A REVIEW ARTICLE ON PRONIOSOMES

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ABSTRACT

In recent times, no single drug delivery system fulfills all the criteria, but attempts have been made through novel approaches. Many novel approaches emerged covering various routes of administration, to achieve either controlled or targeted delivery. The prime aim of novel drug delivery is maintenance of the constant and effective drug level in the body and minimizing the side-effects and it also localizes the drug action by targeting the drug delivery by using drug carriers. Vesicular drug delivery is one of the approaches, which encapsulate the drug e.g.: Liposomes, niosomes, transferosomes, pharmacosomes, and proovesicles such as proniosomes and proliposomes. Advantages of liposomes and niosomes over other conventional dosage forms are their particulate nature, which act as a drug reservoir. Few modifications can also be carried out in order to adjust the pattern and the drug release. It was also found out that modified vesicles had properties that successfully delivered drugs into deeper layers of the skin.

INTRODUCTION

From early 1980s, proniosomes have gained wide attention by researchers for their use as drug targeting agents and drug carriers to have a variety of merits while avoiding demerits associated with the conventional form of drugs. Niosomes are water soluble carrier particles, and these are dried to form a niosomal dispersion on brief agitation in hot aqueous media.
This dehydrated product is called proniosomes. The resulting niosomes are very correlative to conventional niosomes and of higher size uniformity. The proniosomal approach reduces the problems associated with dry, free-flowing product, which is more stable during the storage and sterilization. The proniosomes are a versatile delivery system because of the ease of distribution, measuring, transfer, and storage.

Proniosomes were studied as alternatives to liposomes and other carrier systems for entrapping both polar and nonpolar or hydrophobic and hydrophilic drugs. The additional merits with proniosomes are low toxicity owing to non-ionic nature, no requirement of special precautions and conditions for formulation and preparations. In addition, it is the simple method for the routine and large scale production of proniosomes without the use of undesirable solvents. However, stability is a main concern in the advancement of any formulation and even proniosomes have advantages as drug carriers, such as cost productivity, chemically stability in comparison to liposomes. They also minimize problems of physical stability such as fusion, leakage, sedimentation, and aggregation on storage.

- All these advantages of dry niosomes often termed as proniosomes have made them a promising industrial product.

2. Structure of Proniosomes
Proniosomes are microscopic lamellar structures. They combine a non-ionic surfactant of the alkyl or dialkyl polyglycerol ether class and cholesterol followed by hydration in aqueous media. The surfactant molecule direct themselves such that the hydrophilic ends of the non-ionic surfactant orient outward, while the hydrophobic ends are in the opposite direction to form the bilayer. Like liposomes proniosomes are also made up of a bilayer. In proniosomes the bilayer is made of non-ionic surface active agents.

On the basis of method of preparation proniosomes are unilamellar or multi-lamellar. The niosome is made of a surfactant bilayer with its hydrophilic ends exposed on the outside and inside of the vesicles while the hydrophobic chains face each other within the bilayer. Hence the vesicle holds hydrophilic drugs within the space enclosed in the vesicle and the hydrophobic drugs are embedded within the bilayer.
3. COMPONENTS OF PRONIOSOMES

3.1. Surfactants
Surfactants are the surface active agent usually organic compounds that are amphiphilic in nature. They have a variety of functions including acting as solubilizers, wetting agents, emulsifiers and permeability enhancers. The most common non-ionic surfactants used for vesicle formation are alkyl ethers, alkyl esters, alkyl amides and esters of fatty acids.

Selection of surfactant should be done on the basis of HLB value which is a good indicator of the vesicle forming ability of any surfactant. The formation of bilayer vesicles instead of micelles not only depends upon the HLB values of the surfactant but also on the chemical structure of component and the critical packing parameter.

The HLB value of a surfactant plays a key role in controlling drug entrapment of the vesicle it forms. As Hydrophilic Lipophilic Balance is a good indicator of the vesicle forming ability of any surfactant, HLB number in between 4 and 8 was found to be compatible with vesicle formation.

3.2. Carriers
The carrier when used in the proniosomes preparation permits the flexibility in the ratio of surfactant and other components that incorporated. In addition to this, it increases the surface area and hence efficient loading. The carriers should be safe and non-toxic, free flowing, poor solubility in the loaded mixture solution and good water solubility for ease of hydration.
Commonly used carriers are listed below
a) Malodextrin.
b) Sorbitol.
c) Spraydried lactose.
d) Glucosemonohydrate.
e) Lactosemonohydrate.
f) Sucrose stearate.

3.3. Solvents and Aqueous phase
Alcohol used in proniosome has a great effect on vesicle size and drug permeation rate. Vesicles formed from different alcohols are of different size and they follow the order: Ethanol > Propanol > Butanol > Isopropanol. Phosphate buffer 7.4, 0.1% glycerol, hot water is used as aqueous phase in preparation of proniosomes.

3.4. Lecithin
They are generally named depending on their source of origin such as soya lecithin from soya beans and egg lecithin from egg yolk Phosphatidyl choline is auch a major component of lecithin.

In the vesicular system it plays a number of important role such as:
a) It acts as permeation enhancers.
b) Prevents the leakage of drug.
c) Enhanced the percent drug entrapment due to high Tc (phase transition temperature).

Soya lecithin forms the vesicles of larger when compared to egg lecithin whereas when we compared these two on the basis of the penetration capability soya lecithin is a better candidate to select as it contain unsaturated fatty acid, oleic and linoleic acid whereas the egg lecithin contain the saturated fatty acid.

3.5. Cholesterol
Cholesterol is naturally occurring steroid used as membrane additive. Steroids are important components of cell membrane and their presence in membrane brings about significance changes with regard to bilayer stability, fluidity and permeability. It prevents aggregation by the inclusion of molecules that stabilize the system against the formation of aggregate by repulsive steric or electrostatic effects.
El-Laithy et al. reported that as the cholesterol content increase there is a significant increase in entrapment efficiency (%) but after a certain limit further cholesterol increase result in significant decrease in entrapment efficiency. The increase in entrapment efficiency shows that the cholesterol, which acts as the “vesicular cement” in the molecular cavities of surfactant bilayer, and abolishes the gel to sol transition, thereby form less leak vesicles. Therefore, increase in the rigidity decrease the permeability of the entrapped drug and hence improves the entrapment efficiency. However, when cholesterol amount was increased after a certain limit, the opposite result occurred. The reason behind decreased entrapment efficiency may be due to the reason that a cholesterol molecule will compete with drug for the space within the bilayer, remove the drug from the bilayer and in addition to this will disrupt the vesicular membrane structure.

4. Types of Vesicular Drug Delivery Systems

1. Liposomes.
2. Virosomes.
4. Proniosomes.
5. Transferosomes.
6. Proteasomes.
7. Sphingosomes.
8. Archæosome.

4.1. Liposomes: Liposomes are artificially prepared vesicle composed of a bilayer of lipids. These can be used as a vehicle for administration of nutrients and pharmaceutical drugs. Liposomes can be prepared by disrupting biological membranes. They are composed of natural phospholipids and may also contain mixed lipid chains with surfactant properties.

4.2. Virosomes: Virosomes are drug or vaccine delivery mechanism consisting of unilamellar phospholipid membrane, which is either a mono or bi-layer vesicle incorporating virus derived proteins to allow the virosomes to fuse with target cells.

4.3. Niosomes: A niosome is a non-ionic surfactant-based liposome. Niosomes are formed mostly by cholesterol incorporation as an excipient. Other excipients can also be used. Niosomes have more penetrating capability than the previous preparations of emulsions.
They are structurally similar to liposomes in having a bilayer; however, the materials used to prepare niosomes make them more stable and thus niosomes offer many more advantages over liposomes.

4.4. Proniosomes: Proniosomes are dry formulation of water soluble carrier particles that are coated with surfactant. They are rehydrated to form niosomal dispersion immediately before use on agitation in hot aqueous media within minutes. Proniosomes are physically stable during storage and transport. Drug encapsulated in vesicular structure of proniosomes prolong the existence of drug in the systematic circulation and enhances the penetration into target tissue and reduce toxicity.

4.5. Transferosomes: A transferosome carrier is an artificial vesicle designed to be such as a cell vesicle or a cell engaged in exocytosis and thus suitable for controlled and potentially targeted drug delivery.

4.6. Proteosomes: Proteasomes are cytoplasmic organelle, composed of a cylindric core particle bound by two regulatory particles at each end, responsible for degrading endogenous proteins. Proteins to be destroyed are recognized by proteasomes because of the presence of ubiquitin conjugated to the targeted protein's lysine residue.

4.7. Sphingosomes: Sphingosomes are bilayered vesicles in which an aqueous volume is entirely enclosed by membrane lipid bilayer mainly composed of natural or synthetic sphingolipid. Sphingosomes solve the major drawback of vesicle system (liposomes, niosomes) such as less stability, less in vivo circulation time, low tumor loading efficacy in case of cancer therapy. Sphingosomes are clinically used delivery system for chemotherapeutic agent, biological macromolecule and diagnostics. Owing to flexibility in size and composition, different types of sphingosomes have been developed.

4.8. Archaeosome: Archaeosomes are liposomes made from the polar ether lipids of Archaea. These lipids are unique and distinct in structure from the ester lipids found in Eukarya and Bacteria.

4.9. Ethosomes: Ethosomes are soft, malleable vesicles tailored for enhanced delivery of active agents. It has been shown that the physicochemical characteristics of ethosomes allow this vesicular carrier to transport active substances more efficaciously through the stratum corneum into the deeper layers of the skin than conventional liposomes.
5. Mechanism of action of Proniosomes

Proniosomes show their action after they are converted to niosomes on hydration. Proniosomes → Niosomes (on hydration). The hydration may occur by the addition of aqueous solvents. Proniosomes can entrap both hydrophilic and lipophilic drugs [Table 1].

Table 1: Different materials used and their action in the preparation of proniosomes. According to the type of carrier and method of preparation of proniosomes they are of two types.

![Proniosomes Technique](image)

**Dry granular proniosomes**

1. Sorbitol based proniosomes.
2. Maltodextrin based proniosomes.

- Sorbitol based proniosomes is a dry formulation that involves sorbitol as a carrier, which is further coated with non-ionic surfactant and is used as a niosome within minutes by the addition of hot water followed by agitation.
- Maltodextrin based proniosomes are prepared by fast slurry method.

**Liquid crystalline proniosomes**

- This type of proniosomes are reservoirs for transdermal delivery of the drug. The transdermal patch involves an aluminum foil as a baking material along with a plastic sheet. Proniosomal gel is spread evenly on the circular plastic sheet followed by covering with a nylon mesh.
6. Methods of preparation of Proniosomes

The proniosomes consist of a number of ingredients such as the non-ionic surfactant, cholesterol or lecithin being the main ingredient. Some of the methods, which were reported for the preparation of proniosomes are as follows:

1. Hand shaking method.
2. Slurry method.

6.1. Hand shaking method: The mixture of vesicles forming ingredients such as cholesterol and surfactants are dissolved in ether, methanol or chloroform in a round bottom flask. The organic solvent evaporates at room temperature (20°C) in the rotary evaporator leaving a thin layer of solid mixture deposited on the walls of the round bottomed flask. The dried surfactant film can be rehydrated with the aqueous phase at 0-60°C with little agitation. This process produces typical multi-lamellar niosomes.

6.2. Slurry method: A 250μmol stock solution of surfactant and membrane stabilizer was prepared in chloroform:methanol (2:1) solution. A definite volume of stock solution and drug dissolved in chloroform:methanol (2:1) solution was added to a 100ml round bottom flask containing the carrier material. Additional organic solvent solution added to form a slurry if lower surfactant loading occurs. The flask was attached to a rotary flash evaporator, which evaporates solvent at 60 -70 rpm, a temperature was 45 ± 2°C, and a reduced pressure of 600 mmHg until the mass in the flask had become a dry, free flowing product. These materials were dried in a desiccator overnight at room temperature under vacuum. This dry preparation is referred to as “proniosomes” and was used for preparations and for further study on powder properties. These final products, that is proniosomes were stored in a tightly closed container at refrigerator temperature until further evaluation.

6.3. Slow spray coating method: A 100 ml round bottom flask containing desired amount of carrier can be attached to rotary evaporator. The evaporator has to be evacuated and rotating flask can be rotated in a water bath under vacuum at 65-70°C for 15-20 min. This process is repeated until all of the surfactant solution has been applied. The evaporation should be continued until the powder becomes completely dry.
7. Factors affecting the formulation of proniosomes

Various processing and formulation variables affect the proniosomes characteristics. They include surfactant chain length, cholesterol content, drug concentration, total lipid concentration, charge of lipids, pH of the dispersion medium and type of alcohol used in the preparation.

7.1. Surfactant chain length: Spans are commonly used in the preparation of proniosomes. Spans have the same head group and different alkyl chain. By increasing the alkyl chain length leads to higher entrapment efficiency. The entrapment efficiency follows the trend such as Span 60 (C18)>Span 40 (C16)>Span 20 (C12)>Span 80 (C18). Span 60 and Span 80 have the same head groups but Span 80 has an unsaturated alkyl chain. The introduction of double bonds into the paraffin chains causes a marked enhancement of the permeability of liposomes, possibly explaining the lower entrapment efficiency of the Span 80 formulation.

7.2. Cholesterol content: Cholesterol increases or decreases the percentage encapsulation efficiency depending on either the type of the surfactant or its concentration within the formula.

7.3. pH of the hydration medium: The percentage encapsulation efficiency of niosomes prepared by hydration of proniosomal gels of Span 60/cholesterol (9:1) was found to be greatly affected by the pH of the hydrating medium. For example, the fraction of flurbiprofen encapsulated was increased to about 1.5 times as the pH decreased from pH 8 to 5.5. The increase in the percentage encapsulation efficiency of flurbiprofen by decreasing the pH could be attributed to the presence of the ionizable carboxylic group in its chemical structure.
Decreasing the pH could increase the proportions of the unionized species of flurbiprofen, which have higher partitioning to the bilayer lipid phase compared to the ionized species.

7.4. Total lipid concentration: The percentage encapsulation efficiency of flurbiprofen was increased as the lipid concentration was increased from 25 to 200mol/ml, respectively. The increase in percentage encapsulation efficiency of flurbiprofen as a function of total lipid concentration was linear. On the other hand, the amount of flurbiprofen entrapped was decreased on increasing the lipid concentration from 25 to 200mol/ml, respectively. This leads to the fact that the fraction of lipid taking part in encapsulation decreases as the concentration of lipid increases.

7.5. Drug concentration: Increasing flurbiprofen concentration from 25 to 75 mg/mmol lipids in the proniosomes prepared from Span 60/cholesterol (9:1), showed an increase in both percentage encapsulation efficiency and the amount of drug encapsulated per mol total lipids upon hydration and formation of niosomes.

7.6. Charge of the lipids: Incorporation of either dicetyl phosphate (DCP) which induces negative charge or stearylamine (SA) which induces positive charge decreased the percentage encapsulation efficiency of flurbiprofen into niosomal vesicles.

8. VESICLE FORMATION IN PRONIOSOMES

The ability of non-ionic surfactant to form bilayer vesicles instead of micelles is not only dependent on the hydrophilic-lipophilic balance (HLB) values of the surfactant and the chemical structure of the components, but also on the critical packing parameter (CPP).

In proniosomes the vesicle-forming tendency is similar to niosomes. The relationship between the structure of the surfactant including size of hydrophilic head group, and length of hydrophobic alkyl chain in the ability to form vesicles is described as CPP = v/ lca Where v = hydrophobic group volume, l = the critical hydrophobic group length and a = the area of the hydrophilic head group. A CPP of between 0.5 and 1 indicates that the surfactant is likely to form vesicles. A CPP of below 0.5 (indicating a large contribution from the hydrophilic head group area) is said to give spherical micelles and a CPP of above 1 (indicating a large contribution from the hydrophobic group volume) should produce inverted micelles, the latter presumably only in an oil phase, or precipitation would occur 27, 28, 29. Addition of cholesterol suppresses the tendency of the surfactants to form aggregates and also provides
greater stability to the bilayer membranes by increasing the gel liquid transition temperature of the vesicle and also attributes to the higher HLB and smaller critical packaging parameters.

Cholesterol addition also enables more hydrophobic surfactants to form vesicles. Apart form this addition of cholesterol also influences membrane permeability, encapsulation efficiency and bilayer rigidity. Stabilization and permeability can also be enhanced by the addition of lecithin and by the addition of charged molecules like, diacetyl phosphate (DCP) and stearyl amine (SA) to the bilayer. Preparation of Niosomes from Proniosomes by Hydration Prepared proniosome powder is weighed and filled in screw cap vials.

- Water or saline at 80°C is added and the vials are capped. The vials are attached to a vortex mixer and agitated for 2 minutes to get niosomal suspension as shown in figure no.2. Conversion of Proniosome Gel into Niosomes Proniosome gel is an intermediate state of formation of niosome. Minimum quantity of continuous phase, leads to the formation of liquid crystalline compact mass of proniosomes.

- Proniosome gel thus obtained has some advantages over conventional niosomes due to their compact gel nature, which helps in degradation, transportation and stability. The conversion of proniosome gel into niosomes can be achieved in two ways. Hydration by skin: The hydration is achieved by skin itself i.e. the water in the skin is used to hydrate the proniosome formulation and conversion to niosomes.

- Hydration by solvents: Aqueous systems i.e. purified water, saline solution and buffers are used to convert proniosomes to niosomes with or without agitation and sonication. The proniosome gel system is directly being formulated in the patch for used in dermal and transdermal applications without the requirement of polymeric matrix for dispersion. The formulation takes water from the skin and converts into niosomes.

- The addition of aqueous phase from outside also leads to the formation of niosomes. After the addition of aqueous phase, agitation and sonication leads to formation of niosomes with small size vesicles.

- The addition of water into compact mass of proniosome leads to the swelling of bilayers as well as vesicles due to the interaction of water with polar groups of the surfactant. Due to the inclusion of water in the bilayers, the stacked structures tend to separate. Above a limiting concentration of solvent bilayers tends to form spherical structure which gives rise to unilamellar to multilamellar vesicular structures. Addition of shaking step in hydration process leads to complete hydration and formation of niosomes 6, 13.
9. Characterization of Proniosomes

Evaluation studies are further carried out for the prepared proniosomes in order to find out the

- Measurement of angle of repose.
- Scanning electron microscopy (SEM).
- Optical microscopy.
- Measurement of vesicle size.
- Drug content.
- Entrapment efficiency.
- In-vivo release studies.
- Stability studies.

a) Measurement of angle of repose: The angle of repose of dried proniosomes was measured by funnel method and cylinder method. Angle of repose is calculated by the below equation.

b) Funnel method: The funnel, which was fixed at a position and the proniosomal powder was poured into it so that the outlet orifice of the funnel is 10cm above the level of surface. The powder flowed down from the funnel to form a cone on the surface and then angle of repose was further calculated by measuring the height of the cone and the diameter of its base.

c) Cylinder method: The proniosomes powder was poured into a cylinder, which was fixed at a position so that the outlet orifice of the cylinder is 10 cm above the level of surface. The powder flowed down in the cylinder to form a cone on the surface. The angle of repose was further calculated by measuring the height of the cone and the diameter of its base.

d) SEM: Particle size of proniosomes is a factor of prime importance. The surface morphology and size distribution of proniosomes were studied by SEM. A double-sided tape that was affixed on aluminum stubs and the proniosomal powder was spread on it. The aluminum stub was placed in a vacuum chamber of scanning electron microscope (XL 30 ESEM with EDAX, Philips, Netherlands). The morphological characterization of the samples was observed using a gaseous secondary electron detector (working pressure of 0.8 torr, acceleration voltage-30.00 KV) XL 30, (Philips, Netherlands).
e) **Optical microscopy:** The niosomes were mounted on glass slides and viewed under a microscope (Medilux-207RII, Kyowa-G etner, Ambala, India). The microscope has a magnification of ×1200 used for morphological observation after sufficient dilution. The photomicrograph of the preparation was obtained from the microscope by using a digital Single lens reflex (SLR) camera.

f) **Measurement of vesicle size:** The vesicle dispersions were diluted about 100 times in the same medium, which was used for their preparation. Vesicle size was measured on a particle size analyzer. The apparatus consist of a He-Ne laser beam of 632.8nm focused with a minimum power of 5Mw using a Fourier lens (R-5) to a point at the center of multi-element detector and a small volume sample holding cell. The samples were stirred with a stirrer before determining the vesicle size.

g) **Drug content:** Proniosomes equivalent to 100 mg were taken in a standard volumetric flask. They were lysed with 50 ml methanol by shaking for 15 min. The solution was diluted to 100 ml with methanol. Then 10 ml of this solution was diluted to 100 ml with saline phosphate buffer at certain pH. Aliquots were withdrawn and absorbance was measured at a certain wavelength and drug content was further calculated from the calibration curve.

h) **Entrapment efficiency:** Separation of unentrapped drug from the niosomal suspension was carried out by exhaustive dialysis method and centrifugation method. Theniosomal suspension was taken into a dialysis tube to which osmotic cellulose membrane was securely attached to one side, the dialysis tube was suspended in 100 ml saline buffer at certain pH, which was stirred on a magnetic stirrer. The niosomal suspension and the unentrapped drug were seperated into the medium through osmotic cellulose membrane. After 6 h of exhaustive dialysis, optical density values were noted and the estimation of the entrapped drug was carried out by UV spectrophotometric method. Entrapment Efficiency was calculated using the formula.

i) **In vivo release studies:** The release of the drug from the proniosomal formulations was determined using different techniques such as Franz diffusion cell, Keshary-Chien diffusion cell, Cellophane dialyzing membrane, United states pharmacopeia (USP) dissolution apparatus Type-1, spectrapor molecular porous membrane tubing. Drug release from proniosomes derived niosomal vesicles can follow any one or more of the following
mechanisms; desorption from the surface of vesicles or diffusion of drug from bilayered membrane or a combined desorption and diffusion mechanisms.

j) Stability studies: Stability studies were carried out by storing the prepared proniosomes at various temperature conditions such as refrigeration temperature (2°-8°C), room temperature (25° ± 0.5°C) and elevated temperature (45° ± 0.5°C) from a period of 1 month to 3 months. Drug content and variation in the average vesicle diameter were periodically monitored. International conference on harmonization (ICH) guidelines suggests stability studies for the dry proniosome powders meant for reconstitution should be studied for accelerated stability at 40°C/75% relative humidity as per international climatic zones and climatic conditions (WHO, 1996). For long term stability studies the temperature is 25°C/60% RH for the countries in zone I and II and for the countries in zone III and IV the temperature is 30°C/65% Relative humidity (RH). Product should be evaluated for appearance, color, assay, pH preservative content, particulate matter, sterility, and pyrogenicity.

10. Evaluation of Proniosomes

a) Stability Studies: Stability studies carried out by storing the prepared proniosomes at various temperature conditions like refrigeration on (2-8°C) room temperature (25°±0.5°C) and elevated temperature (45°±0.5°C) from a period of one month to 3 months. Drug content and variation in the average vesicle diameter were periodically monitored. ICH guidelines suggests stability studies for dry proniosomes powder meant for reconstitution should be studied for accelerated stability at 75% relative humidity as per international climatic zones and climatic conditions.

b) Vesicle Size Determination: It was carried out using an optical microscopy with a calibrated eyepiece micrometer. About 200 niosomes were measured individually, average was taken, and their size range, mean diameter were calculated.

c) Drug Content: Proniosomes preparation equivalent to 40 mg is taken into a standard volumetric flask. Then they were lysed with 100ml of propane-1-ol by shaking. Then 1ml of this was subsequently diluted with phosphate buffer (pH 7.4). The absorbance was measured by UV spectrophotometer.
d) **surface morphology**: Surface morphology means roundness, smoothness and formation of aggregation. It was studied by screening electron microscopy, optical microscopy, transmission electron microscopy16.

e) **Separation of Free Unentrapped Drug**: The encapsulation efficiency of proniosomes is determined after separation of the un-entrapped drug using these techniques.

**A. Dialysis**

- The aqueous niosomal dispersion is dialysed tubing against suitable dissolution medium at room temperature then samples are withdrawn from the medium at suitable time interval centrifuged and analysed for drug content using UV spectroscopy.

**B. Gel Filtration**

- The free drug is removed by gel filtration of niosomal dispersion through a sephadex G50 column and separated with suitable mobile phase and analysed by suitable analytical techniques.

**C. Centrifugation**

- The niosomal suspension is centrifuged and the surfactant is separated after this the pellet is washed and then re-suspended to obtain a niosomal suspension free from unentrapped drug.

11. **Advantages of Proniosomes**

1. Both the non-ionic surfactants and phospholipids in proniosomes can act as penetration enhancers and help in diffusion of the drug.

2. Proniosomes have higher advantages such as additional convenience of dosing, storage, transportation, and distribution.

3. They avoid the problems associated with either the aqueous noisome dispersion, such as problems of physical stability, aggregation, fusion, and leakage.

4. Proniosomes also avoid problems associated with liposomes like degradation by hydrolysis or oxidation as well as sedimentation, aggregation or fusion during storage.

5. Proniosomes not only offer a promising means of drug delivery, but also could enhance the recovery rate of the skin barrier.
12. Clinical Applications

Drug targeting

1) Applications in cardiology

- Proniosomes are used as carriers for the transdermal delivery of captopril for the treatment of hypertension. The study shows that the proniosomal system causes extended release of the drug in the body. Encapsulation of the drug is carried out using Sorbitan esters, Cholesterol and lecithin.

2) Application in diabetes

- Skin permeation mechanism of furesamide proniosomes is performed in which span, soya, lecithin, diacetyl phosphate, and cholesterol were used. Overall findings suggest that the proniosomes serve as non-invasive delivery of furesamide.

3) Hormonal therapy

- Work had been performed on proniosome based transdermal delivery of levonorgestrel the emergency contraceptive. The structure of the niosome was liquid crystalline compact hybrid. The system was tested for particle size, encapsulation efficiency, stability study, \textit{in vivo} and \textit{in vitro} study. Bioassay for progestational activity was also performed. It included endometrial assay and blockade of development of corpora lutea.

4) Delivery of peptide drugs

- Oral peptide drug delivery has a drawback of bypassing the enzymes, which would breakdown the peptide and protein bonds. Niosomes were used to successfully protect the peptides from gastrointestinal peptide breakdown. Oral delivery of vasopressin derivative entrapped in niosomes showed that entrapment of the drug significantly increased the stability of the peptide.

5) Uses in studying immune response

- Immune response was studied using niosomes due to their immunological selectivity, low toxicity and greater stability. Niosomes and proniosomes are being used to study the nature of the immune response provoked by antigens.
6) Niosomes as carriers for hemoglobin
   - Blood has many carrier proteins present in it. Niosomes can be used as carriers for hemoglobin within the blood. The niosomal or the proniosomal vesicle is permeable to oxygen and hence it acts as a carrier for hemoglobin in patients.

7) Other applications
   Sustained release
   - Sustained release action of niosomes can be applied to drugs with low therapeutic index and low water solubility since those could be maintained in the circulation via niosomal encapsulation.

   Localized drug action
   - Drug delivery through niosomes is one of the approaches to achieve localized drug action, since their size and low penetrability through epithelium and connective tissue keeps the drug localized at the site of administration. Localized drug action results in enhancement of efficacy of potency of the drug and at the same time reduces its systemic toxic effects e.g., Anti-monials encapsulated within niosomes are taken up by mononuclear cells resulting in localization of drug, increase in potency and hence decrease both in dose and toxicity. The evolution of niosomal drug delivery technology is still at an infancy stage, but this type of drug delivery system has shown promise in cancer chemotherapy and anti-leishmanial therapy.

CONCLUSION
   - Lately, there has been a magnanimous growth in drug delivery technologies, of which proniosomes are one of the sterile drug delivery systems, that are highly used in cancer therapies. The concept of incorporating the drug into niosomes for a better targeting of the drug at appropriate tissue destination is widely accepted by researchers and academicians. Proniosomes derived niosomes represent a promising drug delivery module. They are known to avoid many of the problems associated with either the aqueous noisome dispersion as problems of physical stability such as aggregation, fusion, and leakage. They provide additional convenience of transportation, distribution, storage and dosing. Proniosomes not only offer a promising means of drug delivery, but also could enhance the recovery rate of the skin barrier. Proniosomes represent a promising drug delivery technologies and much research has to be inspired in this to filter out all the
potential in this novel drug delivery systems. All this make proniosomes, that is “dry niosomes,” a promising industrial and research product.

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