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A REVIEW ON PRONIOSOMES - CONTROLLED DRUG DELIVERY SYSTEM

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Abstract:

Nanotechnology is a promising technology in the development of controlled drug delivery system including liposomes, niosomes, implants etc. Skin has a very tough diffusion barrier inhibiting penetration of drug moiety which is rate limiting barrier for penetration of drugs. There are several approaches that deal with penetration enhancement across the skin. Vesicular and provesicular systems are promising amongst them. Vesicular systems including (niosomes, ethosomes, transfersomes and liposomes) are promising systems to cross this permeation barrier. But their major drawback is their unstability, which can be overcome by using provesicular approaches like proniosomes, protransfersomes and proliposomes. Proniosoms are dry product which could be hydrated immediately before use to avoid many of the problems associated with aquous neosome dispersion and problems of physical stabilities would be minimized these proniosome are as good as or even better than conventional niosomes.

Keywords: *Proniosomes, slurry method, coacervation phase separation method, spray coated method.*

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INTRODUCTION:

Controlled release dosage forms are widely used in now a days. It has a prolonged action formulations which gives continues release of their active ingredients at a predetermined rate and for a predetermined time. Vesicular drug delivery is one of the approaches which encapsulate the drug e.g.: Liposomes, niosomes, and provesicles like proliposomes and proniosomes. Vesicular system like liposomes or niosomes has specific advantages while avoiding demerits associated with conventional dosage forms because the particulate carriers can act as drug reservoirs, but these particulate carriers has disadvantages rather than advantages.

To overcome these disadvantages vesicular system of proniosomes are used. Proniosomes are dry product which could be hydrated immediately before use to avoid many of the problems associated with aqueous niosome dispersion and problems of physical stabilities would be minimized. These dry formulations of surfactant coated carrier can be measured out as needed and rehydrated by brief agitation in hot water. These are water soluble carrier particles coated with surfactant and can be hydrated to form niosomal dispersion immediately before use on brief agitation with hot aqueous medium. These proniosomes has additional convenience of the transportation, distribution, storage and designing would be dry niosomes a promising industrial product. The additional merits with proniosomes are low toxicity owing to non-ionic nature, no requirement of special precautions and conditions for formulation and preparations. In addition, it is the simple method for the routine and large scale production of proniosomes without the use of undesirable solvents Proniosomes are dry, free flowing granular product which upon hydration gives multilamellar niosomal dispersion suitable for administration by oral or other routes.

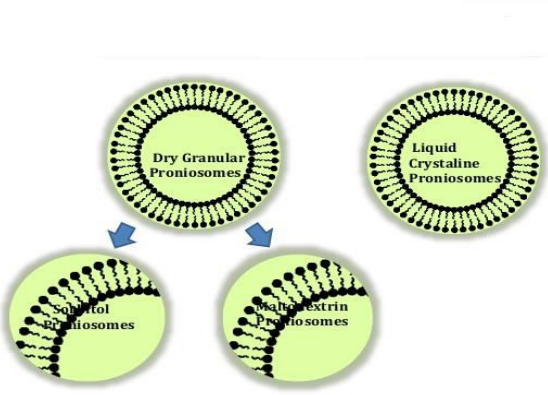

Fig 1: Structure of proniosomes

Structure

Proniosomes are microscopic lamellar structures. They combine a non-ionic surfactant of the alkyl or dialkyl polyglycerol ether and cholesterol followed by hydration in aqueous media. The surfactant molecule direct themselves such that the hydrophilic ends of the non-ionic surfactant orient outward, while the hydrophobic ends are in the opposite direction to form the bilayer. Like liposomes proniosomes are also made up of a bilayer. In proniosomes the bilayer is made of non-ionic surface active agent the basis of method of preparation proniosomes are unilamellar or multi-lamellar. In these systems both type of drugs, hydrophilic and lipophillic drugs can be incorporated.

Types of proniosomes

According to the type of carrier and method of preparation of proniosomes they are of two types.

Dry granular proniosomes

- Sorbitol based proniosomes
- 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.[1]. Maltodextrin based proniosomes are prepared by fast slurry method.

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.[2]

ADVANTAGES

- Improvement in bioavailability and permeation of the drug,
- Ease of manufacture and scale up, reduction in drug toxicity because of their non-ionic nature of the surfactant,
- More physical and chemical stability as compared to niosomes,
- Used for targeted drug delivery of drugs and also used for sustained as well as controlled drug delivery system.

Preparation of Proniosomes

Proniosomes are prepared by three methods

- Slurry method
- Coacervation phase separation method
- Spray coated method

Slurry Method

Proniosomes can be prepared from a stock solution of surfactants and cholesterol in suitable solvent. The required volume of surfactant and cholesterol stock

solution per gram of carrier and drug should be dissolved in the solvent in round bottom flask containing the carrier (maltodextrin or lecithin). Additional chloroform can be added to form the slurry in case of lower surfactant loading. The flask has to be attached to a rotary flash evaporator to evaporate solvent at 50-60rpm at a temperature of 45±20^{o}C and a reduced pressure of 600mm of Hg until the mass in the flask had become a dry, free flowing product. Finally, the formulation should be stored in tightly closed container under refrigeration in light.[3]

Coacervation phase separation method

Accurately weighed or required amount of surfactant, carrier (lecithin), cholesterol and drug can be taken in a clean and dry wide mouthed glass vial (5ml) and solvent should be added to it. All these ingredients have to be heated and after heating all the ingredients should be mixed with glass rod. To prevent the loss of solvent, the open end of the glass vial can be covered with a lid. It has to be warmed over water bath at 60- 70^{O}C 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 proniosome.[4]

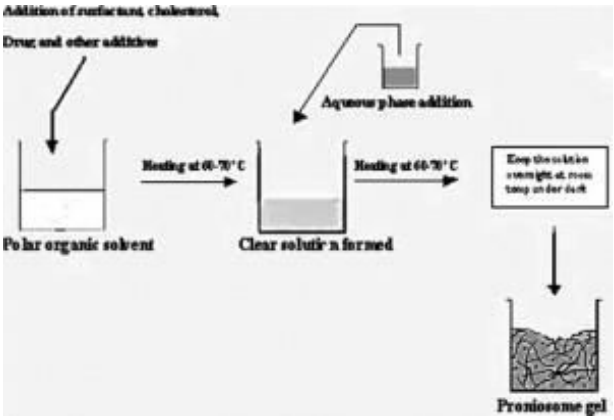

Fig 2: Coacervation phase separation method

Spray coated method

A 100ml round bottom flask containing desired amount of carrier can be attached to rotary flash evaporator. A mixture of surfactants and cholesterol should be prepared and introduced into round bottom flash on rotary evaporator by sequential spraying of aliquots onto carrier's surface. The evaporator has to be evacuated and rotating flask can be rotated in water bath under vacuum at 65-70^{o}C for 15-20min. This process has to be repeated until all of the surfactant solution had been applied. The evaporation should be continued until the powder becomes completely dry. [5]

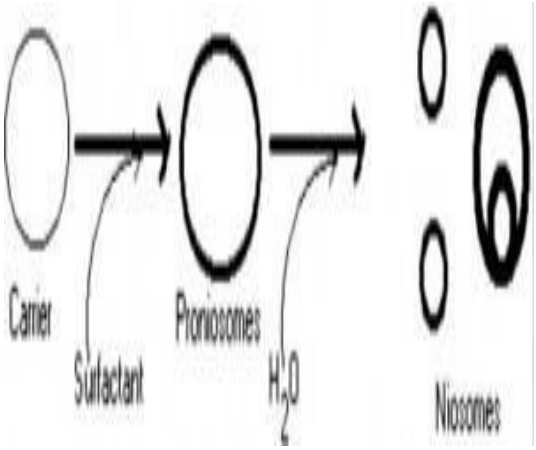

Fig 3: Spray coated method

Characterization of proniosomes

Evaluation studies are further carried out for the prepared proniosomes in order to find out the following.

- Measurement of angle of repose
- Scanning electron microscopy (SEM)
- Optical microscopy
- Measurement of vesicle size
- Drug content
- Entrapment efficiency
- In-vivo release studies
- Stability studies

Measurement of angle of repose

The angle of repose of dried proniosomes was measured by 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 10cm above the level of surface. The powder flew down from the funnel to form a cone on the surface and then angle of repose was further calculated by measuring the height of the cone and the diameter of its base.[6]

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 10cm above the level of surface. The powder flew 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. [7]

SEM

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 scanning electron microscope. The morphological characterization of the samples was observed using a gaseous secondary electron detector. [8]

Optical microscopy

The niosomes were mounted on glass slides and viewed under a microscope. The microscope has a magnification of 1200X 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.[9]

Measurement of vesicle size

The vesicle dispersions were diluted about 100 times in the same medium, which was used for their preparation. Vesicle size was measured on a particle size analyzer. The apparatus consist of a He-Ne laser beam of 632.8nm focused with a minimum power of 5mW using a Fourier lens (R-5) to a point at the center of multi-element detector and a small volume sample holding cell. The samples were stirred with a stirrer before determining the vesicle size. [10]

Drug content

Proniosomes equivalent to 100mg were taken in a standard volumetric flask. They lyses with 50ml methanol by shaking for 15min. The solution was diluted to 100ml with methanol. Then 10ml of this solution was diluted to 100ml with saline phosphate buffer at certain pH. Aliquots were withdrawn and absorbance was measured at a certain wavelength and drug content was further calculated from the calibration curve. [11]

Entrapment efficiency

Separation of unentrapped drug from the niosomal suspension was carried out by exhaustive dialysis method and centrifugation method. Then niosomal suspension was taken into a dialysis tube to which 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 unentrapped drug were separated into the medium through 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. [12]

In vivo release studies

The release of the drug from the proniosomal formulations was determined using different techniques such as Franz diffusion cell, Keshary-Chien diffusion cell, cellophane dialyzing membrane, United States Pharmacopeia (USP) dissolution apparatus Type-1, spectrapore molecular porous membrane tubing. Drug release from proniosomes derived from niosomal vesicles can follow any one or more of the following mechanisms; desorption from the surface of vesicles or diffusion of drug from bilayered membrane or a combined desorption and diffusion mechanisms. [13]

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 to 3 months. Drug content and variation in the average vesicle diameter were periodically monitored.

ICH guidelines suggests stability studies for the dry proniosome powders meant for reconstitution should be studied for accelerated stability at 40°C/75% RH as per international climatic zones and climatic

conditions. 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% RH. Product should be evaluated for appearance, color, assay, pH, preservative content, particulate matter, sterility and pyrogenicity. [14]

Applications of Proniosomes:

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

Drug Targeting:

One of the most useful aspects of niosomes is their ability to target drugs. Niosomes can be used to target drugs to the reticulo-endothelial system. The reticulo-endothelial system (RES) preferentially takes up niosome vesicles. The uptake of niosomes is controlled by circulating serum factors called opsonins. These opsonins mark the niosome for clearance. Such localization of drugs is utilized to treat tumors in animals known to metastasize to the liver and spleen. This localization of drugs can also be used for treating parasitic infections of the liver. Niosomes can also be utilized for targeting drugs to organs other than the RES. A carrier system can be attached to niosomes to target them to specific organs. Many cells also possess the intrinsic ability recognize and bind specific carbohydrate determinants and this can be exploited by niosomes to direct carrier system to particular cells. [15]

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. Niosomal entrapment of Doxorubicin and Methotrexate showed beneficial effects over the unentrapped drugs, such as decreased rate of proliferation of the tumour and higher plasma levels accompanied by slower elimination. [16]

Leishmaniasis:

Leishmaniasis 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 in higher concentrations can cause cardiac, liver and kidney damage. 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. [17]

Delivery of peptide drugs:

Oral peptide drug delivery has long been faced with a challenge of bypassing the enzymes which would breakdown the peptide. Use of niosomes to successfully protect the peptides from gastrointestinal peptide breakdown is being investigated. In an in vitro study oral delivery of a vasopressin derivative entrapped in niosomes showed that entrapment of the drug significantly increased the stability of the peptide.[18]

Uses in studying immune response:

The niosomes 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. [19]

Niosomes as carriers for haemoglobin:

It was reported that the 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 haemoglobin in anemic patients. [20]

Transdermal drug delivery systems utilizing niosomes:

One of the most useful aspects of niosomes is that they greatly enhance the uptake of drugs through the skin. Transdermal drug delivery utilizing niosomal technology is widely used in cosmetics; in fact, it was one of the first uses of the niosomes. Topical use of niosome entrapped antibiotics to treat acne is done. The penetration of the drugs through the skin is greatly increased as compared to un-entrapped drug.[21]

Other Applications:

Sustained Release:

The roles of liver as a depot for methotrexate after niosomes are taken up by the liver cells. Sustained release action of niosomes can be applied to drugs with low therapeutic index and low water solubility since those could be maintained in the circulation via niosomal encapsulation. [22]

Localized Drug Action:

Drug delivery through niosomes 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.: Antimonial encapsulated within niosomes 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 niosomal drug delivery technology is still at an infancy stage, but this type of drug delivery system has shown promise in cancer chemotherapy and anti-leishmanial therapy.[23]

CONCLUSION:

The provesicular systems have been gaining a lot of interest of various researchers and scholars, because

of their advantages of controlled and sustained release action, stability and versatility as a drug carrier. These carrier systems have immense scope in future. Proniosomes contain both non ionic surfactant and phospholipids, both can act as penetration enhancer and useful in increasing permeation of many drugs. However future experiments should explore the suitability of proniosomes with more drugs designed for improved and effective intended therapy. So, that proniosomes are represented as promising drug carrier and promising drug delivery module.

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