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Proniosomes: A Superior Drug Delivery System

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ABSTRACT
Proniosomes are solid colloidal particles which may be hydrated immediately before use to yield aqueous niosomes dispersions similar to those produced by more cumbersome conventional methods. The proniosomes minimize the problems associated with niosomes in terms of its physical stability such as aggregation, fusion and leaking. They also offer an additional convenience in transportation, distribution, storage, and dosing. The proniosomes derived niosomes are better than conventional niosomes in terms of their morphology, particle size, particle size distribution, and drug release. A slurry method was commonly used to produce proniosomes using maltodextrin as carrier. The time required to produce proniosomes by this simple method is independent of the ratio of surfactant solution to carrier material and appears to be a scalable process. The encapsulation efficiency of proniosomes is depends upon the amount of maltodextrin used in the process. The present review describes the method of preparation, characterization, applications of proniosomes as a potential drug delivery system.

Keywords: Proniosomes, stability, drug release, permeability.

INTRODUCTION

Colloidal particulate carriers such as liposomes or niosomes have been widely employed in drug delivery systems. Recent day's proniosomes produced from niosomes offers distinctive advantages over them. These carriers can act as drug reservoirs and the rate of drug release can be controlled by modification of their composition. The lipid vesicles contain both hydrophilic drugs (by encapsulation) and hydrophobic drugs (in lipid domain). [1] Due to their capability to carry a variety of drugs, these lipid vesicles are extensively used in various drug delivery systems like drug targeting, controlled release and permeation enhancement of drugs. But there are certain draw backs to be addressed and can be avoided if they are prepared in dry form.

Proniosomes as drug carriers

Proniosomes are promising drug carriers, because they possess greater chemical stability and have many disadvantages associated with liposomes. Proniosomes are dry formulations of surfactant coated carrier vesicles, which can be rehydrated on requirement and resulting niosomes are very similar to conventional niosomes of uniform in size. [2] Being dry, free flowing product, proniosomes minimizes stability problems during storage and sterilization. They also exhibit the merits of ease of transfer, distribution, measuring and storage which makes proniosomes a pronouncing versatile delivery system.

Advantages of proniosomes over the niosomes [3]

1. Proniosomes avoids the problems of physical stability like aggregation, fusion and leaking of drugs.
2. It avoids hydrolysis of encapsulated drugs which limits the shelf life of the dispersion.
3. Ease on storage and handling.
4. Moreover, unacceptable solvents are avoided in proniosomal formulations. The systems can also be formulated into transdermal patches and doesn't require the dispersion of vesicles into polymeric matrix.
5. The storage makes proniosomes a versatile delivery system with potential and wide range of active compounds.

Types of proniosomes

Dry granular proniosomes

Sorbitol based proniosomes

They are the dry formulation containing sorbitol as a carrier and coated with non-ionic surfactant using water by simple agitation method.

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Maltodextrin based proniosomes

Maltodextrin based proniosomes were prepared by fast slurry method.

Liquid crystalline proniosomes

This type of proniosomes is acting as reservoirs for transdermal delivery of drug. The transdermal patch contains a backing layer along with plastic sheet. Gel is spread evenly on the sheet.

Surfactants

Selection of surfactant was done on the basis of their HLB value. As hydrophilic lipophilic balance (HLB) is a good indicator of vesicle forming ability of any surfactant, HLB number in between 4 and 8 was found to be compatible with vesicle formation. It is also reported that the hydrophilic surfactant owing to high aqueous solubility on hydration do not reach a state of concentrated systems in order to allow free hydrated units to exist aggregates and coalesced to form lamellar structure. The water soluble detergent polysorbate 20 forms niosomes in the presence of cholesterol. This is despite the fact that the HLB number of this compound is 16.7 and the degree of entrapment is affected by the HLB of a surfactant. Transition temperature of surfactants also affects the entrapment of drug in vesicles. Spans with highest phase transition temperature provide the highest entrapment for the drug and vice versa. Span 40 and Span 60 produces vesicles of larger size with higher entrapment of drug. The drug leaching from the vesicles is reduced due to high phase transition temperature and low permeability. Higher HLB value of Span 40 and Span 60 results reduction in surface free energy which allows forming vesicles of larger size hence large area exposed to the dissolution medium and skin. No significant difference is observed in the skin permeation profile of formulation containing Span 60 and Span 40 due to their higher phase transition temperature that is responsible for their lower permeability. The encapsulation efficiency of tween is relatively low as compared to span. The geometry of vesicle to be formed from surfactants is affected by its structure, which is related to critical packing parameters. On the basis of critical packing parameters of surfactants can predicate geometry of vesicle to be formed. Critical packing parameters can be defined using following equation.

$$CPP = \frac{v}{lc \times ao}$$

CPP ≤ 0.5 micelles form

CPP= 0.5 – 1 spherical vesicles form

CPP = 1 ≥ inverted vesicles form

V– Hydrophobic group volume lc = the critical hydrophobic group length, ao= the area of hydrophilic head group. Span 60 is the good surfactant because it has CPP value between 0.5 and1.

Stabilizers

Cholesterol is essential component of vesicles and its incorporation increases vesicle stability and permeability. Concentration of cholesterol plays an important role in entrapment of drug in vesicles. There are reports that entrapment efficiency increase with increasing cholesterol content and by the usage of Span 60 which has higher transition temperature. It is observed that very high cholesterol content had a lowering effect on drug entrapment to the vesicles. This could be due to the fact that cholesterol beyond a certain level starts disrupting the regular bi-layered structure leading to loss of drug entrapment. Lecithin provides stability but to a lesser extent as compared to cholesterol.

Carriers

Maltodextrin

The use of maltodextrin as carrier in proniosomes preparation permitted flexibility in the ratio of surfactant and other components which can be incorporated. Coating sorbitol results in solid cake like mass.

Table 1: Materials and their role in the preparation of proniosomes

S. No	Materials	Example	Role
1.	Surfactants	Span 20, 40, 60,80, 85, Tween 20, 40, 80	Formation of vesicles
2.	Stabilizers	Cholesterol, lecithin	To prevent leakage of drug formulation
3.	Carriers	Maltodextrin, sorbitol	Provides flexibility in surfactant and other component ratio.

METHODS OF PREPARATION OF PRONIOSOMES

Spraying method

Proniosomes were prepared by spraying the surfactant in an organic solvent into 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 load has been achieved. [4] The surfactant coating on the carrier comes out to be very thin and hydration of this coating allows multilamellar vesicles to form.

Slurry method

Proniosomes were produced by slurry method by using maltodextrin as a carrier. The time required to produce proniosomes by this is independent of the ratio of surfactant solution to carrier material. In slurry method, the entire volume of surfactant solution is added to maltodextrin powder in a rotary evaporator and vacuum is applied until the powder appears to be dry and free flowing. [5] Drug containing proniosomes-derived niosomes can be prepared in manner analogous to that used for the conventional niosomes, by adding drug to the surfactant mixture prior to spraying the solution onto the carrier (sorbitol, maltodextrin) or by addition of drug to the aqueous solution used to dissolve hydrate the proniosomes.

Coacervation phase separation method

In this method, accurately weighed amount of surfactant, carrier (lecithin), cholesterol and drug are taken in a clean and dry wide mouthed glass vial (5 ml) and solvent is be added to it followed by simple mixing. To prevent the loss of solvent, the open end of the glass vial can be covered with a lid and heated over water bath at 60-70ºC for 5 minutes until the surfactant dissolved completely. The mixture should be allowed to cool down at room temperature till the dispersion gets converted to a proniosomes.

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.

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.

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.

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. [6] 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.

4. Total lipid concentration

The percentage encapsulation efficiency of flurbiprofen was increased as the lipid concentration was increased from 25 to 200 mol/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 200 mol/ml, respectively. This leads to the fact that the fraction of lipid taking part in encapsulation decreases as the concentration of lipid increases.

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.

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.

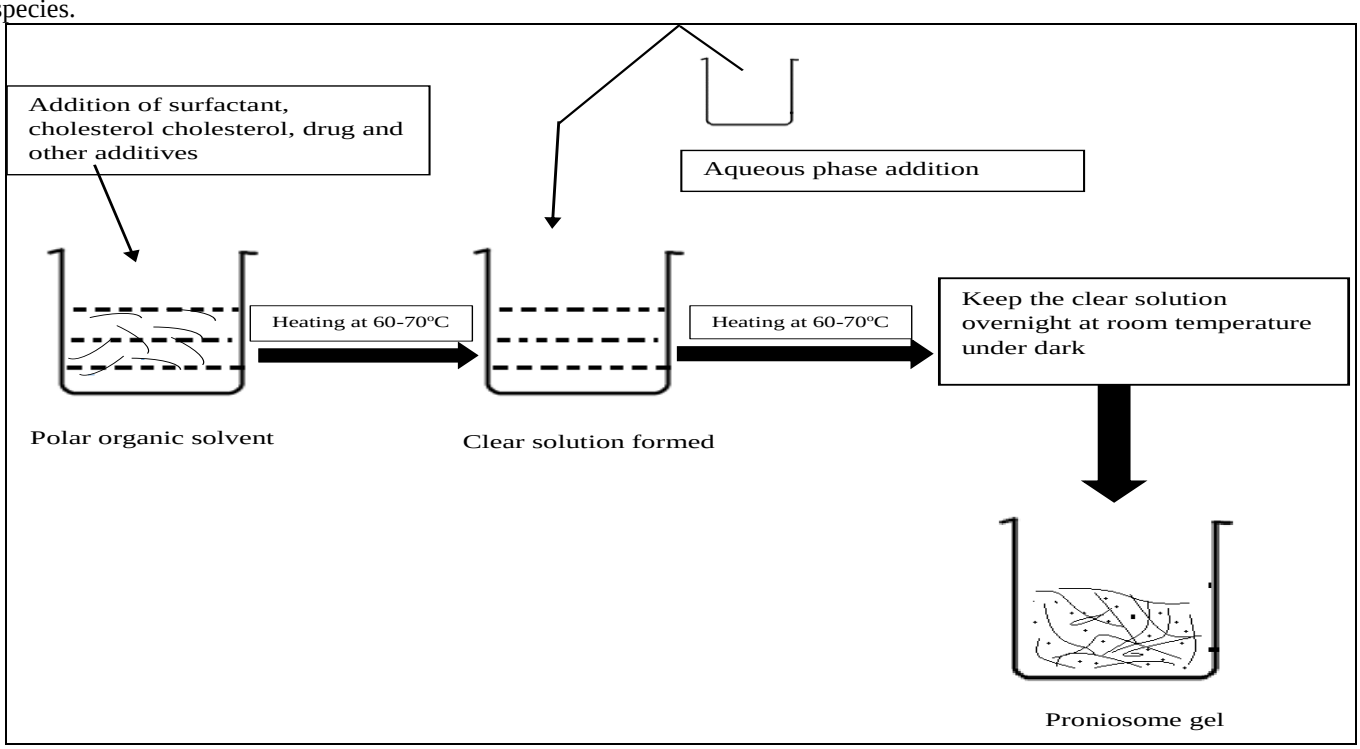

Fig. 1: Coacervation phase separation method

CHARACTERISATION OF PRONIOSOMES

Vesicle morphology

Vesicle morphology involves the measurement of size and shape of proniosomal vesicles. Size of proniosomal vesicles can be measured by dynamic light scattering method in two conditions: without agitation and with agitation. Hydration without agitation results in largest vesicle size. Scanning electron microscopy (SEM) can also be used for the measurement of vesicle size and shape. Determination of vesicle size is important for the topical application of vesicles. Size of captopril vesicles was found after agitation of dispersion as energy applied in agitation resulted in the breakage of the larger vesicles to small vesicles. The size of captopril vesicles was found 11.38-25.06 mm (without agitation) and 4.14-8.36 mm (with agitation). Hence, it can be concluded that increasing hydrophobicity of the surfactant monomer leads to a smaller size vesicles, since surface energy decreases with increasing the hydrophobicity. [7] Haloperidol proniosomes with lower HLB values seemed to be mostly spherical and discrete with sharp boundaries having smooth and rigid surfaces. The main difference between deformable and rigid vesicles was found due to fluidity of the lipid bilayer of the deformable vesicles.

Shape and surface morphology

Surface morphology means roundness, smoothness and formation of aggregation. It was studied by scanning electron microscopy (SEM), optical microscopy, transmission electron microscopy (TEM). [8]

Encapsulation efficiency

The encapsulation efficiency of proniosomes is determined after separation of the unentrapped drug.

(1) Separation of unentrapped drug is done by the following techniques

a. Dialysis

The aqueous niosomal dispersion is dialyzed tubing against suitable dissolution medium at room temperature then samples are withdrawn from the medium at suitable time interval centrifuged and analyzed 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 analyzed with analytical techniques.

c. Centrifugation

The niosomal suspension is centrifuged and the surfactant is separated. The pellet is washed and then resuspended to obtain a niosomal suspension free from unentrapped drug.

(2) **Determination of entrapment efficiency of proniosomes**

The vesicles obtained after removal of unentrapped drug by dialysis is then resuspended in 30% v/v of PEG 200 and 1 ml of 0.1% v/v triton x-100 solution was added to solubilize vesicles the resulted clear solution is then filtered and analyzed for drug content. The percentage of drug entrapped is calculated by using the following formula:

Percent Entrapment = Amount of drug entrapped/total amount of drug × 100

***In-vitro* release study by dialysis tubing method**

In-vitro drug release from proniosomes can be estimated through dialysis method. The proniosomes were placed in prewashed dialysis tubing, which can be hermetically sealed. The dialysis sac is then dialyzed by using a suitable dissolution medium at room temperature; the samples are withdrawn from the medium at suitable intervals, centrifuged and analyzed for drug content using suitable method analytical methods like UV spectroscopy, HPLC etc.,

By reverse dialysis

In this technique, a number of small dialysis which contains 1 ml of dissolution medium are placed in proniosomes. The proniosomes are then displaced into the dissolution medium. The direct dilution of the proniosomes is possible with this method; however the rapid release cannot be quantified using this method.

Franz diffusion cell

The *in-vitro* studies can also be performed by using Franz diffusion cell. Proniosomes are placed in the donor chamber of a Franz diffusion cell fitted with a cellophane membrane. The proniosomes is then dialyzed against suitable dissolution medium at room temperature; the samples are withdrawn from the medium at suitable intervals, and analyzed for drug content using suitable method viz UV spectroscopy, HPLC, etc. with suitable sink conditions should be maintained.

***In-vitro* permeation study**

The rate of permeation of drugs from proniosomal formulations can be determined by using Franz diffusion cell, Keshary chien diffusion cell and drug content can be determined by suitable analytical method. The interaction between skin and proniosomes plays an important contribution to the improvement of transdermal drug delivery. One of the possible mechanisms for niosomal permeability enhancement is structural modification of stratum corneum. Both phospholipids and non-ionic surfactants used in proniosomes act as penetration enhancers, leading to increase the permeation of the many drugs. The permeation of haloperidol from proniosomal formulations was determined by flow through diffusion cell. [9] Direct contact and adherence of vesicles with skin surface is important for the drug to penetrate and partition between the stratum corneum and formulation.

Zeta Potential Analysis

Zeta potential analysis is done for determining the colloidal properties of the prepared formulations. The suitably diluted proniosomes derived noisome dispersion was determined using zeta potential analyzer based on electrophoretic light scattering and laser doppler velocimetery method at a temperature of 25°C.

Stability Studies on Proniosomes

Physical stability study was carried out to investigate the degradation of drug from proniosome during storage. Stability studies are carried out by storing the prepared proniosomes at various temperature conditions like refrigeration on (2-8°C), room temperature (25±0.5°C) and at elevated temperature (45±0.5°C) from a period of one month to 3 months. Drug content and variation in the average vesicle diameter are 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.

APPLICATION OF PRONIOSOMES

Proniosomes are used as carriers in transdermal delivery of captopril in the treatment of hypertension. Proniosomal system causes extended release of drug in the body. The drug is encapsulated with sorbitol esters, lecithin and cholesterol.

Targeting of bioactive agents

One of the most useful aspects of proniosomes is their ability to target drugs to particular area. Proniosomes can be used to target drugs to the reticulo-endothelial system. The reticulo-endothelium system (RES) preferentially takes up proniosomes vesicles. [10] The uptake of proniosomes is controlled by circulating serum factors called opsonins. Such localization of drugs is utilized to treat tumors in animals known to metastasize to the liver and spleen. This localization of the drugs can also be used for treating parasitic infections of the liver. Proniosomes can also be utilized for targeting drugs to organs other than the RES. A carrier system (such as antibodies) can be attached to proniosomes (as immunoglobin bind readily to the lipid surface of the noisome) to target them to specific organ.

Anti-neoplatic treatment [11]

Most of the antineoplastic drugs cause severe side effects. Proniosomes can alter the metabolism; prolong circulation and half life of the drug, thus decreasing the side effects of the drugs. Proniosomal entrapment of doxorubicin and methotrexate showed beneficial effects over the unentrapped drugs, such as decreased rate of proliferation of the tumor and higher plasma levels accompanied by slower elimination. [12-13]

Treatment of leishmaniasis [14]

Leishmanasis is a disease in which a parasite of the genus *leishmania* invades the cells of the liver and spleen. Commonly prescribed drugs for the treatment are derivatives of antimony (antimonials), which are in higher

concentrations causes cardiac, liver and kidney damage. Use of proniosomes showed that it was possible to administer higher levels of the drug without triggering the side effects, and thus allowed greater efficacy in treatment.

Delivery of peptide drugs [15]

Oral peptide drug delivery has long been faced with a challenge of bypassing the enzymes which would breakdown the peptide. Use of proniosomes aimed to successfully protect the peptides from gastrointestinal peptide breakdown. In a study, oral delivery of a vasopressin derivative entrapped in proniosomes showed highest entrapment of the drug and significant increase in the stability of the incorporated peptide.

Uses in studying immune response

Proniosomes are used in studying immune response due to their immunological selectivity, low toxicity and greater stability. Proniosomes are being used to study the nature of the immune response provoked by antigens.

Transdermal drug delivery systems [16]

One of the most useful aspects of proniosomes is that they greatly enhance the uptake of drugs through the skin. Transdermal drug delivery utilizing proniosomal technology is widely used in cosmetics; In fact, it was one of the first uses of the niosomes. Topical use of proniosome entrapped antibiotics to treat acne is done. The penetration of the drugs through the skin is greatly increased as compared to un-entrapped drug. Recently, transdermal vaccines utilizing proniosomal technology is also being researched. The proniosomes (along with liposomes and transferomes) can be utilized for topical immunization using tetanus toxoid. However, the current technology in proniosomes allows only a weak immune response, and thus more research to be done in this field.

Sustained release drug delivery [17]

Sustained release action of proniosomes can be applied to drugs with low therapeutic index and low water solubility since those could be maintained in the circulation via proniosomal encapsulation.

Localized drug action [18]

Drug delivery through proniosomes 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. Antimonials encapsulated within proniosomes 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 proniosomal drug delivery technology is still at an infancy stage, but this type of drug delivery system has promise in cancer chemotherapy and anti-leishmanial therapy.

Proniosomes derived niosomes represent a promising drug delivery module. These systems have been found to be more stable during sterilization and storage than niosomes. Proniosomes are thought to be better candidates of drug delivery as compared to liposomes and niosomes due to various factors like cost, stability etc. Proniosomes have been tested to encapsulate lipophilic as well as hydrophilic drug molecules. The use of proniosomal carrier results in delivery of high concentration of active agent(s), regulated by composition and their physical characteristics. Various types of drug deliveries can be possible using proniosomes based niosomes like targeting, ophthalmic, topical, parenteral, peroral vaccine etc. More researches are carried out in this field to know the exact potential in this novel drug delivery system.

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