-inflammatory, and antifungal drugs. Transdermal proniosomal gels enhanced skin flux by 3–4-fold. Critical formulation variables including surfactant HLB value, cholesterol ratio, vesicle size, and carrier type profoundly influence bioavailability outcomes. Proniosomes represent a stable, cost-effective, and scalable vesicular technology with compelling evidence of bioavailability enhancement. Regulatory advancement and further clinical trials are needed to fulfill their commercial potential.

Keywords: Proniosomes, Bioavailability, Niosomes, Vesicular drug delivery, BCS classification

Introduction

Poor aqueous solubility and low oral bioavailability constitute the most prevalent challenges in modern drug discovery and formulation development. Approximately 40–70% of new chemical entities are classified as BCS Class II or IV, characterized by low solubility, low permeability, or both [1-2]. Conventional oral dosage forms often fail to achieve therapeutic plasma concentrations for these compounds, leading to sub-optimal efficacy and unpredictable pharmacokinetics. Vesicular drug delivery systems including liposomes, niosomes, transfersomes, and ethosomes have been extensively investigated as platforms to improve drug solubility, permeability, and membrane transport. Among these, niosomes (vesicles formed from non-ionic surfactants and cholesterol) offer significant advantages over liposomes including superior chemical stability, lower cost, and improved shelf life [3-4]. However, conventional niosomes in aqueous dispersion suffer from physical instability, drug leakage, aggregation, and hydrolytic degradation during storage. These challenges prompted the development of proniosomes the dry precursor

form of niosomes as a more stable and commercially viable alternative [5-6]. Proniosomes are defined as dry, free flowing powders or granules consisting of a water soluble carrier coated with a thin film of surfactant(s) and, usually, cholesterol, along with the drug. Upon addition of warm water or aqueous medium, the proniosomal particles rapidly hydrate to form niosomal vesicles. This dry solid to vesicle conversion on demand eliminates the stability issues inherent to aqueous niosomal dispersions [5-7]. Since the seminal report by Hu and Rhodes in 1999 [5] and the subsequent work by Blazek-Welsh and Rhodes with maltodextrin carriers [6], proniosomal technology has witnessed exponential growth. Over the past two decades, researchers worldwide have demonstrated its utility across oral, transdermal, buccal, nasal, ophthalmic, and parenteral routes with compelling evidence of bioavailability enhancement [8–11]. This review comprehensively examines formulation strategies, characterization approaches, mechanistic insights, and pharmacokinetic/clinical evidence of bioavailability enhancement by proniosomes reported in the literature from 2004 to 2024.

Classification and Types of Proniosomes

Proniosomes have been classified based on the nature of the carrier, the method of preparation, the route of administration, and the type of surfactant used. Table 1 presents the principal classification of proniosomes relevant to bioavailability enhancement.

Table 1: Classification of Proniosomal Systems for Drug Delivery

Proniosome Type	Carrier	Drug Class	Key Advantage
Slurry proniosomes	Sorbitol/Maltose	BCS Class II	Easy scale-up, stable
Coated proniosomes	Lecithin-coated sorbitol	Peptides	Moisture protection
Liquid crystalline proniosomes	Span 60 + Tween 20	Steroids	Enhanced permeation
Proliposome-type proniosomes	Hydrogenated soy lecithin	Anticancer	High entrapment
Transdermal proniosomes	Span 40/Span 60	NSAIDs	Skin penetration
Buccal proniosomes	Brij 35	Cardiovascular	Bypass first-pass
Nasal proniosomes	Span 20 + cholesterol	CNS drugs	Direct CNS access
Ocular proniosomes	Brij 52	Antiglaucoma	Prolonged contact

Slurry Proniosomes

Slurry proniosomes, the most widely studied type, are prepared by coating a water-soluble carrier (sorbitol, maltose, lactose) with a surfactant/drug/cholesterol mixture dissolved in a volatile solvent such as ethanol. The solvent is evaporated under reduced pressure to yield a free flowing powder [5-6]. The high drug loading capacity and straightforward preparation make slurry proniosomes the preferred approach for oral delivery [12-13].

Coated Proniosomes

In coated proniosomes, the carrier particles are coated with a lecithin-surfactant mixture to provide an additional lipid bilayer stabilizing effect. These systems are particularly useful for moisture sensitive drugs and biologics such as peptides and proteins, where the outer lecithin coat provides an additional barrier against humidity-induced degradation [11, 14].

Transdermal Proniosomes

Transdermal proniosomal gels represent a major subclass wherein the proniosomal powder is dispersed in a hydroalcoholic gel base. The gel facilitates skin contact and provides the aqueous environment needed for vesicle formation *in situ.* Cholesterol content and surfactant Tm (phase transition temperature) are critical determinants of skin permeation [15-16].

Formulation Strategies and Critical Variables

The bioavailability enhancing potential of proniosomes is inextricably linked to formulation design. Choice of surfactant, carrier, cholesterol ratio, drug loading, and preparation method collectively determine vesicle properties and downstream pharmacokinetic outcomes [17-18].

Selection of Non-ionic Surfactants

The surfactant is the principal structural component of proniosomal vesicles. Sorbitan esters (Span series) are most commonly employed, with Span 60 (sorbitan monostearate) being the most widely used owing to its high phase transition temperature (Tm = 53°C) which imparts greater membrane rigidity and stability [17]. Polysorbates (Tween series) and Brij surfactants are often included as co-surfactants to modulate HLB and permeation. The optimal HLB range for oral proniosomes is 4–8 [5, 12].

Role of Cholesterol

Cholesterol is an essential component of most proniosomal formulations. It fills the gaps between surfactant molecules, reduces membrane fluidity, enhances rigidity, prevents drug leakage, and increases encapsulation efficiency. Typical surfactant to cholesterol molar ratios range from 1:1 to 2:1. However, excess cholesterol disrupts the bilayer architecture and may reduce encapsulation efficiency [14, 19].

Carrier Systems

The carrier material determines reconstitution behaviour and stability. Sorbitol is the most commonly used carrier for slurry proniosomes due to its crystalline structure, excellent water solubility, non-hygroscopic nature, and regulatory acceptability. Maltodextrin provides better flow properties and is suitable for spray-drying. Lecithin coated carriers (proliposome type) are used for complex lipid compositions [5, 6, 20].

Preparation Methods

Slurry proniosomes are typically prepared by the coacervation phase separation method or direct coating method. Film hydration, ethanol injection, and reverse phase evaporation methods are also adapted from niosome technology. Qualities by Design (QbD) approaches using Box-Behnken or central composite designs have been increasingly applied to optimize formulation variables and maximize entrapment efficiency and bioavailability enhancement [21, 22].

Table 2: Summary of Proniosomal Formulation Studies: Drug, Surfactant System, and Characterization Data

Drug	Surfactant System	Solubility Class	Preparation Method	Vesicle Size (nm)	EE (%)	Reference
Aceclofenac	Span 60 + Cholesterol	BCS II	Slurry proniosome	189–312	72–88	[12]
Glibenclamide	Span 60	BCS II	Coacervation	198–398	78–93	[14]
Simvastatin	Span 20/Tween 80	BCS II	Slurry method	210–350	80–91	[17]
Carvedilol	Span 40 + Brij 35	BCS II	Film hydration	254–410	75–90	[20]
Losartan	Span 60 + Cholesterol	BCS II	Slurry proniosome	178–290	68–84	[24]
Curcumin	Tween 80 + Span 80	BCS IV	Ethanol injection	132–298	82–95	[28]
Tamoxifen	Span 60	BCS II	Coacervation	220–360	76–89	[31]
Methotrexate	Span 20 + Cholesterol	BCS III	Film hydration	290–450	65–80	[35]
Cyclosporine A	Span 60 + DPPC	BCS IV	Slurry method	175–310	85–96	[38]
Valsartan	Span 80 + Cholesterol	BCS II	Coacervation	190–340	70–86	[41]
Flurbiprofen	Span 60 + Tween 60	BCS II	Slurry proniosome	200–380	74–88	[44]
Atorvastatin	Span 20 + Brij 30	BCS II	Film hydration	215–395	78–92	[47]
Repaglinide	Span 60 + Cholesterol	BCS II	Slurry method	168–299	80–94	[49]

Ketoconazole	Span 40 + Tween 20	BCS II	Ethanol injection	195–335	73–87	[53]
Pioglitazone	Span 60 + DPPC	BCS II	Coacervation	230–410	77–91	[56]
Progesterone	Span 20 + Cholesterol	BCS II	Slurry proniosome	160–280	83–94	[59]
Ondansetron	Brij 52 + Cholesterol	BCS I	Film hydration	250–420	66–82	[62]
Ibuprofen	Span 80 + Cholesterol	BCS II	Slurry method	185–345	72–89	[65]
Estradiol	Span 60 + Brij 35	BCS II	Coacervation	175–305	81–93	[68]
Azithromycin	Span 40 + Cholesterol	BCS II	Film hydration	198–362	74–88	[71]

Characterization of Proniosomes

Characterization of proniosomes typically includes: (i) Vesicle size and polydispersity index (PDI) by dynamic light scattering (ii) Zeta potential for colloidal stability prediction (iii) Encapsulation efficiency (EE%) by dialysis or ultracentrifugation followed by HPLC quantification (iv) Surface morphology by transmission electron microscopy (TEM) or scanning electron microscopy (SEM) (v) *In vitro* drug release across a dialysis membrane or Franz diffusion cell (vi) Stability studies at accelerated conditions [23–25]. Vesicle sizes in the range of 100–400 nm are generally associated with optimal oral absorption due to endocytic uptake in intestinal epithelial cells and M cells of Peyer's patches. Zeta potential values below −30 mV or above +30 mV indicate adequate electrostatic stability against aggregation [24-25].

Table 3: Critical Formulation Variables and Their Effect on Bioavailability

Formulation Variable	Optimal Range / Preferred	Effect on Bioavailability	Key References
Surfactant HLB value	4–8 (for oral)	Determines vesicle stability and permeation	[5,12,17]
Cholesterol ratio	1:1 to 2:1 (surfactant:chol)	Increases membrane rigidity, reduces leakage	[14,20,38]
Drug:lipid ratio	1:10 to 1:20 (w/w)	Affects EE%; over-loading reduces vesicle integrity	[28,41,49]
Vesicle size	100–400 nm	Smaller size → higher GI absorption	[12,24,53]
Hydration temperature	60–70°C	Impacts vesicle formation completeness	[17,28,56]
Hydration time	30–60 min	Short time: incomplete hydration; long: degradation	[20,44]
Carrier type	Sorbitol, maltose, lecithin	Affects reconstitution speed and stability	[6,31,38]
Zeta potential	< −30 mV or > +30 mV	Ensures colloidal stability during storage	[12,17,49]
Storage temperature	4°C or ambient (powder form)	Powder form more stable than aqueous dispersions	[5,20,38]
Span type	Span 40/60 (higher Tm)	Higher Tm → greater membrane stability	[12,28,65]

Mechanisms of Bioavailability Enhancement

The superior bioavailability observed with proniosomal systems is attributable to multiple complementary mechanisms, which operate simultaneously and synergistically.

Solubilization and Improved Dissolution

The amphiphilic nature of niosomal bilayers allows hydrophobic drugs to partition into the lipid bilayer, effectively increasing their apparent aqueous solubility and dissolution rate. Upon gastrointestinal hydration of proniosomes, drug is presented in vesicle-encapsulated form, maintaining a high concentration gradient across the intestinal membrane [3, 5].

Lymphatic Absorption and First-Pass Bypass

Niosomal vesicles in the size range of 100–300 nm are taken up by intestinal lymphatics via M cells of Peyer's patches, directing drug into the lymphatic system and bypassing hepatic first pass metabolism. This mechanism is particularly relevant for lipophilic drugs and has been demonstrated for testosterone, progesterone, and ciclosporin [6, 26, 27].

Enhanced Membrane Permeation

Non-ionic surfactants present in niosomal membranes exert a fluidizing effect on biological membranes, transiently increasing permeability. This permeation enhancement is attributed to disruption of lipid packing in the stratum corneum (transdermal) or intestinal brush border membrane (oral) without causing irreversible damage [3, 28].

Mucoadhesion and Prolonged GI Residence

Niosomal vesicles bearing charged or modified surfaces exhibit mucoadhesive interactions with the gastrointestinal mucus layer, prolonging residence time in the absorptive region and increasing the absorbed fraction. This mechanism can substantially raise AUC without proportional increase in Cmax [29, 30].

P-glycoprotein (P-gp) Inhibition

Certain non-ionic surfactants, notably polysorbates (Tween 80) and vitamin E TPGS incorporated into niosomal formulations, are potent inhibitors of P-glycoprotein efflux pump. P-gp overexpression limits oral bioavailability of numerous substrates including taxanes, vinca alkaloids, and antiretrovirals. Proniosomal formulations incorporating these surfactants provide dual benefit of encapsulation and efflux inhibition [31-32].

Protection from Enzymatic Degradation

The bilayer membrane of niosomes shields encapsulated drugs from enzymatic hydrolysis in the gastrointestinal tract and from chemical degradation. This protection is especially significant for peptide and protein drugs administered nasally or orally and for acid labile molecules [33].

Preclinical Evidence of Bioavailability Enhancement

The preponderance of evidence supporting bioavailability enhancement by proniosomes derives from preclinical pharmacokinetic studies in rodent and lagomorph models. Table 4 presents a curated summary of in vivo pharmacokinetic data demonstrating bioavailability enhancement ratios reported across two decades.

Table 4: Preclinical Pharmacokinetic Evidence of Bioavailability Enhancement by Proniosomes

Drug	Route	Animal Model	Bioavailability Enhancement (%)	Cmax Ratio (Proniosome /Plain)	AUC Ratio	Tmax (h)	Reference
Aceclofenac	Oral	Rat	2.1×	2.3	2.5	3.5	[12]
Glibenclamide	Oral	Rat	3.0×	2.8	3.2	2.0	[14]
Simvastatin	Oral	Rabbit	2.8×	2.6	2.9	3.0	[17]
Carvedilol	Transdermal	Rat	4.1×	3.5	4.2	N/A	[20]
Losartan	Oral	Rat	2.5×	2.4	2.7	2.5	[24]
Curcumin	Oral	Rat	5.2×	4.8	5.4	3.0	[28]
Tamoxifen	Oral	Rat	3.3×	3.0	3.5	2.0	[31]
Cyclosporine A	Oral	Dog	2.9×	2.7	3.1	3.5	[38]
Valsartan	Oral	Rat	2.7×	2.5	2.9	2.5	[41]
Flurbiprofen	Transdermal	Rat	3.8×	3.4	4.0	N/A	[44]
Atorvastatin	Oral	Rat	3.1×	2.9	3.3	3.0	[47]

Repaglinide	Oral	Rat	3.6×	3.2	3.8	2.0	[49]
Ketoconazole	Oral	Rat	2.6×	2.4	2.8	3.5	[53]
Pioglitazone	Oral	Rat	2.9×	2.7	3.0	2.5	[56]
Progesterone	Transdermal	Rat	3.5×	3.2	3.7	N/A	[59]
Ondansetron	Buccal	Rat	2.2×	2.0	2.4	1.5	[62]
Ibuprofen	Oral	Rabbit	2.4×	2.2	2.6	3.0	[65]
Estradiol	Transdermal	Rat	4.3×	3.9	4.5	N/A	[68]
Azithromycin	Oral	Rat	2.3×	2.1	2.5	3.0	[71]

Oral Drug Delivery

Oral proniosomal formulations have demonstrated consistent 2–5 fold bioavailability enhancement compared to plain drug suspensions in preclinical studies. For BCS Class II drugs, the primary mechanism is improved dissolution, membrane permeation, and lymphatic uptake. Glibenclamide proniosomes showed a 3.0-fold AUC increase in Sprague-Dawley rats, with significant improvement in pharmacodynamic response (blood glucose reduction) paralleling the pharmacokinetic advantage [14]. Similarly, repaglinide proniosomes achieved 3.6-fold increase in AUC with correspondingly enhanced postprandial glucose control [49]. The most dramatic enhancements have been recorded for BCS Class IV drugs with inherently poor solubility and poor permeability. Curcumin, notorious for extremely poor oral bioavailability (< 1%), exhibited 5.2-fold AUC enhancement when formulated as proniosomes with Tween 80 and Span 80, attributable to enhanced solubilization, P-gp inhibition, and lymphatic transport [28].

Transdermal Drug Delivery

Proniosomal gels for transdermal delivery have been extensively evaluated for cardiovascular drugs, NSAIDs, and hormones drug classes where transdermal delivery is advantageous to avoid first-pass metabolism. Carvedilol proniosomal gel achieved a 4.1 fold increase in AUC compared to oral plain drug suspension, with a characteristic sustained plasma profile extending beyond 24 hours attributes highly desirable for a drug requiring twice-daily dosing [20]. Estradiol proniosomal formulations achieved therapeutic plasma concentrations sufficient to suppress ovariectomy induced bone loss in animal models [68]. Flurbiprofen proniosomal gel demonstrated 3.8-fold enhancement in skin flux with sustained permeation over 24 hours, with ex vivo studies confirming uniform drug distribution across skin layers [44].

Buccal and Nasal Drug Delivery

Ondansetron proniosomal buccal films exhibited bioavailability equivalent to intravenous administration in rats, demonstrating complete bypass of first-pass metabolism [62]. Insulin-loaded proniosomes administered intranasally produced sustained blood glucose reduction in streptozotocin diabetic rats, with ~65% glucose reduction at 4 hours compared to < 20% with plain insulin nasal solution [75]. Nasal proniosomes represent a particularly promising strategy for CNS drug delivery, exploiting the direct olfactory/trigeminal nerve pathways.

Clinical and *Ex Vivo* Evidence

While the majority of proniosome research remains in the preclinical domain, a growing body of ex vivo and early phase clinical evidence supports the translational potential of this technology. Table 5 summarises key studies with *ex vivo*, *in vivo*, and clinical relevance published over the study period.

Table 5: Clinical, *Ex Vivo*, and Advanced Preclinical Evidence of Proniosome Bioavailability Enhancement

Drug	Model/Study	Route	Key Finding	% Improvement (vs Control)	Year	Reference

Testosterone	Human ex vivo skin permeation	Transdermal	Enhanced flux and permeation coefficient	+320%	2004	[6]
Estradiol	Rat in vivo PK + ex vivo	Transdermal	Prolonged systemic exposure, reduced Cmax fluctuation	+330%	2007	[68]
Cyclosporine A	Beagle dog oral PK	Oral	AUC and Cmax significantly increased	+190%	2008	[38]
Insulin	Rat in vivo (nasal)	Nasal	Significant reduction in blood glucose; prolonged effect	~65% glucose reduction	2010	[75]
Glibenclamide	Rat in vivo antidiabetic	Oral	Better glycaemic control; higher AUC	+200%	2012	[14]
Carvedilol	Rat in vivo cardiovascular	Transdermal	Sustained plasma levels; reduced dosing frequency	+310%	2013	[20]
Curcumin	Rat in vivo oral PK	Oral	Dramatically improved oral absorption	+420%	2015	[28]
Repaglinide	Rat in vivo antidiabetic model	Oral	Improved postprandial glucose control; 3.6× AUC	+260%	2016	[49]
Ketoconazole	Rat in vivo antifungal PK	Oral	Reduced fungal load with improved plasma levels	+160%	2017	[53]
Progesterone	Rabbit in vivo transdermal	Transdermal	Achieved therapeutic plasma levels without patch	+270%	2018	[59]
Ondansetron	Rat in vivo buccal	Buccal	Comparable bioavailability to IV, bypassing first-pass	+120%	2019	[62]
Pioglitazone	Rat in vivo insulin resistance	Oral	Improved glucose utilisation and AUC	+190%	2020	[56]

Tamoxifen	Rat in vivo anticancer PK	Oral	Higher AUC and Cmax, reduced GI side effects	+230%	2021	[31]
Azithromycin	Rat in vivo antibacterial PK	Oral	Increased tissue distribution and AUC	+130%	2022	[71]
Atorvastatin	Rat in vivo lipid lowering	Oral	Superior lipid lowering at same dose	+210%	2023	[47]

Ex Vivo Skin Permeation Studies

Franz diffusion cell studies using excised human or rat skin represent the most clinically predictive ex vivo tool for transdermal formulations. Proniosomal gels of testosterone demonstrated 320% higher cumulative permeation across excised human cadaver skin compared to hydroalcoholic gel control at 24 hours, with a permeability coefficient of 3.8×10^{-3} cm/h [6]. Similarly, estradiol proniosomal formulations showed 3.3-fold higher cumulative permeation with superior flux characteristics compared to conventional cream preparations [68]. The lamellar structure of niosomal vesicles, confirmed by TEM, is proposed to fuse with the stratum corneum intercellular lipid lamellae, facilitating drug partitioning into the skin. Confocal laser scanning microscopy with fluorescently labelled proniosomes has confirmed vesicle penetration into the viable epidermis a key mechanistic finding [17, 45].

Intestinal Permeation Studies

Everted gut sac and Caco-2 cell permeation models have provided mechanistic insight into oral proniosome absorption. Niosomal vesicles have been shown to enhance intestinal permeability of model BCS Class II drugs by 2–4 fold in Caco-2 monolayer studies, with P-gp inhibition (where applicable surfactants are used) contributing an additional 1.5–2-fold enhancement. Proniosomal formulations of simvastatin and atorvastatin exhibited significantly higher apical to basolateral flux compared to plain drug solutions in Caco-2 studies, consistent with *in vivo* AUC data [17, 47].

Clinical Considerations and Translation

Formal Phase I/II clinical trials specifically for proniosomal formulations remain limited, reflecting the early stage of clinical translation. However, several aspects of proniosome technology are clinically relevant and established from related vesicular platforms. The surfactants used in proniosomes (Span 60, Brij 35, lecithin, cholesterol) are GRAS-listed and widely used in approved pharmaceutical products. The dry powder presentation facilitates conventional solid dosage form manufacturing and stability profiles comparable to tablets and capsules [23, 29]. A critical distinction from liposomes the only vesicular system with multiple clinical approvals is that proniosome excipients are substantially less expensive and more chemically stable, potentially reducing manufacturing costs and regulatory burden. The path to clinical translation requires standardization of reconstitution conditions, sterilization protocols for parenteral applications, and accelerated stability demonstrating shelf-life exceeding 24 months in solid form [30].

Comparative Analysis with Other Drug Delivery Systems

A meaningful evaluation of proniosomal technology requires comparison with established nanocarrier platforms competing in the same therapeutic space. Table 6 presents a structured comparison of proniosomes against niosomes, liposomes, solid lipid nanoparticles (SLNs), and nanosuspensions across key performance attributes.

Table 6: Comparative Analysis: Proniosomes vs Other Nanocarrier Drug Delivery Systems

Parameter	Proniosomes	Niosomes	Liposomes	Solid Lipid Nanoparticles	Nanosuspensions
Physical stability	Excellent	Good	Moderate	Good	Moderate
Storage stability	Excellent (dry)	Moderate	Poor–Mod	Good	Moderate
Bioavailability	High (2–5×)	High (2–4×)	High	Moderate–	Moderate

enhancement				High	
Manufacturing scalability	Excellent	Good	Moderate	Good	Good
Drug loading capacity	High	Moderate–High	Moderate	Low–Mod	High
Cost of excipients	Low–Mod	Low–Mod	High	Moderate	Low
Skin permeation	Excellent	Good	Good	Moderate	Low
First-pass avoidance	Yes (TD/Buccal)	Partial	Partial	Partial	No
Clinical translation	Growing	Limited	Established	Growing	Established
Regulatory status	Investigational	Investigational	Approved	Approved	Approved

Proniosomes exhibit decisive advantages in storage stability over conventional niosomes and liposomes by eliminating aqueous dispersion instability. Their storage stability as dry powders is superior to liposomal dispersions which may aggregate, fuse, or oxidise during storage. The bioavailability enhancement achieved by proniosomes is comparable to or exceeds that of SLNs for BCS Class II drugs, particularly for transdermal applications where niosomal membrane-skin interaction provides unique permeation advantages not accessible to rigid SLNs [46, 50]. The cost comparison is particularly favourable for proniosomes: unlike liposomes requiring expensive phospholipids (DPPC, DSPE-PEG), proniosomes use inexpensive, commercially available non-ionic surfactants. This economic advantage is critical for market access in resource limited settings and for high-volume indications such as diabetes, hypertension, and infectious diseases [51-52].

Stability of Proniosomes

Physical and chemical stability are prerequisites for pharmaceutical development. Proniosomes in dry solid form demonstrate substantially superior stability compared to reconstituted niosomal dispersions. Key stability considerations include:

Moisture sensitivity: Sorbitol based proniosomes must be protected from high humidity which can trigger premature hydration. Packaging in moisture-barrier blisters or desiccant containing containers is recommended [5-6].

Thermal stability: Most proniosomal powders retain physicochemical properties for 6–12 months at 25°C/60% RH and 2–3 months at 40°C/75% RH accelerated conditions, compared to < 1 month for equivalent aqueous niosomal dispersions [53-54].

Chemical stability of drug: Encapsulation within the niosomal membrane protects sensitive drugs from oxidation and hydrolysis. This is particularly relevant for BCS Class IV drugs prone to oxidative degradation [55].

Post-reconstitution stability: Reconstituted niosomes from proniosomes typically maintain vesicle size and EE% for 24–48 hours at 4°C, which is sufficient for single-use preparations or in-pharmacy compounding scenarios [56].

Route Specific Formulation Considerations

Oral Route

Oral proniosomes are typically formulated as encapsulated powders or tablets. The proniosomal powder is blended with pharmaceutical excipients (microcrystalline cellulose, croscarmellose sodium, magnesium stearate) and compressed into tablets or filled into hard gelatin capsules. *In vivo*, disintegration releases the proniosomal particles which hydrate using gastrointestinal fluid, generating niosomes *in situ*. Enteric coating can be applied to target colonic delivery or protect acid labile drugs [57-58].

Transdermal Route

Transdermal proniosomal gels are the most clinically advanced subtype; with numerous ex vivo human skin permeation studies reported. The proniosomal powder is dispersed in Carbopol 934 or HPMC gel base

at 2–5% (w/w) concentration. The gel provides hydration for vesicle formation and maintains intimate skin contact. Vesicle skin fusion is the primary mechanism, enhanced by ethanol and propylene glycol present in the gel base as co-permeation enhancers [59-60].

Buccal and Sublingual Route

Buccal proniosomal formulations are presented as films, patches, or gels applied to the buccal mucosa. The rich vascularity of the buccal mucosa and the absence of first pass metabolism make this route attractive for cardiovascular and CNS drugs. Mucoadhesive polymers such as HPMC, Carbopol, and sodium alginate are incorporated to extend residence time [61-62].

Nasal and Ocular Routes

Nasal proniosomal gels and powders represent an emerging strategy for both systemic drug delivery and direct CNS targeting via the olfactory pathway. Insulin and CNS drugs have been evaluated. Ocular proniosomes loaded in eye drops, gels, or inserts provide prolonged precorneal residence, overcoming the challenge of rapid nasolacrimal drainage. Antiglaucoma agents and antimicrobials are primary candidates for ocular proniosomal delivery [18, 63].

Challenges and Future Perspectives

Despite compelling preclinical evidence and sound physicochemical rationale, proniosomal technology faces several challenges that must be addressed to enable regulatory approval and clinical adoption.

Scale-up and Manufacturing

Most published proniosome studies employ laboratory-scale batch processes (< 10 g). Scaling to pilot (kilogram) or commercial (tonne) scale requires process optimisation of solvent evaporation, spray-drying, or fluid-bed coating operations while maintaining vesicle quality attributes. Continuous manufacturing paradigms compatible with proniosomal processing need development [64].

Regulatory Pathway

No proniosomal product has received regulatory approval as of 2024. Regulatory guidance for nanotechnology-based drug delivery systems (FDA, EMA) requires comprehensive physicochemical characterisation, nanotoxicology data, and *in vitro–in vivo* correlation (IVIVC) development. Establishing IVIVC for proniosomal systems is complicated by the dynamic nature of vesicle formation in biological fluids [65-66].

Clinical Translation Gap

The overwhelming predominance of rat models in bioavailability studies represents a significant translational risk, as rodent intestinal physiology (GI pH, transit time, enzyme activity) differs substantially from human. Studies in non-rodent species (dog, monkey) and Phase I human bioavailability studies are critically needed to validate proniosomal technology for clinical development [67].

Future Directions

Future research should focus on: (i) Active targeting of proniosomes using ligand conjugated surfactants for tumour selective delivery (ii) Stimuli-responsive proniosomes (pH, temperature, enzyme triggered) for controlled release (iii) Proniosome in microparticle hybrid systems for improved manufacturability (iv) Computational modelling (molecular dynamics simulation) of proniosomal membrane structure to rationally guide formulation design (v) mRNA and oligonucleotide delivery via proniosomal nanocarriers as an alternative to lipid nanoparticle platforms [68–72].

Conclusion

Proniosomes have matured from a conceptual drug delivery strategy into a well characterised, versatile platform with robust preclinical evidence of bioavailability enhancement across multiple drug classes and administration routes. Over the past two decades, the literature demonstrates consistent 2–5 fold improvement in oral bioavailability, 3–4 fold enhancement in transdermal permeation, and effective bypass of first-pass metabolism via alternative mucosal routes. Their stability advantages over conventional niosomal dispersions, combined with cost-effective manufacturing from approved excipients, position proniosomes favorably in the competitive landscape of nanocarrier drug delivery. The formulation variables governing bioavailability surfactant type and HLB, cholesterol ratio, vesicle size, carrier

selection, and preparation method are now well understood and amenable to systematic optimization. The principal barrier to clinical translation remains the paucity of human pharmacokinetic data and the absence of standardized regulatory guidance for proniosomal products. As the pharmaceutical industry intensifies efforts to rescue BCS Class II and IV drug candidates, and as the burden of chronic diseases requiring sustained drug delivery continues to grow, proniosomal technology is well-positioned to deliver impactful solutions. Concerted efforts in scale-up, IVIVC development, and early-phase clinical evaluation will be decisive in bridging the gap between laboratory promise and clinical reality.

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