REVIEW ARTICLE

Emerging Trends in Proniosomal Drug Delivery Systems and Their Pharmaceutical Applications

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Abstract

Proniosomes are advanced vesicular drug delivery systems that improve drug stability, bioavailability, and controlled release. They can encapsulate both hydrophilic and hydrophobic drugs and convert them into Niosomes upon hydration, making them suitable for targeted and sustained drug delivery. Proniosomes are commonly prepared using slurry, spray drying, and coacervation phase separation methods. Formulations generally contain non-ionic surfactants, cholesterol, and carrier materials. The prepared proniosomes are evaluated for vesicle size, entrapment efficiency, surface charge, and stability.Proniosomal systems demonstrated improved drug solubility, enhanced bioavailability, prolonged drug release, and better stability compared with conventional formulations. They successfully delivered proteins, vaccines, antibiotics, and anticancer drugs through oral, transdermal, and ocular routes.The flexibility of proniosomal formulations allows optimization of drug release and tissue targeting. Their ability to overcome biological barriers and reduce drug degradation enhances therapeutic efficacy and patient compliance.Proniosomes are promising carriers for modern drug delivery because of their stability, versatility, and controlled release properties. Continued research may further improve their clinical applications and therapeutic outcomes.

Key words: Characterization, drug delivery, entrapment efficiency, niosomes, proniosomes

INTRODUCTION

Proniosomes are emerging nanotechnology-based drug delivery systems developed to improve drug bioavailability, stability, and therapeutic efficacy while reducing adverse effects. They are dry formulations composed of non-ionic surfactants, cholesterol, and stabilizing agents that form niosomal vesicles upon hydration. These vesicles can encapsulate both hydrophilic and hydrophobic drugs, enabling controlled and targeted drug delivery. Compared with conventional niosomes, proniosomes exhibit greater stability, longer shelf life, easier handling, and improved transportability, making them suitable for delivery across challenging biological barriers such as the skin, gastrointestinal tract, and ocular tissues.[1,2]

The development of proniosomes evolved from vesicular systems such as liposomes and niosomes. Although liposomes improved drug encapsulation, they were limited by high cost and instability. Niosomes provided a more stable and economical alternative but still faced storage-related issues.[3] Proniosomes were introduced in the early 2000s to overcome these limitations by providing a stable dry precursor that can be hydrated before use.[4] Proniosomes have been investigated for the delivery of antibacterial, antiviral, anti-inflammatory, and anticancer drugs. They also show promise in dermatological and cosmetic applications because of their biocompatibility and reduced irritation potential.[5-8] Overall, proniosomes represent an important advancement in vesicular drug delivery systems with significant pharmaceutical potential.[9,10]

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Proniosomes [Figure 1] are semi-solid gel formations that are thought to be a combination of hexagonal, cubic, and lamellar liquid crystal phases. Proniosomes are microscopic lamellar formations. Proniosomes are composed primarily of non-ionic surfactants and cholesterol. Non-ionic surfactant's hydrophobic portion orients itself inward, while the hydrophilic portion orients itself outward to form a bilayer. Medications are incorporated into vesicles when hydrophilic medications are encapsulated, while hydrophobic drugs are lodged in the bilayer.[12,13]

Non-ionic surfactants

The fundamental elements of proniosomes and niosomes that are in charge of creating the bilayer vesicles are called non-ionic surfactants. Alkyl ethers, polysorbates (Tween 20, Tween 80), and sorbitan esters (Span 20, Span 60, Span 80) are examples of surfactants that are frequently employed. The vesicles' size, charge, stability, and ability to encapsulate drugs are all impacted by the surfactant selection. Higher hydrophilic-lipophilic balance (HLB) surfactants are known to generate smaller vesicles and improve medication solubility, whereas lower HLB surfactants form larger, more stable vesicles.[14]

Cholesterol

Cholesterol is included in the formulations, as it supports the niosomal bilayer. This stabilizes the drug delivery system since cholesterol rigidifies the vesicles. Cholesterol does not allow the leakage of pharmaceuticals that are encapsulated. Besides this, cholesterol influences the regulation of vesicle permeability, which makes it capable of controlled release drug delivery.[15]

Solvent

Ethanol or chloroform is mainly used as a volatile organic solvent in the preparation of proniosomes. The solvent dissolves surfactants and cholesterol. During drying, this solvent evaporates and leaves a thin layer of lipid and surfactant that can be hydrated to form niosomes.[16]

Carrier material

The most commonly used solid carriers in the formulation with which free-flowing proniosomal powder can be produced are sorbitol or maltodextrin. On hydration of the surfactant, the large surface area of the carrier allows easy adsorption of the surfactant, followed by the formation of niosomes.[17]

Drugs

Proniosomes can encapsulate both hydrophilic and hydrophobic drugs. The hydrophobic drugs are retained within the lipid bilayer, while the hydrophilic drugs get entrapped within the aqueous core of the vesicles. As a result, a wide variety of therapeutic compounds, such as proteins, vaccines, antibiotics, and anticancer medications, can be encapsulated in it.[18]

MECHANISM OF TRANSPORTATION AND RELEASE

Proniosomes are biodegradable vesicles that deliver drugs step-wise, starting from the wetting of a dry granular form to final drug release in the target tissue. Proniosomes

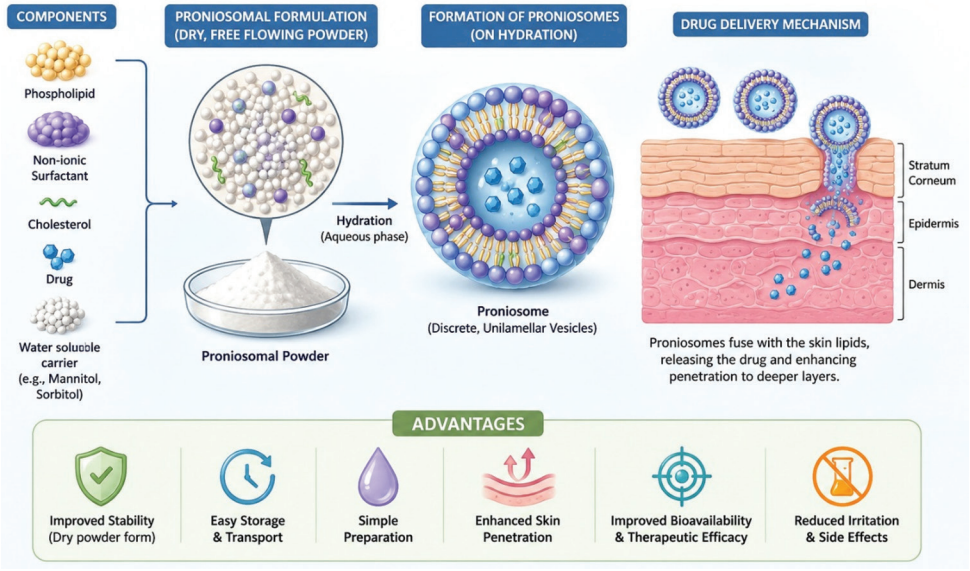

Figure 1: Proniosomes drug delivery system[11]

spontaneously convert to niosomes in aqueous environments, such as water and biological fluids. This is because hydrated non-ionic surfactants typically form bilayer vesicles, commonly known as niosomes.[19] Hydration expands the vesicles and encapsulates the drug molecules inside them and increases the thickness of a surfactant's bilayer. Once proniosomes mature into niosomes, the hydrophilic or hydrophobic drug molecules are either entrapped in the aqueous core or confined in the lipid bilayer, respectively. Niosomal vesicles encapsulate the medication inside them and protect it from degradation by enzymes and the chances of premature release; therefore, this improves its stability in circulation or other biological milieus. Because they are nanosized and contain lipids, niosomes have better penetration across the cell-cell barrier compared to free drug molecules.[20]

Vesicle-cell interactions

Niosomal vesicles generated from proniosomes interact with cellular membranes through adsorption, fusion, lipid exchange, and endocytosis. The bilayer structure of the vesicles resembles biological membranes, promoting membrane fusion and facilitating direct intracellular drug delivery. These interactions enhance drug permeation across epithelial and endothelial barriers, improving bioavailability and therapeutic effectiveness.[21]

Cellular internalization and endosomal escape

After cellular uptake, vesicles are commonly internalized through clathrin-mediated endocytosis, caveolae-mediated endocytosis, or macropinocytosis. Once inside the endosomes, efficient drug delivery requires escape from the endosomal compartment before lysosomal degradation occurs. Endosomal escape may occur through membrane destabilization, osmotic swelling, or fusion of the vesicular bilayer with the endosomal membrane, allowing the encapsulated drug to reach the cytoplasm and exert its pharmacological action.[22]

Surface functionalization strategies

Recent advances have focused on modifying the surface of proniosome-derived vesicles to improve circulation time, stability, and targeting efficiency. Surface coating with polyethylene glycol, chitosan, hyaluronic acid, or other polymers can reduce opsonization, prolong systemic residence, and enhance mucoadhesion. Functionalization also improves vesicle stability under physiological conditions and facilitates controlled drug release.[23]

Ligand-mediated targeting

Targeted proniosomal systems can be developed by conjugating specific ligands such as antibodies, peptides, folic acid, transferrin, aptamers, or carbohydrates onto the vesicle surface. These ligands recognize overexpressed receptors on diseased cells and tissues, promoting receptor-mediated endocytosis and selective drug accumulation at the target site. Such active targeting strategies can increase therapeutic efficacy while minimizing off-target effects and systemic toxicity.[24]

PRODUCTION OF PRONIOSOMES [FIGURE 2]

Slurry method

Proniosomes are dry, free-flowing powder precursors that convert into niosomes upon hydration, and the slurry method is considered one of the most efficient techniques for their preparation. This method is widely preferred because of its simplicity, scalability, and ability to produce stable proniosomal formulations with extended shelf life. Proniosomes prepared by the slurry method are commonly used in transdermal, oral, and specialized drug delivery systems. In this method, non-ionic surfactants such as Span 60 or Tween 80, cholesterol, and the drug are dissolved in an organic solvent such as ethanol or chloroform. Cholesterol helps stabilize the vesicular membrane and regulate fluidity. A solid carrier such as maltodextrin, sorbitol, or lactose is then added gradually to adsorb the surfactant-drug mixture and promote formation of dry proniosomes. The solvent is removed by evaporation under vacuum or at room temperature, producing a dry powder in which the surfactant and cholesterol coat the carrier surface. Upon hydration with water or an aqueous phase, the surfactant molecules self-assemble into bilayer vesicles, forming niosomes that encapsulate the drug molecules within their structure.[25,26]

Coacervation phase separation

The coacervation phase separation technique is one of the most commonly used methods for preparing proniosomes. In this method, surfactant molecules are concentrated from an organic solvent solution to form a separate phase, producing dry proniosomes that convert into niosomes upon hydration. This technique is suitable for encapsulating both lipophilic and hydrophilic drugs. The process involves dissolving the drug, surfactant, lecithin, and cholesterol in a volatile organic solvent such as ethanol or chloroform. As the solvent evaporates, the surfactant molecules undergo phase separation and form a thin film around the drug particles. Due to their amphiphilic nature, surfactants self-assemble into bilayer structures in the presence of water, leading to niosome formation. Cholesterol is added to stabilize the bilayer membrane and improve vesicle rigidity.[27] After solvent evaporation, a thin lipid layer remains, which can be easily rehydrated with an aqueous phase. Upon hydration, proniosomes transform into niosomes, entrapping the drug

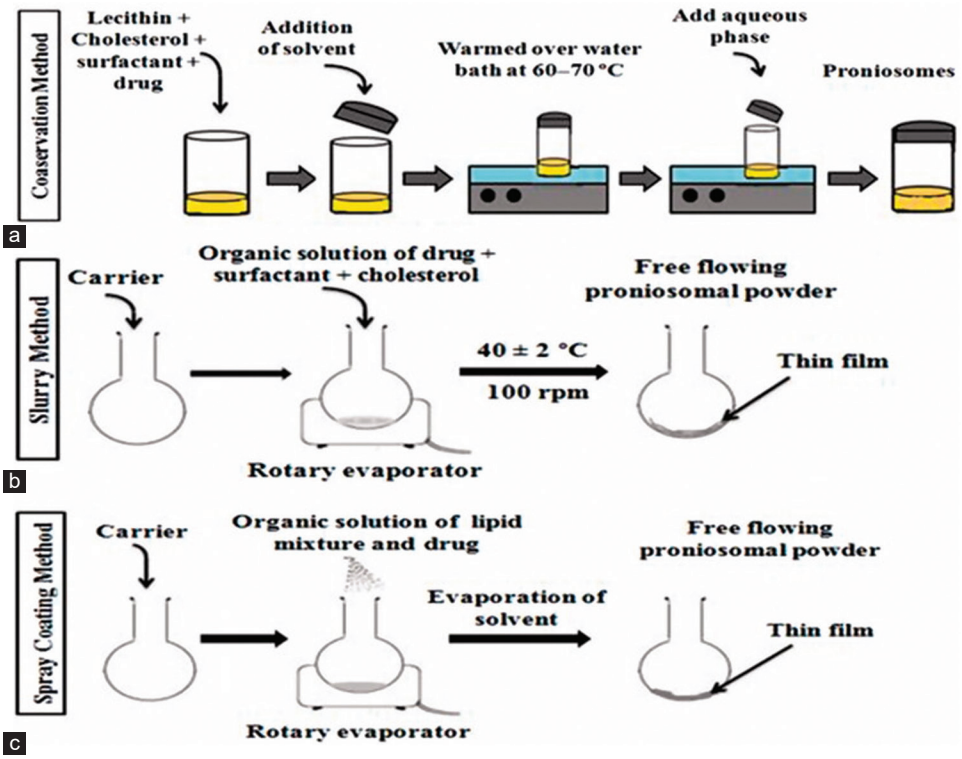

Figure 2: Proniosome preparation techniques include: (a) Coacervation phase separation; (b) Slurry; and (c) Spraying[10]

within their bilayer structure and enabling efficient drug delivery.[28]

Spray coating method

Spray coating is a widely used method for preparing proniosomes, which are dry, free-flowing particles that convert into niosomes upon hydration. This technique is preferred because of its simplicity, scalability, and ability to produce a uniform surfactant coating on carrier materials, ensuring consistent proniosome formation. In this method, surfactants such as Span or Tween, along with cholesterol and the drug, are dissolved in a volatile organic solvent such as ethanol or chloroform. The resulting solution is sprayed onto a solid carrier material, commonly lactose, sorbitol, or maltodextrin, using a spray dryer or atomizer.[29] As the solvent evaporates during spraying, a thin layer of surfactant and drug is deposited on the surface of the carrier particles, forming a dry powder. The coated particles are further dried to remove residual solvent and obtain a free-flowing proniosomal formulation. Upon addition of water or an aqueous medium, the proniosomes spontaneously hydrate and form niosomes capable of encapsulating the drug for effective delivery.[30]

Film hydration method

One of the most well-known and popular methods for creating proniosomes dry formulations that become niosomes when hydrated is the film hydration method. Because of its ease of use and capacity to encapsulate both hydrophilic and hydrophobic medications, this approach is very well-liked. The film hydration method is based on the dissolution of cholesterol and surfactants (e.g., Span or Tween) in a volatile organic solvent, such as methanol or chloroform, followed by solvent evaporation to produce a thin lipid film. After the solvent is extracted from this solution using rotary evaporation, a thin lipid layer forms on the inside of a flask with a circular bottom. Surfactants, cholesterol, and the medication, if added at this stage, make up the film shown in Figure 3.[31] Multilamellar vesicles (MLVs), also known as niosomes, are formed when the film becomes hydrated with an aqueous solution (such as phosphate-buffered saline) while being stirred after the solvent has evaporated. The medication, cholesterol, and surfactants are all dissolved in an organic solvent. Using a rotary evaporator, the solvent is evaporated at low pressure, leaving a thin lipid film on the flask walls. An aqueous phase is added to the dry film, causing the surfactants to self-assemble into bilayers and the creation of niosomes. To produce more homogenous niosomes, the generated vesicles might be shrunk down by extrusion or sonication.[32]

Microfluidization

Microfluidization [Figure 4] is an advanced technique used for the preparation of proniosomes, producing small and homogeneous vesicles through the application of high pressure. In this method, a mixture of surfactants, cholesterol, drug, and organic solvent is passed through narrow

microchannels of a microfluidizer at pressures ranging from 500 to 20,000 psi. The high shear forces and turbulence generated during the process reduce vesicle size and improve drug encapsulation and stability.[34] This technique produces uniformly sized nanoscale proniosomes with narrow particle size distribution, which enhances bioavailability and enables controlled drug release. Microfluidization is suitable for encapsulating both hydrophilic and lipophilic drugs and is highly reproducible and scalable for industrial applications. It also improves drug loading efficiency, physical stability, and formulation consistency.[35] Although specialized equipment increases production cost, microfluidization remains a promising approach for developing proniosomes intended for intravenous, oral, and transdermal drug delivery systems.

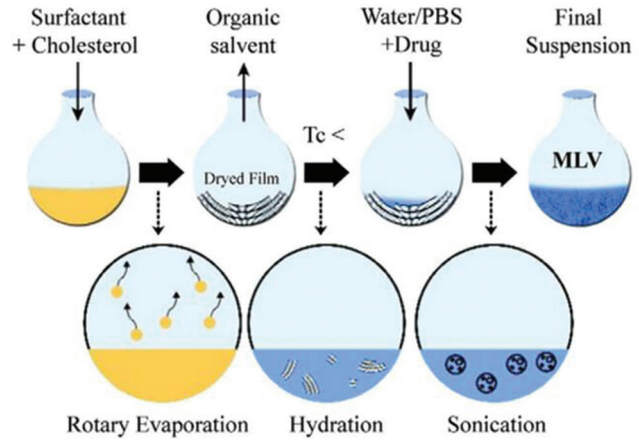

Figure 3: Production of proniosomes by film hydration[33]

Freeze-thaw method

The freeze-thaw technique is an effective method used to improve the stability and encapsulation efficiency of proniosomes. In this process, surfactants such as Span or Tween, cholesterol, and the drug are dissolved in an organic solvent to form a thin film after solvent evaporation. An aqueous phase is then added to produce vesicular suspensions.[37] The formulation is repeatedly subjected to freezing and thawing cycles, usually 3–10 times, to stabilize the vesicles and achieve uniform drug encapsulation within the bilayer or aqueous core. These cycles reduce MLVs into more uniform niosomes through mechanical stress generated during freezing and thawing. The technique improves membrane integrity, enhances vesicle stability, and minimizes drug leakage.[38] It is suitable for both hydrophilic and hydrophobic drugs and has broad applications in drug delivery. However, optimization is necessary to prevent possible drug leakage during thawing.[39]

CHARACTERIZATION OF PRONIOSOMES

The characterization of these systems is very essential to determine whether they are potent or not in their drug delivery activity. For the desired therapeutic effect, characterization should be measured against some set of attributes such as

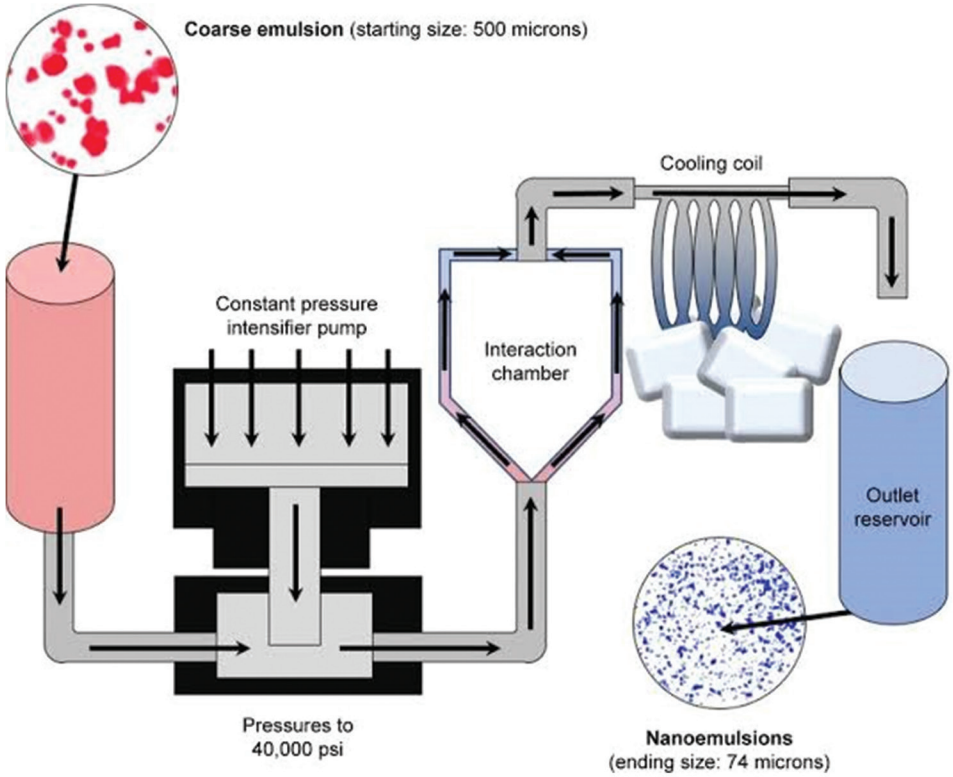

Figure 4: Microfluidization process[36]

size, shape, stability, entrapment efficiency of the drug, and release profile. The following are the major methods and parameters used for proniosomes characterization:

Morphology and particle size

The size and shape of proniosomes highly affect their permeation through biological barriers and subsequent drug release. Morphological studies on proniosomes are primarily carried out with the help of transmission electron microscopy and scanning electron microscopy. This technique provides information about the surface characteristics and the structure of the vesicles, along with the particle size. The particle size and distribution are evaluated by dynamic light scattering, which checks the proniosomal formulation for homogeneity.[40]

Entrapment efficiency

The drug entrapment efficiency of proniosomes is highly important in determining the amount of drug that has successfully been encapsulated within the vesicle. This is usually done by free separation of (unentrapped) drug from encapsulated drug via centrifugation or ultracentrifugation.[41] The concentration of the medication within the supernatant is ascertained, and EE is then calculated using the following formula:

$$EE\% = \frac{\text{Amount of entrapped drug}}{\text{Total amount of drug}} \times 100$$

Zeta potential

The surface charge of proniosomes is attracted in order to obtain the zeta potential that is crucial for the stability of proniosomes. A high value of zeta potential is either positive or negative; it simply means it gives good stability since it stops the aggregation of vesicles, which is from the repulsive interaction between like charges. A zeta potential analyzer is normally used to assess zeta potential.[42]

In vitro drug release

The release profile of drugs from proniosomes can often be studied *in vitro* by making use of a dialysis membrane and diffusion cells. This mimics the actual release of the drug from proniosomes in a biological environment. Formulation-based study of time-dependent drug release kinetics can also be studied using zero-order, first-order, or Higuchi models.[43]

Stability studies

The physical and chemical stability of proniosomes is determined based on time, especially during storage. Vesicles may also be sensitive to temperature, humidity, and light. Stability studies will monitor the change of particle size and zeta potential with time and the leakage of drugs. Freeze-drying or lyophilization is often used to improve stability for long-term storage.[44]

Vesicular lamellarity

Proniosome lamellarity is the bilayer number in the vesicle. This depends on the method of its manufacture, but whether to produce MLVs or unilamellar vesicles, it produces proniosomes. Freeze-fracture electron microscopy and nuclear magnetic resonance are routine techniques for bilayer counting.[45]

Thermodynamic analysis

Thermogravimetric analysis and differential scanning calorimetry determined the thermal properties of proniosomes. The methodology allows one to gain insight in a drug excipient interaction, phase transitions as well as heat stability of the formulation. Proniosomal formulations that have good stability over a wide range of temperatures and a sharp melting point are likely to be robust.[46] Studies on permeability, in the case of topical or transdermal delivery, would be important to verify if the drug is penetrating the skin sufficiently. Most studies are put together using Franz diffusion cells and excised animal or human skin. By relying on its better penetration, compared with other formulations or free drugs, proniosomes can be administered transdermally.[47] Sensitivity to pH – this is one of the possible ways to achieve stability and drug release profile irrespective of the pH level, which may be useful in formulations targeted to specific pH habitats, such as the stomach or tumor tissues. It might thus be possible to determine whether the vesicles can be qualified for drug delivery through routes such as the intravenous or oral route by determining their stability in different pH settings.[48]

APPLICATIONS OF PRONIOSOMES IN DRUG DELIVERY

Oral drug delivery

Even though proniosomes have extremely low solubility and bioavailability, they are especially useful for the oral delivery of medications. Proniosome encapsulation improves drug absorption throughout the gastrointestinal system; hence, proniosomes become niosomes when consumed in the stomach's water content. This makes the drug's controlled release from the capsule even easier. Medication absorption is slowed, and therapeutic medication levels are prolonged by this kind of controlled

release. Because peptides protect the substance from gastrointestinal tract-derived enzymatic degradation, peptides also increase the bioavailability of sensitive medicines. Higher bioavailability was shown by oral dosage forms with proniosomal drug delivery systems comprising nimesulide, acyclovir, and indomethacin.[49]

Transdermal drug delivery

Another common application for proniosomes is transdermal medication administration. Proniosomes are specifically helpful for medications that need to be released gradually or have little skin penetration because of their capacity to increase skin permeation. The stratum corneum can be penetrated by the niosomes that are created following hydration. This improves the medication distribution to the skin's deeper layers. This is mainly useful for medications such as hormones, analgesics, or anti-inflammatory compounds that need to be delivered systemically through the transdermal route. Proniosomal preparations, which provide controlled and sustained drug release throughout time, lower dose frequency, and enhance patient compliance, have been created for transdermal delivery of medications such as ketorolac, estradiol, and diclofenac.[50]

Topical drug delivery

Proniosomes assist in the dermal delivery of drugs and transdermal delivery in those cases where the drug has to act locally at the outer layer of the skin or at the dermis. Proniosomes provide deeper penetration for a dermatological preparation through the barrier of the skin and also facilitate localized release at the site of its action. More importantly, proniosomes protect unstable or sensitive drugs from degradation by prolonging the therapeutic action of drugs. For example, the application of proniosomes is on topical drug delivery of medications such as tretinoin and clotrimazole for better retention of drugs in the skin, thereby avoiding systemic side effect.[51]

Pulmonary drug delivery

Proniosomes are being used to transport medications to the lungs' systemic circulation and to treat the respiratory system locally, due to the growing interest in their usage in pulmonary medication administration. Proniosomal formulations provide direct alveolar or inhalation entry into the lung, hence enabling the non-invasive technique of medication delivery. Asthma and chronic obstructive pulmonary disease (COPD) are only two of the many conditions that this approach may effectively treat and manage when it comes to lung diseases. The hydrophilic or lipophilic medications that these proniosomes may contain could enable the carefully regulated, prolonged delivery of treatment into the lungs. Furthermore, when the frequency of dosage is reduced, these also help to improve patient compliance.[52]

Targeted drug delivery

Proniosomes have many applications, especially in targeted drug delivery, where drugs are delivered exclusively to tissues or cells that have been damaged with minimal systemic exposure and side effects. This can be achieved through the conjugation of prions with ligands such as peptides, antibodies or folate molecules that bind and recognize various receptors present on the specific target cells, thereby carrying the drug directly to the site of action. The most important advantage of proniosomes is that chemotherapeutic drugs are delivered directly to the targeted cancer cells without causing much damage to the healthy organs. This formulation is, therefore, highly useful in chemotherapy. Formulations of proniosomes of drugs such as paclitaxel and doxorubicin have been shown promisingly selective for targeting cancerous cells while sparing the healthy ones.[53]

Intravenous drug delivery

Since proniosomes can also control the drug release and improve the solubility of poorly soluble drugs, it is also used in intravenous drug delivery. Intravenous proniosomes hydrate *in vivo* to form niosomes in the blood after intravenous injection, which makes continuous drug release possible. It reduces re-dosing since the therapeutic concentration of the drug is maintained for a more extended period. The entrapped drugs with narrow therapeutic indices become safer because the release rate is controlled, which minimizes the possibility of toxicity.[54]

Vaccination and immunization

Indeed, research work on proniosomes as carriers for vaccines and immunotherapeutic agents is already underway. Since proniosomes can encapsulate antigens, they stabilize them so that it is possible to transport the antigen in a controlled way, perhaps intensifying the immune response. Indeed, even the potency of vaccines can be enhanced using this mode of application precisely to target cells within the immune system. Proniosomal formulations have been studied as needleless and patient-friendly delivery systems of antigens in oral, transdermal, and nasal vaccines.[55,56]

LATEST INVENTIONS IN PRONIOSOMAL DRUG DELIVERY

Formulation of proniosomes by high-pressure homogenization (HPH)

HPH is an important technique used in proniosome processing to reduce particle size, improve drug encapsulation

efficiency, and enhance formulation stability. Proniosomes are dry surfactant-coated carriers that convert into niosomes upon hydration, and HPH helps produce uniform nano-sized vesicles for improved drug delivery.[57] In this process, the hydrated proniosomal dispersion is forced through a narrow gap under high pressure (100–1500 bar), generating shear forces, turbulence, and cavitation that break large vesicles into smaller and more homogeneous niosomes. This results in reduced polydispersity index, improved stability, enhanced drug retention, and controlled drug release.[45] The process generally involves hydration of the proniosomal powder with an aqueous medium to form a coarse dispersion, followed by multiple homogenization cycles to achieve the desired vesicle size. Optimized formulations are then evaluated for particle size distribution, drug encapsulation efficiency, stability, and *in vitro* drug release behavior. HPH offers several advantages, including improved bioavailability, enhanced cellular uptake, better formulation uniformity, and reduced aggregation during storage.[58] It is also suitable for large-scale industrial production in pharmaceutical, nutraceutical, and cosmeceutical applications. Studies have demonstrated that HPH-based proniosomes provide sustained drug release, prolonged circulation time, and improved therapeutic efficacy in applications such as transdermal, pulmonary, and anticancer drug delivery.[59] Despite challenges such as high energy consumption and possible degradation of sensitive drugs, HPH remains a valuable technique for producing stable nano-sized proniosomal formulations with controlled release properties.[60]

Proniosomal gel for transdermal treatment [Figure 5]

Proniosomal gels are advanced transdermal drug delivery systems containing dry surfactant-coated vesicles that form niosomes upon hydration. They enhance drug penetration through the stratum corneum, enabling controlled and sustained drug release with improved bioavailability and reduced side effects.[61,62] These gels typically contain non-ionic surfactants, cholesterol, and gel bases such as carbopol or hydroxypropyl methylcellulose.[63] Upon skin application, proniosomes convert into niosomes and gradually release the drug through skin layers. Proniosomal gels improve patient compliance due to their non-greasy nature and prolonged therapeutic action and are widely studied for anti-inflammatory, hormonal, and antihypertensive drug delivery.[64-66]

Proniosomes in sonophoresis for enhanced transdermal drug delivery

Proniosomes combined with sonophoresis represent an effective non-invasive transdermal drug delivery approach. Sonophoresis uses low-frequency ultrasound to temporarily disrupt the stratum corneum through cavitation, heating, and microstreaming, thereby enhancing skin permeability and drug penetration.[68] Upon hydration, proniosomes form niosomes that encapsulate drugs and provide controlled release, improving bioavailability and reducing systemic side effects. These formulations commonly contain non-ionic surfactants such as Span and Tween, cholesterol, and penetration enhancers.[69] Proniosome-based sonophoresis has shown improved delivery of drugs such as insulin, diclofenac, and lidocaine for applications including pain management, hormone therapy, and wound healing.[70] Despite promising results, challenges such as optimization of ultrasound parameters and formulation stability remain.[9,47]

Proniosomes for a pulmonary drug delivery system

Proniosomes have shown significant potential in pulmonary drug delivery for treating respiratory disorders such as asthma, COPD, and pulmonary infections.[52] These dry surfactant-coated vesicles convert into niosomes upon hydration in the lungs, enabling controlled drug release, improved bioavailability, and enhanced drug stability. Their small vesicle size promotes deep lung penetration and efficient alveolar deposition, thereby prolonging therapeutic effects while reducing systemic side effects.[71] Proniosomal pulmonary formulations commonly contain non-ionic surfactants such as Span and Tween, cholesterol, and carriers such as lactose or mannitol. They can be administered through dry powder inhalers, nebulizers, or pressurized metered-dose inhalers.[72] Studies have demonstrated promising outcomes with bronchodilators, corticosteroids, antibiotics, and antitubercular drugs such as isoniazid and rifampicin. Proniosomal budesonide formulations also showed enhanced anti-inflammatory effects in asthma treatment. However, challenges, including formulation stability, particle size optimization, and large-scale production, remain areas for further research.[73]

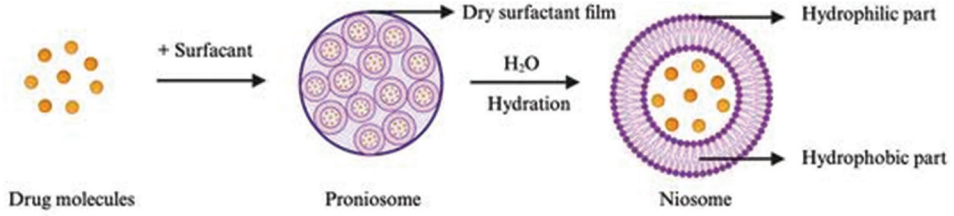

Figure 5: Development of proniosomal gel formation[67]

Proniosome for ocular drug delivery

Ocular drug delivery is challenging because protective barriers such as the corneal epithelium, blinking, and tear drainage reduce drug absorption and bioavailability. Proniosomes have emerged as promising nanocarriers for ocular delivery due to their ability to enhance drug permeability, stability, and sustained release.[74,75] Upon hydration, proniosomes form niosomes that prolong ocular retention time and reduce dosing frequency. These formulations commonly contain non-ionic surfactants such as Span and Tween, along with cholesterol, which improve vesicle stability and drug retention.[76] Proniosomal systems have shown improved delivery of drugs such as ciprofloxacin, timolol maleate, and ketorolac compared with conventional eye drops. Recent advancements include *in situ* gelling proniosomal formulations and chitosan-coated proniosomes, which enhance ocular bioadhesion and permeability.[77] Despite their advantages, challenges related to drug release kinetics and patient comfort remain. Ongoing research focuses on biodegradable and stimuli-responsive proniosomal systems for targeted and controlled ocular drug delivery.[78]

CONCLUSION

Proniosomes are advanced drug delivery systems that offer significant advantages over conventional formulations. They can encapsulate both hydrophilic and lipophilic drugs, providing improved stability, controlled release, and enhanced bioavailability. Their ability to self-assemble into niosomes upon hydration makes them suitable for multiple routes of administration, including oral, transdermal, topical, pulmonary, intravenous, and targeted drug delivery. Proniosomes protect drugs from degradation and improve drug permeation across biological barriers such as the skin and gastrointestinal tract. They also enhance therapeutic efficacy while reducing systemic side effects, particularly in targeted therapies such as cancer treatment. Owing to their stability, flexibility, and controlled release properties, proniosomes have the potential to improve patient compliance and therapeutic outcomes. Continued research on advanced and surface-modified proniosomal systems may further expand their pharmaceutical and clinical applications.

AUTHORS' CONTRIBUTIONS

Shaik Meharaj: Conceptualization, study design, methodology development. Badri Sireesha: supervision. Data interpretation, manuscript drafting, and final review. Saravanan Ravindran: Experimental work, chromatographic analysis, data collection, validation studies, and manuscript preparation. All authors reviewed, revised, and approved the final version of the manuscript.

AI USE STATEMENT

The authors used Grammarly and OpenAI for grammar checking, language refinement, sentence restructuring, and improving the clarity of scientific writing. Bio render software is used for figure improvement and drawing. The authors carefully reviewed, edited, and validated all generated content and take full responsibility for the final manuscript.

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