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Proniosomes: A New Development in Vesicular Drug Delivery System

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ABSTRACT

Nanotechnology-based drug delivery is evolving at a steady pace, contributing significantly to the creation of novel dosage formulations. A technology created through the use of nanoforms is the vesicular drug delivery system. Niosomes and proniosomes are one such innovation in nano-vesicular drug delivery. Proniosomes are a surfactant-coated, dry formulation of water-soluble carrier particles that may be hydrated in a matter of minutes to create a niosomal dispersion, which is ideal for use on short agitation in hot aqueous medium. Provesicular systems, like proniosomes, which are an example of a nanotechnology innovation, reduce issues with vesicular systems including drug aggregation, fusion, and leakage while offering more convenience in terms of distribution, storage, transportation, and dosing. Stability is a challenge for conventional vesicular systems like liposomes and niosomes. This novel and developing idea has shown promise in enhancing oral bioavailability, directing medication to a particular location, and facilitating drug penetration through the stratum corneum. It ultimately lessens the toxicity of the medicine by extending its time in systemic circulation.

Keywords: Vesicular Drug Delivery, Proniosomes, Surfactant, Niosomes.

INTRODUCTION

No single distribution system has been able to meet all the requirements in modern times, although attempts have been made using creative strategies. In order to accomplish regulated or targeted drug delivery, a number of innovative approaches covering different routes of administration have arisen. Maintaining a steady and effective drug level in the body while reducing adverse effects is the major goal of innovative drug delivery. It also uses drug carriers to target drug delivery, which localizes the drug's activity.1A lot of interest has been shown in vesicular systems as a vehicle for cutting-edge medication delivery. One such technique is the encapsulation of the medication in vesicular structures, which is anticipated to increase the amount of time the drug remains in systemic circulation while reducing toxicity by selective uptake.2Drug delivery systems that employ colloidal particulate carriers, like liposomes or niosomes, have shown to have a number of advantages over traditional dosage forms. These advantages include the particles' ability to function as drug reservoirs, to carry hydrophilic drugs by encapsulating hydrophobic drugs and dividing them into hydrophobic domains, and to modify the surface or composition of the particles to alter the affinity or rate of drug release. In a dispersed aqueous system, the vesicles may experience physical issues such liposome fusion, sedimentation, or aggregation during storage, as well as some chemical issues related to hydrolysis or oxidation-induced deterioration.3In order to generate proliposomes and develop niosomes employing non-ionic surfactants as an alternative to phospholipids in the vesicle preparation process, two unique approaches were taken to address these issues. While niosomes show strong chemical stability when stored, their shelf life may be limited by physical stability issues such as aggregation, fusion, drug leakage, or hydrolysis when niosomes are suspended in water. The most recent development in the field of vesicular delivery combines the two previously discussed methods by extending the pro-vesicular strategy to niosomes via the production of “proniosomes,” which upon hydration transform into niosomes.[1,2]

Similar to liposomes, niosomes are non-ionic surfactant vesicles that have the ability to ensnape a solute. They boost the stability of the entrapped pharmaceuticals in addition to being osmotically active and stable on their own[4,5]. Because niosomes have an architecture made up of both hydrophilic and hydrophobic moieties, they may hold a variety of medicinal compounds with varying solubilities[6]. Niosomes are minuscule, existing on a nanometric scale. The range of particle sizes is 10 nm to 100 nm.[5]

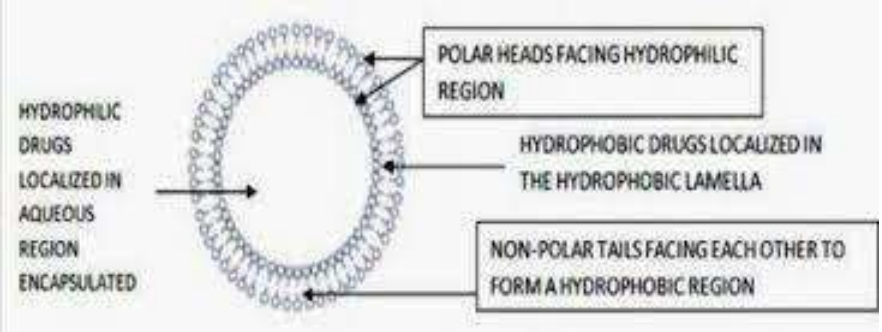


Fig – Representation of Proniosomes

Proniosomes

Proniosomes are dry formulations of surfactant-coated carrier, according to Hu and Rhodes et al[(7)]. They can be weighed out as needed and rehydrated with a quick stir in hot water. These "proniosomes" reduce niosome physical stability issues like fusion, aggregation, and leakage while also offering more convenience in dosage, distribution, transit, and storage.

When it comes to ease of dosage, storage, and transportation, niosomes generated from promethoids are superior to regular niosomes.

Dry proniosome stability is anticipated to be higher than that of a niosomal formulation that has been pre-manufactured. Proniosomes seem to be comparable to regular niosomes in release studies. Because the size distributions of niosomes formed from proniosomes are marginally better than those of normal niosomes, the release performance is improved in more demanding situations.[12–9]

ADVANTAGES OF PRO-NIOSOMES

The advantages of pro-niosomes are as follows:

1. Refraining from fusion, aggregation, sedimentation, and leakage during storage, which are issues with physical stability.
2. Preventing issues with chemical stability, such as the hydrolysis of medications enclosed, which shortens the dispersion's shelf life.
3. Handling and storing made simple.
4. There are no issues with scaling up, homogeneous dosage storage, transportation, distribution, or sterilizing.
5. Medication administration increases bioavailability and reduces adverse effects.
6. It demonstrates the depot formation-induced controlled, targeted, and prolonged release of medications.
7. Drugs that are hydrophilic or hydrophobic can be entrapped by it.
8. The drug niosomes is biodegradable, biocompatible, and does not cause immunological reactions in the body.
9. The drug's size, content, form, and fluidity can be adjusted as needed.

Advantages of proniosomes over the niosomes[10-13] .

Preventing physical stability issues such as fusing, leakage, and aggregation

Preventing the hydrolysis of pharmaceuticals enclosed, which can shorten the dispersion's shelf life.[26]

Structure of Proniosomes:

These represent tiny lamellar structures. They mix hydration in the aqueous medium with a nonionic surfactant of the alkyl or dialkyl polyglycerol ether type of cholesterol. The non-ionic surfactant's hydrophilic end points outward, while the hydrophobic end points in the opposite direction to create the bilayer.

This is how the surfactant molecules align themselves. Proniosomes are composed of two layers, just like liposomes. This bilayer of proniosomes is composed of a non-ionic surface active component. Proniosomes can be either unilamellar or multilamellar depending on the preparation technique used. [14]

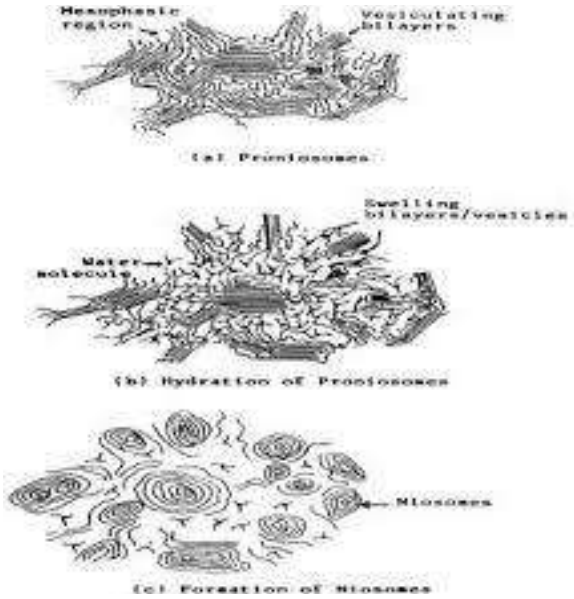


Fig 2: Structure of proniosomes and their formation into niosomes

TYPES OF Proniosomes[10, 12, 14.]

- Sorbital based proniosomes
- Maltodextrin based proniosomes
- Liquid crystalline proniosomes

Sorbitol based proniosomes-
When hot water is added and agitated, orbital base proniosomes—a dry formulation made of proniosomes as the carrier—are further coated with a non-ionic surfactant and can be utilized as niosomes in just a minute. Typically, this is created by spraying the sorbitol powder with a surfactant mixture generated in an organic solvent, then letting the solvent evaporate. Because the sorbitol carrier dissolves in organic solvents, it is necessary to repeat the procedure until the appropriate surfactant coating is obtained.The size distribution of sorbitol-based proniosomes is uniform. In situations where the active substance is hydrolyzable, it is helpful. Entrappment efficiency is reduced to less than half of what is seen with sorbitol when there is residual sorbitol present. This calls for a decrease in the ultimate carrier fraction.

Maltodextrin based proniosomes
It is made using the quick slurry process. The amount of surfactant solution needed to be used does not affect how long it takes to create proniosomes using the slurry approach. It is possible to use proniosomes with a high surface to carrier ratio. It is possible to create prionoids with a high surface to carrier ratio. It is relatively easy to extract niosomes for drug administration from such proniosomes. Sorbital is used in an analogous technique that yields a solid surfactant/sorbitol cake. Hollow blown maltodextrin particles can be employed to achieve a considerable increase in surface area since the morphology of maltodextrin is conserved. The rehydration process is more effective because of the thinner surface coating that is produced by the larger surface area. This formulation may be used to deliver amphiphilic and hydrophobic medicinal molecules.

Liquid crystalline proniosomes
There are three ways that lipophilic surfactant chains might change into a disordered, liquid state known as the lipophilic liquid crystalline state (neat phase) when the surfactant molecule is kept in contact with water. The three methods include raising the Kraft temperature (Tc), adding a solvent that dissolves lipids, and combining the use of solvent and temperature. A bilayer of molecules layered on top of one another in an intervening aqueous layer is found in the neat phase, often referred to as the lamellar phase.

Under a polarized microscope, this kind of material exhibits thread-like birefrigerant structure and characteristic x-ray diffraction. At greater concentrations, the lamellar crystalline phase transforms into niosomes. Proniosomal gel and liquid crystalline proniosomes serve as reservoirs for transdermal medication administration.

Liquid crystalline proniosomes display a number of advantages:

1) Stability
2) High entrapment efficiency
3) As a penetration enhancer
4) Easy to scale up as no lengthy process is involved; moreover it avoids the use of pharmaceutically unaccept

COMPONENTS OF PRONIOSOMES

The essential components of the delivery system are as follows Surfactants:[16]

Surfactants are organic molecules that possess both hydrophobic and hydrophilic groups, making them amphiphilic surface active agents. They serve as emulsifiers, permeability enhancers, wetting agents, and solubilizers, among other purposes. The most often utilized non-ionic amphiphiles for vesicle formation are fatty acid esters, alkyl ethers, alkyl amides, and alkyl esters. The HLB value should be the basis for surfactant selection. Because Hydrophilic Lipophilic Balance (HLB) is a reliable measure of a surfactant's capacity to produce vesicles. In the presence of cholesterol, the water-soluble detergent polysorbate 20 also produces niosomes. This is true even if the compound's HLB value is 16.7. A surfactant's HLB has an impact on the degree of entrapment.The drug's entrapment in vesicles is also influenced by the transition temperature of surfactants. The medication is most entrapped in spans with the highest phase transition temperature, and vice versa. The production of bigger vesicles with increased drug entrapment is achieved by Span 40 and Span 60. Low permeability and a high phase transition temperature prevent drugs from leaking out of the vesicles. A high HLB value of Span 40 and 60 causes a decrease in surface free energy, allowing for the formation of bigger vesicles and a higher surface area exposed to the skin and dissolving media. Because of their higher phase transition temperature, which causes them to have lesser permeability, formulations containing Span 60 and Span 40 surfactant do not differ significantly in their skin permeation profiles.

Membrane Stabilizers

Lecithin and cholesterol are the two key ingredients in membrane stabilizers. The presence of steroids in the membrane causes notable alterations in the bilayer's stability, fluidity, and permeability. Steroids are essential components of cell membranes. A naturally occurring steroid utilized as a membrane addition is cholesterol. By adding molecules that stabilize the system against the formation of aggregates by repulsive steric or electrostatic properties, it inhibits aggregation. It facilitates the niosome system's transition from the gel to liquid phases. Lecithin contains a significant amount of phosphatidylcholine. It has a low water solubility and, depending on temperature and hydration, can form lamellar structures, micelles, bilayer sheets, or liposomes.Egg lecithin and soy lecithin are the names given to them based on the source from which they originate. It serves as a penetration enhancer and stabilizing agent. It is discovered that the vesicles made of soy lecithin are bigger than those made of egg lecithin, most likely because of the differences in their inherent makeup. Depending on the type of surfactant and its concentration in the formula, cholesterol can either raise or lower the percentage encapsulation efficiency. Instead of only a surfactant forming a gel, cholesterol and surfactant together produce a homogenous noisome dispersion. Since cholesterol is known to prevent the gel to liquid phase transition in most formulations, it is often added in a 1:1 molar ratio.[20, 19]

Solvent and Aqueous Phase

Vesicle size and medication absorption rate are significantly impacted by the alcohol used in prometheosomes. The size and arrangement of vesicles made from various alcohols varies: Isopropanol > Butanol > Propanol > Ethanol. Because ethanol is more soluble in water than isopropanol, which forms vesicles with smaller sizes because of its branched chain, ethanol generates vesicles with larger sizes. Proniosome preparation uses phosphate buffer pH 7.4, 0.1% glycerol, and hot water as the aqueous phase.

Drug The drug selection criteria could be based on the following assumptions. [19]

1. Low aqueous solubility of drugs.
2. High dosage frequency of drugs.
3. Short half-life.
4. Controlled drug delivery suitable drugs.
5. Higher adverse drug reaction drugs.

Hydration medium

The most popular hydration media for creating niosomes produced from proniosomes is phosphate buffer, which comes in different pH ranges. The actual pH of the hydration medium depends on how soluble the medicine is that is being

encapsulated. The self-assembly of non-ionic surfactant into vesicles is influenced by temperature of hydration, which also has an effect on the size and form of these particles. When preparing proniosomal gel, the hydration temperature utilized to form niosomes should typically be higher than the system's gel to liquid phase transition temperature. [16, 22, 7]

Nature of encapsulated drug

The impact of an amphiphilic medication on vesicle formation is the primary factor taken into account. Aggregation happened when the medication was enclosed in niosomes, but it was prevented by adding a steric stabilizer. Saturation of the medium may lead to an increase in drug encapsulation when more medicines are introduced. This implies that encapsulating some weakly soluble medications in niosomes can boost their solubility—but only to a point, beyond which drug precipitation will happen. As the concentration of the drug increased, so did the percentage encapsulation efficiency and the quantity of drug encapsulated per mole of total lipids after niosome formation and hydration. [16, 7]

Formation of niosomes from proniosomes

By adding the drug-containing aqueous phase to the proniosomes and briefly agitating them at a temperature higher than the surfactant's mean transition phase temperature, niosomes can be synthesized from proniosomes.

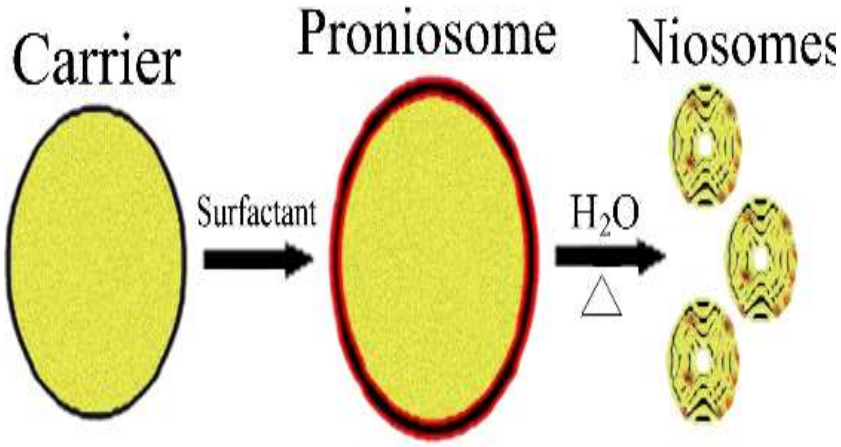


Figure 3: Proniosome conversion to Niosome

Mechanism of Action

The precise process by which the drug enters the vesicles and passes through the skin is still unknown, but it will rely on the kind and nature of the drug, the morphology of the vesicles, and the temperature at which the proniosomes hydrate to become niosomes. The lipids utilized in the proniosome production process serve as carriers, forming a depot at the site of action and thereby sustaining it.

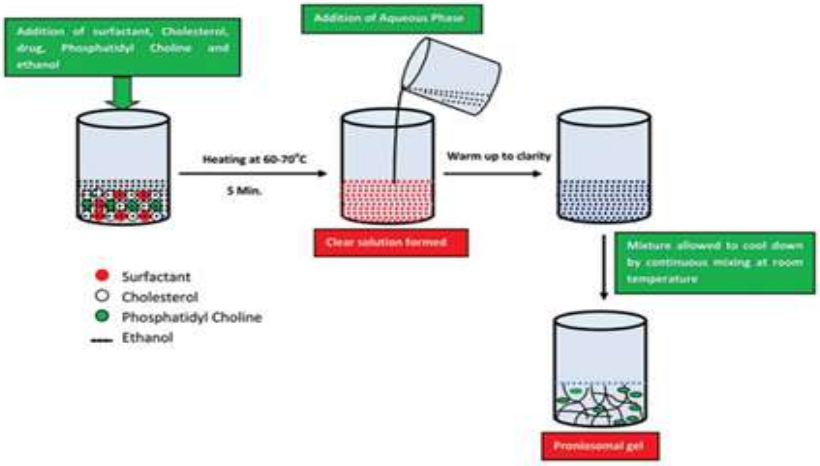
The ceramides, which are lipids and are densely packed as a bilayer by hydrogen bonding, are the step that limits the rate at which a drug can penetrate the stratum corneum during transdermal drug administration. The lipid bilayer will be stabilized and strengthened by the hydrogen bonding, which will give the stratum corneum its barrier quality. When applied to skin, promiosomes will hydrate to become niosomes. High thermodynamic activity at the interface results from the niosomes' adsorption of the skin's surface, which fuses and loosens the ceramides by competitively disrupting the hydrogen bond network.

This will raise the concentration gradient and, in turn, the diffusion pressure necessary to push the medication through the stratum corneum.[30–28]

METHOD OF PREPARATION OF PRONIOSOMES

Coacervation phase separation method

This approach, which involves placing a medication, lipid, and surfactant in a wide-mouthed glass vial with a tiny amount of alcohol within, can be used to make proteosomal gels. The liquid is heated for five minutes over a water bath at 60–700C to fully dissolve the surfactant combination. After adding a small amount of aqueous phase to the vial above and warming it further, a clear solution forms. When it cools, this solution transforms into proniosomal gel. Proniosomes are transformed into niosomes with a consistent size after hydration.[21,22]



Advantages of this method

a) The procedure is straightforward and doesn't require any special equipment because it doesn't take much time.
b) Specifically used to prepare gels
c) Lab-scale preparation of small amounts or small dose formulation is possible.

CONCLUSION

Niosomes produced from proniosomes are a potentially useful medication delivery system. When compared to niosomes, these systems have been proven to be more stable after sterilization and storage. Because of their affordability, stability, and other advantages over liposomes and niosomes, pioniosomes are considered superior options for drug administration. It has been demonstrated that proneosomes can encase both hydrophilic and lipophilic medicinal molecules. Delivery of a high concentration of the active agent or agents is facilitated by the employment of proniosomal carriers, which are controlled by their physical and compositional properties. Proniosome-based niosomes can be used for a variety of drug delivery applications, including topical, parenteral, ophthalmic, targeting, and vaccination. To determine the precise potential of this innovative medication delivery method, more study is being done in this area.[36,37]

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