REVIEW ARTICLE

A Review on Proniosomes as a Novel Drug Delivery System

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ABSTRACT

Proniosomes are desiccated versions of surfactant-coated, water-soluble carrier particles. Before usage, on agitation in heated aqueous solution, they are rehydrated in a matter of minutes to create niosomal dispersion. In storage and transit, proniosomes maintain their physical stability. The drug contained within the proniosomes' vesicular structure increases the drug's potency, improves its absorption into the target tissue, and lowers its toxicity. Niosomes are technically more promising than liposomes as drug carriers since they are more chemically stable and don't have many of the glitches of liposomes, like high cost and problems with phospholipid purity. Focusing on proniosome preparation, characterization, and application in targeted drug delivery, this study highlights their general approaches.

Keywords: Proniosomes, Niosomes, Vesicular, Characterization, applications.

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INTRODUCTION

There has been a lot of interest in using vesicular systems to administer cutting-edge drugs. One such technique is the encasing of the drug in vesicular structures, which should extend the period the drug is in the bloodstream while also lowering its toxicity through selective absorption. Over the following years, a lot of progress was made in our knowledge of the molecular and cellular interactions between vesicular systems and the biological milieu.[1] Drug delivery technologies have unquestionably demonstrated the benefits of colloidal particle carriers over traditional dosage forms. These particles can serve as drug reservoirs and transport hydrophilic or hydrophobic drugs to the target site. In addition to physical issues, certain chemical problems related to degradation may arise in a dispersed aqueous solution.[2]

Utilizing non-ionic surfactant substitutes for phospholipids in vesicle preparation, two innovative strategies were used to address these issues: pro-liposome and niosome development. Although the physical stability of the preparation is improved by proliposomal formulations over conventional liposome dispersions, chemical instability still exists. As such, preparing and storing the preparation under an environment of nitrogen or vacuum is advised to prevent phospholipid oxidation.[3]

In the latter method, niosomes show strong chemical stability throughout storage; however, niosomes in aqueous suspension may display physical stability problems.[4] Combining the two previously described methods, the most recent development in vesicular delivery extends the pro-vesicular strategy to niosomes by forming "proniosomes" that, when hydrated, transform into niosomes.[5] Low solubility and low bioavailability can be addressed using a variety of formulation strategies.

Proniosome technology provides new approaches to drugs with low solubility. Proniosome is a granular product that is dry, free-flowing, and can be hydrated right before usage, dispensing with many of the issues related to aqueous niosome dispersions, including problems with physical stability.[6]

Structure

Figure 1 depicts the structure of proniosomes**.** Microscopic lamellar formations are known as Proniosomes. After hydration in aqueous fluids, they blend cholesterol with a non-ionic surfactant of the alkyl or dialkyl polyglycerol ether type. Comparable to liposomes, proniosomes comprise two layers. Non-ionic surface-active substances comprise the proniosome bilayer.[7,8]

Based on the formation process, proniosomes can have one or more lamellar structures. Hydrophobic drugs are thus incorporated in the bilayer, whereas hydrophilic pharmaceuticals are restricted to the vesicle's aqueous portion [8].

Mechanism of Proniosomes[9-10]

There are conflicting findings about the mechanism of drug transport across the skin using vesicles. Therefore, the variables that affect the interactions between skin and vesicles

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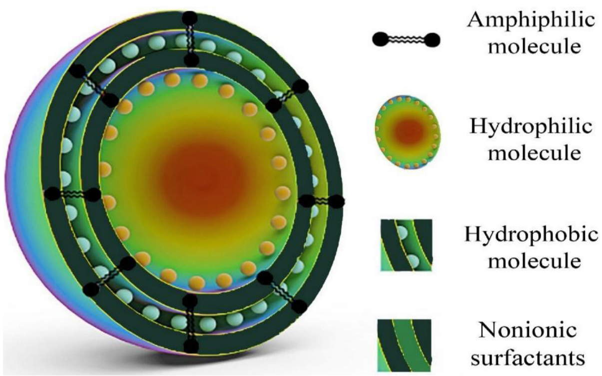

Figure 1: Structure of proniosomes

and determine how well drugs are transported through the skin remain unknown. However, prior to the drug being released and entering the skin, the pro-vesicular system needs to be transformed into vesicles. The drug's rate-limiting barrier is the bilayer found in the vesicles, which also contain phospholipids and non-ionic surfactants, both of which can improve drug penetration. The stratum corneum barrier characteristics are diminished by the permeation enhancers' effect on vesicles. Changes to the stratum corneum's structure that allow drugs encased in vesicles to permeate are another potential mechanism.

Advantages of Proniosomes[11-12]

- Phospholipids and surfactants in proniosomes aid in the drug's diffusion and penetration.
- Another benefit of Proniosomes is their ease of distribution, transportation, storage, and sterilization.
- They avoid stability problems during storage, such as fusion, leakage, aggregation, and sedimentation.
- The drug has a longer shelf life.
- Encapsulates both hydrophilic and hydrophobic drugs.
- This demonstrates controlled and prolonged drug release by depot formulation.
- The size, content, shape, and fluidity can all be altered.
- It can be administered topically, parenterally, or orally.
- They also increase the drug's skin penetration over the skin and oral bioavailability of poorly absorbed medications.

Components of Proniosomes

Surfactant

The surface-active substances known as surfactants are typically amphiphilic organic molecules, meaning they include both hydrophobic and hydrophilic groups. Consequently, the water-soluble (hydrophilic) and water-insoluble (lipophilic) components of a surfactant molecule are both present. They act as permeability enhancers, wetting agents, emulsifiers, and solubilizers.[13] To produce vesicles, non-ionic amphiphiles such as fatty acid esters, alkyl ethers, alkyl esters, and alkyl amides are most frequently used.

Carrier materials

When the carrier is employed in the assembly of proniosomes, it allows flexibility in the proportion of integrated surfactant to other components.[14] Examples of commonly used carriers are sorbitol, mannitol, glucose, lactose, and sucrose.

Membrane stabilizers

The primary functions of lecithin and cholesterol are as membrane stabilizers. Cell membranes contain sterols, which significantly alter the fluidity, permeability, and stability of the bilayer significantly. Steroids are an essential component of membranes. A naturally occurring steroid, cholesterol, is added to membranes. It prevents aggregation by adding particles that alleviate the system and the formation of aggregates through electrostatic or repulsive steric forces.[15]

A major component of lecithin is phosphatidylcholine. It forms liposomes, micelles, or lamellar structures depending on temperature and hydration levels. It is poorly soluble in water. They are called soy lecithin and egg lecithin, depending on where they derive from. It serves as an amplifier of penetration in addition to stabilizing. Because of the apparent difference in intrinsic makeup, vesicles made of soy lecithin are observed to be larger than those made of egg lecithin.

Solvents

Drug penetration rate and vesicle size are significantly impacted by the alcohol used in Proniosomes.
The order of the size of formatted vesicles is:

Ethanol > Propanol > Butanol > Isopropanol

Because of its branched chain, isopropanol produces the smallest vesicles, whereas ethanol produces the largest.[16]

Types of proniosomes

Dry granular proniosomes

With the help of surfactants, water-soluble carriers are coated to produce dry granular proniosomes.

- *Sorbitol-based proniosomes*

Sorbitol is covered with a non-ionic surfactant and then employed as a niosome by adding hot water and agitating it. Classically, sorbitol powder is coated with a surfactant blend created in an organic solvent, which is then spread on, and the solvent is allowed to evaporate to create sorbitol-based proniosomes. The procedure needs to be repeated until the desired coating is obtained.

- *Maltodextrin-based proniosomes*

The slurry method is used to manufacture this type of proniosomes. As a carrier substance in the formulation, maltodextrins are readily soluble in water and increase the surface area of hollow particles. Potential uses for maltodextrin-based proniosomes include the transport of amphiphilic drugs.

Liquid crystalline proniosomes

Surfactant molecules interact with water in three different ways that cause their lipophilic chains to alter into a disordered liquid form acknowledged as the lyotropic liquid crystalline state.
The following are the three methods.

- Temperature increase at Kraft's location

- Solvent addition for lipid dissolution
- Employing both solvent and temperature

Methods of Preparation

Slurry method

A measured amount of cholesterol and surfactants dispersed in an appropriate solvent, to put it briefly. A round-bottom flask (RBF) with the carrier was filled with the resulting solution. If there is less surfactant loading, extra solvent can be added to form the slurry. The flask was fastened to a rotating flash evaporator, and at 45 ± 2ºC, the organic solvent was evaporated under low pressure. Proniosomes that flow freely and become dry in the flask are produced. In the end, they were kept in a firmly closed container awaiting further assessment.

Coacervation phase separation method

Precisely weighed drug, lipid, and surfactant were combined with organic solvent in glass vials and heated in a water bath. Until all of these materials had completely dissolved, the glass vials The liquids were left to cool at room temperature, and any production of a white, creamy proniosomal gel or a transparent, translucent solution was noted. After adding a stabilizer, the resulting gel was kept in the dark until characterization.

Modified coacervation method

A precisely weighed drug containing lipid, lecithin, and surface-active agent was combined with a solvent and heated in a water bath at 65 ± 3°C for five minutes. Phosphate buffer (pH 7.4) and the blend was added to the water bath till a clear solution was attained. After allowing the mix to cool, the dispersion began to form proniosomal gel.

Hand-shaking method

Surfactants and cholesterol, which are components of vesicles, are dissolved in an organic solvent-filled RBF. At normal temperature, the solvent blend in the rotary flash evaporator evaporates. The spherical bottom of the flask develops a thin layer of dried solid material. Rehydrating the dry solid mixture film requires an aqueous phase at 0 to 60°C and moderate shaking and yields multi-lamellar niosomes.

Slow spray coating method

It includes scattering a surfactant diluted in the organic solvent over a carrier and letting the solvent evaporate. To do this, aliquots are constantly sprayed at a regulated rate of application onto the carrier's surface, introducing a blend into the RBF, holding the required quantity of carrier. After the last aliquots are added, the flask must be rotated under vacuum until the powder is fully dry. It must then be placed in a water bath that is between 65 and 70°C. Continue doing this until the required degree of surfactant loading is achieved. Next, obtain a very thin surfactant-coatedcarrier, which dissolves as the coating becomes hydrated. The material is subsequently dried for an entire night under vacuum in a desiccator. It provides a free-flowing, dry preparation of "proniosomes," which is subsequently utilized for the preparation and characterization.

Characterization

Analysis of particle size

Researchers can study the size distribution and surface appearance of individual particles with scanning electron microscopy (SEM).

Optical microscopy

It is necessary to spread out the niosome suspension on a glass slide, let it dry at room temperature, and then look at it under a microscope to capture photomicrographs of the niosome suspension as a thin, dry layer during the development of vesicles.

Angle of repose

Powdered dry proniosomes were measured for the angle of repose using a funnel technique. A fixed funnel was filled with the proniosomes that had been powdered. Following the powder's release from the funnel and the formation of a cone on the surface, the cone's height and base diameter were measured.

Drug content

A standard volumetric flask was filled with 100 mg of proniosomes. After 15 minutes of shaking, 50 mL of methanol were added. Using methanol, the solution was diluted to 100 mL. Next, by saline phosphate buffer at a certain pH, 10 mL of this solution were diluted to 100 mL. After aliquots were removed, the drug content was further computed using the standardization curve and absorbance at a specific wavelength.

Measurement of zeta potential

To ascertain the colloidal characteristics of the produced formulations, the study is conducted. The greater the value of the ZP, the more will be the surface charge.

Measurement of vesicle size

The size of the sample was estimated using a particle size analyzer. The resulting dispersion was obtained after bath-sonicating the powder for three minutes and hydrating it with phosphate buffer.

Entrapment efficiency

From the proniosomal suspension, the unentrapped drug was separated using the

- *Dialysis technique*

The proniosomal suspension was positioned in a dialysis tube with a magnetic stirrer, and one side of the tube was sealed with an osmotic cellulose membrane. Via the osmotic cellulose membrane, the drug that was not entrapped and the niosomal suspension were separated into the medium. Following six hours of intensive dialysis, optical density readings were recorded, and the UV spectrophotometric technique was used to evaluate the quantity of drug that had been entrapped.

- *Centrifugation method*

Using centrifugation, the produced proniosomes were separated from the drug that was entrapped. Using a chilled centrifuge, hydrated proniosomes were centrifuged for five minutes at 14000 rpm. The supernatant was then examined using UV spectrophotometry to determine the amount of free drug present.

The provided formula was used to calculate entrapment efficiency (EE).

$$EE = \frac{Total\ drug\ loaded - free\ drug}{Total\ drug}\ x\ 100$$

Fourier Transform Infrared (FTIR) Spectroscopy

Using an FTIR spectrophotometer and the traditional KBr pellet technique, a spectrum of the improved proniosome powder was attained from 4000 to 5000 cm^{-1}.

In-vitro Diffusion Studies

The most widely used technique is the Franz diffusion cell, which uses phosphate buffer and requires a temperature of 37 ± 0.5°C. To keep the volume constant, a 5-mL aliquot was taken at prearranged intermissions and substituted with a fresh medium. UV spectroscopy was used to analyze the samples. The skin of albino rabbits/rats; both dorsal and flank, can be used for in vitro skin permeation experiments.

In-vitro Drug Release

The suspension was introduced in a dialysis bag secured in the receptor compartment with 50 mL of phosphate buffer (7.4). Aliquots are removed at appropriate intervals and subjected to UV spectrophotometer analysis.

Osmotic Shock

The shift in vesicle dimensions can be established by osmotic studies. For 3 hours, proniosomal formulations are incubated in solutions that are hypotonic, isotonic, and hypertonic. The alterations in vesicle sizes inside the formulations are then observed via optical microscopy.

Stability Studies

For stability experiments, the produced proniosomes were kept for 1 to 3 months at room temperature (25 ± 0.5°C), refrigerator temperature (2–8°C), and high temperature (45 ± 0.5°C).

Applications

In cardiology

Proniosomes are utilized as carriers to deliver captopril transdermally for the treatment of hypertension.

In diabetes

The skin penetration process of furosemide proniosomes is delivered non-invasively using proniosomes.

Anti-cancer

Most antineoplastic drugs have serious adverse effects. Proniosomal entrapment of methotrexate (in two different investigations) and doxorubicin (in an unentrapped drug) has shown benefits, with a reduced rate of lump development and higher plasma levels with a delayed elimination period.

Hormonal therapy

The emergency contraceptive levonorgestrel is delivered via a proniosome. A pregestational activity bioassay was also conducted. It consisted of an endometrial test and corpora lutea development blockage.

Delivery of peptide drugs

Peptide and protein bonds break down when peptide drugs are administered orally. The peptides are shielded from gastrointestinal peptide degradation by niosomes. Moreover, a vasopressin derivative contained in niosomes demonstrated greater stability.

Studying the immune response

The nature of the immunological response brought on by antigens is studied using niosomes and proniosomes.

Carriers for haemoglobin

Haemoglobin (Hb) in the blood can be transported by proniosomes. Due to its oxygen permeability, the proniosomal vesicle can transport Hb in anaemic individuals.

Transdermal drug delivery systems

Proniosomal technique for transdermal drug administration is extensively employed in cosmetics. For the topical treatment of acne, antibiotics with proniosome entrapment are used. When drugs are entrapped in proniosomes, their skin penetration is knowingly higher. Proniosomal technology-based transdermal vaccinations have also been the subject of a recent study (Table 1).

Treatment of leishmaniasis

The disease known as leishmaniasis is triggered by a parasite belonging to the genus Leishmania invading the spleen and

Table 1: Some of the studies conducted on proniosomes as drug delivery systems

S. No.	*Active pharmaceutical ingredient*	*Category*	*Composition*
1	Ketorolac [38]	Non-steroidal anti-inflammatory drug	Span 60, ethanol
2	Estradiol [39]	Hormonal therapy	Span (40,60,85); Tween (20,40), lecithin, cholesterol
3	Ritonavir [40]	Anti-retroviral agent	Spans, Tweens, lecithin, cholesterol, carbopol-934.
4	Valsartan [41]	Angiotensin II inhibitor	Span 40,60, soya lecithin
5	Cromolyn sodium [42]	Anti-inflammatory agent	Span, lecithin, cholesterol
6	Pioglitazone [43]	Anti-hypoglycemia	Span, lecithin, cholesterol
7	Terconazole [44]	Anti-fungal	Surfactants, lecithin, cholesterol
8	Benzocaine [45]	sedatives	Span 60/cholesterol

liver cells. Derivatives of antimony, in greater quantities, can cause harm to the kidneys and liver and are frequently used as drugs for treatment.

Sustained release

Since niosomal encapsulation can keep drugs with a lower therapeutic index and low water solubility in the bloodstream, proniosomes can be used to provide sustained release action for these types of pharmaceuticals.

CONCLUSION

Compared to traditional vesicular systems, proniosome development marks a substantial advancement. The notion of encapsulating the drug into proniosomes to enhance its targeting at suitable tissue locations and enable regulated distribution is extensively acknowledged by scientists. Proniosomes are osmotically active and stable as a drug delivery vehicle. Special handling, storage, or industrial manufacturing conditions are not needed for them. A proniosomal drug delivery method can also administer a broad range of active substances with distinct therapeutic activities as tablets, beads, or capsules. Numerous issues related to the dispersion of niosomes in water or issues related to physical stability, like fusion, leakage, and aggregation, are known to be avoided by proniosomes particles. This proniosomal delivery technique can also be used to deliver amphiphilic medicines. Because of its benefits, including its non-toxicity, the ability of surfactants to increase penetration, and its ability to effectively modify drug release, proniosomes have garnered increased interest in the transdermal delivery of pharmaceuticals. Proniosomes are extensively studied as drug carriers because of all these benefits. To the fullest extent possible, there is still much to learn about the potential of novel carrier materials for proniosome preparation

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