



Proniosomes: Innovative Vesicular Drug Delivery System: A Review

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ABSTRACT

In recent years, a novel drug delivery system has been realized as a major drug delivery system. Especially, a vesicular system such as proniosomes (a non-ionic surfactant vesicular system) is a novel and potential for topical drug delivery. Proniosomes can improve the bioavailability of the encapsulated drug and establish therapeutic activity in a controlled manner for a prolonged period. Niosomes and other vesicular systems have various drawbacks like problems during drug dispersion such as leakage fusion aggregation and low solubility, sedimentation, short half-life of the dispersion and hydrolysis of the active compounds. In the proniosomal gel formulation cholesterol is used as a stabilizer to enhance penetration to vesicles by minimizing all these problems. This narrative review elaborates one of the pro-vesicular carriers commonly called as proniosomes and emphasizes on a various method of preparation, mechanism, advantages over other vesicular systems, structure, components used in the formulation, characterization, drug release and current clinical applications of proniosomal as a various drug delivery carrier.

Keywords: Vesicular system, Bioavailability, Proniosomal gel, Characterization, Applications.

INTRODUCTION

Now a days, various attention has been focused on the development of a novel drug delivery system (NDDS). The numbers of novel drug delivery systems have been developed in different routes of administration, to enhance sustained, controlled and targeted drug delivery. NDDS play important role in the sustain drug release at a predetermined rate or by maintaining a relatively constant drug at the site of administration, Presence of effective concentration of drug in the body which reduces the undesirable side effects. The encapsulation of the drug in a vesicle is one such system, and a several vesicular drug delivery system i.e. cubosomes, liposomes, phytosomes, niosomes, transferosomes, proniosomes etc. were developed.¹

However, like niosomes, liposomes have unilamellar or multilamellar vesicles are capable of entrapping both hydrophilic and hydrophobic substance.

From the technical point of view, niosomes are osmotically active, shows good chemical stability during storage, but they have problems during dispersion such as aggregation, leakage, fusion and hydrolysis of encapsulated drug from the vesicles and also, they have,

1. Short half-life of the dispersion and sedimentation.
2. production cost is high

3. Low solubility
4. Oxidation and hydrolysis of phospholipid occur during storage.

These problems can be avoided by proniosomes.²

Proniosomes are dry, free-flowing solid colloidal carrier particles that are coated with surfactants and can be converted to niosomal dispersion by hydrating instantly before use on agitation in hot aqueous media within few minutes. Proniosome can entrap both hydrophilic and lipophilic drugs (figure1).^{3, 4} Proniosomal gels are usually present in white semisolid gel texture or transparent and translucent. Proniosomal gels are physically stable throughout storage and transport.⁵

Though the oral administration is a most favourable route for delivery of drugs but it has limited importance especially in the treatment of topical infection. because they face problems like an unpleasant taste, odour, gastric, drug/enzyme instability and low bioavailability.⁶ NDDS an alternative to conventional dosage formulations, are becoming popular due to their exclusive advantages. Increases bioavailability, improves absorption, uniform plasma concentration levels, painless, reduces side effects and easy application. The present article is elaborating components used in the formation of proniosomal gel along with its method of preparation and evaluation studies.⁷



Figure 1: Action of proniosomes

Advantages of Proniosomes Over the Other Vesicular Systems⁸⁻¹¹

- Proniosomes reduces the physical stability problems of niosomes such as fusion, aggregation, leaking on storage.
- It also controls hydrolysis of encapsulated drugs which limiting the shelf life of the dispersion.^{8,9}
- The entrapment of both hydrophilic and hydrophobic drugs can be done easily by this vesicular system.
- Sustained and controlled release of drugs can be done due to depot formation.
- Proniosomal formulation requires generally low-cost materials.
- More stable and Ease of use.
- It leads to ease the transportation, better size distribution and storage uniformity of dose.
- These formulations are biodegradable, biocompatible and non-immunogenic to the body.^{10,11}

Proniosomes Exist in Two Forms¹²

The following two forms of the proniosomes are mainly used for topical application.

Semisolid liquid crystal gel

When the non-ionic surfactant molecules are interacted with water, the lipophilic chains of surfactants can be converted into a liquid state called as lyotropic liquid crystalline state. There are three ways to convert liquid crystalline state, they are;

- Increasing temperature at kraft point (T_c)
- Addition of lipid soluble solvent
- Utilizing both temperature and solvent.

Dry granular powder¹³

Dry granular type proniosomes involves the coating of water-soluble carriers i.e. sorbitol and maltodextrin with surfactant, the coating process is a dry formulation. These are further classified as follows:

Sorbitol based Proniosomes

It is a dry formulation, in this sorbitol is used as a carrier, which is further coated with thin layer of non-ionic surfactant. These are normally made by spraying non-ionic surfactant mixture prepared by organic solvent onto

the surface of sorbitol powder and then solvent get evaporated. the process is repeated until the desired coating has been achieved. The surfactant coating is very thin layer on carriers and hydration of this surfactant coating allows dissolving the multilamellar vesicles.

Maltodextrin based proniosomes¹⁴

The maltodextrin based proniosomes are recently developed formulation which contains maltodextrin as a carrier. Which mainly used to deliver of hydrophobic or amphiphilic drugs and used to hollow particle having surface area. In this formulation the amount of carrier used to support the surfactant can be easily modify, also proniosomes with high mass ratios of surfactant to carrier can be easily formulated.

Mechanism of Proniosomes^{15,16}

Mechanism of drug transport through the skin with the help of vesicles shows conflicting results. So, it is still not clear which factors influence the skin-vesicle interactions and determining the efficiency of drug transport through the skin (figure 2).¹⁵ But it is clear that pro-vesicular system should be converted to vesicles before the drug is released and permeates across the skin. The bilayer present in the vesicles which act as drugs rate-limiting barriers. Also, which contains surfactants (non-ionic) and phospholipids, both can act as a penetration enhancer and increases permeation power of many drugs. The penetration enhancers effect on vesicles to decrease stratum corneum barrier properties. Another possible mechanism is modifications in the structure of stratum corneum for the permeation of vesicle- encapsulated drug.¹⁶

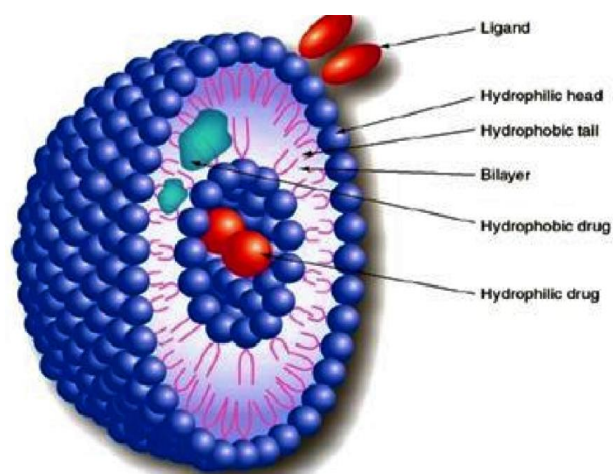


Figure 2: Structure of proniosomes

Methods of Preparation of Proniosomes²⁰

Proniosomal formulations may be prepared by,

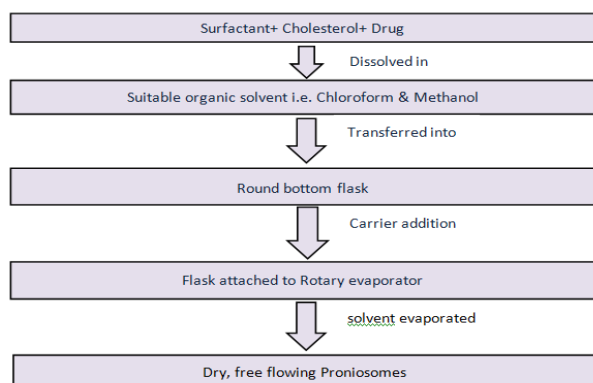
1. Slurry method.
2. Coacervation phase separation method
 - a) Modified coacervation method
 - b) Handshaking method
3. Slow spray coating method.

Slurry method^{21, 22}

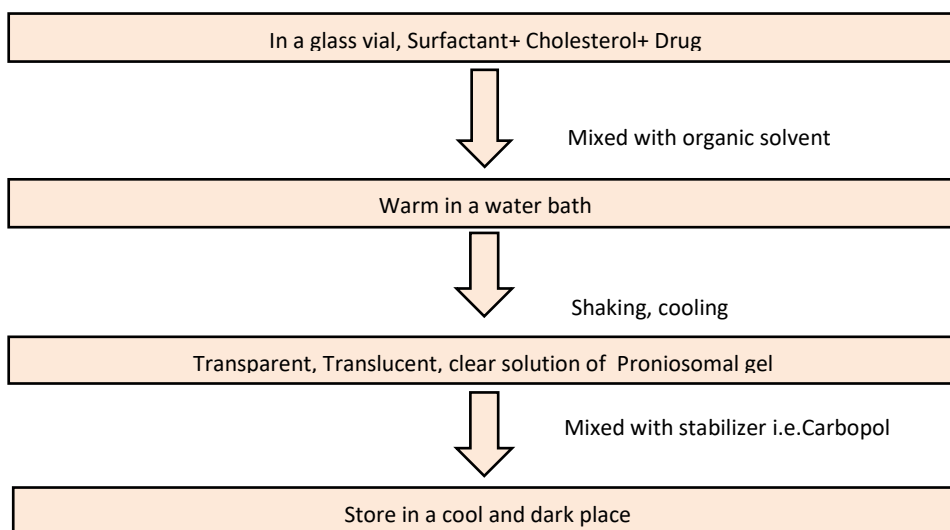
Proniosomes were prepared by the slurry method. In brief, a weighed quantity of surfactants and cholesterol dissolved in suitable solvent. The resultant solution was transferred into a round bottom flask containing the carrier. Additional solvent can be added to form the slurry if lower surfactant loading. The flask was attached to a rotary flash evaporator and the organic solvent was evaporated under reduced pressure at a temperature of $45 \pm 2^{\circ}\text{C}$. Become in the flask dry and free-flowing proniosomes are obtained. Finally, they were stored in a tightly closed container until further evaluation.

Table 1: Components Used Commonly in the Preparation of Proniosomal Gel.^{17, 18, 19}

Sl. no.	Components	Examples	Uses
1.	Surfactants	Span(20,40,60,80) Tween (20,40,60,80)	To enhance the drug flux rate across the skin. ¹⁸
2.	Stabilizer	Cholesterol	To control leakage of the drug formation. ¹⁹
		Soya & egg lecithin	Penetration enhancer
3.	Carriers	Sorbitol	Alter or changes the drug distribution
		Maltodextrin	It provides flexibility in surfactant and other components
4.	Solvents	Methanol, ethanol, etc	Skin permeation
5.	Aqueous phase	Buffer, hot water, glycerol	Entrapment efficiency
6.	Others	Magnesium aluminium silicate, mcc, glucose monohydrates, Carbopol etc.	It Controls leakage of formulation and gelling agent as stabilizer

**Coacervation phase separation method:²³**

In glass vials, an accurately weighed or required amount of surfactant, cholesterol and drug were mixed with organic solvent and warmed in a water bath. Shaking the glass vials until complete dissolution of all these ingredients. The mixtures were allowed to cool down at room temperature and observed for the formation of a transparent and translucent solution or white creamy proniosomal gel. The obtained gel mixed with stabilizer, then preserved in dark until Characterization.



Modified coacervation method²⁴

This is the modified method of coacervation. As per the formulation an accurately weighed drug with cholesterol, lecithin, and surfactant, were mixed with solvent in a wide mouth glass tube. Open-end of the glass tube was covered with a lid and mixtures warmed in a water bath at $65\pm 3^\circ\text{C}$ for 5 min. Then pH 7.4 phosphate buffer was added and further warmed the mixture in the water bath until the clear solution obtained. The mixture was allowed to cool down until the dispersion will be converted to proniosomal gel.

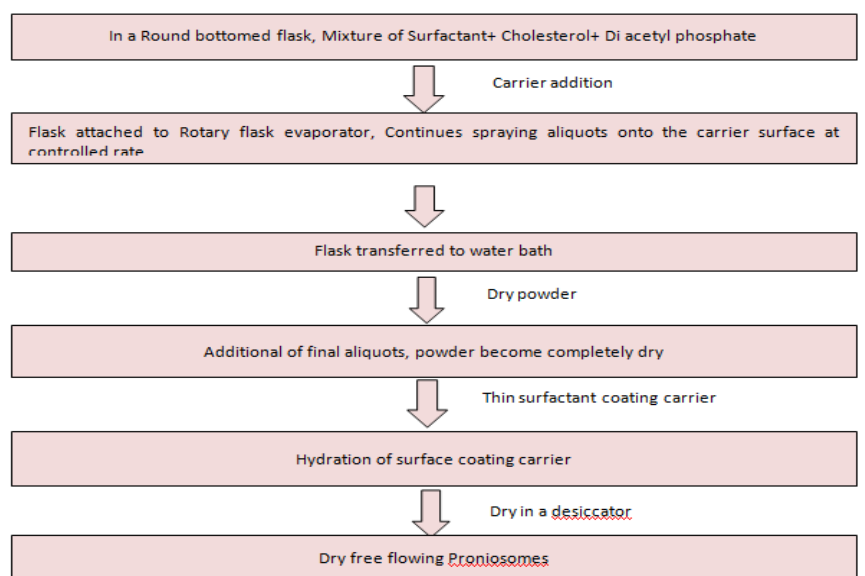
Hand-shaking method²⁵

The vesicles forming ingredients such as cholesterol and surfactants are dissolved in a round bottom flask containing an organic solvent. The solvent mixture get evaporates in the rotary flash evaporator at room temperature. A thin layer of dried solid mixture deposited on the walls of the round bottom flask. The dried solid mixture film can be rehydrated with the help of aqueous

phase at $0-60^\circ\text{C}$ with mild shaking. This method gives a typical multi-lamellar niosomes.

Slow spray coating method^{26,27}

Proniosomes are prepared by spraying surfactant in organic solvents onto a carrier followed by evaporation of remaining solvent. For this, A mixture of surfactants, cholesterol, and diacetyl phosphate is introduced into the round-bottomed flask containing the desired amount of carrier on the rotary evaporator by continuous spraying of aliquots onto the carrier's surface at a controlled rate of application. The flask has to be transferred to a water bath of $65-70^\circ\text{C}$, rotates the flask after the addition of the final aliquots under vacuum until powder becomes completely dry. Repeat the process until the surfactant loading reaches the desired level. Then get a very thin surfactant coating carrier and hydration of this coating allows carrier dissolves. The material is further dried in a desiccator under vacuum overnight. It gives a dry, free-flowing preparation of "proniosomes" then it is used for the characterization and preparation.

**Evaluation of Proniosomes****% Entrapment Efficiency²⁸**

It can be determined by separating the untrapped drug. In this, a sample of proniosomal gel was taken in a glass tube, and to this phosphate buffer (pH 7.4) was added. The obtained aqueous suspension was sonicated in a sonicator bath followed by centrifugation. The supernatant was taken and assayed by using U.V spectrophotometer at a specific wavelength for an untrapped drug. The percentage of drug [EE%] was determined by the following equation:

$$\text{EE\%} = \left(\frac{\text{Total amount of drug} - \text{Untrapped drug}}{\text{Total amount of drug}} \right) \times 100.$$

Characterization of proniosomes²⁹**Vesicle size**

The mean vesicle size is determined by using a microscope, the proniosomal gel was dissolved in Phosphate buffer solution in a small glass test tube by manual shaking. And proniosomes get hydrated to form niosomes. To determine the vesicle size the sample was observed under an optical microscope. The average size of vesicles can be calculated by using calibrated ocular and stage micrometer in the microscope.

Optical microscopy analysis

A few drops of niosomal dispersion prepared from proniosomes were spread on a glass slide and examined for the presence of insoluble drug crystals and vesicle structure under an ordinary light microscope with varied

magnification power. (10x, 40x) Photomicrographs were taken for niosomes using a digital camera.

Scanning electron microscopy (SEM)³⁰

SEM is used to illustrate the role of cholesterol in the vesicle formation and also used to study surface characteristics (i.e. shape and size) of proniosomes. Niosomes suspension formed from the proniosomal gel by hydration were sprinkled on an aluminium stub having double-sided adhesive carbon tape. Then the vesicles were spray-coated with gold/palladium using a vacuum evaporator and examine dry thin film of niosomal suspension using SEM equipped with a digital camera.

Transmission electron microscopy (TEM)³¹

The surface morphology like smoothness, roundness, formation of aggregation is determined by TEM. A drop of diluted proniosomal suspension was applied to a carbon-coated copper grid mesh and leave, some of the proniosomes to adhere to the carbon substrate. The remaining suspension was removed by using a piece of filter paper. Rinsing the grid twice using deionized water. Then added a drop of 2% aqueous solution of uranyl acetate. Further, the remaining solution was removed by absorbing the liquid with the help of a piece of filter paper and the sample was air-dried. Then sample was observed with TEM at 80 KV.

Spreadability of proniosomal gel³²

It is the most important characteristic of any topical administration as far as patient compliance is concerned. Prepared gel was placed between the two glass slides onto which weights were allowed to rest. Then the top slide was subjected to pull up. The time required for the top slide to travel 30 cm distance was noted.

Stability studies^{33,34}

The stability testing of proniosomes is important to determine the leaching of a drug from the vesicles. In this method, samples were sealed in 20 ml glass vials and stored at refrigeration temperature (4°C - 8°C) and at 30°C for 90 days. After 90 days, the hydration step was carried out and as well as the mean particle size and entrapment efficiency of each sample was determined then results are compared with freshly prepared proniosomes-derived niosomes.

In-vitro methods for the assessment of drug release from proniosomes

In-vitro drug release can be determined by followings,

Franz diffusion cell³⁵

The in-vitro diffusion studies can be done by using Franz diffusion cell. Proniosomal formulation is placed in the donor chamber of the cell fitted with a cellophane membrane. Then the proniosomes is dialyzed with a suitable dissolution medium at room temperature. At a specific time of interval, the samples are withdrawn from the medium and analyzed for the presence of drug

content using a suitable method (i.e. U.V. spectroscopy, HPLC, etc). The sink condition maintenance is essential.

Dialysis tubing³⁶

In vitro drug release can be achieved by using dialysis tubing. The proniosomes is placed in cleansed dialysis tubing which can be completely sealed. The dialysis sac containing proniosomes is then dialyzed against a suitable dissolution medium at room temperature. At a suitable period of the interval, the samples are withdrawn from the medium, centrifuged then obtained supernatant was taken and analyzed. To determine the drug content using a suitable method. During this process keeping sink condition is essential.

Reverse dialysis³⁷

This method is rarely used due to their slow release of drug. In this method containing number of small dialysis tube. In which 1 ml of dissolution medium and proniosomes are placed. From this method direct dilution of proniosomes is possible.

Drug content uniformity³⁸

Drug content uniformity of proniosomal gel was determined by analyzing the drug concentration. From the four different points of sample are taken. Then samples were dissolved in phosphate buffer solution (pH 6.8) and stirred to dissolve the vesicles. The presence of drug contents was determined using the U.V spectrophotometer at a specific wavelength.

Physical appearance and Homogeneity³⁹

They were tested due to their appearance and the presence of any aggregates. A test can be done by visual observations after the gels have been set in the container.

pH Determination⁴⁰

The pH of the proniosomal dispersion was measured by using digital pH meter. An accurately weighed amount of gel was dispersed in a purified water. Then calibrate the pH of proniosomes before use with standard buffer solution later which gives pH of the gel.

Viscosity⁴¹

Viscosity was measured by using a Viscometer. In this, an accurately weighed amount of the gel was taken into a beaker, viscosity was measured by rotating the spindle in a beaker.

Zeta potential⁴²

Zeta potential is another method to characterize proniosomes. It can be determined by using suitable zeta potential analyser, mainly based on the electrophoretic light scattering method. It measures charge of the particles, in this larger the absolute zeta potential value indicates more amounts of surface charge on particles. Logically, it shows particle stability. It means, higher zeta potential value exists more repulsive interaction of particles which leads to uniform size distribution. A



physically stabled formulation is stabilized by electrostatic stability prevents aggregation of proniosomal repulsion of min. zeta potential i.e. $\pm 30\text{mV}$ and this formulation.

Table 2: Some of The Current Research Work Carried Out A Proniosomes as Drug Delivery.

Sl. No.	Drug	Category	Method of preparation	Purpose/reason	Ref.
1	Tolnaftate	Antifungal	Coacervation phase separation method	To increase duration of action & improve systemic absorption	43
2	Celecoxib	Anti-inflammatory, analgesic, anti- pyretic	Modified coacervation method	To reduce 1 st pass metabolism and enhance bioavailability	44
3	risperidone	Anti-psychotic drug	Coacervation phase separation method	To increase bioavailability because it has low systemic absorption (orally)	45
4	Isoniazid	Anti-tubercular drug. Anti-bacterial	Coacervation phase separation method	To improve therapeutic efficacy .and reduces side effects	46
5	Ritonavir	Anti-viral, HIV treatment	Modified coacervation method	To improve stability of formulation and sustain release of drug	47
6	Olmesartan medoximil	Anti-hypertensive	Slurry method	To enhance the bioavailability due to their poor water solubility orally (26%)	48
7	Glimepiride	Hypo-glycemic activity	Coacervation phase separation method	To improve its therapeutic efficacy	49
8	Cefuroxime axetil	Anti-biotic (2 nd generation)	Slurry method	To enhance bioavailability	50
9	Carvedilol	Anti-hypertensive (b-blocker)	Coacervation phase separation method	To improve entrapment efficiency and bioavailability	51
10	Clotrimazole	Anti-fungal (imidazole)	Coacervation phase separation method	To enhance solubility	52
11	Acyclovir	Anti-viral	Coacervation phase separation method	To facilitate sustain release of drug and improve bioavailability	53
12	Lovastatin	Hyper cholesterolemia	Coacervation phase separation method	To reduce risk of cardiovascular diseases	54
13	Irinotecan	Anti-cancer drug	Slurry method	To treat colon cancer and reduces severe adverse effect	55
14	Bromocriptine	Anti-parkinsonism	Coacervation phase separation method	To treat pituitary tumour, infertility, menstrual disorder	56
15	Ofloxacin	Anti-biotic (broad spectrum)	Slurry method	To enhance sustain release of drug	57

Clinical Applications of Proniosomes⁵⁸

Anti-neoplastic treatment

Proniosomes can alter the metabolism and decreasing the side effects of antineoplastic drug because which causes severe side effects and also prolong circulation and half-life of the drug.

Leishmaniasis disease

Use of the drug in the form of proniosome for the treatment of leishmaniasis disease. Which shows the administration of higher levels of the drug without causing side effects, and also shows greater efficacy in the treatment.

Immune response studies

Proniosomes vesicles are used in studying immune response because of their greater stability, low toxicity, and immunological selectivity, low toxicity and greater stability.

Treatment of cardiac disorders

Proniosomal carrier used in Cardiac Disorders (e.g. Hypertension). To improve the deliverance of drugs over an extended period.

Carriers for haemoglobin

Proniosomes can be used as carriers for haemoglobin with in the body particularly in anaemic patients, because of these vesicles are permeable to oxygen.



Drug targeting

Proniosomes can be used as drug targeting to the reticuloendothelial system.

E.g. Drug targeting to the parasitic infection of the liver.

Antibacterial therapy

Used for antibacterial therapy, during storage of an anti-bacterial drug which increases the physical stability and prevent the oxidation of phospholipids.

Cosmetic formulation

In Cosmetics Formulation. The therapeutic agents which can be utilized for incorporation into the proniosomal carrier systems (e.g. cleansing, moisturizing, sunscreen particles, nutritional, anti-wrinkle, anti-ageing etc.

CONCLUSION

A vesicular system such as proniosomes is a novel and tremendous drug delivery. Generally, for an anti-cancer, anti-infective and topical route of administration. Extensively Proniosomal formulation is used in the dermatology for the treatment of skin disorders like melanoma, psoriasis, a bacterial and fungal infection. Proniosomes are osmotically active, which possess enhanced stability and decreased drug toxic effects compare to other vesicular systems. Proniosomal gel formulation is better comfort, majorly used in drug targeting for controlled, sustained release of drugs (hydrophobic and hydrophilic). Because it has the most desirable skin penetration and entrapment efficiency. They having good physicochemical properties while industrial manufacturing, handling, and storage. Overall, proniosomes are a very effective vesicular drug delivery system for various therapeutically active drugs. And they provide satisfactory treatment than conventional drug delivery systems.

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