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PRONIOSOMES: AN EMERGENT DRUG DELIVERY SYSTEM

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ABSTRACT

Controlled release drug products are often formulated to permit the establishment and maintenance of drug concentration at target site for longer interval of time. One such technique of drug targeting is 'niosome'. In order to minimize the problems associated with niosome physical stability such as aggregation, fusion and leaking and to provide additional convenience in transportation, distribution, storage and dosing etc. a dry product can be prepared from niosome called proniosome. In all comparisons, proniosomes are as good as or better than conventional niosome. Because proniosome are a dry powder, further processing is possible. To provide convenient unit dosing, the proniosome powder may be processed to make beads, tablets or capsules. The hydration of proniosome powder is much easier than the long shaking process required hydrating surfactant in the conventional dry film, method Proniosome derived niosome suspension to be as good or better than conventional niosome preparation; and may be an appropriate preparation to use as a hydrophilic drug carrier.

KEYWORDS: Proniosomes, Controlled release, Conventional niosomes.

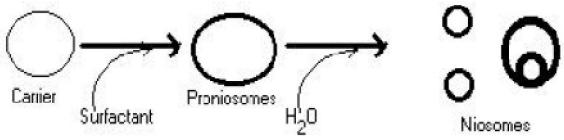
INTRODUCTION

Proniosomes are non-ionic based surfactant vesicles, which may be hydrated immediately before use to yield aqueous noisome dispersions. Proniosomes are now days used to enhance drug delivery in addition to conventional niosomes. Proniosomal system serves as a rate limiting barrier for absorption of drugs. These systems can overcome the permeation barrier of the skin and act as a penetration enhancers for the drugs. The vesicles may serve as non toxic penetration enhancer for drug because of the ampiphillic nature of the vesicles; they are more stable and compatible with the skin. Provesicular

system can be simply converted into vesicular system, which presents a useful vesicular delivery concept with potential to deliver drugs via transdermal route. Proniosomes are dry formulations of surfactant-coated carrier, which can be deliberate out as needed and rehydrated by brief agitation in hot water. These "proniosomes" minimize problems of niosomes physical stability such as aggregation, fusion and leaking and provided additional convenience in transportation, distribution, storage and dosing. Stability of dry proniosomes is probable to be more stable than a premanufactured niosomal formulation. In release studies proniosomes become visible to be

equivalent to conventional niosomes. Size distributions of proniosome derived niosomes are fairly better that those of conventional niosomes so the release performance in more significant cases turns out to be superior[1].

Proniosome: Proniosomes are water soluble carrier particles that are coated with surfactant and can be hydrated to form niosomal dispersion immediately before use on brief agitation in hot aqueous media. The resulting niosomes are very similar to conventional niosomes and more uniform in size. The additional convenience of the transportation, distribution, storage, and dosing would make 'dry niosomes' a promising industrial product. Proniosome derived niosomes are as good as or even better than conventional niosomes[2].



Interaction Between skin and proniosomes:

There is a direct contact of proniosome formulation with skin after applies, so it is better to discuss the potential interactions between skin and vesicles formed in proniosome formulations. As we know that proniosomes are composed of non-ionic surfactants, and the vesicles are composed of these non-ionic surfactant only. So it is advisable to study the interactions between non-ionic surfactants and the skin. The non ionic surfactants are amphipathic molecules consisting of a hydrophobic (alkylated phenol derivatives, fatty acids, long chain linear alcohols, etc.) and a hydrophilic part (usually ethylene oxide chains of variable length). Nonionic surfactants are used widely in pharmaceuticals to increase their stability, solubility and permeation. There is a strong indication that the degree of interaction between vesicles and skin mainly depends on physicochemical properties of the surfactant molecules of which the niosomes or proniosomes are composed. Skin consists of a range of bioactive material like membrane phospholipids, proteins, amino acids, peptides, etc.

Surfactants are known to increase the permeability of vesicles and phospholipid membranes, causing low molecular mass compounds to leak. The interaction between biological membranes and non-ionic surfactant tested for phospholipid composition and rate of biosynthesis of major phospholipid components indicate no significant change in the phospholipid composition, where as biosynthesis and turnover rates of phospholipids were increased two to four times[3, 4, and 5].

Preparation of proniosome

Carrier which is selected for proniosomes preparation should have following characteristics like free flow ability, non-toxicity, poor solubility in the loaded mixture solution and good water

solubility for ease of hydration. Different carriers and non ionic surfactants and membrane stabilizers used for the proniosome preparation are shown in **table 1.**

Table 1: Commonly used materials for proniosomes preparation

S.No	Class	Examples	Use
1.	Surfactants	Span 20, 40, 60, 80,85 Tween 20, 40, 80	To increase drug flux rate across the skin.
2.	Cholesterol	Cholesterol	To prevent leakage of drug formulation.
3.	Lecithin	Lecithin	Penetration Enhancer.
4.	Maltodextrin	Maltodextrin	Provides flexibility in surfactants and other components.
5.	Sorbitol	Sorbitol	Alters the drug distribution.

There are 3 methods for preparation

1. Slurry method: Maltodextrin powder as carrier is added to a 250-mL round-bottom flask and the entire volume of surfactant solution was added directly to the flask to form slurry. If the surfactant solution volume is less, then additional amount of organic solvent can be added to get slurry. The flask was attached to the rotary evaporator and vacuum was applied until the powder appeared to be dry and free flowing. The flask was removed from the evaporator and kept under vacuum overnight. Proniosome powder was stored in sealed containers at 4°C. The time required to produce proniosomes is independent of the ratio of surfactant solution to carrier material and appears to be scalable[6, 7].

2. Coacervation phase separation method: weighed amounts of surfactant, lipid and drug are taken in a clean and dry wide mouthed glass vial of 5.0 ml capacity and alcohol (0.5 ml) is added to it. After warming, all the ingredients are mixed well with a glass rod; the open end of the glass bottle is covered with a lid to prevent the loss of solvent from it and warmed over water bath at 60-70°C for about 5 min until the surfactant mixture is dissolved completely. Then the aqueous phase (0.1% glycerol solution) is added and warmed on a water bath till a clear solution was formed which is then converted into proniosomal gel on cooling[8].

3. Slow spray-coating method: This method involves preparation of proniosomes by spraying surfactant in organic solvent onto sorbitol powder and then evaporating the solvent. Because the sorbitol 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. The

resulting niosomes are very similar to those produced by conventional methods and the size distribution is more uniform[9].

Characterization of proniosomes[10, 11, 12, 13]

Provesicles are characterized for vesicle size and morphology, entrapment efficiency, *In vitro* release and permeation studies, *In vivo* studies, stability studies *etc*.

Vesicle size and morphology Vesicle morphology

It involves the measurement of size and shape. The size of the vesicles can be measured by light scattering method and optical microscopy in two conditions *i.e:* with agitation and without agitation. Hydration without agitation results in largest vesicle size. Surface morphology means roundness, smoothness and formation of aggregation; it can be studied by scanning electron microscopy and transmission electron microscopy.

Optical microscopy

In optical microscopy, small amounts of the formed niosomes are spread on a glass slide and examined for the vesicles structure and the presence of insoluble drug crystals using ordinary light microscope with varied magnification power 100x.

Scanning electron microscopy

Particle size of proniosomes is very important characteristic. The surface morphology (roundness, smoothness, and formation of aggregates) and the size distribution of proniosomes were studied by Scanning Electron Microscopy (SEM). For scanning electron microscopy, the niosomes are mounted on an aluminum stub using double sided adhesive carbon tape. Then the vesicles are sputter coated with gold palladium (Au/Pd) using a vaccum evaporator and examined using a Scanning electron microscopy equipped with a digital camera at 25kV accelerating voltage.

Transmission electron microscopy

The morphology of hydrated niosome dispersion prepared from proniosome was also determined using transmission electron microscopy (TEM). The noisome dispersion is applied to a carbon-coated 300 mesh copper grid and left to allow some of the niosomes to adhere to the carbon substrate. The remaining dispersion is removed by absorbing the drop with the corner of a piece of filter paper. Then drop of aqueous solution of uranyl acetate is applied. The remaining solution is removed by absorbing the liquid with the tip of a piece of filter paper and the sample is air dried and observed under transmission electron microscope.

Entrapment efficiency

Various methods can be used to evaluate the loading capacity of proniosomal systems such as dialysis method, gel filteration and centrifugation method. In dialysis method, amount of entrapped drug can be obtained by subtracting the amount of untrapped drug from total drug incorporated.

Entrapment efficiency (EE) = Amount of drug entrapped/total amount of drug × 100

In vitro release and permeation studies

In vitro release and skin permeation studies for proniosomes were determined by different techniques like franz diffusion cell, dialysis tubing and reverse dialysis. In case of dialysis, the prewashed dialysis tubing is used which can be hermatically sealed, the proniosomes are placed in it and then dialysed against a suitable dissolution medium at a room temperature. The samples are withdrawn from the medium at suitable interval, centrifuged and analysed spectrophotometrically (UV, HPLC).

Stability studies

Stability studies are carried out by storing the proniosomes at various temperature conditions like refrigeration, room temperature and elevated temperature according to ICH guidelines. Drug content and variation in the average vesicles diameter is periodically monitored. According to ICH guidelines the stability studies for dry proniosomes powder should be studied for accelerated stability at 75% relative humidity as per international climate zones and climate conditions[14].

Clinical Applications of Proniosomes[15, 16]

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

1. Anti-neoplastic Treatment: Most antineoplastic drugs cause severe side effects. Niosomes can alter the metabolism; prolong circulation and half life of the drug, thus decreasing the side effects of the drugs.

2. Leishmaniasis: Leishmaniasis is a disease in which a parasite of the genus Leishmania invades the cells of the liver and spleen. Use of pronoisome 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.

3. Uses in Studying Immune Response: Proniosomes are used in studying immune response due to their immunological selectivity, low toxicity and greater stability. Niosomes are being used to study the nature of the immune response provoked by antigens.

4. Proniosomes as Carriers for Haemoglobin: Niosomes can be used as carriers for haemoglobin within the blood. The niosomal vesicle is permeable to oxygen and hence can act as a carrier for hemoglobin in anemic patients.

5. Proniosomes used in Cardiac Disorders: Proniosomal carrier system for captopril for the treatment of hypertension that is capable of efficiently delivering entrapped drug over an extended period of time.The potential of proniosomes as a transdermal drug delivery system for captopril was

investigated by encapsulating the drug in various formulations of proniosomal gel composed of various ratios of sorbitan fatty acid esters, cholesterol, lecithin prepared by coacervation-phase separation method.

6. Antibacterial treapy: Amphotericin-b proliposomes could be stored for 9 months without significant changes in distribution of vesicle size and for 6 months without loss of pharmacological activity.Even though physical stability of the preparation can be increased, a vacuum or nitrogen atmosphere is still required during preparation and storage to prevent oxidation of phospholipid.

7. Cosmetics formulation: Large number of cosmetic preparations available in the market is utilizing niosomes and liposomes as a carrier for delivery of actives. Liposomes were prepared using unacceptable organic solvents, whose traces in the final preparation can cause harm to the skin. It is proved that proniosomes are as effective as noisome and liposomes, but their preparation, handling, storage and transportation make them superior over others. The therapeutic agents which can be utilized for incorporation into proniosomal carrier systems include, moisturizing, nutritional, anti wrinkle, anti-ageing, cleansing, sunscreen particles, etc.

CONCLUSION

Compared to liposome or niosomes, proniosomes are very promising as drug carriers. Compared to liposome and niosome suspension, proniosome represents a significant improvement by eliminating physical stability problems, such as aggregation or fusion of vesicles and leaking of entrapped drug's during long term storage. Proniosome are convenient to store, transport and for unit dosing since proniosome's have similar release characteristics as conventional niosomes, it may offer improved bioavailability of some drugs with poor solubility controlled release formulations or reduced adverse effects of some drugs.

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