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A Review on Proniosomes: Preparation, Characterization, and Applications

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ABSTRACT

The term "nanotechnology" refers to a developing field of technology that is focused on the study of manipulating matter at the nanoscale, and it includes the creation and engineering of functional systems at the atomic level. Numerous unique drugs kinds have been developed as a result of nanotechnology. Liposomes, microparticles, liposomes, and proniosomes are examples of delivery methods. There are some drawbacks to liposomes and niosomes, such as leakage, fusion, aggregation, dispersion, transportation, and storage. Proniosomes are dry formulations of water soluble carriers coated with the surfactant and drug encapsulated in the peroxisomal vesicles, which helps in prolonging the duration of retention of drug in systemic circulation and by reaching the target organs. This helps to overcome the drawbacks of both liposomes and niosomes. This review mainly focusses on the demerits of liposomes and niosomes, methods of preparation, characterization, and applications of Proniosomes.

1. INTRODUCTION

With the goal of achieving targeted and controlled medication administration with reduced or minimal adverse effects when compared to the conventional system, significant efforts are being made in the field of pharmaceutical sciences to research and develop numerous innovative drug delivery systems. The duration of the drug in the systemic circulation should be prolonged by drug encapsulation in any of the vesicular systems, improving therapeutic efficacy and bioavailability.

Liposomes

They have the capability of entrapping both lipophilic and hydrophilic agents, in the lipid membrane and in the aqueous core, respectively. The size of these nearly spherical lipid vesicles can range from a few nanometers to several micrometers. However, liposomes applied to medical use range between 50 and 450 nm.(1)

DEMERTIS (2)

- High production costs.
- Drug or molecular leakage and fusion that has been encapsulated.
- Phospholipid occasionally experiences processes like oxidation and hydrolysis.
- Minimal half-life.
- Limited solubility

To deal with these problems of liposomes proliposomal approach has been provided.

PRONIOSOMES

Proniosomes are either dry, free-flowing formulations of water-soluble surfactant coated carriers or non-ionic surfactant liquid crystals with a viscosity similar to jelly(3). It results in multi-lamellar liposomal suspension when water is added(4).

Demerits

Technical challenges such the need for vacuum (or) nitrogen gas during preparation and storage to prevent phospholipid oxidation (5–6).

Niosomes are being developed as drug carriers and drug targeting agents to solve the drawbacks of proliposomes and liposomes (7-8).

Niosomes

When synthetic nonionic surfactants are hydrated, whether or not cholesterol or other lipids are included, nonionic surfactant vesicles called niosomes are produced(9).They are vesicular structures that resemble liposomes and can transport both amphiphilic and lipophilic drugs(10).

Niosomes and liposomes are contrasted in that:

• Niosomes are less expensive than liposomes.

• Niosomes do not need any particular handling or storage procedures when compared to liposomes (11).

• Liposomes contain neutral or charged phospholipids, whereas niosomes contain non-ionic surfactants (12).

Demerits

- Aggregation.
- Physical instability.
- Entrapped medication leakage on storage.
- Traditional preparation methods take a lot of time.
- Requires specialised tools.
- Drugs that are encapsulated undergo hydrolysis, which shortens the liposomal suspension's shelf life[13].

Niosomes are created by preparing and reconstituting proniosomes in order to solve the drawbacks of niosomes.

2. PRONIOSOMES

Proniosomes are either dry, free-flowing formulations of water-soluble surfactant coated carriers or non-ionic surfactant liquid crystals having a viscosity similar to jelly (14,3,15). By

briefly agitating both medicinal dosage forms with heated aqueous medium, it is possible to create a niosomal suspension that can be administered orally as well as through other routes(16,17,18,19). Drugs that are both hydrophilic and hydrophobic can be captured using proniosomes(20). Proniosomes' additional benefit over other vesicular drug delivery technologies is their low toxicity because they are non-ionic(21).

There are no unique precautions or circumstances needed for peroxisome formation. Proniosomes can also be produced on a regular basis and in big quantities using a straightforward approach without the need for unfavourable solvents. Additionally, they reduce issues with fusion, leakage, sedimentation, and aggregation during storage(22,23,24). Drug entrapment in the proniosome's vesicular structure extends its time in the body's regular circulation, improves its penetration of the target tissue, and lessens its toxicity. The fundamental ideas and most recent research findings on the extremely promising use of proniosomes will be clarified by this review.

Advantages of Proniosomes over Niosomes (25)

- Proniosomes are water-soluble carrier particles that can prevent problems with physical stability such as fusion, aggregation, and leakage.

- They can also prevent hydration of drugs that are encapsulated, which shortens the shelf-life of the dispersion.

- Proniosomal formulations are also simpler to transport, distribute, and store because they don't include undesirable solvents.

- Proniosomes are a versatile delivery technique with the capacity to be utilized with a variety of active substances due to their preservation. The systems don't require the dispersion of vesicles into polymeric matrix and may be instantly moulded into transdermal patches.

2.1 Preparation of proniosomes

Materials used in the formulation of both types of proniosomes include a non-ionic surfactant, the membrane stabilizer, a small amount of water and alcoholic solvent ‘‘such as absolute ethanol, propanol, isopropanol, butanol, propylene glycol or liquid polyethylene glycols’’ to formulate proniosomal gels. However, to prepare dry free flowing proniosomal powders, the non-ionic surfactant, carrier material, membrane stabilizer and coating material

are also required. A desirable characteristic of the carrier material used in the formulation of dry proniosomes comprises safety and non-toxicity, free flow, poor solubility in the loaded mixture solution and good water solubility for ease of hydration. Carrier material used in the formulation of dry proniosomes permits the flexibility of surfactant and other components. Furthermore, it increases the surface area and encourages the efficient loading of the drug inside the proniosomes.(20,22,23,24) The presence of steroids in the cell membrane provides stability to the membrane; therefore, cholesterol is mainly used as a membrane stabilizer in the preparation of proniosomes. The surfactant has varieties of function such as permeability enhancer, emulsifier wetting agent and solubilizers. Vehicles used in the reconstitution of proniosomes include phosphate buffer (pH7.4), hot water and 0.1% glycerol (Figure 1.1).

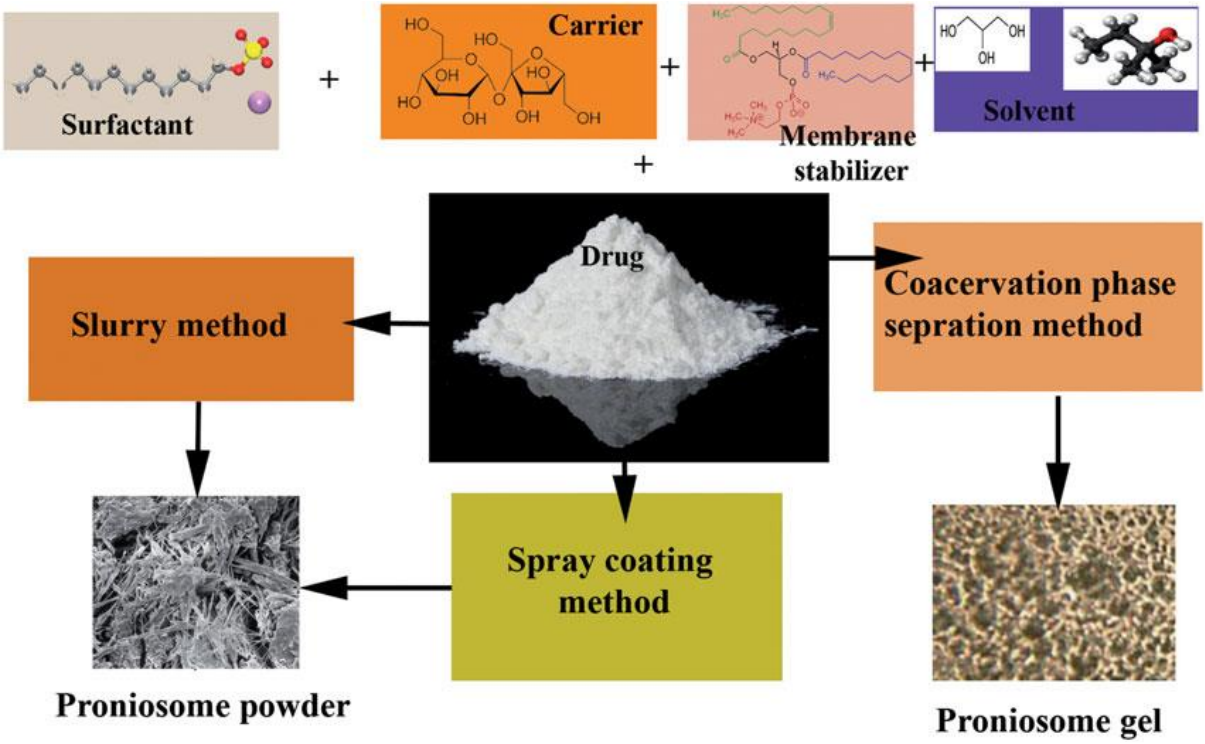

Figure 1.1. Illustration for materials and methods used for the preparation of proniosome.

- **Surfactants**

Surfactants, which are typically organic molecules with both hydrophobic and hydrophilic groups, are the surface-active agents. As a result, the molecule of a surfactant consists of both a water-insoluble (lipophilic) and a water-soluble (hydrophilic) component. They can work as emulsifiers, solubilizers, wetting agents, and permeability enhancers, among other things.

The most often employed non-ionic amphiphiles for vesicle production are alkyl ethers, alkyl esters, alkyl amides, and esters of fatty acids (26).

- **Carrier materials**

When a carrier is utilised in the creation of proniosomes, the ratio of surfactant and other ingredients can be altered. Additionally, it expands the surface area, resulting in effective loading. The carriers must be free-flowing, safe, efficient, non-toxic, poorly soluble in the loaded mixed solution, and easily soluble in water (27).

- **Membrane stabilizer**

Lecithin and cholesterol are primarily utilised as membrane stabilisers. Steroids are essential parts of cell membranes, and their presence in the membrane causes significant changes in the stability, fluidity, and permeability of the bilayer . A naturally occurring steroid utilised as a membrane addition is cholesterol. By including molecules that stabilise the system against the formation of aggregate by repulsive steric or electrostatic effects, it prevents aggregation. 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 (25).

- **Solvent and Aqueous phase**

Vesicle size and drug permeation rate are significantly affected by alcohol usage in a protosome. Different alcohols produce vesicles of varying sizes that appear in the following order: Ethanol > Propanol > Butanol > Isopropanol. The development of the largest vesicles occurs when ethanol is added to water as opposed to isopropanol, which creates the smallest vesicles because of its branched chain. Proniosomes are prepared or formed using an aqueous phase consisting of hot water, phosphate buffer pH 7.4, 0.1% glycerol, and other ingredients (28).

2.1.1 Drug

The drug selection criteria could be based on the following assumptions (26).

- Low aqueous solubility of drugs.
- High dosage frequency of drugs.

- Controlled drug delivery suitable drugs
- Short half-life.
- Higher adverse drug reaction drugs.

2.1.2 Types of proniosomes

- Dry granular proniosomes
- Liquid crystalline proniosomes

2.1.3 Dry Granular Proniososmes

Dry granular proniosomes involves the coating of water-soluble carrier such as sorbitol and malt dextrin with surfactant. The result of coating process is a dry formulation in which water water-soluble particle is covered with thin film of surfactant. It is essential to prepare vesicles at a temperature above the transition temperature of the non-ionic surfactant being used in the formulation. These are further categorized as follows:

2.1.4 Sorbitol based Proniosomes

A dry formulation called sorbitol-based proniosomes uses sorbitol as the carrier. It is then coated with a non-ionic surfactant and employed as niosomes within minutes by adding water and stirring. Typically, they are created by spraying a surfactant mixture generated in an organic solvent onto sorbitol powder and then letting the solvent evaporate. The technique must be repeated in order to acquire the desired surfactant coating because the sorbitol carrier is soluble in organic solvent. The surfactant coating on the carrier is very thin, and as the carrier dissolves, hydration of the coating causes multilamellar vesicles to form(29).

2.1.5 Maltodextrin based proniosomes

Recently, a maltodextrin-based proniosome formulation was created that may be used to deliver hydrophobic or amphiphilic medicines. The more effective version of this formulation included hollow particles with very large surface areas. With this formulation, it was possible to construct proniosomes with very high mass ratios of surfactant to carrier and readily change the quantity of carrier needed to support the surfactant (29).

2.1.6 Liquid Crystalline Proniosomes

When the surfactant molecules are kept in contact with water, there are three ways through which lipophilic chains of surfactants can be transformed into a disordered, liquid state called lytorophic liquid crystalline state (neat phase). These three ways are –

- Increasing temperature at kraft point (Tc)
- Addition of solvent, which dissolves lipids
- Using both temperature and solvent.

Bilayers are stacked in sheets over one another in the neat phase or lamellar phase, which has an intervening aqueous layer. Under a polarised microscope, these kinds of structures produce bi-refractive structures that resemble threads and conventional X-ray diffraction patterns.

2.2 Methods

2.2.1 Proniosomal gel preparation ‘‘coacervation–phase separation technique’’

The proniosomal gel can be prepared by the method reported by Vora et al. and modified by Ibrahim et al. Accurately weighed surface active agent were mixed with the appropriate amount of cholesterol in glass vials. Absolute ethanol (small amount enough to solubilize the lipids; about half the weight of total lipids) were added to the surfactant or surfactant/cholesterol mixtures then vials were tightly sealed and warmed in a water bath (55–60^{o}C) for 5 min while shaking until complete dissolution of lipids.

To each of the formed transparent hot lipid solutions, little amount of distilled water ‘‘about 40% of the total solvent added’’, heated to 55–60^{o}C were added to the lipid solution while warming in the water bath for 3–5 min until a clear or translucent solution was produced. The mixtures were allowed to cool down at room temperature and observed for the formation of transparent solution, two-phase liquids, translucent, transparent or white creamy proniosomal gels (Figure 1.2a).

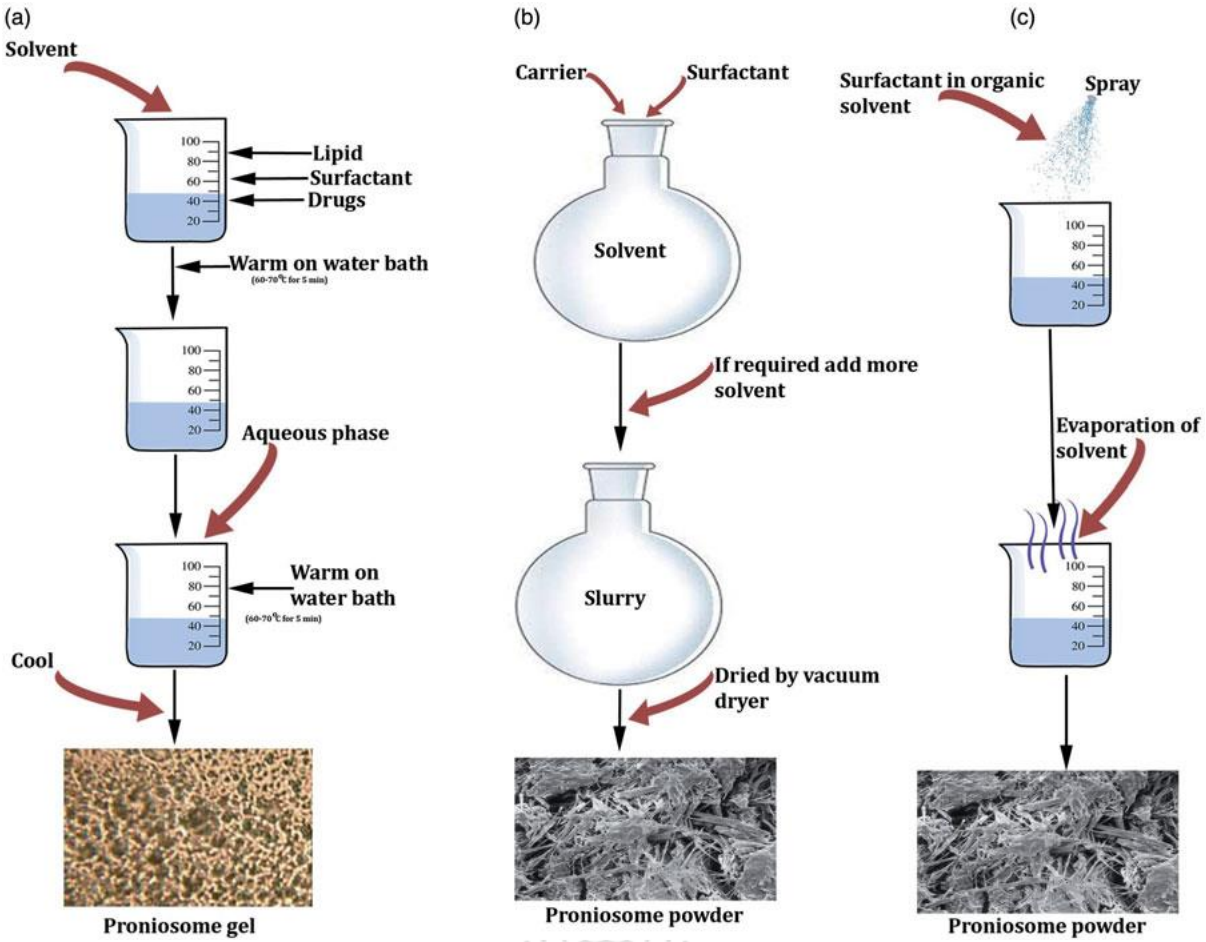

Figure 1.2: (a) Coacervation phase separation method for the preparation of proniosome gel. (b) Slurry method for the preparation of proniosome powder. (c) Spray coating for the preparation of proniosome powder method.

2.2.2 Drug loading into proniosomal gel formulations

The drug could be added to the non-ionic surfactant/cholesterol mixture and dissolved by the aid of absolute ethanol while warming at 50–60°C in a water bath if it is lipid-soluble. However, it might be dissolved first either in the alcohol or in distilled water and added to the hot lipid solution before cooling down to gel state according to the drug physicochemical properties (14). It is important to note that the addition of the drug did not show turbidity or precipitated crystals in liquid preparations before gelation and also it should not precipitate into the gel phase.

2.2.3 Free flowing proniosomal dry powder preparation

- **Slurry method**

In this method, the slurry is prepared by using the carrier and surfactant/drug solution in a round-bottom flask. The additional organic solvent solution may be added to form slurry if lower surfactant loading occurs. The flask is attached to the rotary evaporator and vacuum is applied until the powder appeared to be dry and free flowing (Figure 1.2b). The powder should be stored in sealed containers at 4°C. The time required to produce proniosomes is independent of the ratio of surfactant solution to the carrier material and appears to be flexible (30,31).

- **Spray-coating method**

This method involves preparation of proniosomes by spraying surfactant/drug in an organic solvent onto a carrier or coating material and then evaporating the solvent. Because the carrier is soluble in the organic solvent, it is necessary to repeat the process until the desired surfactant loading has been achieved. The surfactant coating on the carrier is very thin and hydration of this coating allows multilamellar vesicles to form as the carrier dissolves (Figure 2c) (32).

- **Niosome from proniosome by hydration**

Niosome can be prepared by hydration of proniosomes. Here, the aqueous phase containing the drug is added to proniosomes with brief agitation at a temperature higher than the mean transition phase temperature of non-ionic surfactant used in the preparation of proniosomes (Figure 1.3).

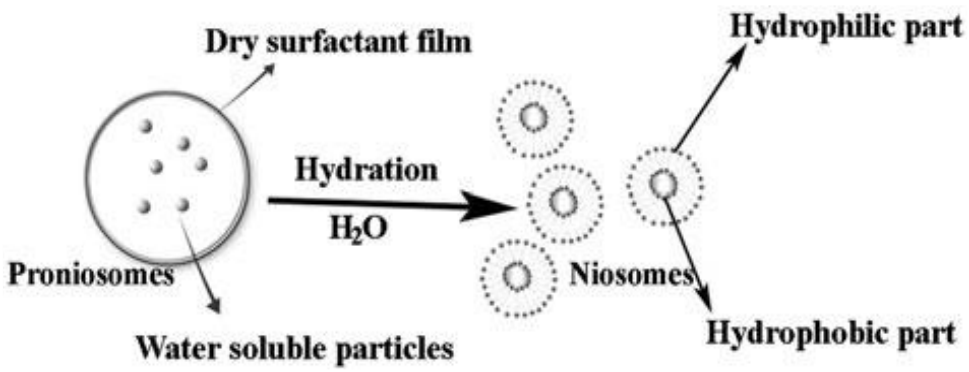

Figure 1.3. Niosome formation from proniosome by hydration

3. Characterization of proniosomes

Different parameters and techniques employed for characterization of proniosomes include measurement of vesicle size and size distribution, morphological characteristics, angle of repose, measurement of particle charge, rate of hydration (spontaneity), aerodynamic behaviour, separation of unentrapped (free) drug, drug entrapment efficiency, drug content, in vitro drug release, skin permeation studies and stability of proniosomes.

3.1 Measurement of angle of repose

- **Funnel method**

The proniosomal powder was poured into the funnel, which was set in place, so that the funnel's exit orifice was 10 cm above the level of the surface. Angle of repose was further determined by measuring the cone's height and base diameter after the powder trickled down from the funnel to create one on the surface(30).

- **SEM**

Proniosome particle size is a crucial consideration. Proniosomes' surface shape and size distribution were investigated using SEM. Aluminium stubs had double-sided tape attached to them, and the proniosomal powder was then applied to them. The scanning electron microscope's vacuum chamber contained the aluminium stub. The morphological characterization of the samples was observed using a gaseous secondary electron detector(30).

3.2 Measurement of vesicle size

The identical media that was utilised to create the vesicle dispersions was diluted approximately 100 times. On a particle size analyser, the size of the vesicles was assessed. The device consists of a small volume sample holding cell and a multi-element detector with a point focused at its centre by a 632.8 nm He-Ne laser beam using a Fourier lens (R-5) with a minimum power of 5Mw. Before evaluating the vesicle size, the samples were agitated with a stirrer.

3.3 Morphology of proniosomes

3.3.1 Proniosomal gels

Using light microscopy, it has been reported that the structures of the gel were affected by the surfactant type(3). The dominant coherent gel phase is built up by surfactant/cholesterol lamellae with water phase mainly bound interlamellar to the hydrophilic head groups of surfactant/cholesterol lamellae. This resulted in an interconnected network of a mixture of lamellar liquid crystals resembling palisades or tubular aggregates and vesculating lamellae. The different gel structures according to the surfactant type investigated that Span 20 and Span 80 gels were consisted of twisted matted lamellar strands with transparent appearance and no drug precipitates, where the gels of Span 40 and Span 60 were formed of floccules of small tubular and vesculating particles which have creamy opaque appearance and also no drug precipitates (Figure 1.4). The units of the gel are often bound together by vander Waals forces so as to form crystalline regions throughout the entire system.

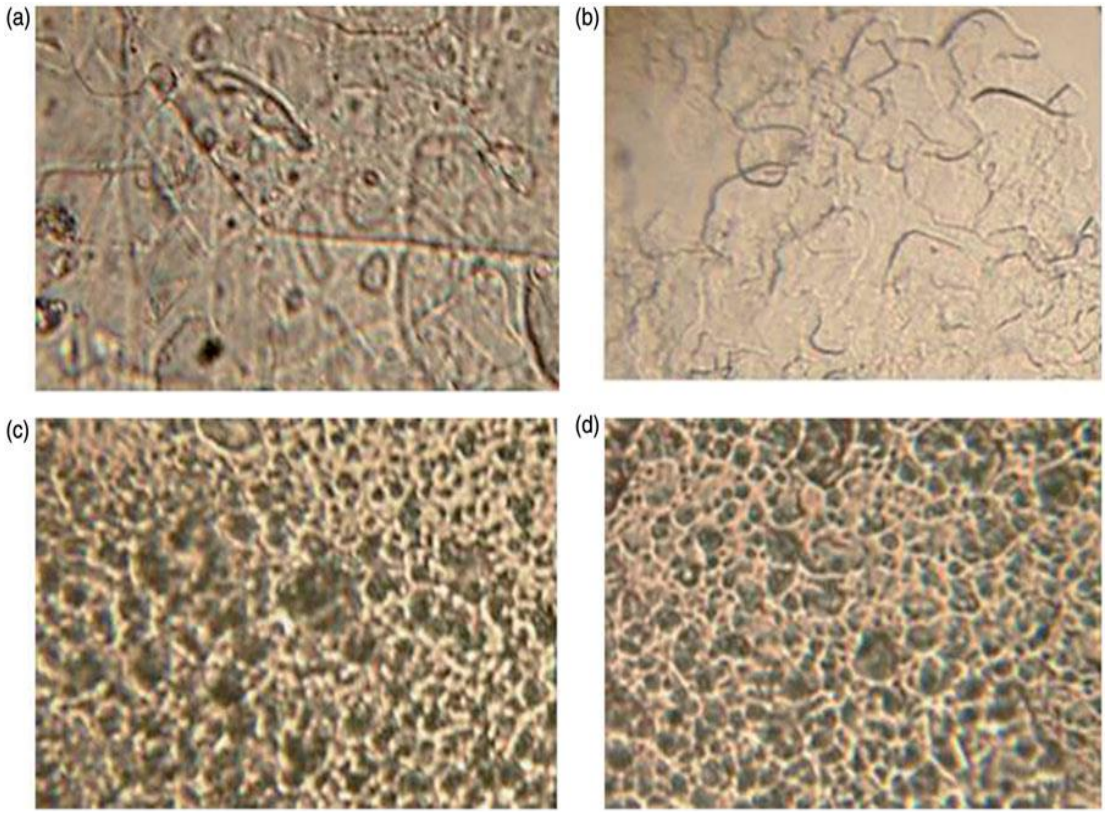

Figure 1.4: Photomicrograph of proniosomal gel of (a) Span 20/20% cholesterol, (b) Span 80/30% cholesterol, (c) Span 40/0% cholesterol and (d) Span 60/0% cholesterol (with permission from (3).

3.3.2 Proniosomal powders

Hu and Rhodes observed through the SEM that the surface of proniosome powder appeared to be smoother and have fewer‘‘fine features’’ such as whiskers and sharp corners. The surface change is probably caused by some brief dissolution of surface molecules of the carrier (particularly, thin or sharp features) in the organic solvent used as a carrier for surfactants sprayed onto the surface of the carrier (22,23)(Figure 1.5).

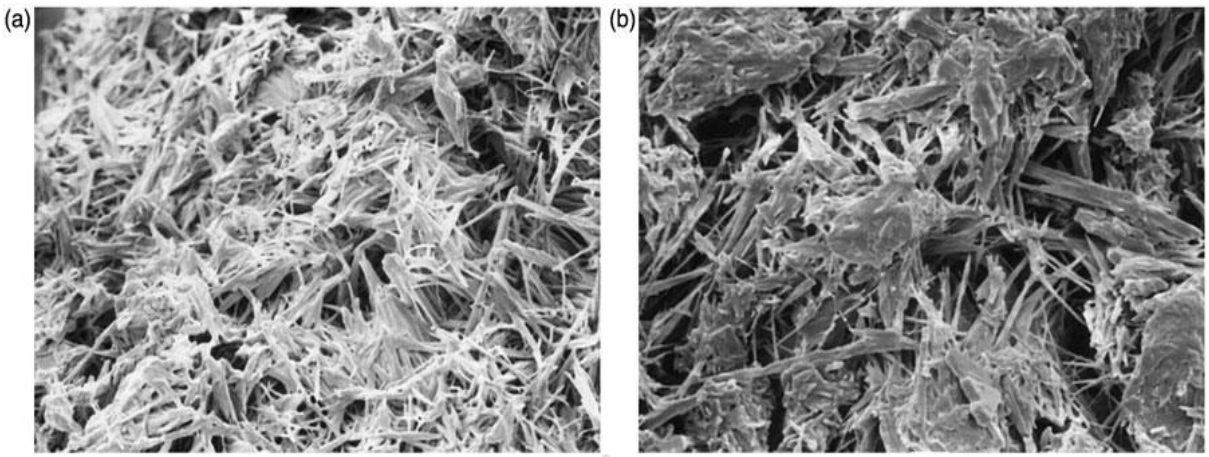

Figure 1.5: Photomicrograph of proniosomal powders (a) sorbitol carrier exhibits crystals with sharp edges and fine structure versus (b) proniosomal powder have somewhat less well defined features (22).

3.3.3 Separation of unentrapped (free) drug

- **Dialysis**

In dialysis techniques, the aqueous niosomal suspension is transferred to a dialysis tube suspended in a suitable dissolution media, the unentrapped drug is separated into the media through osmotic cellulose membrane at appropriate time interval aliquots were withdrawn and analyzed for drug content by using suitable spectrophotometric and high-performance liquid chromatography (HPLC) methods(13,14).

- **Gel filtration**

In gel filtration separation of unentrapped drug from niosomal dispersion is carried out by using a Sephadex-G-50column, eluted with suitable mobile phase and analyzed with suitable analytical techniques(33).

- **Centrifugation**

Centrifugation is another technique used for separation of unentrapped drug from niosomal suspension in which the pellets and supernatant are separated by centrifugation. The obtained pellets are washed and re suspended to get a niosomal suspension free from unentrapped drug(5,30–32,21).

- **Entrapment efficiency**

After separation of unentrapped drug from the niosomal dispersions, the entrapment efficiency can be determined by complete disruption of the vesicles or by solubilizing the vesicles:

3.4 In vitro drug release and skin permeation studies

In vitro drug release and skin permeation studies can be carried out by using different techniques. For in vitro skin permeation studies, flank skin, dorsal skin of albino rabbit, female albino rat, Wistar rat skin (7–9-weeks old)(35) can be used.

4. APPLICATIONS OF PRONISOMES

4.1 Proniosomes as drug carriers

Proniosomes serve as drug carriers for a range of medications. Drug delivery has been explored using a variety of administration techniques, including intramuscular, peroral, transdermal, and lV. Proniosomes will behave similarly to liposomes in vivo(36).

4.2 Proniosomes as haemoglobin carriers

In the blood, proniosomes serve as haemoglobin transporters. The proniosomes can transport haemoglobin under conditions of illness because they are permeable to oxygen(37).

4.3 Cardiological application

Proniosomes are utilised to transport medications with cardiac activity. Captopril is mostly administered topically to treat hypertension, and it also aids in the drug's prolonged absorption into the body(38).

4.4 Antibacterial therapy

When an antibacterial medicine is stored for antibacterial therapy, proniosomal preparations are employed to boost the drug's physical stability and stop formulation oxidation.(39)

4.5 Anti-neoplastic Treatment

The majority of anti-cancer medications have serious adverse effects. The circulation and half-life of the medicine can be prolonged, the metabolism can be changed, and the negative effects of the drug can be reduced. Proniosomes are also frequently employed in cancer treatments(40).

4.6 In diabetes

Transdermal injections of furosemide proniosomes for diabetes lower blood glucose levels(41).

5. CONCLUSION

Proniosomes are a promising drug delivery technique because of their structural resemblance to liposomes. Thus, they can take the place of conventional vesicular systems. It is known that niosomes made from pioniosomes can stop leakage, fusion, aggregation, and problems with physical stability. They also provide benefits for transportation, distribution, storage, and dosing. The aforementioned article leads to the conclusion that many academics and researchers agree with the idea of entrapment or incorporation of the drug into proniosomes for improved targeting of the correct tissue target.

6. ACKNOWLEDGEMENT

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