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PRONIOSOMES - A NOVEL DRUG DELIVERY CARRIER: A REVIEW

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ABSTRACT

Drug targeting is described as the capacity of a drug molecule to selectively accumulate in the target organ or tissue so that the concentration of the drug at the site of the disease is large whereas its concentration in non-target organs and tissues is preferably lower than a certain minimum level to avoid any toxic effect. Drug targeting can thus overcome the non-specific toxic effect of standard drug delivery. Various drug targeting pharmaceutical carriers are polymer micelles, liposomes, proliposomes, niosomes, proniosomes. A method for generating a dry product that is hydrated instantly before use has been outlined to generate an aqueous niosomal dispersion comparable to those generated by more cumbersome standard techniques. Proniosomes are a compact non-ionic surfactant semi-solid liquid crystalline product readily created to dissolve the surfactant in a minimum quantity of solvent and a minimum quantity of aqueous stage. This paper provides an understanding of the kinds of proniosomes, composition, vesicle formation mechanism, advantages, applications, formulations on the market and focuses primarily on preparation techniques.

INTRODUCTION

Recently, no single drug delivery system meets all.Together with surfactant, the carrier results in the creation of proniosomes that convert to niosomes after hydration.They are transformed by following methods

- Solvent hydration.
- Skin hydration

Solvent hydration: Buffers and aqueous solutions such as saline solution, purified water are used by sonication and agitation to convert proniosomes to niosomes. ***Skin hydration***: Water in the skin is used to hydrate the proniosomal formulation and to convert it into niosomes.

Composition ofproniosomes:

Non-ionic surfactants: Non-ionic surfactants are surface active agents of an Amphiphilic nature [7]. They are frequently used as wetting agents, solubilizers, emulsifiers and enhancers of permeability. After considering the following variables, they are chosen:

HLB Value: The HLB value of 4-8 is great for vesicle formation. The HLB value of 8-6 provides the greatest trapping effectiveness for vesicles. Up to 14-17 surfactant is not appropriate for vesicle formation.Alkyl ethers, alkyl esters, alkyl amides and fatty acid esters are the most frequently used surfactants.

CPP: It is a critical packing parameter. It is characterized as the connection between the surfactant structure including the size of the hydrophilic head group and the length of the hydrophobic alkyl chain in the vesicle forming capability.They affect the drug's trap

effectiveness. The effectiveness of surfactants with stearyl(c_{18}) chains is greater than those with lauryl(c_{12}) chains.

Phase-transition temperature: As transition temperature rises, the effectiveness of trapping increases and the permeability of surfactants decreases.Spans with the lowest phase-transition temperature provide the drug's maximum trapping.

Eg: Tween 20, Tween 40, Tween 60, Tween 80, Span 20, Span 40etc

Carrier materials:

They are the materials of coating themselves. Carriers used to promote flexibility in the ratio of surfactants to surfactants and other components embedded in proniosomes. They also increase the surface area and efficient drug loading[8].

Eg: sucrose stearate, spray dried lactose, sorbitol, lactose monohydrate, maltodextrin, glucose monohydrate.

Membrane stabilizer: Cholesterol and lecithin are primarily used to stabilize the membrane. Naturally, cholesterol is a steroid used as a membrane additive. It avoids aggregation by molecular inclusion [9]. Phosphotidyl choline is a significant element of lecithin. It is two kinds – egg lecithin and soy lecithin. It functions as a stabilizing and penetration enhancer.

Solvent and aqueous phase [9]: Alcohol is widely used as a solvent and also affects vesicle size and drug permeation rate. Vesicle size relies on distinct kinds of used alcohols. Ethanol > Propanol >Butanol> Isopropanol

Ethanol has higher water solubility, which in comparison with isopropanol vesicle size generates the largest vesicle proniosomes. In the preparation ofproniosomes, phosphate buffer pH-7.4,0.1 %glycerol, hot water is used as aqueous phase.

Drug: Drug is the active pharmaceutical ingredient that generates therapeutic response. Drug trapping improves the vesicle size primarily by interacting with the surfactant head groups, which increases the surfactant bilayers load and mutual repulsion [8,9].

Types of proniosomes [10]: Proniosomes are categorized into the following kinds which are shown in figure 3.They are

• Dry granular type proniosomes.
• Liquid crystalline proniosomes.

Dry granular type proniosomes: These types of proniosomes have a water-soluble carrier layer such as sorbitol, maltodextrin with surfactant.

- Sorbitol-based proniosomes: This includes sorbitol as a carrier that is covered with non-ionic surfactant. They are transformed into niosomes by adding warm water within minutes. They are prepared by spray-coating.
- Proniosomes based on maltodextrin: Maltodextrin is frequently a polysaccharide that is totally water-soluble. They are prepared using a slurry method. This form of proniosomes has lately been created.

Liquid crystalline proniosomes: They act as a reservoir for the transdermal delivery of drugs. Surfactants comprising liphophilic chains are disordered to form liquid state known as lyotropic liquid crystalline state. This state is accomplished when surfactant molecules come into contact with water in three ways: Use of solvent and temperature. Increasing temperature at kraft point (T_c) Addition of solvent which dissolves lipids.

Methods for preparation of proniosomes:

Proniosomes are prepared by the following techniques which are depicted in figure 4.

Coacervation-phase seperation: This technique includes the production of proniosomal gel. Drug together with surfactant, cholesterol, phosphotidyl choline and alcohol are added to the wide-mouthed glass vial. The mixture has been heated and blended with glass rod. Glass vial has been covered with the lid to avoid solvent loss. The mixture was heated over the water bath at 60-70o for 5 minutes until all the surfactants were dissolved and allowed to cool down until the dispersion became proniosomal gel [11].

Advantages of coacervation-phase seperation method:

- Method is easy and not time consumable.
- Little quantities only can be prepared in lab scale.
- Proniosomal gel is prepared by this method.

Slurry method: This method involves the production of proniosome powder. Drug together with the carrier (maltodextrin) is mixed in a round bottom flask with a non-ionic surfactant solution. It results in the creation of slurry. Organic cholesterol solution has also been added. The round bottom flask comprising the combination is linked to the rotary evaporator. Organic solution has been evaporated at 60-70rpm, temperature of 43-47◦c and at a pressure of 600mm Hg.This process was continued until powder appears to be dry and free flowing[12].

Advantages of slurry method:

Active ingredients and surfactants are protected from the oxidation and hydrolysis due to uniform coating on carrier. Rehydration process becomes more efficient because of the higher surface area results in thinner surface coating. The carrier material (e.g., maltodextrin is a polysaccharide) is easily soluble in such a way that the carrier particles can be easily coated by simply adding surfactant to dry carrier particles in organic solvents

Spray coating method: Required amount of carrier was taken in round bottom flask which is connected to rotary evaporator. A mixture of surfactant, cholesterol along with the drug was prepared and poured into round bottom flask. The formed mixture was slowly sprayed onto the carrier. Flask was rotated in water bath under vaccum at 65-70° c for 15-20 minutes. This process was repeated until all the surfactant solution has been applied. Organic solvent was evaporated until the powder becomes dry[11,12].

Advantages of spray coating method: It is simple method. It is a straightforward technique appropriate for hydrophobic drugs without instability or susceptibility to hydrolysis of the active pharmaceutical ingredient.

Characterization of proniosomes: Characterization of proniosomes involves the studying of the following parameters. They are

Vesicle size determination: The vesicles were diluted with the same medium which was used for preparation for about 100 times. Measurement of size was done by particle size analyzer. The equipment consists of He-Ne laser beam of 632.8nm focused with minimum power of 5mW using Fourier lens (R-5) to point at the centre of multi element detector and small volume holding cell(Su cell).Samples were stirred using stirrer before determining the vesicle size[13].

Shape and surface morphology:

Surface morphology of vesicles was determined by scanning electron microscopy (SEM),optical microscopy and transmission electron microscopy(TEM).

Scanning electron microscopy[SEM]:

Proniosomes are sprinkled onto the double-sided tape to be attached to the aluminum stubs that are further placed in SEM's vaccum room and rendered electrically conductive by coating with a thin layer of gold. Photographs were gathered when a gaseous secondary electron detector is used for morphological determination[14].

Optical microscopy: Proniosomes were mounted under a microcope after rehydration on the glass slide with a magnification of 1200x after dilution. Photomicrographs were acquired using SLR camera[14].

Transmission electron microscopy: Niosome dispersion after 10-fold dilution with deionized water is applied to carbon-coated 300 mesh copper grid and is permitted to stand for some moment to allow niosomes to stick to the carbon substratum. Grid has been rinsed and a drop of 2% aqueous uranyl acetate solution is applied.Sample is dried and observed with 80kv.

Angle of repose [10,14]: The angle of repose of the dried proniosomes is measured using the following methods:

a. Cylinder method: Proniosomes were poured over a cylinder above 10 cm from the ground in order to create a cone. The height of the cone and the base diameter were drawn and the angle of rest was calculated.

b. Funnel method: This method is also the same as the cylinder method, but the funnel was used in this technique instead of the cylinder.

$$\text{Angle of repose}(\theta)=\tan^{-1}(h/r)$$

Drug content: Formulation was drawn and mixed with the appropriate amount of propanol by shaking. The resulting mixture was diluted with phosphate buffer(7.4) so that stock solution was obtained. Aliquots were taken and the absorption was spectroscopically measured at 218 nm and the drug content was measured from the calibration curve [10,14].

Encapsulation efficiency [15]: Encapsulation efficiency of proniosomes is determined after separation of the unentrapped drug.

1. Separation of unentrapped drug: It is done by following methods

a. Dialysis: Aqueous niosomal dispersion is dialyzed at room temperature against the appropriate medium. Samples are removed at periodic intervals, centrifuged and evaluated using UV spectroscopy for drug content.

b. Gelfiltration: Free medication is removed from dispersion by gel filtration through the Sephadex G50 column and separated and evaluated at the appropriate mobile phase.

c.Centrifugation:

Surfactant is separated from dispersion by centrifugation. Pellet is cleaned and then resuspended to achieve a drug-free niosomal suspension.

2. Determination of entrapment efficiency of proniosomes: Vesicles acquired after removal of untrapped medication by dialysis and then 30 % v / v of PEG 200 and 1 ml of 0.1 % v / v triton X-100 solution were added to solubilize vesicles.

Percent Entrapment=amount of drug entrapped /total*100

Osmotic shock: Osmotic studies can determine the change in vesicle size. Hypotonic, isotonic, hypertonic solutions of niosomal formulations are incubated for 3 hours. In optical microscopy, changes in the size of vesicles in the formulations are then viewed or observed[3,15].

In-vitro methods[4,10,15]: ***a. Dialysis:*** Dispersion or suspension is dialysed using dialysis tubing dissolution medium at room temperature. Samples are withdrawn and centrifuged and checked under UV spectroscopy, HPLC etc.,

b. Reverse dialysis: A number of small dialysis tubes containing 1ml of dissolution medium are placed. Proniosomes are then displaced into the dissolution medium. Direct dilution of proniosomes is possible. Rapid release of drug cannot be quantified.

c. Franz Diffusion Cell: Proniosomes were placed in the donor chamber which were separated by the receptor chamber with cellophane membrane. Samples are withdrawn at regular time intervals and analysed.

Drug release kinetics and data analysis[15,16]:

Results of *In-vitro* drug release study of proniosomes are fitted with various kinetic equations like

A .Zero-Order: In this a graph of cummulative percentage release Vs time was plotted.

$$C = k_o t$$

Where, k_o-zero-order constant

t- Time

b .Higuchis model: In this graph of cumulative % drug release Vs square root of time was plotted.

$$Q = K_H \sqrt{t^{1/2}}$$

Where, K_H-Higuchis constant. t-time

c. korse-mayerspeppas model: In this graph of lo g cumulative % drug release vs. log time was plotted.

$Mt / M\infty = btn$

Where, Mt - amount of drug release at time t,

M∞ - overall amount of the drug,

b -constant

n –release exponent indicative of the drug release mechanism.

If exponent n = 0.5 or near, then the drug release mechanism is Fickian diffusion,

If n have value near 1.0 then it is non-Fickian diffusion

Zeta potential analysis: Zeta potential analysis is used for determining the colloidal properties of the formulations. The diluted proniosomes were determined by Zeta potential analyzer based on electrophoretic light scattering and laser Doppler velocimetermethod.Charge on vesicles and their potential values with standard deviation are obtained directly from the measurement [16]

Stability studies: Proniosomes are stored for 1-3 months under different temperature circumstances such as refrigeration (2-8°c), room temperature (25±0.5°c) and high temperature (45±0.5°c). The drug content and variation of the average vesicle diameter shall be monitored. Accelerated stability experiments

shall also be performed at 75 percent relative humidity [17].

Applications of proniosomes: Proniosomes has wide variety application. Some are listed in table1.

Anti-neoplastic treatment: Severe side effects are caused by most antineoplastic drugs. Niosomes can change the metabolism; prolong the drug's circulation and half-life, thereby reducing the drug's side effects. Doxorubicin and Methotrexate niosomal trapping (in two distinct research) showed positive impacts on untrapped drugs, such as reduced tumor proliferation rate and greater plasma concentrations followed by slower elimination[3,8].

Drug targeting: One of the most helpful elements of proniosomes is the capacity to target drugs. Proniosomes can be used in the reticule-endothelial system to target drugs. The preferential reticulo-endothelial system (RES) requires vesicles from the proniosomes. Proniosomal absorption is regulated by circulating serum factors known as poisonings(opsonins).These poisonings mark the proniosomes clearance. Such drug localization is used in animals known to metastasize to the liver and spleen to treat tumors. This drug localization can also be used to treat parasitic liver infections. Proniosomes may also be used to target organs other than the RES with drugs. In order to target particular organs, a carrier system (such as antibodies) can be connected to proniosomes (as immunoglobulin binds easily to the lipid surface of the niosome)[5,8].

Proniosomes as haemoglobin carriers: Proniosomes can be used as blood haemoglobin carriers. The proniosomal vesicle is oxygen-permeable and can therefore act in anaemic patients as a carrier for haemoglobin[10].

Leishmaniasis: Leishmaniasis is a disease in which the liver and spleen cells are invaded by a Leishmania genus parasite. Commonly prescribed drugs for therapy are antimony derivatives (antimonials), which may cause heart, liver, and kidney damage at greater levels. The use of niosomes in the trials performed showed that higher concentrations of the medication could be administered without causing the side impacts, thus enabling greater therapy effectiveness [3,10].

Used in studying immune response: Due to their immunological selectivity, low toxicity and higher stability, niosomes are used in the study of immune response. Niosomes are used to study the immune response that are caused by antigens.[15].

Oral delivery of peptides: The delivery of oral peptide drugs has long experienced a challenge to bypass the enzymes that would break the peptide. proniosomes are used to effectively safeguard peptides against gastrointestinal peptide breakdown. Oral delivery of a vasopressin proniosomes showed that entrapment of the drug significantly increased the stability of the peptide[3,5,8].

Transdermal drug delivery: Transdermal drug delivery is commonly used in cosmetics using proniosomal technology. For the treatment of acne, topical use of niosome trapped antibiotics was performed. The penetration of drugs through the skin is significantly improved compared to drugs that have not been trapped Transdermal vaccines using niosomal technology are also being investigated recently. Using tetanus toxoid, niosomes (with liposomes and transferosomes) may be used for topical immunization. The present niosome technology, however, enables only a weak immune response, and therefore more study is needed in this area[15].

NSAID: Ketorolac, a powerful anti-inflammatory non-steroidal drug, is developed using spans, tweens, lecithin and cholesterol with ethanol as a solvent as a proniosomegel[16,17].

Hypertension: Proniosomes are manufactured by using various non-ionic surfactants such as span 20,span40,span60,span80,tween 20,tween 40 and tween 80 for transdermal delivery of losartan potassium where asproniosomal formulation are more effective in hypertension control[17].

Skin disorders: Chlorpheniramine maleate (CPM) which was developed as proniosomal gel for transdermal drug delivery which was formulated with span40 and has high penetration property.[17].

Hormonal insufficiencies: A proniosome-based levonorgestrel (LN) transdermal drug

delivery system was created and extensively described both in vitro and in vivo. The proniosomal structure was hybrid liquid crystalline compact proniosomes that could be converted to niosomes by hydration.. The system was assessed in vitro for drug loading, hydration rate (spontaneity), vesicle size, polydispersity, effectiveness of trapping and drug diffusion across the skin of rats[16,17].

Sustained release action: Proniosomes also sustained release action of drugs which are having low therapeutic index and low water solubility since they could be maintained in the circulation via niosomal encapsulation.

Eg-Methotrexate proniosomes acts as depot in which drug has been taken up by the liver cells which shows sustained release [18].

Antibacterial therapy: Amphotericin-b proliposomes without important modifications are stored for 9 months in vesicle size distribution and for 6 months without the loss of pharmacological activity[19].

Used in cardiac disorders: Proniosomes entrapping captopril are used for hypertension treatment which are capable of efficiently providing drug over an extended period of time. Different proniosomal formulations were prepared by using sorbitan fatty acid esters, cholesterol and lecithin by coacervation-phase separation method which describes the potential of proniosomes as transdermal drug delivery[19].

Localized drug Action:

Localized drug action can be achieved by proniosomes due to their size and also low penetrability through the epithelium and connective tissue which usually keeps the drug localized at the administration site. Localized drug action reduces systemic toxic effects and also there is an enhancement of efficacy of the potency of the drug.

Eg- proniosomes encapsulating antimonials are taken up by mononuclear cells which results in localized drug action [20].

CONCLUSION:

Proniosomes are promising forward - looking drug carrier because of their physical, chemical stability and possibly scalable business viability[5].Proniosomes derived niosomes are better alternatives to the liposomal vesicular system. It is also possible to incorporate amphiphilic drugs into the proniosomal delivery system[18].Proniosomes have drawn more attention for drug delivery through transdermal route owing to benefits like non-toxicity,surfactant penetration improving impact and efficient drug release alteration. Secure proniosomal powder makes them appropriate for the preparation of unit dosage forms like tablets,beads and capsules[10].Because of all the benefits, proniosomes as drug carriers are extensively researched. There is plenty of scope to investigate new carrier material for preparation of proniosomes and their potential remains to be investigated to full extent.

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