PRONIOSOMES: A NOVEL DRUG DELIVERY CARRIER

Shubham Yadav¹* and Santosh Kumar Rada²

¹M. Pharmacy, Department of Pharmaceutics, Gitam School of Pharmacy, (Gitam Deemed to be a University), Rushikonda, Visakhapatnam, Andhra Pradesh, India, PIN- 530045.
²Department of Pharmaceutics, Gitam School of Pharmacy, Rushikonda, Visakhapatnam, Andhra Pradesh, India, PIN- 530045.

ABSTRACT

The basic goal of drug therapy is to deliver a medication's therapeutic action to a specific location inside the body quickly and control the desired drug amount to provide the preserved effect. The essential drug distribution in non-targeted tissues and body liquids necessitated remedial dosages that could greatly surpass the necessary amount in targeted cells and the stronger dosage typically led to harmful health during and after treatments. Standard pharmaceutical dosage forms are unable to control the delivery rate of drugs to the specific target site. One such method is the vesicle-based drug delivery system, which includes niosomes, proniosomes, liposomes, and pharmocosomes, among others, and serves to extend the drug duration in pulmonary circulation and reduces toxicity. Niosomes have caught attention as drug-targeting agents and carriers to address the drawbacks of liposomes and proliposomes. In comparison to the traditional dosage form, this article compares the benefits and drawbacks of vesicular drug delivery, Proniosomes definition, its kinds, and its method and uses. Any substrate utilised for drug delivery is referred to as a drug carrier. A suitable drug carrier that aims to increase the selectivity, efficacy, and safety of medication administration is the fundamental part of the drug delivery system. Proniosomes are so prospective drug carriers that are non-ionic surfactant-based unilamellar or multi-lamellar vesicles that are currently used in place of liposomes because of their biocompatible, biodegradable, and non-immunogenic composition. They share a bilayer structure with liposomes and are comparable structurally, however Proniosomes are more stable due to chemical changes in the monomer units. Both hydrophilic as well as lipophilic
drugs can be trapped by them in the vesicular membrane or an aqueous layer. Proniosomal carriers are appropriate for the transdermal distribution of the wide range of pharmacological drugs, comprising antioxidant, anticancer, anti-inflammatory, antimicrobial, and antibacterial compounds.

**Graphical abstract**

**KEYWORDS:**- Niosomes, Proniosomes, Proniosomal gels, vesicular delivery system, advantage, drug carrier, application.

**INTRODUCTION**

Proniosomes are the water-soluble carrying particles covered with surfactants in a dry formulation. They are promptly saturated for creating niosomal dispersion before being stirred in hot flowing media within few minutes. The main goal of developing controlled and targeted release dose forms is to raise the plasma concentration of high potency drugs in order to expand their safety margin and lessen adverse effects while also improving therapeutic impact.[1] The primary objective of the novel vesicular drug delivery system is to deliver drugs that are effective for the body's needs throughout the course of therapy and that have controlled and targeted effects on the location of action. This helped to prolong the drug action. Bingham bodies initially reported the biological genesis of these vesicles in 1965. The method of delivering the therapeutic substance to the target tissue is known as targeted drug delivery. Drug targeting refers to the distribution of drugs to organs with receptors or to any other particular bodily area. [2] Drugs are transported by a variety of carriers, including Niosomes, Proniosomes, Liposomes, Microspheres, Electrosomes, Phytosomes, etc., to the target spot in body parts such as tissue organs. These vesicular drug delivery methods deliver...
specific drugs to the site of action.\cite{3} Similar to colloidal particles, vesicular drug delivery uses amphiphilic molecules to form concentric bilayers that are then encased in an aqueous compartment. Cholesterol is combined or added alone with amphiphilic molecules such as nonionic surfactants and phospholipids (phosphatidylcholine, phosphatidylserin, etc.).\cite{4} They also avoided issues with niosomes such as aggregation, physical stability, sedimentation, leaking drug aggregation and fusion. Pronisosomes are the dried, free-flowing formulation of a coated surfactant carrier that can be rehydrated into multilamellar niosomes with a quick stir in hot water.\cite{5} Over niosomes and liposomes, proniosomes have some advantages, including simplicity in distribution, sterilisation, and storage. Niosomes that are produced from proniosomes are both more stable when compared to regular niosomes and niosomes that are not.\cite{4} Liposomes and niosomes have comparable structures and characteristics. Proniosomes are dry formulations, making hydration simple and minimising issues with niosome dispersions.\cite{6} Proniosomes have been investigated as potential replacements for liposomes along with other drug carriers for entrapping both non-polar and polar or hydrophilic and hydrophobic drugs. Recently, a formulation of maltodextrin proniosomes was created that can deliver both hydrophobic and amphiphilic drugs. In this formulation, the surfactant supports the carrier so that it can be adjusted easily and the surfactant and carrier are generated with the maximum mass of proniosomes.\cite{7} The transdermal method is popular due to its ease of use, safety, and better advantages over traditional dosage forms, including GI intolerance, variable absorption, first-pass metabolism, improved bioavailability, reduced administrative frequency, and improved compliance of patient. When cholesterol, dicetyl phosphate, and non-ionic surfactant are combined together and then hydrated in aqueous environments, microscopic lamellar structures known as niosomes are created.\cite{8} Niosomes as well as liposomes are highly susceptible to fusion, drug leakage, and aggregation during dispersion. Proniosome is a promising product that is dry and granular and dissolves into niosome suspension when water is added. Additionally, it makes transportation, distribution, storage, and dosage simple.\cite{9} Comparing proniosomes to traditional niosomes, they have demonstrated performance in drug release that is equivalent to or better. The majority of surfactants utilised to create non-ionic surfactant vesicles are not very soluble in water. On hydration, however, highly soluble non-ionic surfactants such as tween can create micelles when there is cholesterol present.\cite{10}
Advantages of proniosomes

1. Niosomes have some limitations, such as aggregation, fusion, leakage, and physical stability. To address these limitations, proniosomes or proniosomal gel formulations were developed.\cite{11}

2. Drug release is prolonged by proniosome vesicles, which act as a repository for the drug.\cite{12}

3. When used for ocular distribution, proniosomal gel meets all requirements, lengthens the contact period, and prevents drug breakdown by metabolic enzymes found in tears.\cite{13}

4. Hydrolysis of the medicine that is entrapped can be used to treat medications with a limited shelf life.\cite{14}

5. The dry powder form of proniosomes is one of the best parameters for simplicity of use; capsules beads are also produced in this form.\cite{15}

6. Proniosomes also solve the issues with liposomes such hydrolysis, oxidation, sedimentation, and storage.\cite{16}

7. The percutaneous absorption of proniosomal gel is superior than that of other semisolid dose forms.\cite{17}

8. Proniosomes have the benefit of being able to be stored, making them a flexible drug delivery mechanism.\cite{18}

9. Proniosomes have a promising drug delivery method and speed up skin healing.\cite{19}

10. Lecithin works to improve penetration while cholesterol alters the fluidity of the buffer. Proniosomes and proniosomal gel components serve as membrane stabilisers.\cite{20}

Composition of proniosomes

Proniosomes comprises of several main components as given below. Components used in the formation of Proniosomes are shown in Table 1.

a) Surfactant- Surfactants, which are typically organic molecules with amphiphilic properties, are the surface-active agents. They are used as emulsifiers, permeant enhancers, solubilizers, and wetting agents, among other things. For vesicle production,
alkyl amides, esters, and ethers, and fatty acid esters are the most often utilized non-ionic surfactants.\textsuperscript{[21]} The HLB value, a reliable indicator of any surfactant's capacity to form vesicles, should be used in the selection of the surfactant. Bilayer vesicles, as opposed to micelles, can form depending on the crucial packing parameter, the chemical makeup of the component, and the HLB values of the surfactant. A surfactant's HLB value is crucial for regulating drug entrapment in the vesicle it creates. HLB numbers around 4 to 8 were discovered to be consistent with vesicle production since they are a good indicator of any surfactant's potential to create vesicles.\textsuperscript{[22]}

b) Carrier- When a carrier is employed in the manufacture of proniosomes, there is some flexibility in the quantity of other ingredients that are included along with the surfactant. Additionally, it extends the area of surface, resulting in effective packing. The carriers must be non-toxic, free-flowing, weakly soluble in the loaded mixture and highly water-soluble for hydration.\textsuperscript{[23,24]} Below is a list of frequently used carriers:

a. Lactose monohydrate
b. Sorbitol
c. Sucrose stearate
d. Spray dried lactose
e. Malodextrin
f. Glucose monohydrate

c) Aqueous and Solvent phase- Vesicle size and drug permeation rate are greatly affected by alcohol usage in proniosomes. Different alcohols produce vesicles of varying sizes that appear in this order: Ethanol, having the largest size, followed by Butanol, Propanol and Isopropanol, having the smallest size. Buffer of phosphate having 7.4 percent, hot water along with glycerol having 0.1 percent were used to prepare proniosomes in the form of aqueous phase.\textsuperscript{[25]}

d) Lecithin- They are typically named according to where they come from, for example, soy lecithin comes from soy beans, while egg lecithin comes from egg yolk.\textsuperscript{[26]} Lecithin contains a significant amount of phospholipid choline. It has various critical roles in the vesicular system, including:\textsuperscript{[27]}

a. Minimizes medication leakage.
b. Increased drug entrapment rate as a result of high Tc (phase transition temperature).
c. It serves to improve permeability.
When compared to egg lecithin, soya lecithin creates larger vesicles, but when it comes to penetration ability, soya lecithin is a superior choice because it comprises of unsaturated fatty acids such as linoleic and oleic acids whereas egg lecithin comprises of saturated fatty acids.\cite{28}

e) Cholesterol- It is a commonly occurring steroid utilized as a membrane addition. The presence of steroids in the cell membrane affects the stability, fluidity, and permeability of the bilayer, which are all critical elements of the cell membrane. By including molecules that inhibit the system from aggregating due to repellent steric or electrostatic forces, it suppresses aggregation.\cite{29} According to El-Laithy, the percentage of entrapment efficiency increases significantly as cholesterol content rises, but beyond a certain point, further cholesterol rises lead to a major decline in the entrapment efficiency. Improvement in entrapment efficiency demonstrates that cholesterol, which eliminates gel to sol transition and serves as the "vesicular bond" in the surfactant bilayer’s molecular spaces, produces fewer leak vesicles. Therefore, an increase in stiffness reduces the drug's permeability while increasing the effectiveness of drug entrapment. However, the reverse outcome occurred when cholesterol levels were raised above a specific point. Reduced entrapment efficiency can be caused by the fact that the cholesterol molecule will engage with the drug for the bilayer space, remove that drug from there, and disturb the structure of the vesicular membrane on top of that.\cite{30,31} Diagram of proniosomes is shown in Figure 1.

![Diagram of proniosomes](image)

**Fig. 1: Diagrammatic representation of proniosomes.**\cite{32}
**Table 1: Different components used in formation of proniosomes.**[33]

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Class</th>
<th>Example</th>
<th>Uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Lecithin</td>
<td>Egg lecithin, soya lecithin</td>
<td>Emulsifiers, Permeability enhancers</td>
</tr>
<tr>
<td>2</td>
<td>Surfactant</td>
<td>Tween 40, 80, 20</td>
<td>Enhances transfer of drugs around the skin</td>
</tr>
<tr>
<td>3</td>
<td>Solvent</td>
<td>Ethyl alcohol, Chloroform</td>
<td>Affects vesicle size and drug permeation rate</td>
</tr>
<tr>
<td>4</td>
<td>Carrier</td>
<td>Sorbitol, Malodextrin</td>
<td>Flexibility of surfactant and expansion of surface area</td>
</tr>
<tr>
<td>5</td>
<td>Cholesterol</td>
<td>Cholesterol</td>
<td>Stop leaking after drug creation</td>
</tr>
</tbody>
</table>

**Mechanism of action of proniosomes**

1. Vesicle fusion and absorption onto the skin surface raise the drug's thermodynamic gradient activity at the boundary, which serves as a catalyst for lipophilic medicines to pass the stratum corneum.[34]

2. By using small angle x-ray scattering along with the freeze fracture electron microscope, it is possible to see how the stratum corneum's ultra-structural alterations affect the skin's deeper layers and intracellular lipid area.[35]

3. Niosomes' bilayer serves as a rate-limiting barrier for medicines.[36]

4. Non-ionic surfactants and phospholipids, which are both important in enhancing the penetrability of many drugs, are both found in proniosomes.[37]

5. Vesicles' penetration-enhancing effects cause the stratum corneum barrier characteristics to decrease.[38]

6. To create niosomal suspension, add the aqueous form of the drug into proniosomes and stir them briefly for two minutes at 80°C. With little remaining carrier, it offers quick reconstruction of niosomes.[39] Formation of proniosomes is shown in **Figure 2**.
Preparation techniques for proniosomes

The non-ionic surfactant, cholesterol, or lecithin, which is the primary component, are some of the elements that make up proniosomes. The following are some of the reported techniques for making proniosomes:

a) Slow spraying method

By sprinkling the solution of surfactant dissolved in the organic solvent over a carrier accompanied by the evaporation of that solution, proniosomes are prepared using this technique. The carrier is soluble in the organic dissolving agent; therefore, the procedure must be repeated until the required surfactant storing has been accomplished. As the carrier dissolves, multilamellar vesicles can develop because of the surfactant coating's hydration, which is a very thin coating on the carrier. The created niosomes exhibit homogeneous size distribution and resemble those made using traditional techniques. The key benefit of this approach is that it offers a way to synthesise hydrophobic pharmaceuticals in a lipid solution with or without issues with suspension instability or the active ingredient's sensitivity to hydrolysis. Since the sorbitol carrier used to cover the surfactant is soluble in the solvent, this process has been described as time-consuming. It has also been discovered to prevent some drugs from becoming encapsulated. Diagram of this method is shown in Figure 3.
b) **Phase separating method**

This approach, which includes a little amount of alcohol and a wide-mouthed glass vial with the drug, surfactant, and lipid, can be used to create proniosomal gels. The mixture gets heated well in a water bath from 60-70°C up to five minutes, or until this surfactant combination is completely dissolved. After adding the aqueous phase and warming it further, a clear solution is created in the above vial that, when cooled, transforms into proniosomal gel. Proniosomes are transformed into equally sized niosomes after hydration.\[^{43,44}\] Diagram of this method is shown in Figure 4.

![Diagram of Phase separating method](image)

**Fig. 4: Phase separating method.\[^{45}\]**

c) **Slurry method**

Proniosomes are made by adding the whole surfactant solution along with the drug carrier to the flask with a flat bottom that is fixed to the rotary flash evaporator, followed by applying vacuum to create a free-flowing dried powder. Last but not least, the formulation needs to be kept in a tightly covered container with refrigeration and light. Proniosome synthesis

![Diagram of Slurry method](image)
appears to take a consistent amount of time that is unaffected by the amount of surfactant solution in the carrier material. The benefit of this approach is that the active chemicals and surfactants are shielded from oxidation and hydrolysis thanks to the uniform coating on the carrier. Additionally, the thinner surfactant coating produced by the increased surface area leads to an effective rehydration process.\[46,47\] Diagram of this method is shown in Figure 5.

![Diagram of Slurry Method](image)

**Fig. 5: Slurry method.**[48]

**Factors influencing proniosomal formulation**
Processing and formulation factors are determining the properties of proniosomes. They include surfactant chain length, amount of cholesterol, amount of total lipids, lipid charge, dispersion medium’s pH, and alcohol type employed in the mixture.[49]

1. **Lipid charge**
Negative charge created by a substance known as Dicetyl phosphate (DCP), and positive charge produced by the substance sterylamine (SA), have both minimized the amount of flurbiprofen that was successfully encapsulated into niosomal vesicles.[50]

2. **Cholesterol content**
Depending on the formula’s surfactant type and concentration, cholesterol can either improve or decrease the percentage of encapsulation efficiency.[51]

3. **Total lipid concentration**
Flurbiprofen’s % encapsulation efficiency improved when the lipid amount went from 25 up to 200 mol/ml separately. As a result of total lipid amount, Flurbiprofen’s % encapsulated efficiency increased linearly. On the other hand, when the lipid amount was improved from
25-200 mol/ml, amount of flurbiprofen that was entrapped reduced. This results in a decrease in the lipid part involved in encapsulation as lipid amount rises.\textsuperscript{[52]}

4. **Surfactant chain length**

Proniosomes are frequently prepared using spans. Spans have a distinct alkyl chain along with identical head groups. A chain length having a longer alkyl group results in greater trapping effectiveness. The efficiency of entrapment moves in the following order: Span 60 (C18), followed by Span 40 (C16), Span 20 (C12) and the least element, Span 80 (C18). The head groups are common in Span 60 and Span 80, but an unsaturated alkyl chain is present in Span 80. It is possible that reduced entrapment efficiency of Span 80 formulation can be attributed to the double bonding of the paraffin chains, which significantly increases the permeability of liposome.\textsuperscript{[53]}

5. **Drug concentration**

When proniosomes created from cholesterol (9:1) and Span 60 were hydrated and formed into niosomes, the flurbiprofen amount was increased from 25-75 mg/mmol lipids. This resulted in the improvement of both drug encapsulated efficiency percentage and encapsulated drug amount per mol total lipids.\textsuperscript{[54]}

6. **pH of the hydration medium**

It has been discovered that the hydrating medium’s pH had a remarkable impact on the niosomal encapsulated efficiency percentage created by hydrating proniosomal gels from Span 60 or cholesterol (9:1). As the pH fell from pH 8 to 5.5, for instance, amount contained in flurbiprofen grew nearly up to 1.5 times the original amount. The inclusion of ionizable carboxylic group into flurbiprofen’s chemical structure may be responsible for the rise in percentage encapsulation efficiency that occurs when the pH is lowered. Flurbiprofen’s unionised species have higher splitting to the bipid layer phase than its ionised species, hence lowering the pH might enhance the proportions of these species.\textsuperscript{[55]}

**Characterization studies of proniosomes**

For the prepared proniosomes, evaluation studies are also conducted to determine the

1. **Entrapment efficiency**

The unentrapped drug was detached from the niosomal suspension using a thorough dialysis procedure and centrifugating method. The niosomal suspension was contained within a dialysis tube that had an osmotic cellular membrane firmly connected to one side. After that,
the dialysis tube was floated inside a 100 ml solution of saline buffer with a predetermined pH and stirred using a magnetic stirrer. Through an osmotic cellulose membrane, the unentrapped drug and the niosomal solution were separated and added to the medium. Optical density measurements were recorded after a 6-hour lengthy dialysis, and a UV spectrophotometric approach was used to estimate the amount of medication that had been trapped. The formula was used to calculate Entrapment Efficiency.\(^5\)

\[
\text{Entrapment Efficiency} = \frac{\text{Amount of entrapped drug} \times 100}{\text{Total amount of drug}}
\]

2. Repose angle measurement

Both the funnel and cylinder approach were used for measuring repose angle of dried proniosomes.

a) Funnel method

The proniosomal powder were added to the funnel that was secured in place, filling it to the point where the funnel's exit orifice was 10 cm beyond surface level. Repose angle was further determined by measuring the height and base diameter of the cone after the powder was poured down the funnel to create the surface cone.\(^5\)

b) Cylinder method

Proniosome powder was added to a cylinder that had been secured in place and positioned so that its outflow orifice was 10 cm beyond surface level. A cone-shaped cloud of powder emerged from the top of the cylinder. By taking measurements of the cone's height and base diameter, the angle of repose could then be computed.\(^5\)

The given equation determines the repose angle.

\[\theta = \tan^{-1}(h/r)\]

3. Optical microscopy

A microscope called Medilux-207RII, manufactured from Ambala, India, was used to view the niosomes that had been put on glass slides. After adequate dilution, morphological observation can be performed under the microscope's 1200x magnification. Digital Single Lens Reflex (SLR) cameras were used to capture the photomicrographic presentation under the microscope.\(^5\)
4. **In-vivo release studies**
Franz diffusion cell, Cellophane dialyzing membrane, spectrapor molecular porous membrane tubing, United States Pharmacopoeia (USP) Type-1 dissolution apparatus and Keshary-Chien diffusion cell were the following methods used to measure the drug release from the proniosomal formulations. Mixture of diffusion and desorption mechanisms, drug desorption of vesicle surface, and drug diffusion from the bilayered membrane were the mechanisms that can be used to release drugs from niosomal vesicles generated from proniosomes.\(^{[60]}\)

5. **Measurement of vesicle size**
The identical media that was utilised to create the vesicle dispersions was diluted approximately 100 times. Using a particle size analyser, vesicle size was determined. The device consists of a sample holding a small volume cell and a multi-element detector with a point focused at its centre by a 632.8 nm He-Ne laser beam using the Fourier Lens (R-5) with minimum power of 5Mw. Before measuring the vesicle size, the samples were mixed using a stirrer.\(^{[61]}\)

6. **Stability studies**
The manufactured proniosomes were stored for a period of one to three months at several temperatures, including body temperature (25° to 0.5°C), high temperature (45° to 0.5°C), and refrigerated temperature (2° to 8°C). Monitoring of the average vesicle diameter variation and drug content was done on a regular basis.

ICH (International Conference on Harmonization) Guidelines have stated that the accelerated stability studies used for proniosome dry powders planned for the purpose of reconstitution should be conducted at relative humidity of 75% and temperature of 40°C in accordance with internal climatic zones and circumstances as prescribed by WHO in 1996. For long-term stability studies, countries in zones I and II have a temperature of 25°C and relative humidity of 60% while countries III and IV should have a temperature of 30°C and relative humidity of 65 percent, respectively. The product should be assessed by the following factors like assay, particle matter, pyrogenicity, color, preservative content’s pH, appearance and sterility.\(^{[62]}\)
7. SEM
Proniosome particle size is a crucial consideration. Proniosomes' surface shape and size distribution were investigated using SEM. The proniosomal powder was applied on aluminium stubs with double-sided tape. SEM vacuum chamber known as XL 30 ESEM with EDAX, created from Netherlands, was used to house the aluminium stub. XL 30 is a volatile secondary electron detector having a 0.8 torr working pressure and 30,000 KV acceleration which was used to observe the morphological characteristics of the samples (Philips, Netherlands).[63]

8. Drug content
100 mg of proniosomes were administered in a typical volumetric flask. They were shaken for 15 minutes with 50 ml of methanol to lyse them. Methanol was used to dilute the 100 ml solution. Then, using phosphate-buffered saline at a fixed pH, 10 ml of that solution was diluted into the 100 ml solution. Aliquots were taken out, absorbance at a specific wavelength was measured, and the drug component was then determined by using a calibration curve.[64]

Applications of proniosomes
1. Drug targeting
Niosomes' capacity to target drugs is one of their most advantageous features. The reticulo-endothelial system can be targeted by drugs using niosomes. Niosome vesicles are occupied preferably by the reticulo-endothelial systems (RES).[65] Opsonins, molecules found in circulating serum, regulate the uptake of niosomes. The niosome is marked for clearing by these opsonins. Animal tumours known to reach the liver and spleen are treated with localisation of such drugs.[66] This drug localisation can also be utilised to treat liver parasite infections. Other than the RES, other organs can also be targeted with drugs using niosomes. Since immunoglobulin binds easily to the lipid surface of niosomes, a carrier system such as antibodies, can be connected to direct them to distinct organs.[67] Numerous cells have the innate capacity to recognize and attach particular determinants of carbohydrates; niosomes can take use of this to direct the carrier system to articular cells.

2. Cardiological applications
Captopril is delivered transdermally to treat hypertension using proniosomes as the carrier. According to the study, the proniosomal system prolongs the time that a drug is released into the body. Lecithin, Sorbitan esters, and cholesterol are used to encapsulate the drug.[68]
3. **Peptide drug delivery**
The disadvantage of oral delivery of peptide drugs is that it avoids the enzymes that would otherwise break down the links between peptides and proteins. The peptides were successfully shielded from gastrointestinal peptide degradation using niosomes. Oral administration of the vasopressin by-product trapped in niosomes showed that the entrapment of drug considerably boosted the stability of peptides.\(^{69}\)

4. **Niosomes as hemoglobin carriers**
Numerous carrier proteins are found in blood. Hemoglobin can be transported through the blood via niosomes. Patients' niosomal or proniosomal vesicles serve as carriers for haemoglobin because they are permeable to oxygen.\(^{70}\)

5. **Therapy of hormones**
Work was done on transdermal delivery of an important contraceptive drug known as levonorgestrel, by using proniosomes. The noisome had a crystal liquid, stable hybrid structure. Stability, particle size, in-vivo, in-vitro release studies and encapsulated efficiency were performed on this system. Progestational activity bioassays were also carried out. It includes inhibition of corpora lutea formation and endometrial assay.\(^{71}\)

6. **Immunity response studies**
Niosomes were used for studying immunity response because of their low toxicity, improved stability and their immune selection. Researchers are examining the immunity response nature triggered by antigens using proniosomes and niosomes.\(^{72}\)

7. **Diabetic applications**
Span, soy, diacetyl phosphate, cholesterol and lecithin were employed in the skin permeation process of furesamide proniosomes. Overall results point to proniosomes as a non-invasive method of furesamide administration.\(^{73}\)

8. **Leishmaniasis treatment**
A parasite from the genus Leishmania infects the liver and spleen cells to cause leishmaniasis. Antimonials, which are compounds of antimony that are frequently recommended for treatment, can harm the heart, liver, and kidneys when they are present in higher doses. Proniosome use shown that bigger doses of the medication could be given without causing side effects, increasing therapy effectiveness.\(^{74}\)
9. Treatment of Anti-neoplastic drugs
Most of the anti-neoplastic drugs have dangerous side effects. Proniosomes can change a drug's metabolism, prolong its half-life in the body, and decrease its ability to cause negative effects.\textsuperscript{[75]} Doxorubicin and methotrexate proniosomal entrapment demonstrated advantages over the unentrapped medicines, including a lowered rate of tumour proliferation and higher plasma levels with a delayed rate of clearance.\textsuperscript{[76,77]}

10. Other drug applications
   a) Local drug action
Niosomes are the single method of delivering drugs since they are small and have poor penetration into connective tissue and the epithelium, which keeps the drug localised where it is administered. When a drug acts locally, its potency and effectiveness are increased, and its integral toxic effects are decreased at the same time. For example, when anti-monials enclosed in niosomes are absorbed by mononucleate cells, the drug has been localized, its potential is increased, resulting in the reduction of drug's amount and toxicity. Technological drug delivery of niosomes is still in developing stage, but it has already shown success in leishmaniasis treatment and cancer chemotherapy.\textsuperscript{[78]}

   b) Sustained release
Drugs having poor water solubilities and lower therapeutic indexes can gain from the sustained release of niosomes because these substances are kept in bloodstream by the encapsulation of niosomes.\textsuperscript{[79]}

11. Proniosomes used in drug delivery
   a) Drug carrier
In order to get over the drawbacks of niosomes and liposomes as effective drug carriers in comparison to other forms of traditional drug delivery, proniosomal gel has been developed. Proniosomes do not experience these issues, which are related to niosomes' stability and aggregation.\textsuperscript{[80]}

   b) Ocular delivery
Proniosomal gel's ocular medication delivery addresses the issues with ocular drug delivery and maintains drug activity. This would resolve the issue with metabolism, prevent medication breakdown by a metabolic enzyme found in tears and on the surface of the
corneal epithelium, and improve drug retention. When compared to traditional eye drops, loméfloxacin proniosomal gel is effective for bacterial conjunctivitis.\cite{81}

c) Gene delivery
There are some non-viral vectors that can replace viral gene delivery techniques. Proniosomes are non-viral vectors that have showed promise as gene delivery systems since they are inexpensive, simple to make, stable, simple to produce, and less harmful because they contain a non-ionic surfactant.\cite{82}

d) Transdermal drug delivery
The fact that proniosomes significantly improve the uptake of medications through the skin is one of their most advantageous features. In fact, one of the first applications of niosomes was for the drug’s transdermal administration by using proniosome technology in cosmetics. Antibiotics with proniosome entrapment are applied topically to treat acne. In comparison to unentrapped medicines, the drug penetration through the skin is significantly boosted. Proniosomal technology-based transdermal vaccinations are also being studied recently. The proniosomes can be used for topical tetanus toxoid immunisation, together with liposomes and transferomes. It is necessary to conduct more study in this area because proniosome technology now available only permits a modest immune response.\cite{83}

e) Anti-inflammatory and Anti-biotic delivery
Antibiotics and anti-inflammatory drugs can be delivered using proniosomal carriers. These carriers were extensively utilized to increase ineffective penetration of skin and to improve drug retention in the skin. Topical delivery aims to effectively distribute the drug to the target tissue by passing it via the stratum corneum. Jacob's proniosomal gel showed that acyclovir could be delivered successfully by topical application.\cite{84}

f) Anti-cancer delivery
Many anti-cancer medications have poor tumour tissue penetration and substantial negative effects on healthy cells, which both reduce their therapeutic efficacy. Proniosomes have been used as an unique drug delivery mechanism in a number of attempts to get around these limitations. Proniosomes can change metabolism, extend drug circulation, and extend the drug's half-life, all of which help to lessen negative effects. Proniosomes have a slower rate of clearance along with higher plasma levels and a slower rate of tumour proliferation.\cite{85}
CONCLUSION
Proniosomes have a better future development in other drug delivery systems as compared to niosomes. Proniosomes have a lot of components stored in it like surfactants, lecithin, drug carriers, cholesterol. They have a lot of advantages such as simple distribution, sterilization and storage as compared to niosomes and liposomes. They also avoided necessary issues with niosomes such as fusion, physical stability, leaking drug aggregation, sedimentation, and aggregation. They are useful for delivering transdermal drugs because of their penetrating impact and non-toxicity of the surfactant. The lipid charge, total lipid amount, surfactant chain length, cholesterol content, dispersion medium’s pH, and alcohol type are responsible for influencing the formulation of proniosomes. There are many evaluation parameters used for studying proniosomes like optical microscopy, repose angle, drug content, entrapment efficiency, vesicle size, stability and in-vivo release studies, SEM. They are having more advancements in research like targeting drugs, treating cardiac disorders and diabetes and leismaniasis, studying immune responses, acting as hemoglobin carriers, creating anti-neoplastic drugs, and delivering peptide drugs. They are also used in other drug delivery systems like ocular, transdermal and genetic. They are also used for creating anti-cancer, anti-inflammatory and anti-biotic drugs, giving them a better scope of advancement in medical research and drug development.

ACKNOWLEDGEMENT
I would like to thank Professor Dr. Santosh Kumar Rada for his guidance in my article. He is Assistant Professor in Gitam Institute of Pharmacy.

Ethical considerations
Ethics approval and consent to participate- Not Applicable

Consent for publication- Other author has given consent for publication

Availability of Data and Material- Not Applicable

Competing interest- There was no completing interest found between the authors.

Funding- Not Applicable

Author’s contribution- Both the authors has given equivalent contribution in this article.
REFERENCES


10. Yoshiko T, Stemberg B, Florence AT.; preparation and properties of vesicles (niosomes) of sorbitan monoesters (span 20, 40, 60, and 80) and sorbitan trimester (span 85); Int j pharm, 1994; 105(1): 1-6.


