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PRONIOSOMES: A VERSATILE DRUG DELIVERY SYSTEM

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ABSTRACT

In recent times nanotechnology is considered a technology that could revolutionize the field of life sciences including drug delivery. Further, one of the recent advancements in the field of nanotechnology is proniosomes. Proniosomes are a dry formulation of water-soluble carrier particles that are coated with surfactant and can be measured out as needed and dehydrated to form niosomal dispersion immediately before use on brief agitation in hot aqueous media within minutes. Prevesicular systems, such as proniosomes overcome the problems of vesicular systems such as aggregation, fusion, and leakage of drugs and provide additional convenience in transportation, distribution, storage, and dosing. Conventional vesicular systems such as liposomes and niosomes are particulate and face stability related problems. This new emerging concept has demonstrated the potential in improving the oral bioavailability, targeting drugs to the specific site and also permeation of drugs across the stratum corneum. It prolongs the existence of the drug in systemic circulation and reduces the toxicity. This review provides information regarding the formulation and evaluation of proniosomes including morphology, particle size, drug release, and their advantages over the niosomes.

KEYWORDS: Proniosomes; Niosomes; Permeation; Vesicular systems; Skin.

INTRODUCTION

Novel drug delivery systems have been delivered through various routes of administration, to attain the targeted and controlled drug delivery. Drug encapsulation in the vesicles will help to prolong the drug duration in systemic circulation and decreases the toxicity by selective uptake. Based on this technique, vesicular drug delivery systems such as liposomes, niosomes, and proniosomes have been developed. Liposomes are colloidal, vesicular

structures that are organized in one or several concentric phospholipidic bilayers with an aqueous core inside which encloses a wide variety of substances and drugs.[1] However, liposomes have limited success in terms of oral delivery and suffer from physicochemical stability problems such as sedimentation, aggregation, fusion, phospholipids hydrolysis, and/or oxidation. Further, to overcome the above-mentioned limitations in the early ’80s niosomes have been developed as an alternative to liposomes as drug carriers and drug-targeting agents.[2,3] Niosomes can be considered as a potential alternative to liposomes as drug carriers with greater chemical stability, entrapment efficiency of both hydrophobic and hydrophilic drugs, and less toxic due to their non-ionic nature.[4] They overcome the disadvantages associated with liposomes such as phospholipids purity, difficulty in sterilization, and high cost.[5,6] However, niosomes possess some disadvantages like leakage, fusion, aggregation, and sedimentation which can be overcome by formulating proniosomes.[7]

Apart from that Proniosomes were studied as alternatives to liposomes and other carrier systems for entrapping both hydrophobic and hydrophilic drugs. The additional advantages with proniosomes are low toxicity owing to non-ionic nature, no requirement of special precautions and conditions for formulation and preparations. Besides, the method of formulation for both small and large scale batches can be done without using undesirable solvents. However, stability is the 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 and niosomes.[8] All these advantages of dry niosomes often termed as proniosomes have made them a promising industrial product. In the current review, an attempt has been made to understand the formulation and evaluation aspects of proniosomes.

Merits[9]

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

Demerits[10]

1. During the hydration to niosomes complete drug, entrapment may not be possible, sometimes Hence the amount of un-entrapped drug should be analyzed.

Structure of proniosomes

Proniosomes are transparent, translucent, or semisolid gel in nature because of containing a limited solvent and these are a mixture of lamellar, hexagonal, and cubic liquid crystals. Further, the lamellar phase shows sheets of surfactants arranged in a bilayer, the hexagonal phase shows the cylindrical compact structure, and these are arranged in hexagonal fashion whereas the cubic phase consists of curved continuous lipid bilayer extending to three dimensions. While formulating a gel loaded with proniosomes, in the primary step the less viscous composition is formed in some cases but the addition of water leads to interaction between water and a polar group of surfactant resulting swelling of bi-layer. If the amount of solvent is increased further, a spherical structure is formed which is termed as multi-lamellar and multi-vesicular resulting in complete hydration thereby niosomes are formed.[11,12]

Classification of proniosomes

According to the type of carrier and method of formulation of proniosomes can be classified into two types as shown in Fig.1.

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 noisome within minutes by the addition of hot water followed by agitation.[13]

Maltodextrin based proniosomes are prepared by the fast slurry method. These are formulations in which maltodextrin, surfactant solution in the organic solvent are added together to form a slurry. Later organic solvent is evaporated and to form a dry powder.[14]

Liquid crystalline proniosomes

These types 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. Liquid crystalline proniosomes possess various advantages like stability; high entrapment efficiency; as a penetration enhancer and easy to scale up.[15]

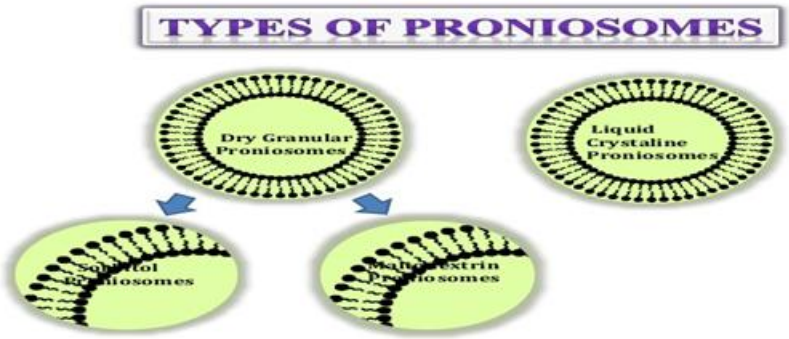

Fig. 1. Types of proniosomes.

Formulation of proniosomes

The proniosomes consist of several 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. Coacervation phase Separation method
2. Slurry method
3. Spray Coating method

Coacervation phase separation

It is the most commonly used method for the preparation of Proniosomal gel. In this method accurately weighed quantity of drug along with surfactant, cholesterol, and lecithin is taken in a wide mouth glass vessel. Then a sufficient quantity of solvent (ethanol) was added and the mixture was heated in a water bath at a temperature of 50-60 °C. The open end of the glass vial is covered with a lid to prevent the evaporation of the solvent. To this mixture, aqueous phase phosphate buffer pH 7.4 was added and heated the mixture over a water bath at 50-60 °C until the drug dissolved in the surfactant mixture. The Proniosomal gel is formed by either cool the mixture at room temperature or by adding a suitable gelling agent to the heated mixture and cool it on an ice bath.[16, 17]

Slurry method

In this method, maltodextrin is used as a carrier. A 250 µ molar 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. Further, an organic solvent solution added to form a slurry. The flask was attached to a rotary flash evaporator and rotated at 60-70 rpm at a temperature of 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 stored in a tightly closed container.[18]

The slow spray coating method

Proniosomes are generally formulated by spraying surfactants in the organic solvent into sorbitol powder and evaporating the solvent. A 100 ml round bottom flask containing the desired amount of carrier can be attached to the 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 solutions have been applied. The evaporation should be continued until the powder becomes completely dry and to form multicellular vesicles.[19,20]

Niosomes formation from proniosomes by hydration

The niosomes can be prepared by hydration of proniosomes, where aqueous phase containing the drug should be added to the proniosomes with brief agitation at a temperature greater than the mean transition phase temperature of the surfactant as shown in Fig. 2.[20] Different research works where the above-mentioned techniques were used to formulate proniosomes is presented in Table 1.

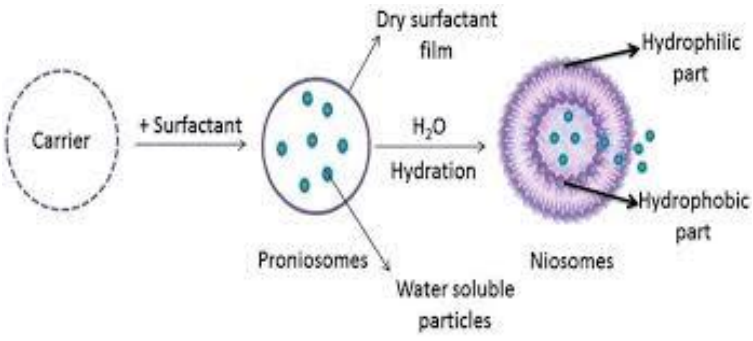

Fig. 2: Formation of niosomes from proniosomes.

Table 1: Research works carried out on the above mentioned techniques to formulate proniosomes.

Name of author	Name of drug	Type of procedure used	Year	Reference
Madan JR et al	Lornoxicam	Coacervation phase separation	2016	[21]
Amal Saber Mohammed Abu El-Enin et al	Fluconazole	Coacervation phase separation	2019	[22]
S.Ramkanth et al	Atenolol	Coacervation phase separation	2018	[23]
Tamizharasi Sengodan et al	Indomethacin	Slurry method	2009	[24]
Almira I. Blazek-Welsh et al	Maltodextrin	Slurry method	2001	[25]
Ajay B Solanki et al	Ketoprofen	Slurry method	2009	[26]
H.O.Ammar et al	Tenoxicam	Slow spray coating method	2011	[27]

Evaluation of proniosomes

Measurement of angle of repose

The angle of repose of dried proniosomes was measured by the funnel method and cylinder method.

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 10 cm above the level of surface. The powder flowed down from the funnel to form a cone on the surface and then the angle of repose was further calculated by measuring the height of the cone and the diameter of its base.

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.[20]

The angle of repose is calculated by the below equation

$\text{Tan}(\Theta) = h/r$

Scanning electron microscopy (SEM)

The 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 the scanning electron microscope. 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).[28]

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.[29]

Measurement of vesicle size

Vesicle size was measured on a particle size analyzer. The vesicle dispersions were diluted about 100 times in the same medium, which was used for their preparation. The apparatus consists of a He-Ne laser beam of 632.8 nm focused with a minimum power of 5Mw using a Fourier lens (R-5) to a point at the center of a multi-element detector and a small volume sample holding cell. The samples were stirred with a stirrer before determining the vesicle size.[30]

Drug content

Proniosomes equivalent to 100 mg was 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 10ml 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.[31]

Entrapment efficiency

Separation of the un-entrapped drug from the niosomal suspension was carried out by exhaustive dialysis method and centrifugation method. The niosomal suspension was taken into a dialysis tube to which the 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 un-entrapped drug were separated into the medium through the 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.[32]

***In-vitro* release studies**

The *in-vitro* diffusion studies can be performed by using Franz diffusion cells. Proniosomes is placed in the donor chamber of a Franz diffusion cell fitted with a cellophane membrane. The proniosomes are then dialyzed against a suitable dissolution medium at room temperature; the samples were withdrawn from the medium at suitable intervals and analyzed for drug content using the suitable method (U.V Spectroscopy, HPLC, etc). The maintenance of the sink condition is essential.[33]

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 proniosomes 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). The product should be evaluated for appearance, color, assay, pH preservative content, particulate matter, sterility, and pyrogenicity.[34]

Clinical applications

The application of proniosomal technology is widely varied and can be used to treat several diseases. The following are the few uses of proniosomes which are either proven or under research:

A. Glipizide for treatment of diabetes

Glipizide is an anti-diabetic medication belonging to the sulfonylurea class which is used to treat type-2 diabetes. By formulating into proniosome the glipizide will be successfully entrapped within the bilayer of the vesicles with high entrapment efficiency and is a promising approach to sustain the drug release for an extended period and by that reducing the side-effects related to gastric irritation.[35]

B. Delivery of peptide drugs

Oral peptide drug delivery has a drawback of bypassing the enzymes, which would breakdown the peptide and protein bonds. Proniosomes were used to successfully protect the peptides from gastrointestinal peptide breakdown. The investigations done by Yoshida et al suggested that oral delivery of vasopressin derivative entrapped in proniosomes showed that entrapment of the drug significantly increased the stability of the peptide.[36]

C. Risperidone in treating schizophrenia

Risperidone is a potent benzisoxazole derivative used in the treatment of schizophrenia and other psychiatric disorders and is commercially available in various formulations. Risperidone belongs to Biopharmaceutics Classification System (BCS) class II drug, i.e. bears low solubility and high permeability. The major drawback associated with risperidone therapy is its low oral bioavailability due to its extensive hepatic first-pass metabolism mediated via Cytochrome P-450 enzymes. Further, work done by Sharda Sambhakar et al suggested that relative bioavailability was 92% after transdermal administration of proniosomes, and the t_{max} was increased to 8 h when compared with pure drug and concluded that developed proniosome formulation would be a promising alternative to improve the bioavailability problems of risperidone.[37]

D. Antineoplastic treatment

Most antineoplastic drugs can cause severe side effects. So by designing into proniosomes, they can alter the metabolism; prolong circulation, and half-life of the drug, thus decreasing the side effects of the drugs. Proniosomes can decrease the rate of proliferation of tumors and higher plasma levels accompanied by slower elimination. Further, a study performed by Azmin MN et al suggested that by formulating niosomes loaded with methotrexate, absorption of the drug from the gastrointestinal tract following oral ingestion appeared to be increased and brain uptake was also increased.[38]

E. Treatment of leishmaniasis

Leishmaniasis is a disease in which a parasite of the genus Leishmania invades the cells of the liver and spleen. The use of niosomes in tests conducted showed that it was possible to administer higher levels of the drug without the triggering of the side effects, and thus allowed greater efficacy in treatment. A typical study performed by Deepika Aggarwal et al suggested that niosomes loaded with timolol maleate had shown a sustained release up to 8h

while the standard solution had shown complete release by 2h.[39] Some of the recent research works carried out on proniosomes as drug carriers are reported in Table 2.

Table 2: Recent research works that carried out on proniosomes as drug carriers.

Drug	Category	Experimental model	Reference
Capecitabine	Chemotherapy agent	*In-vitro* diffusion study by Franz diffusion cell	[40]
Duloxetine	Anti-psychotic	*In vitro* release study by membrane diffusion technique and *Ex vivo* permeation studies using goat mucosal surface	[41]
Lovastatin	Cholesterol-lowering agent	*In-vitro* diffusion study by Franz diffusion cell, *Ex vivo* permeation studies using male Wister rat skin and pharmacokinetic studies using male Wister rats	[42]
Aceclofenac	Nonsteroidal anti-inflammatory drug	Rheological characterization of proniosomal based gel and conventional gel using a rotational type rheometer	[43]
α-Mangostin	Antineoplastic agent	*In-vitro* diffusion study by Franz diffusion cell and skin retention studies	[44]
Chlorpheniramine maleate	Antihistaminic agent	*In-vitro* diffusion study by Franz diffusion cell	[45]
Captopril	Anti-hypertensive agent	*In-vitro* diffusion study by Franz diffusion cell	[46]
Ketorolac Tromethamine	Nonsteroidal anti-inflammatory drug	*In vitro* release study by membrane diffusion technique and *In-vivo* anti-inflammatory study	[47]
Levofloxacin	Antibiotic	*In-vitro* diffusion study by Franz diffusion cell and *In vivo* ocular irritancy test	[48]
Tretinoin	Anti-acne agent	*In-vitro* diffusion study by Franz diffusion cell and skin irritation studies on healthy subjects	[49]
Docetaxel	Antineoplastic agent	*In-vitro* diffusion study by everted gut sac method and pharmacokinetic studies using rats	[50]

Future trends

Proniosomal formulations are considered as an alternative approach to deliver and target the loaded drugs. Still, there is a need for discovering the new delivery systems using proniosomes in the field of cosmetics, nutraceuticals, herbal actives, and other synthetic formulations. Hence, wider research should be done to develop scale-up batches for drug and natural preparations.

CONCLUSION

From the above article, it is concluded that the concept of incorporating the drug into niosomes for 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 represent a structure similar to liposome and hence they can represent alternative vesicular systems for liposomes, due to the niosome ability to encapsulate the different types of drugs within their multi environmental structure. Proniosomes based niosomes can be considered as better candidates for drug delivery as compared to liposomes due to various factors like cost, stability, etc. Thus proniosomes present itself as a potential alternative to deliver and target commercially available therapeutics.

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CONFLICT OF INTEREST

The author confirms that this article content has no conflict of interest.

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