WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
Coden USA: WJPRAP Impact Factor 8.63
Volume 15, Issue 8, 212-243. Review Article ISSN 2277–7105

PRONIOSOMAL DRUG DELIVERY SYSTEMS: FABRICATION APPROACHES, MECHANISTIC INSIGHTS, AND MULTIFUNCTIONAL THERAPEUTIC APPLICATIONS

Mujammil[1], Swati Joshi*[2], Jyoti Gupta[3], Maneesh Banyal[4]

[1]Student, [2]Assistant Professor, [3]Head of Department,
Department of Pharmacy, IEC University, Baddi, Himachal Pradesh.
[4]Assistant Professor, ICFAI University, Baddi, Himachal Pradesh.

Article Received on 16 March 2026,
Article Revised on 06 April 2026,
Article Published on 16 April 2026,

https://doi.org/10.5281/zenodo.19589600

***Corresponding Author**
Swati Joshi
Assistant Professor, Department of Pharmacy, IEC University, Baddi, Himachal Pradesh.

How to cite this Article: Mujammil[1], Swati Joshi*[2], Jyoti Gupta[3], Maneesh Banyal[4]. (2026). Proniosomal Drug Delivery Systems: Fabrication Approaches, Mechanistic Insights, And Multifunctional therapeutic applications. World Journal of Pharmaceutical Research, 15(8), 212–243.

ABSTRACT

Proniosomes have emerged as a versatile and advanced provesicular drug delivery system designed to overcome the limitations associated with conventional vesicular carriers such as liposomes and niosomes. These dry, free-flowing formulations are composed of non-ionic surfactants, lipids, and carrier materials, and upon hydration, they spontaneously convert into niosomal vesicles capable of encapsulating both hydrophilic and hydrophobic drugs. This unique transformation enhances physicochemical stability, minimizes drug leakage, and improves shelf-life compared to traditional systems.The present review highlights the structural design, mechanistic aspects, fabrication strategies, and physicochemical characterization of proniosomes, along with their functional modifications for targeted and controlled drug delivery. Advanced engineering approaches, including ligand-mediated targeting, polymer hybridization, and stimuli-responsive systems, further expand their applicability by enabling site-specific drug release and improved therapeutic efficiency. Proniosomes demonstrate significant potential across multiple routes of administration, including oral, parenteral, transdermal, ocular, pulmonary, intranasal, and vaginal delivery. Their ability to enhance drug solubility, protect labile molecules from degradation, and improve bioavailability has been validated through various

pharmacokinetic and preclinical studies. Despite these advantages, challenges such as scale-up complexities, cost considerations, and limited clinical data remain barriers to their widespread application. Nevertheless, ongoing advancements in formulation design and manufacturing technologies are expected to facilitate their clinical translation. Overall, proniosomes represent a promising platform for next-generation drug delivery with improved efficacy, safety, and patient compliance.

KEYWORDS: Proniosomes; Vesicular drug delivery; Provesicular systems; Niosomes; Controlled drug release, Nanocarriers; Bioavailability enhancement.

INTRODUCTION

Vesicular drug encapsulation represents a significant breakthrough in modern pharmaceutical research, providing a highly efficient platform for targeted drug delivery. By facilitating the direct transport of drugs to specific sites in the body, vesicular systems reduce the distribution of active agents in non-target tissues, thereby minimizing systemic toxicity and enhancing therapeutic efficacy.[1,2] This revolutionary concept has spurred the development of a variety of vesicular and provesicular systems, including liposomes, niosomes, proliposomes, and proniosomes, each of which has unique structural and functional characteristics that determine its suitability for particular therapeutic applications.[3,4]

Liposomes were among the earliest vesicular systems to be widely studied. These vesicles consist of concentric phospholipid bilayers surrounding an aqueous core, enabling the encapsulation of both hydrophilic and hydrophobic drugs. Hydrophilic drugs are sequestered within the aqueous interior, whereas hydrophobic drugs are integrated into the lipid bilayers. This unique architecture facilitates improved drug solubility, stability, and bioavailability.[5] Despite these advantages, liposomes face considerable limitations, particularly when administered orally. The lipid bilayers are prone to physicochemical instability, including fusion, hydrolysis, and oxidation, which can result in premature drug leakage and reduced therapeutic efficacy. In addition, liposomes often suffer from a limited shelf-life, sensitivity to temperature variations, and challenges in large-scale industrial production, constraining their practical use in pharmaceutical applications.[6]

To overcome these limitations, proliposomes were introduced as a dry, provesicular system capable of converting into liposomes upon hydration. By storing the lipid components in a dry state, proliposomes minimize aqueous stability issues such as hydrolysis and oxidation,

thereby enhancing shelf-life and ease of handling. However, proliposomes heavily rely on phospholipids, which are expensive and can present challenges regarding biocompatibility and large-scale production.[7]

Building on this foundational concept, proniosomes were developed as a more versatile provesicular system. Proniosomes utilize tunable non-ionic surfactants instead of phospholipids, resulting in dry, free-flowing powders that spontaneously form multi-lamellar niosomal vesicles upon hydration.[8,9] This dry formulation offers several advantages: increased chemical stability, reduced susceptibility to leakage, fusion, or aggregation, and enhanced ease of transport, packaging, and storage. Moreover, proniosomes can encapsulate both hydrophilic and hydrophobic drugs efficiently, outperforming conventional liposomes and niosomes in terms of stability, safety, and versatility.[10,11]

Since their emergence in the 1980s, proniosomes have gained considerable attention in drug delivery research. Unlike conventional vesicles, proniosomes not only improve chemical stability but also offer functional versatility across multiple administration routes, including oral, topical, parenteral, and pulmonary pathways. The dry nature of proniosomes allows for easy conversion into unit dosage forms, which is highly advantageous for large-scale industrial manufacturing and commercial applications.[12,13]

Table 1: Comparative evaluation of vesicular drug delivery systems.

Feature	Liposomes	Niosomes	Proniosomes	Transfersomes	Ethosomes
Physical state	Liquid	Liquid/Gel	Dry powder	Flexible vesicles	Ethanol-based vesicles
Stability	Moderate	Moderate	High	Moderate	Low-Moderate
Drug encapsulation	Hydrophilic/ hydrophobic	Hydrophilic/ hydrophobic	High efficiency	Moderate	Moderate
Shelf-life	Short	Moderate	Long	Moderate	Moderate
Targeting	Passive	Passive	Passive + Active	Transdermal	Transdermal
Scalability	Limited	Moderate	High	Low	Moderate
Handling	Moderate	Moderate	Excellent	Moderate	Moderate

Proniosomes' evolution represents a critical step from passive drug carriers to engineered composite systems capable of controlled and targeted drug delivery. By integrating functional excipients, polymers, and ligands, proniosomes overcome many limitations of traditional vesicular systems, offering enhanced therapeutic efficacy, improved patient compliance, and broad applicability across diverse drug delivery scenarios.[14,15]

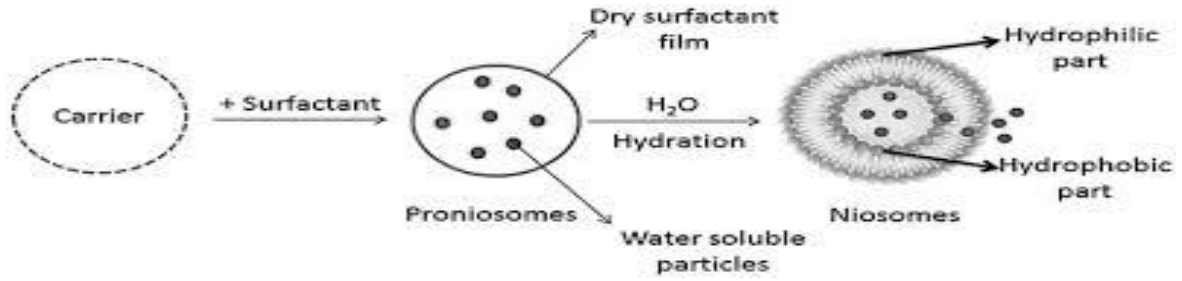

Figure 1: Schematic representation of proniosomes transforming into niosomes.

Mechanistic insights into proniosomal drug delivery

Proniosomes exist in an inactive provesicular form and convert into functional niosomal vesicles upon hydration. This transformation can occur through direct absorption of moisture from the skin or mucosal surfaces, or via immersion in aqueous media, such as water or buffer solutions.[16,17] The hydration process is pivotal, as it activates the vesicular structure and facilitates encapsulation of the drug payload within the vesicle, ensuring protection from external environmental factors.

Upon hydration, proniosomes reorganize into multi-lamellar vesicles. Hydrophilic drugs are trapped in the aqueous core, while hydrophobic drugs reside within the lipid bilayers. This structural arrangement facilitates controlled and sustained drug release, which can be further fine-tuned using stimuli-responsive strategies, including pH, temperature, or redox-sensitive triggers.[18,19] This capability is critical for targeting specific pathological sites such as tumors or inflamed tissues, enhancing drug accumulation at the target while minimizing systemic exposure and toxicity.[20,21]

The protective matrix of proniosomes shields sensitive drugs from enzymatic degradation, oxidation, and hydrolysis, extending the drug's in vivo half-life. Additionally, the hierarchical architecture of proniosomes allows for modulation of drug release kinetics, enabling prolonged therapeutic activity and reducing the frequency of dosing.[22]

Surface functionalization of proniosomes with targeting ligands, such as folic acid, peptides, or antibodies, facilitates receptor-mediated endocytosis, enabling selective drug delivery to diseased cells while sparing healthy tissues.[23] Furthermore, the inclusion of polymers such as chitosan, carbopol, and hydroxypropyl methylcellulose imparts mucoadhesive properties, increasing retention time at mucosal sites and enhancing absorption.[24,25]

In summary, the mechanistic framework of proniosomal drug delivery combines

1. Controlled drug encapsulation and protection from degradation
2. Stimuli-responsive release mechanisms
3. Surface functionalization for active targeting
4. Mucoadhesive properties for enhanced absorption.

These characteristics position proniosomes as highly adaptable, next-generation drug delivery systems capable of overcoming multiple pharmacokinetic barriers.

The architectural blueprint of proniosomes: types and composite nature

Proniosomes are advanced composite systems designed to combine functional versatility, structural stability, and controlled drug delivery. Their architecture is composed of surfactants, lipids, and carrier matrices, forming a solid-phase matrix that allows precise encapsulation and release of drugs.[26,27] Upon hydration, proniosomes convert into niosomal vesicles, whose properties are dictated by the initial formulation composition and processing parameters.[28]

Conventional classification based on vesicular morphology

Proniosomes are typically classified according to the vesicle type generated upon hydration: small unilamellar proniosomes (SUPs), large unilamellar proniosomes (LUPs), and dry granular proniosomes (DGPs).

Table 2: Proniosomes classification according to the vesicle type.

Proniosome Type	Vesicle Size	Composition	Preparation Method	Applications
SUPs	25–100 nm	Non-ionic surfactants (Span 60, Tween 80), cholesterol	Sonication, microfluidization	High drug ncapsulation, controlled release, hydrophilic/hydrophobic drugs
LUPs	100–1000 nm	Surfactants, cholesterol, additives	Ether injection, reversed-phase evaporation	Large aqueous core for hydrophilic drugs; lipid bilayer for hydrophobic drugs
DGPs	Dry powder	Surfactants, cholesterol, fillers (sorbitol/maltodextrin)	Freeze-drying	Extended shelf-life, controlled release, industrial scalability

- **Sorbitol-based DGPs** provide structural stability, ease of storage, and reproducible drug release.

- **Maltodextrin-based DGPs** serve as fillers to maintain powder integrity while enhancing mucoadhesion and drug release efficiency.[29,30]

Proniosomes as engineered composite delivery systems

Proniosomes are not merely passive carriers; they represent **engineered composite platforms** that integrate multiple components to achieve superior performance. The solid-phase matrix contains surfactants, lipids, and carrier materials in precise ratios, ensuring high drug loading, prolonged stability, and controlled release.[31]

Key engineered strategies include

1. **Ligand-anchored targeting:** Surface functionalization with ligands enables selective delivery to target cells, improving therapeutic efficacy and minimizing off-target effects.[32]
2. **Polymer-hybrid vesicles:** Incorporation of biopolymers, such as chitosan or carbopol, enhances mucoadhesive properties, extending retention on mucosal surfaces and improving absorption.[33]
3. **Stimuli-responsive systems:** 'Smart' composites respond to environmental triggers (pH, temperature, redox conditions), ensuring site-specific drug release.[34]
4. **Hybrid lipid–polymer proniosomes:** These synergize lipid biocompatibility with polymeric resilience, achieving mechanical stability and tunable release kinetics.[35]

Proniosomes thus serve as **next-generation platforms**, offering adaptability, multifunctionality, and enhanced drug delivery efficiency for both small molecules and macromolecules.

Fabrication strategies: from conventional techniques to next-generation manufacturing

Proniosome production involves converting surfactants, lipids, and carrier matrices into stable, dry powders. Both conventional and advanced manufacturing approaches are employed to optimize particle characteristics, scalability, and reproducibility.

Conventional techniques

1. **Slurry method:** Ingredients are dissolved in organic solvent to create a slurry, followed by vacuum drying to produce proniosomal powders.[36,37]
2. **Coacervation phase separation:** Components are heated, mixed, and then gradually hydrated to produce vesicles.[38]

3. **Spray-coating:** Surfactant solutions are sprayed onto carrier materials and solvent evaporated to form multilamellar vesicles.[39]

Advanced fabrication approaches

1. **Microfluidics:** Allows precise control over particle size and polydispersity through rapid mixing at the microscale.[40]
2. **Supercritical fluid (SCF) technology:** CO_2 is used as a solvent-free medium, reducing organic solvent residues and simplifying downstream processing.[41]
3. **Quality-by-design (QbD):** Systematic optimization of formulation parameters ensures reproducibility, industrial scalability, and regulatory compliance.[42]

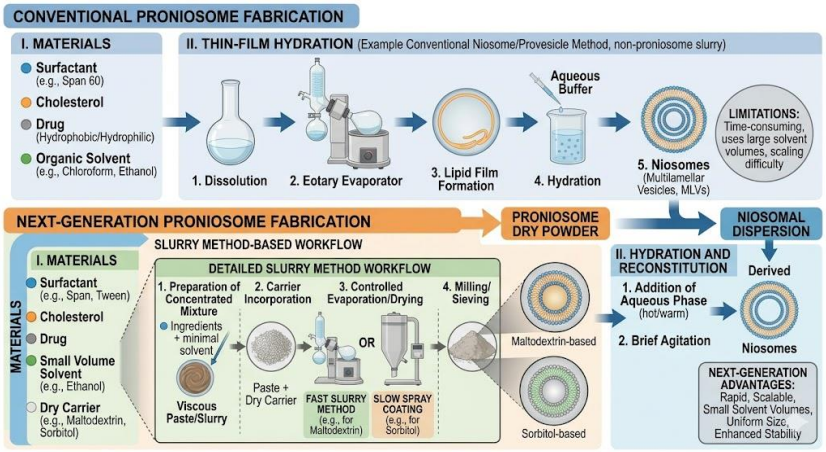

Figure 2: Workflow illustrating conventional and next-generation proniosome fabrication methods.

These manufacturing strategies ensure **consistent particle size, stability, and controlled drug release**, crucial for clinical translation and commercial viability.

Physicochemical profiling of proniosomes

Comprehensive characterization is essential to assess proniosome quality, stability, and therapeutic performance. Key parameters include

1. **Vesicle morphology:** SEM and TEM visualize vesicle size, lamellarity, and structural integrity.[43]
2. **Particle size, PDI, and zeta potential:** DLS quantifies vesicle homogeneity and colloidal stability.[44]
3. **Entrapment efficiency (%EE):** Determines drug loading capacity by separating unentrapped drug via centrifugation and analyzing the supernatant.[45]

4. **In vitro drug release:** Dialysis or dissolution methods evaluate release kinetics under physiological conditions.
5. **Solid-state characterization:** DSC and XRD confirm drug–excipient compatibility and the amorphous nature of encapsulated drugs.
6. **Powder flow properties:** Angle of repose measured using funnel/cylinder methods ensures good handling, packaging, and dosing uniformity.
7. **Stability and safety:** Formulations are tested under variable temperature, humidity, and storage conditions to confirm shelf-life and safety.[46]

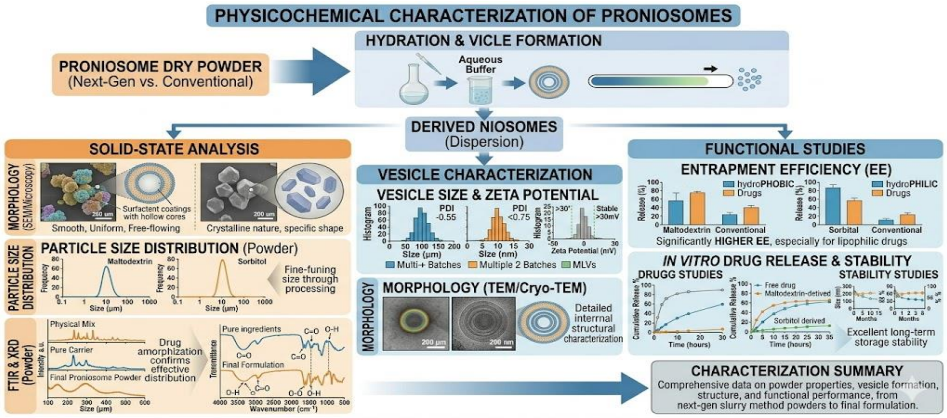

Figure 3: Flowchart depicting the physicochemical characterization of proniosomes, from hydration to in vitro release and solid-state analysis.

Extensive profiling establishes **robust quality assurance**, ensuring that proniosomal formulations are safe, stable, and effective for clinical applications.

Advanced Functional Design of Proniosomes for Drug Delivery

Proniosomes are advanced solid-phase drug delivery systems engineered to encapsulate active pharmaceutical ingredients (APIs) within a composite framework of surfactants, lipids, and carrier materials to optimize stability, structural integrity, and therapeutic performance. Unlike conventional liposomes or niosomes, proniosomes exist as dry powders with enhanced chemical and physical stability, preventing leakage, fusion, or aggregation while facilitating storage and handling. Upon hydration, these powders spontaneously assemble into multilamellar niosomal vesicles capable of targeted drug delivery, allowing proniosomes to overcome limitations commonly observed in traditional vesicular carriers.[47] One of the principal advantages of proniosomes is their capacity for functional customization. Through **functional compositing**, these vesicles can evolve from simple carriers into adaptive delivery platforms by integrating targeting ligands, polymer matrices, and stimuli-responsive

components, collectively improving delivery efficiency and reducing off-target effects. Ligand-mediated targeting, for example, involves surface modification with folic acid, peptides, or antibodies that bind receptors overexpressed on diseased cells. Upon hydration, these proniosomes form active niosomes capable of receptor-mediated uptake, increasing drug concentration at the target site and reducing systemic exposure.[48]

Polymer-hybrid engineering offers further functional enhancement. Incorporation of polymers such as chitosan, carbopol, hydroxypropyl methylcellulose, or maltodextrin imparts mucoadhesion, improved mechanical strength, and stability to dry proniosomal powders. These modifications also enable controlled and sustained drug release, which enhances plasma drug levels and reduces dosing frequency.

Stimuli-responsive proniosomes add another level of precision by releasing their payload only under specific triggers such as pH, temperature, or oxidative conditions typical of tumor or inflamed microenvironments. Smart proniosomes remain stable under physiological conditions but selectively release drugs at target sites, maximizing therapeutic effects while reducing systemic toxicity.[49]

Emerging lipid–polymer hybrid designs combine lipid biocompatibility with polymer resilience and tunable release properties, facilitating enhanced cellular uptake and improved pharmacokinetic profiles. These multifunctional systems can also incorporate targeting ligands and stimuli-responsive elements to achieve adaptive, site-specific delivery in challenging biological environments.[50]

The engineered features of proniosomes provide numerous therapeutic advantages: stable dry form, efficient encapsulation of both hydrophilic and hydrophobic drugs, targeted delivery, improved retention, and controlled release. Proniosomes can be formulated for various routes of administration, including oral, parenteral, pulmonary, and topical, and are amenable to industrial scale-up and unit dosage formulation.[51]

Fabrication Strategies: From Conventional Techniques to Next-Generation Manufacturing

The preparation of proniosomes involves methods that convert surfactants, lipids, and carrier matrices into stable dry powders. Traditional laboratory-scale techniques include the **slurry method**, where surfactants and lipids are dissolved in organic solvent and vacuum-dried to

form free-flowing powders; and **coacervation phase separation**, where controlled cooling after solvent mixing produces uniform proniosomal powders.[57,58] The **spray-coating method** involves spraying a surfactant solution onto a carrier and evaporating the solvent, providing high surface uniformity and scalability.[52]

Next-generation approaches such as **microfluidics** enable precise control over vesicle size distribution, while **supercritical fluid (SCF) technology** uses CO_2 as a non-toxic medium to produce solvent-free vesicles with narrow size distributions and high encapsulation efficiency. Integration of **Quality by Design (QbD) and high-throughput screening** allows systematic optimization of formulation parameters and improves reproducibility for clinical translation.

- (A) Slurry Method – mixture of surfactant, lipid, and solvent in a flask → vacuum drying → dry powder.
- (B) Coacervation Phase Separation – surfactant-lipid mixture heated with solvent → aqueous phase addition → cooling → proniosome formation.
- (C) Spray Coating Method – surfactant solution sprayed onto carrier → solvent evaporation → multilamellar vesicle formation upon hydration.

Table 3: Comparing Traditional and Next-Generation Proniosome Fabrication Methods.

Feature	Slurry Method	Coacervation Phase Separation	Spray Coating	Microfluidics	Supercritical Fluid
Solvent Use	Yes	Yes	Yes	Minimal	None
Scale-up Potential	Moderate	Moderate	High	High	Moderate
Size Control	Moderate	Moderate	Moderate	Excellent	Excellent
Powder Flow	Good	Good	Excellent	Excellent	Excellent
Environmental Impact	Medium	Medium	Medium	Low	Very Low
Reproducibility	Moderate	Moderate	High	High	High

Proniosomes: A Versatile Drug Delivery Platform

Proniosomes are flexible and multifaceted nanocarriers that have garnered considerable interest due to their capacity to deliver therapeutic agents through multiple administration routes. Built as solid, dry formulations that transform into niosomes upon contact with water or physiological fluids, proniosomes combine the advantages of both lipid-based and vesicular systems while mitigating many of their limitations. Their adaptability allows them

to enhance the delivery, absorption, stability, and targeting of a wide range of drugs, making them suitable for oral, parenteral, and dermal/transdermal applications. In the sections that follow, the utility of proniosomes in each of these routes is examined in depth, along with representative examples from the literature demonstrating their effectiveness.

Oral delivery

Oral drug delivery remains the most widely practiced route for administering therapeutic agents due to its convenience, non-invasiveness, and high patient compliance. However, many drugs face significant barriers when delivered orally, which include chemical instability in the gastrointestinal (GI) environment, susceptibility to acidic degradation and digestive enzymes, poor permeability across the intestinal mucosa, and substantial first-pass metabolism in the liver, which can drastically reduce systemic availability[53] For drugs to be absorbed efficiently in the GI tract, they must be present in dissolved form and maintain structural integrity long enough to traverse the intestinal epithelium. These challenges have driven the development of advanced nanocarrier systems designed to overcome the biological hurdles associated with oral administration.

Among the various nanocarriers explored — including liposomes, niosomes, solid lipid nanoparticles, polymeric micelles, and inorganic nanoparticles such as gold and quantum dots — proniosomes are distinguished by their solid, free-flowing powder form, which affords excellent physical stability and ease of formulation. Upon contact with gastrointestinal fluids, proniosomal powders rapidly hydrate to form niosomal vesicles, which can encapsulate poorly soluble drugs and facilitate their absorption.[54] The transformation into niosomes enables these carriers to protect labile drugs from the harsh acidic and enzymatic conditions of the GI tract, improving solubility and enhancing transport across biological barriers.

Several pharmacokinetic studies have demonstrated the effectiveness of proniosomes in improving oral bioavailability. For instance, vinpocetine — a neuroprotective compound with limited water solubility — was formulated into a free-flowing proniosomal powder with the aim of enhancing its GI absorption. When administered orally, vinpocetine-loaded proniosomes exhibited a significant increase in bioavailability (up to ~4.9-fold) compared to the free drug. This enhancement was attributed to the rapid hydration of proniosomes into niosomes in the GI lumen followed by endocytic uptake and lymphatic transport, which helps bypass hepatic first-pass metabolism[55] Such findings underscore the potential of proniosomes to improve systemic exposure for poorly absorbed drugs.

In another study, nateglinide, an oral hypoglycemic agent used in type 2 diabetes, was encapsulated within proniosomal carriers. In rabbit models, proniosomal nateglinide exhibited approximately 32% higher plasma levels relative to the pure drug, demonstrating improved absorption and systemic exposure. Similarly, proniosomal formulations of lipophilic drugs such as irbesartan have shown enhanced pharmacokinetic profiles in rat models, with optimized proniosomal suspensions demonstrating up to a two-fold increase in oral bioavailability compared to conventional suspensions.[56]

Proniosomes are also well suited for co-delivery of multiple drugs. For example, systems comprising non-ionic surfactants, cholesterol, and carriers like maltodextrin have been developed to simultaneously entrap metronidazole and doxycycline hydrochloride. These proniosomal powders exhibited physical stability at refrigerated temperatures for several months, maintained a free-flowing nature, and enabled precise dosing, which enhances ease of handling and patient compliance — important considerations for oral dosage forms.[57]

Despite these promising outcomes, there are challenges associated with scaling up proniosomal oral formulations. Manufacturing at an industrial scale can disrupt the delicate supramolecular arrangement of surfactants, lipids, and drug molecules, potentially leading to performance deviations compared to laboratory batches. Ensuring consistent quality during large-scale production requires careful optimization of formulation and process parameters. Moreover, converting proniosomal powders into final oral dosage forms, such as tablets or capsules, may necessitate additional processes such as coating, which can increase overall production costs. Nonetheless, the substantial improvements in solubility, stability, and absorption make proniosomes a compelling platform for enhancing oral drug delivery.

Parenteral delivery

The parenteral route — including intravenous, intramuscular, and subcutaneous administration — is often employed for drugs with narrow therapeutic windows, poor oral bioavailability, or in clinical scenarios where rapid onset of action is required. This route bypasses the GI tract entirely, ensuring direct access to systemic circulation. Parenteral delivery is particularly critical in emergency medicine, for patients with compromised swallowing or GI function, and for individuals who require precise dosing and immediate therapeutic effects.[58]

However, conventional parenteral formulations present challenges including the need for trained healthcare professionals for administration, rapid systemic clearance of drugs, and the need for frequent dosing. To address these issues, researchers have developed biodegradable nanosystems that allow sustained release of drugs, reducing dosing frequency and mitigating side effects[59] Proniosomes, in their solid, dry form, are particularly advantageous for parenteral use because they can be sterilized and reconstituted without significant changes in particle size or drug release behavior — issues that commonly arise with conventional nanosuspensions or vesicular systems following sterilization procedures such as gamma irradiation or freeze drying.[60]

Proniosomal formulations can be packaged as unit dosage forms suitable for parenteral administration. They are amenable to standard sterilization techniques and show excellent stability during storage and transport. For example, flurbiprofen, a non-steroidal anti-inflammatory drug, was incorporated into a proniosomal system designed for parenteral use. The resulting formulation maintained therapeutic systemic concentrations for up to three days following a single administration, reducing dosing frequency and potentially improving patient tolerance and compliance.[61]

The stability and reconstitution behavior of proniosomes position them as a promising alternative to traditional vesicular and colloidal systems for parenteral drug delivery. Their ability to provide sustained release, maintain stability post-sterilization, and deliver therapeutic concentrations over extended periods make them particularly useful for potent drugs, biologics, and therapies requiring controlled pharmacokinetics.

Topical and transdermal delivery

The skin, the largest organ in the body, serves as a protective barrier against environmental insults while also presenting an accessible route for drug delivery. Transdermal administration offers several advantages, including the avoidance of first-pass metabolism, non-invasiveness, and improved patient compliance. However, the primary hindrance to transdermal drug delivery is the **stratum corneum**, the outermost layer of the epidermis, which effectively limits the permeation of many therapeutic agents.[62]

To overcome these barriers, vesicular systems have been explored as permeation enhancers. Among these, proniosomes have shown particular promise because they can adhere to the stratum corneum, convert into niosomes upon hydration, and facilitate deeper penetration of

drugs through the complex architecture of the skin.[63] Proniosomes act not just as carriers but also as reservoirs, allowing sustained and controlled release at the site of application.

The composition of proniosomal carriers — including the type and ratio of non-ionic surfactants, cholesterol, and other excipients — can be tailored to favor skin permeation and drug entrapment. For instance, proniosomal formulations of flurbiprofen optimized with a higher surfactant concentration and minimal cholesterol demonstrated high drug entrapment efficiency (~39%) and significantly enhanced skin permeability in vitro.[64]

In another noteworthy example, boswellic acid, a compound with inherently poor oral bioavailability, was incorporated into proniosomal gels and demonstrated marked improvements in absorption and release properties. The optimized proniosomal gel showed superior transdermal flux and enhanced bioavailability compared with conventional topical formulations, translating to significantly better anti-inflammatory effects in comparative studies.[65]

Proniosomal systems have also been investigated in other therapeutic contexts, such as treatment of overactive bladder. Proniosomal patches or gels containing tolterodine tartrate provided higher skin permeability (35–42%) and improved therapeutic profiles, while the oral formulations were associated with more adverse effects.[85] The versatility of proniosomes allows them to be formulated into various dosage forms, such as patches, films, and gels, which may be optimized for specific application sites and drug release profiles.

Another important advantage of proniosomal transdermal systems is their bioadhesive properties, which enhance intimate contact between the dosage form and the skin, thereby improving drug uptake and reducing dose variability. The use of cost-effective excipients in such systems also supports their commercial viability and scalability.[66]

Ocular Delivery

Ocular drug delivery has historically been challenged by low bioavailability, primarily due to anatomical and physiological barriers of the eye. Factors such as the blinking reflex, limited ocular surface area, nasolacrimal drainage, and the protective functions of the corneal and conjunctival epithelia collectively reduce the retention and absorption of drug molecules applied to the eye.[67] These barriers necessitate frequent instillation of conventional

ophthalmic formulations to maintain therapeutic levels, which often leads to patient inconvenience and noncompliance.

To overcome these limitations, researchers have developed various advanced ocular drug delivery systems. In situ gelling systems, liposomes, nanosuspensions, nanoparticles, nanoemulsions, and proniosomes represent some of the modern strategies designed to enhance drug retention, absorption, and bioavailability in ocular tissues.[68] Among these, proniosomes have emerged as particularly promising due to their unique solid-state nature and ability to convert into niosomal vesicles upon contact with aqueous ocular fluids.

Proniosomal gels offer several advantages in ocular applications. First, their solid matrix can prolong the contact time of drugs with the corneal surface, effectively increasing the residence time within the corneal cavity. Second, the hydration-induced transformation into niosomes facilitates sustained release of the encapsulated drug and reduces enzymatic degradation by tear components.[96] For instance, ketoconazole-loaded proniosomal gels demonstrated a remarkable up to 20-fold increase in ocular bioavailability. This was attributed to their prolonged residence time on the ocular surface, which enabled sustained therapeutic action at the target site and minimized the rapid clearance typically associated with conventional eye drops.[69]

Further evidence of proniosomes' effectiveness comes from studies on tacrolimus, an immunosuppressive agent. In a rabbit model, tacrolimus-loaded proniosomes exhibited superior corneal penetration and extended retention time compared to traditional ointments. Upon administration, the proniosomal gel hydrated in the ocular fluid to form niosomes, facilitating deeper permeation and prolonged contact with corneal tissues.[70] In a corneal xenograft transplantation study in Sprague-Dawley rats, tacrolimus proniosomes significantly delayed allograft rejection and maintained a retention time of approximately 13.86 ± 0.80 days, outperforming conventional cyclosporine eye drops in both efficacy and duration of action. These findings underscore the potential of proniosomal ocular formulations to achieve targeted, sustained, and efficient drug delivery, reducing dosing frequency and enhancing patient compliance.

Vaginal Delivery

The vaginal route has traditionally been employed for the treatment of localized infections such as vulvovaginal candidiasis and bacterial vaginosis.[12] More recently, this route has

been explored for systemic and local delivery of a variety of therapeutic agents, including antimicrobials, antifungal agents, sex hormones, and peptide-based drugs.[13] The vaginal mucosa presents several advantages, including a rich vascular supply that drains into the inferior vena cava via the iliac veins, thereby circumventing first-pass metabolism. Additionally, the relatively high permeability of vaginal tissues can facilitate systemic absorption of appropriately designed drugs.[71]

However, the vaginal environment also presents unique challenges. Factors such as menstrual cycles, menopause, sexual activity, personal hygiene, and the natural mucus clearance mechanisms can all influence drug retention and bioavailability.[15,16] Rapid mucus turnover and limited residence time of conventional dosage forms can significantly reduce therapeutic effectiveness. Leakage and poor adhesion of the formulation further compromise drug delivery to the target site.[72] As a result, there has been a shift towards designing advanced delivery systems with enhanced mucoadhesion, prolonged retention, and controlled release properties.

Several innovative vaginal drug delivery strategies have been investigated to address these limitations. These include hydrogels, vaginal sponges, nanoparticles, nanocapsules, solid lipid nanoparticles, liposomes, niosomes, and proniosomes.[73] Among these, proniosomal gel systems have shown particular promise due to their intrinsic mucoadhesive properties, which allow the formulation to remain in intimate contact with the vaginal epithelium, thereby enhancing drug retention and efficacy.[74]

Proniosomal gels are designed to convert into niosomes upon contact with the vaginal fluid. This transformation allows for the controlled release of the encapsulated drug over an extended period, while the gel matrix provides additional mechanical support and adhesion to mucosal surfaces.[75] For example, Abdou et al. developed a proniosomal gel system loaded with the antifungal drug terconazole for the treatment of vaginitis. The proniosomes transformed into niosomes upon hydration in the vaginal environment, providing prolonged retention (up to 3 hours) and significantly improved therapeutic outcomes compared to conventional formulations.[76] Such systems not only enhance local drug concentrations but also reduce systemic exposure and potential side effects.

Proniosomal vaginal gels offer several advantages over traditional formulations. Their solid-state nature allows for easier handling, accurate dosing, and extended shelf-life. Moreover,

their capacity to provide controlled, sustained, and targeted drug release makes them suitable for a wide range of vaginal therapies, including antifungals, antibiotics, and hormonal agents. By optimizing the surfactant, lipid, and carrier composition, the physicochemical properties of proniosomes — such as particle size, entrapment efficiency, and mucoadhesive strength — can be finely tuned to maximize both local and systemic therapeutic effects.[77]

In addition to antifungal therapy, proniosomal gels have been explored for hormone replacement and contraceptive delivery. The ability to maintain localized drug concentrations while minimizing systemic exposure is particularly valuable for therapies requiring prolonged action with minimal side effects. The combination of mucoadhesion, controlled release, and biocompatibility makes proniosomal vaginal gels a versatile platform for both prophylactic and therapeutic interventions.[78]

Overall, the ocular and vaginal applications of proniosomes illustrate their adaptability as a drug delivery platform. Their capacity to enhance drug retention, provide controlled and sustained release, and overcome physiological barriers positions them as superior alternatives to conventional dosage forms. By combining the advantages of niosomal vesicles with the stability and convenience of solid formulations, proniosomes address key limitations in traditional drug delivery and open new avenues for site-specific and patient-compliant therapies.

Pulmonary Delivery

The pulmonary route has increasingly become an attractive pathway for drug administration due to the lungs' unique anatomical and physiological properties. The lungs are the primary site of several serious respiratory diseases, including asthma, chronic obstructive pulmonary disease (COPD), pneumonia, and pulmonary fibrosis. Beyond local therapy, they have been recognized as an efficient route for systemic delivery of therapeutic agents, given the lungs' high surface area and specialized vascularization. Human lungs present an absorptive surface area exceeding 100 square meters, combined with ultra-thin alveolar epithelial and capillary endothelial layers optimized for rapid gaseous and molecular exchange. These structural characteristics facilitate the efficient uptake of small molecules, peptides, and nanoparticles, often with higher bioavailability than traditional oral or parenteral administration.[79] A key advantage of pulmonary delivery is the dual blood supply of the lungs. Drugs absorbed through alveolar regions can enter systemic circulation directly via pulmonary veins into the left atrium, bypassing the hepatic first-pass metabolism. This allows rapid onset of action and

improved systemic bioavailability.[80] Moreover, modern advancements in inhalation technology—including nebulizers, metered-dose inhalers (MDIs), and dry powder inhalers (DPIs)—have improved the precision of dose delivery, patient convenience, and adherence. These devices, when combined with nanocarriers, provide a potent strategy for local treatment of lung diseases and systemic therapy through pulmonary absorption.

Proniosomes represent a promising vesicular system for pulmonary drug delivery due to their ability to convert into niosomes upon contact with aqueous fluids. This transformation provides a stable and controlled-release vesicular system capable of aerosolization. For example, Elhissi et al. formulated proniosomal aerosols of beclomethasone dipropionate (BDP) using nebulizer systems. Their findings demonstrated that proniosomes achieved higher drug entrapment efficiency (35.4%) than conventional niosomes (27.5%). Moreover, aerosolized proniosomes exhibited a high fine particle fraction (FPF), ensuring effective deposition in the alveolar region and facilitating systemic absorption.[81]

Similarly, Abd-Elbary et al. developed cromolyn sodium-loaded proniosomal aerosols using sucrose stearate, a nonionic and biodegradable surfactant. The proniosomal system hydrated rapidly within two minutes, releasing the encapsulated drug efficiently in the lungs. The study highlighted enhanced absorption through the pulmonary circulation and superior therapeutic effects compared to conventional nebulized drugs. Proniosomes, therefore, not only improve deposition and bioavailability but also allow sustained drug release, reducing the frequency of administration and improving patient adherence.[82]

The intrinsic advantages of pulmonary proniosomal delivery extend to stability and practical usability. Unlike conventional aerosols, proniosomal formulations are stable as dry powders, can be stored without significant changes in vesicle size or drug release properties, and can be reconstituted just before use. These features are particularly advantageous for long-term treatment of chronic respiratory diseases or acute interventions where immediate availability of the drug is critical. Additionally, the vesicular structure of proniosomes allows encapsulation of both hydrophilic and lipophilic drugs, providing versatility for different therapeutic applications.[83] By enhancing drug entrapment, reducing clearance, and prolonging residence time in the lungs, proniosomal aerosols represent a next-generation approach for pulmonary therapy. They are suitable not only for conventional anti-inflammatory and bronchodilator drugs but also for newer therapeutic molecules, including biologics, peptides, and gene-based therapies. This versatility underscores the potential of

proniosomes to transform pulmonary drug delivery and overcome limitations of traditional inhaled formulations, such as low retention, poor solubility, and enzymatic degradation.[84]

Intranasal Delivery

The intranasal route has gained attention as a non-invasive and efficient pathway for systemic drug delivery, especially for targeting the central nervous system (CNS). The nasal cavity possesses specialized pathways that enable drugs to bypass the blood-brain barrier (BBB), such as the olfactory neurons, trigeminal nerve routes, nasal lymphatics, and porous endothelial structures.[9] These anatomical features allow direct transport of therapeutic agents to the CNS, making the nasal route a promising alternative for neuroactive drugs, peptides, and small molecules that otherwise have limited brain penetration.[85]

Intranasal drug delivery offers several practical advantages. It allows for self-administration, is generally painless, and avoids first-pass metabolism, thus improving the bioavailability of drugs that are extensively metabolized orally. However, the nasal route faces several physiological limitations. Rapid mucociliary clearance, enzymatic degradation, potential irritation of the nasal mucosa, and risks of tissue damage during chronic administration can reduce therapeutic efficacy. To overcome these barriers, nanosized carriers, such as proniosomes, have been extensively investigated. Their nanoscale size (typically 1–100 nm) enables them to cross epithelial barriers efficiently, protect encapsulated drugs from enzymatic degradation, and improve absorption and bioavailability.[86]

Proniosomal gels exhibit additional benefits through their mucoadhesive properties. By adhering to the nasal mucosa, they prolong residence time and enable sustained drug release. This feature is particularly valuable for CNS-targeted drugs, which require prolonged contact with the mucosa to facilitate transport along neuronal pathways to the brain. Khatoon et al. developed a mucoadhesive proniosomal gel of duloxetine, an antidepressant, for intranasal administration. Ex vivo and in vivo studies demonstrated that the proniosomal gel enhanced drug absorption, sustained release, and transmucosal permeation. The formulation achieved 54% drug release over 8 hours, improving bioavailability significantly compared to conventional nasal solutions.[87]

The use of proniosomes for intranasal delivery is particularly advantageous for CNS-targeted therapeutics. It allows non-invasive drug administration while reducing systemic exposure, which minimizes side effects. Furthermore, proniosomal carriers can encapsulate a variety of

drugs, including small molecules, peptides, and larger biomolecules, and provide sustained release for chronic conditions such as depression, neurodegenerative disorders, and epilepsy. The combination of mucoadhesion, controlled release, and vesicular stability makes intranasal proniosomes a versatile and promising platform for CNS drug delivery.[88]

Overall, pulmonary and intranasal proniosomal drug delivery systems exemplify the platform's adaptability and efficacy in overcoming the challenges of conventional routes. In the lungs, proniosomes enhance deposition, retention, and systemic absorption, while intranasally, they facilitate CNS targeting and improve bioavailability through extended mucosal adhesion. These properties make proniosomes a next-generation drug delivery platform capable of addressing unmet clinical needs, reducing dosing frequency, improving patient compliance, and increasing therapeutic efficacy.

Therapeutic Applications of Proniosomes

1. Application in Peptide Drug Delivery

Proniosomal drug delivery systems effectively overcome the limitations associated with oral administration of peptides and proteins by protecting them from enzymatic degradation in the gastrointestinal tract. These systems form vesicular structures that encapsulate the drug, creating a protective coating that shields it from adverse biological conditions and enhances its stability.

A vesicular formulation containing a vasopressin derivative demonstrated improved oral bioavailability along with increased stability and drug entrapment efficiency. Similarly, insulin-loaded proniosomes prepared using cholesterol and non-ionic surfactants protect the drug from enzymatic breakdown and other physiological barriers. This approach enhances insulin bioavailability and allows controlled drug release, providing a more efficient and patient-friendly alternative to conventional injectable formulations.

2. Application in Immune Response Studies

Proniosomes have shown significant potential in immunological research due to their high stability, minimal toxicity, and selective immunological properties. They are widely used to investigate immune responses triggered by various antigens.[89]

Proniosomal formulations developed for malaria vaccine delivery have demonstrated enhanced immunogenicity, resulting in increased antibody production in experimental models compared to conventional delivery systems.

In addition, proniosomes have been explored for delivering CpG oligodeoxynucleotides as adjuvants. This delivery strategy enhances antigen-specific immune responses and induces a stronger T-helper 1 (Th1) immune response in animal studies.

3. Application in Hemoglobin Delivery

Proniosomes can serve as carriers for hemoglobin, facilitating its transport within the body after conversion into niosomes. Due to their oxygen permeability, these vesicular systems can function as artificial oxygen carriers.[90]

They enhance hemoglobin stability, prevent oxidative degradation, and provide controlled release. Furthermore, proniosomes enable targeted delivery to tissues with high oxygen demand, such as ischemic regions. Their capability for non-invasive administration also improves patient comfort and treatment compliance.

4. Application in Gene Delivery

After hydration, proniosomes are converted into niosomes that can efficiently deliver genetic material into cells. These carriers protect nucleic acids from enzymatic degradation and facilitate their uptake into target cells.

A study demonstrated the successful delivery of plasmid DNA (pCMSEGFP) to retinal tissue using niosomal carriers, indicating their potential application in ocular gene therapy.

Additionally, cationic niosomes formulated using lipids such as DOTAP, PEGylated lipids, and surfactants have been used for the delivery of siRNA and miRNA into human mesenchymal stem cells. These systems promote gene transfer and cellular differentiation when optimized for appropriate surface charge and composition.[91]

5. Application in Cardiology

Proniosomal drug delivery systems are considered a promising approach in cardiovascular therapy, particularly for improving the bioavailability of drugs such as statins. Encapsulation within proniosomes enhances drug solubility and stability, leading to improved therapeutic outcomes. For example, atorvastatin incorporated into proniosomal formulations has shown

improved effectiveness in preventing cardiovascular events. Captopril-loaded proniosomes administered transdermally have demonstrated high encapsulation efficiency (approximately 66.7–68.7%) along with sustained drug release, making them suitable for hypertension management. Similarly, lisinopril formulated in proniosomal gels using cholesterol and non-ionic surfactants provides improved solubility, enhanced gastrointestinal absorption, and sustained drug release for up to 24 hours, thereby reducing side effects and improving therapeutic efficacy.[93]

6. Application in Diabetes

Proniosomal systems offer multiple advantages in the treatment of diabetes by enhancing drug solubility, stability, and bioavailability. Glibenclamide-loaded proniosomes have demonstrated improved oral bioavailability and significant reduction in blood glucose levels (approximately 73%) compared to conventional formulations. Proniosomal formulations containing amitriptyline and liraglutide have shown improved management of diabetic neuropathy by reducing pain, inflammation, and oxidative stress, while maintaining better glycemic control and minimizing side effects. Metformin incorporated into proniosomes helps reduce gastrointestinal side effects, improves absorption, and provides controlled drug release, thereby enhancing patient compliance. Similarly, maltodextrin-based proniosomal formulations of nateglinide have shown improved bioavailability by converting rapid drug release into a sustained release pattern.

Additionally, glibenclamide proniosomal gel has demonstrated protective effects against oxidative stress in testicular tissues by enhancing antioxidant enzyme activity and supporting insulin production.[94]

7. Application in Hormonal Therapy

Proniosomes have gained considerable attention in hormone delivery due to their ability to enhance drug permeability and provide sustained release. Levonorgestrel-loaded proniosomes have demonstrated high drug entrapment efficiency along with improved permeability and therapeutic effectiveness, while reducing adverse effects. Letrozole proniosomal formulations have shown controlled drug release and high encapsulation efficiency (approximately 74%), resulting in improved therapeutic outcomes in breast cancer treatment. Estradiol-loaded proniosomes designed for transdermal delivery exhibit nearly complete drug encapsulation and enhanced bioavailability. These systems enable sustained hormone release, reduce systemic side effects, and improve therapeutic efficacy in hormone replacement therapy.

Table 4: Therapeutic Applications of Proniosomes.

Therapeutic Area	Drug/Example	Key Findings	Advantages
Peptide Delivery	Vasopressin derivative	Improved stability and bioavailability	Protection from GI degradation
Peptide Delivery	Insulin	Enhanced stability and absorption	Controlled release, non-invasive
Immune Studies	Antigen response	Selective immune interaction	Useful in immunological research
Immune Studies	Malaria vaccine	Increased antibody production	Enhanced immunogenicity
Immune Studies	CpG ODN	Strong Th1 response	Improved adjuvant activity
Hemoglobin Delivery	Hemoglobin vesicles	Oxygen permeability	Targeted delivery, stability
Gene Delivery	pCMSEGFP plasmid	Retinal gene transfer	DNA protection, uptake
Gene Delivery	siRNA/miRNA	Efficient delivery	Promotes differentiation
Cardiology	Atorvastatin	Improved solubility	Better cardiovascular outcomes
Cardiology	Captopril	66–68% encapsulation	Sustained antihypertensive effect
Cardiology	Lisinopril	24 h release	Improved absorption
Diabetes	Glibenclamide	~73% glucose reduction	Better bioavailability
Diabetes	Amitriptyline + Liraglutide	Reduced neuropathy	Improved efficacy
Diabetes	Metformin	Reduced GI effects	Better compliance
Diabetes	Nateglinide	Controlled release	Improved bioavailability
Diabetes	Glibenclamide gel	Reduced oxidative stress	Tissue protection
Hormonal Therapy	Levonorgestrel	High entrapment	Improved efficacy
Hormonal Therapy	Letrozole	~74% encapsulation	Better therapeutic index
Hormonal Therapy	Estradiol	~100% encapsulation	Sustained release

Other Applications of Proniosome

Application Type	Drug/Example	Key Findings	Advantages
Sustained Release	Paclitaxel	Prolonged drug release	Improved bioavailability, anticancer efficacy
Sustained Release	NSAIDs (transdermal)	~71% release over 24 h	Extended drug action
Sustained Release	Lornoxicam gel	~67% entrapment, >24 h release	Controlled release
Sustained Release	Metformin HCl	~75.9% release in 24 h	Maintains constant drug levels

Targeted Delivery	Gossypin gel	Effective skin penetration	Reduced toxicity, melanoma therapy
Targeted Delivery	Artemether (intranasal)	Enhanced brain targeting	Improved stability and permeation
Targeted Delivery	Benzocaine (buccal)	Sustained local release	Prolonged anesthesia

Biocompatibility and Toxicological Considerations

Proniosomes are widely recognized for their favorable safety profile, primarily due to the incorporation of biocompatible and relatively non-toxic materials in their formulation. Nonetheless, the possibility of toxicity cannot be entirely excluded, as it may depend on the specific characteristics of the surfactants employed. Experimental studies involving both oral and parenteral administration have generally shown no significant harmful effects associated with proniosomes. For example, formulations containing lornoxicam have demonstrated both safety and therapeutic effectiveness. In a similar manner, lomefloxacin-loaded proniosomes have exhibited good ocular compatibility, without inducing irritation or inflammation. Moreover, proniosomal gels incorporating 5-fluorouracil have been reported to enhance therapeutic outcomes while maintaining an improved safety profile in cancer therapy.[95]

Taken together, these findings highlight the overall safety, tolerability, and potential applicability of proniosomes as efficient drug delivery systems.

Opportunities and Challenges of Proniosomes

Proniosomes are increasingly recognized as an advanced vesicular drug delivery system due to their promising characteristics. Nevertheless, addressing their limitations is essential for their rational design and successful clinical translation. One of their key advantages is their ability to enhance the solubility and permeability of poorly water-soluble drugs, thereby improving systemic absorption and achieving better therapeutic plasma levels. Their structural properties also support controlled and sustained drug release, which helps maintain prolonged therapeutic effects and reduces dosing frequency, making them suitable for chronic disease management. In addition, proniosomes exhibit considerable versatility, as they can encapsulate a wide range of therapeutic agents, including small molecules, proteins, and nucleic acids. Through surface modification, these systems can be tailored for targeted drug delivery, enhancing therapeutic outcomes while minimizing unintended side effects. By entrapping drugs within biocompatible vesicles, proniosomes also help decrease systemic exposure to free drugs, thereby lowering the risk of organ-specific toxicity.

From a formulation perspective, their dry state significantly improves physicochemical stability by minimizing degradation processes such as hydrolysis and oxidation, which are common in aqueous systems. Furthermore, the preparation techniques for proniosomes are relatively straightforward, facilitating their scalability for industrial production.

Despite these advantages, several challenges limit their widespread application. The cost of raw materials, including surfactants, cholesterol, and coating agents, may increase production expenses. Additionally, certain surfactants can cause irritation by disrupting epithelial barriers at the site of administration. The lack of extensive clinical studies and the complexity of regulatory approval processes for novel drug delivery systems may further hinder their commercialization. Moreover, since proniosomes require hydration to form niosomes, their practical use in clinical settings can sometimes be inconvenient. Although stable in dry form, their stability may decrease after hydration.[96]

Therefore, a careful evaluation of both the advantages and limitations is crucial for guiding future research and facilitating the successful development and clinical translation of proniosomal drug delivery systems.

Future Roadmap: Bridging the Gap with Emerging Innovations

Looking ahead, proniosomes hold significant promise in advancing long-acting drug delivery systems, enabling effective disease management while reducing adverse effects and improving the therapeutic index through targeted and controlled drug release at specific tissues and cellular sites. Increasing emphasis will also be placed on sustainability, particularly through the adoption of biodegradable and environmentally friendly materials in formulation design.

The integration of artificial intelligence (AI) is expected to play a transformative role in proniosome development, especially through machine learning-based Quality by Design (QbD) approaches. Techniques such as artificial neural networks and deep learning models can be utilized to optimize formulation parameters, including surfactant, cholesterol, and polymer ratios. Additionally, advanced predictive tools like Gaussian process models can estimate post-hydration vesicle size, facilitating the automated design of stable, efficient, and personalized stimuli-responsive proniosomal systems with controlled release behavior.

As this field continues to progress, it will be essential to establish educational initiatives supported by adequate funding to train professionals in this emerging technology. Such efforts will enhance its broader acceptance and support regulatory approval processes.[97] Overall, these advancements position proniosomes as a highly promising and transformative platform with the potential to significantly reshape future drug delivery strategies.

CONCLUSION

Proniosomes represent a significant advancement in the field of drug delivery, offering a robust and adaptable platform that addresses many of the limitations associated with conventional vesicular systems. Their dry, stable nature ensures enhanced shelf-life and ease of handling, while their ability to convert into niosomal vesicles upon hydration enables efficient encapsulation and controlled release of a wide range of therapeutic agents. This dual advantage of stability and functionality makes proniosomes particularly suitable for modern pharmaceutical applications. The integration of functional components such as targeting ligands, polymers, and stimuli-responsive materials has further transformed proniosomes into intelligent delivery systems capable of site-specific action and improved therapeutic outcomes. Their versatility across multiple routes of administration—including oral, parenteral, transdermal, ocular, pulmonary, intranasal, and vaginal pathways—highlights their broad applicability in addressing diverse clinical needs. Moreover, proniosomes have demonstrated considerable potential in enhancing drug bioavailability, reducing systemic toxicity, and improving patient adherence through sustained and controlled drug release. However, challenges such as high production costs, potential surfactant-related toxicity, scalability issues, and limited clinical validation must be addressed to enable their successful commercialization.

Future developments focusing on advanced manufacturing techniques, regulatory standardization, and the integration of artificial intelligence-driven formulation design are expected to accelerate their translation from laboratory research to clinical practice. In conclusion, proniosomes hold substantial promise as next-generation drug delivery systems with the potential to significantly improve therapeutic efficacy and patient outcomes.

REFERENCES

1. Jain NK. Controlled and novel drug delivery. 1st ed. New Delhi, CBS Publishers, 2008.
2. Kaur L, et al. Barriers to oral drug delivery: strategies and solutions. Int J Pharm Sci., 2019; 11(4): 211-26.

3. Florence AT, Attwood D. Physicochemical principles of pharmacy. 4th ed. London: Pharmaceutical Press, 1998.
4. Caddeo C, et al. Liposomes as carriers for oral drug delivery. Expert Opin Drug Deliv., 2017; 14(10): 123-32.
5. Khan MW, et al. Niosomal drug carriers for oral delivery. J Pharm Sci., 2016; 105(7): 2154-64.
6. Kraft JC, et al. Lipid nanoparticles for oral drug delivery. Adv Drug Deliv Rev., 2014; 72: 53-63.
7. Chen Y, et al. Micelles in oral drug delivery. Colloids Surf B Biointerfaces, 2013; 103: 69-80.
8. Chen C, et al. Nanoparticles as oral carriers. J Nanomed Nanotechnol., 2014; 5(6): 238-46.
9. Mittal N, et al. Proniosomes for oral delivery: formulation and evaluation. Pharm Res., 2020; 37(4): 63-75.
10. Song X, et al. Improved oral bioavailability of vinpocetine using proniosomes. Int J Pharm., 2015; 489(1-2): 123-31.
11. Sahoo DK, et al. Proniosomal nateglinide: enhanced bioavailability. Drug Dev Ind Pharm., 2014; 40(9): 1115-22.
12. Mujtaba M, et al. Enhanced bioavailability of irbesartan via proniosomes. J Pharm Sci., 2024; 113(2): 578-89.
13. Gad H, et al. Proniosomal powder for dual drug delivery. Int J Pharm Tech Res., 2014; 6(1): 112-23.
14. Yuksel N, et al. Manufacturing challenges for proniosomes. Eur J Pharm Biopharm., 2016; 107: 31-44.
15. Nkanga C, et al. Parenteral drug delivery systems. J Pharm Sci., 2020; 109(5): 1469-80.
16. Kim J, et al. Biodegradable nanosystems for parenteral delivery. Nanomedicine., 2023; 34: 102454.
17. Din FU, et al. Sustained release polymeric systems. J Drug Target, 2017; 25(6): 512-23.
18. Bozdag S, et al. Sterilization effects on nanoparticle properties. J Pharm Sci., 2005; 94(4): 781-91.
19. Nasr M. Proniosomes: advantages in parenteral delivery. Int J Pharm., 2010; 387(1-2): 234-42.
20. Verma P, et al. Proniosomal flurbiprofen for parenteral use. Drug Deliv Lett., 2016; 6(3): 192-200.

21. Fukushima M, et al. Transdermal drug delivery barriers. Biol Pharm Bull., 2011; 34(1): 1-10.
22. Muzzalupo R. Proniosomes for transdermal drug delivery. Expert Opin Drug Deliv., 2016; 13(2): 285-96.
23. Witika BAG, et al. Vesicular systems for topical delivery. Pharmaceutics, 2021; 13(8): 1218.
24. Kamel R, et al. Proniosomal carriers in dermal therapy. J Drug Deliv Sci Technol., 2013; 23(3): 235-42.
25. Zidan G, Mokhtar K. Enhanced flurbiprofen skin permeability using proniosomes. Saudi Pharm J., 2011; 19(3): 173-81.
26. Mehta SK, et al. Boswellic acid proniosomal gels for topical use. Int J Cosmet Sci., 2016; 38(3): 234-42.
27. Rajabalaya R, et al. Tolterodine tartrate proniosomes for transdermal delivery. Drug Dev Ind Pharm., 2016; 42(7): 1114-23.
28. Khatoon Z, et al. Bioadhesive proniosomes: formulation and applications. J Pharm Educ Res., 2017; 8(1): 11-25.
29. Kaur IP, et al. Challenges in ocular drug delivery. J Control Release, 2012; 163(1): 21-33.
30. Luo L, et al. Limitations in conventional ophthalmic preparations. Int J Pharm., 2011; 403(1-2): 1-9.
31. Gupta P, et al. In situ gelling ocular systems. Int J Pharm., 2015; 487(1-2): 15-23.
32. Dai X, et al. Liposomal delivery for ocular therapy. Drug Deliv., 2013; 20(3-4): 120-7.
33. Luschmann C, et al. Nanosuspensions in ocular drug delivery. J Pharm Sci., 2013; 102(7): 2345-55.
34. Nagarwal RC, et al. Nanoparticle formulations for eye diseases. Curr Drug Deliv., 2012; 9(4): 419-32.
35. Garg R, et al. Nanoemulsions in ophthalmology. J Ocul Pharmacol Ther., 2013; 29(5): 452-62.
36. Abdelkader H, et al. Proniosomes as ocular carriers. Int J Pharm. 2012;426(1-2):60-70.
37. Abdelbary G, et al. Ketoconazole-loaded ocular proniosomes. Int J Pharm., 2017; 518(1-2): 41-50.
38. Li X, et al. Tacrolimus-loaded proniosomes for ocular delivery. J Control Release, 2014; 192: 123-32.
39. Li X, et al. Corneal transplantation and proniosomal tacrolimus. Exp Eye Res., 2014; 124: 112-20.

40. Lin H, et al. Vaginal drug delivery: overview and challenges. Drug Deliv., 2021; 28(1): 1-15.
41. Ensign LM, et al. Advances in vaginal drug delivery. Adv Drug Deliv Rev., 2014; 72: 1-4.
42. Vanić Ž, Škalko-Basnet N. Vaginal mucosa physiology and drug delivery. Eur J Pharm Sci., 2013; 50(1): 2-11.
43. Yang W, et al. Factors affecting vaginal drug absorption. Int J Pharm., 2013; 452(1-2): 88-97.
44. das Neves J, et al. Mucus clearance in vaginal drug delivery. Eur J Pharm Biopharm, 2011; 78(3): 340-6.
45. Neves J, et al. Vaginal drug delivery systems. Int J Pharm., 2014; 469(1): 112-24.
46. Khade P, et al. Hydrogel systems for vaginal administration. Int J Pharm., 2014; 463(1-2): 1-8.
47. Vora B, Srivastava A, Malviya R, et al. Proniosomes: a novel drug delivery system. *Journal of Advanced Pharmaceutical Technology & Research*, 2019; 10(1): 1–14.
48. Pandey A, Prakash S, Khuller GK. Nanotechnology based anti-tubercular drug delivery. *International Journal of Nanomedicine*, 2014; 9: 3759–3775.
49. Kumar R, Bhatt L, Pancholi SS. Functionalization in vesicular drug delivery systems: Recent advances and future prospects. *Journal of Drug Delivery Science and Technology*, 2021; 63: 1–14.
50. Sharma A, Sharma R, Saraogi GK. Targeted drug delivery using ligand-functionalized nanocarriers: recent advances and challenges. *Journal of Controlled Release*, 2020; 321: 271–290.
51. Ahmed TA, Aljaeid BM. Preparation, characterization, and evaluation of polymeric proniosomes for drug delivery. *International Journal of Pharmaceutics*, 2018; 542(1–2): 82–92.
52. Singh S, Bhatia A, Kumar A. Polymer hybrid proniosomes for enhanced drug delivery: formulation and evaluation. *European Journal of Pharmaceutical Sciences*, 2022; 173: 106–117.
53. Li J, Wang Y, Zhao X, et al. Stimuli-responsive vesicular systems for controlled drug delivery. *Advanced Drug Delivery Reviews*, 2021; 171: 152–173.
54. Chen Y, Zhang Y, Wang Z, et al. Lipid-polymer hybrid nanoparticles: synthesis and applications in drug delivery. *Biomaterials*, 2020; 232: 119739.

55. Zhao M, Li S, Gan L. Multifunctional proniosomal systems: combining ligand targeting, stimuli responsiveness, and polymer hybridization. *Journal of Pharmaceutical Sciences*, 2023; 112(4): 789–801.
56. Raza K, Kumar V, Syed R, et al. Proniosomes as versatile drug carriers: design, mechanisms, and applications. *Journal of Drug Targeting*, 2022; 30(8): 776–791.
57. Moghassemi S, Hadjizadeh A. Preparation methods for proniosomes and their applications in drug delivery. *Journal of Liposome Research*, 2019; 29(3): 213–229.
58. Jain S, Singh I, Kaur N, et al. Phase separation and coacervation techniques in proniosomal formulation. *International Journal of Pharmaceutics*, 2020; 584: 119425.
59. Gupta P, Pawar VK. Spray coating and other scalable techniques for proniosome production. *Asian Journal of Pharmaceutical Sciences*, 2021; 16(2): 150–162.
60. Song Z, Han Y, Huang L. Microfluidics and advanced manufacturing for liposomal and proniosomal carriers. *Journal of Controlled Release*, 2021; 329: 763–781.
61. Lee J, Park JW. Quality by Design approaches for vesicular nanocarrier optimization. *Pharmaceutics*, 2022; 14(8): 1549.
62. Misra A, et al. Pulmonary drug delivery: strategies and challenges. Int J Pharm., 2011; 406(1-2): 15-30.
63. Nasr M. Lung as a route for systemic drug delivery. J Pharm Sci., 2010; 99(5): 2180-92.
64. Zhou Q, et al. Pulmonary surface area and drug absorption. Expert Opin Drug Deliv., 2014; 11(3): 353-66.
65. Kuzmov A, Minko T. Drug delivery via lungs. J Control Release, 2015; 219: 500-14.
66. Elhissi AM, et al. Pulmonary proniosomes for aerosol delivery of beclomethasone dipropionate. Int J Pharm., 2013; 453(2): 441-50.
67. Abd-Elbary AA, et al. Nebulizable proniosomes for cromolyn sodium delivery. Drug Deliv., 2008; 15(5): 327-35.
68. Bors L, Erdő F. Intranasal drug delivery to the brain. CNS Drugs., 2019; 33(11): 1101-18.
69. Misra A, et al. Nose-to-brain drug delivery: opportunities and challenges. J Control Release, 2016; 241: 144-61.
70. Bhatt P, et al. Advantages of intranasal drug delivery. Drug Deliv Transl Res., 2015; 5(6): 665-77.
71. Ali A, et al. Limitations of intranasal drug delivery. Curr Drug Deliv., 2010; 7(6): 460-72.
72. Alsarra IA, et al. Proniosomes for nasal delivery of therapeutic agents. Int J Pharm., 2010; 396(1-2): 164-70.

73. Gurrapu S, et al. Nanocarriers for nose-to-brain delivery. Nanomedicine, 2012; 8(7): 1043-54.
74. Khatoon S, et al. Intranasal duloxetine-loaded proniosomal gels: ex-vivo and in-vivo evaluation. Int J Pharm., 2019; 560: 245-55.
75. Yoshida K, Sakurai Y, Kawakami K. Vesicular delivery systems for vasopressin analogues: enhancement of oral bioavailability. *J Pharm Sci*., 1992; 81(10): 949–954.
76. Teaima MH, El-Nabarawi MA, El-Setouhy DA. Proniosomal insulin delivery systems for improved oral bioavailability: formulation and evaluation. *Drug Deliv*., 2022; 29(1): 1234–1245.
77. Chandra A, Sharma PK. Niosomes: a novel drug delivery system. *Pharm Rev*., 2008; 6(1): 1–10.
78. Kakar S. Niosomes as carriers for drug delivery: a review. *Int J Pharm Sci Res*., 2010; 1(3): 1–8.
79. Shegokar R. Proniosomal vaccine delivery systems for enhanced immunogenic response in malaria. *Vaccine*, 2023; 41(5): 1123–1130.
80. Gogoi M, Das MK, Sarma H. CpG oligodeoxynucleotide-loaded niosomes as vaccine adjuvants for enhanced immune response. *Int J Biol Macromol*., 2018; 107: 222–229.
81. Radha GV, Rani TS, Sarvani B. Niosomes as carriers for hemoglobin delivery: preparation and evaluation. *Int J Pharm Sci Nanotechnol*. 2013; 6(3): 2152–2160.
82. Biju SS, Talegaonkar S, Mishra PR, Khar RK. Vesicular systems for drug delivery: an overview. *AAPS PharmSciTech*., 2006; 7(1): E1–E7.
83. Durga S, Veera V. Proniosomal carriers for hemoglobin delivery: recent advances and applications. *Int J Pharm Sci Rev Res*., 2020; 60(2): 45–52.
84. Puras G, Zarate J, Aceves M, et al. Niosome-mediated gene delivery to the retina: a novel approach for ocular gene therapy. *Eur J Pharm Biopharm*., 2014; 87(3): 553–562.
85. Yang Z, Li J, Wang Y, et al. Cationic niosomes for siRNA and miRNA delivery into human mesenchymal stem cells. *Colloids Surf B Biointerfaces*, 2018; 170: 89–97.
86. Eltellawy N, El-Say KM, Samy AM. Proniosomal drug delivery systems for cardiovascular therapy: formulation and evaluation. *Drug Deliv*., 2021; 28(1): 567–578.
87. Gupta A, Prajapati SK, Balamurugan M, Singh M, Bhatia D. Development and characterization of proniosomal transdermal drug delivery system of captopril. *Int J Pharm*., 2007; 337(1–2): 1–6.

88. Ahmad M, Sheikh S, Ali SM, Ahmad FJ. Formulation and evaluation of lisinopril proniosomal gel for improved oral delivery. *AAPS PharmSciTech*., 2011; 12(3): 1021–1029.
89. Alshora DH, Alanazi FK, Alotaibi HF, et al. Development of glibenclamide-loaded proniosomes for enhanced oral bioavailability in diabetes management. *Drug Dev Ind Pharm*., 2023; 49(2): 210–218.
90. Eissa MM, El-Say KM, Samy AM. Proniosomal co-delivery of amitriptyline and liraglutide for management of diabetic neuropathy. *Int J Pharm*., 2023; 635: 122633.
91. Loona R, Bharti N, Madan J. Proniosomal drug delivery system of metformin: formulation and evaluation. *Int J Pharm Sci*., 2012; 4(2): 123–130.
92. Sahoo SK, Dilnawaz F, Krishnakumar S. Maltodextrin-based proniosomes of nateglinide for improved bioavailability. *Colloids Surf B Biointerfaces*, 2014; 116: 192–199.
93. Madan J, Dua K, Khude P. Development and evaluation of proniosomal gel of lornoxicam for sustained drug delivery. *Drug Deliv*., 2016; 23(5): 1507–1515.
94. Teng Y, Chen X, Chen Y. Niosomes and proniosomes as drug delivery systems for controlled release applications. *Int J Pharm*., 2019; 564: 123–135.
95. Najlah M, Ahmed Z, Iqbal M, et al. Development of paclitaxel-loaded proniosomes for improved anticancer activity. *J Liposome Res*., 2018; 28(4): 287–295.
96. Kumar R, Jain SK. Proniosomal transdermal delivery of NSAIDs: formulation and evaluation. *AAPS PharmSciTech*., 2016; 17(3): 1–9.
97. Loona R, Bharti N, Madan J. Proniosomal drug delivery system of metformin hydrochloride: formulation and evaluation. *Int J Pharm Sci*., 2012; 4(2): 123–130.