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Proniosomes: A Novel Vesicular Drug Delivery System

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ABSTRACT

The Improvement in the nanotechnology brings revolutionary changes & helps in preparing the novel formulations. The proniosomes are solid colloidal particles which may be hydrated immediately before use to yield the aqueous niosome dispersions similar to those that are produced by more cumbersome conventional methods. These proniosomes minimize the problems of niosome physical stability such as leaking, aggregation & fusion provide additional convenience in dosing, transportation, storage & distribution. The proniosomes overcome the disadvantages involved with liposomal & niosomal drug delivery systems. This review focuses on different aspects of proniosome such as components , types, preparation, evaluation & applications.

Keywords: Proniosomes, Niosomes, Evaluation, Applications.

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INTRODUCTION

The vesicular drug delivery is one of the approaches, which encapsulate the drug For e.g.: Niosomes, liposomes, pharmacosomes, transferosomes & provesicles such as proliposomes & proniosomes. The advantages of liposomes and niosomes over the other conventional dosage forms is their particulate nature, which act as the drug reservoir. In order to adjust the pattern & the drug release, few modifications can also be carried out. It was also found that the modified vesicles had the properties that successfully delivered the drugs into the skin's deeper layers. For their use as the drug targeting agents & drug carriers ,the proniosomes have gained wide attention by the researchers to have the variety of advantages while avoiding the disadvantages associated with the conventional form of drugs. The niosomes are the water soluble carrier particles & on the brief agitation in the hot aqueous media these are dried to form the niosomal dispersion. Thus, this dehydrated product is called as proniosomes. The resulting niosomes are very correlative to conventional niosomes & of higher size uniformity. The problems associated with dry, free-flowing product, is reduced by proniosomal approach which is more stable during the storage & sterilization. Because of the ease of distribution, measuring, transfer, and storage the proniosomes are the versatile delivery system. For entrapping both polar and nonpolar or hydrophobic and hydrophilic drugs the proniosomes were studied as an alternatives to the liposomes & other carrier systems. Low toxicity owing to non-ionic nature, no requirement of special conditions & precautions for formulation & preparations, are the additional advantages of proniosomes. Apart from this it is the simple method for the routine & large scale production of the proniosomes without the use of the undesirable solvents. In the advancement of any formulation however the stability is the main concern & even the proniosomes have the advantages in comparison to the liposomes as drug carriers such as the cost productivity, chemically stability. They also minimize the problems of physical stability such as the leakage, fusion, sedimentation & the aggregation on storage.[1-2]

Proniosomes

The Proniosomes are the dry formulations of the surfactant-coated carrier, which can be measured out as needed & rehydrated by the brief agitation in the hot water. These proniosomes minimizes the problems of niosomes which include the physical stability such as leaking, fusion , aggregation & provided additional convenience in the dosing, transportation, storage, distribution is reported by Hu and Rhodes et al. As compared to conventional niosomes the proniosome-derived niosomes are superior in convenience of dosing , storage & transport. The stability of the dry proniosomes is expected to be more stable than the pre-manufactured niosomal formulation. The proniosomes

appear to be equivalent to conventional niosomes in the release studies. The size distributions of the proniosome-derived niosomes are somewhat better that that of conventional niosomes so the release performance turns out to be superior in more critical cases.[3-6]

Structure

The proniosomes are microscopic lamellar structures. They combine the non-ionic surfactant of the alkyl or the dialkyl polyglycerol ether class & cholesterol followed by the hydration in the aqueous media. A surfactant molecule directs themselves in such a way that the hydrophilic ends of the non-ionic surfactant orient outward while the hydrophobic ends are in the opposite direction to form a bilayer. The proniosomes are also made up of a bilayer like the liposomes. The bilayer is made of non-ionic surface active agents in proniosomes. The proniosomes are unilamellar or multi-lamellar on the basis of the method of preparation. The niosome is made of the surfactant bilayer with its hydrophobic chains face each other within the bilayer & the hydrophilic ends exposed on the outside & inside of the vesicles. Hence within the space enclosed in the vesicle the vesicle holds hydrophilic drugs & within the bilayer the hydrophobic drugs are embedded.[2]

Advantages Of Proniosomes Over the Niosomes

a. Proniosomes can carry both hydrophobic & hydrophilic drug.

b. Proniosomes avoids the encapsulation of hydrolysis drugs.

c. Proniosomes are extensively used in the various drug delivery system like controlled release, drug targeting & permeation enhancement of drug.

d. It avoids the problems of physical stability drug.

e. Proniosomes show additional convenience in dosing, distribution, transportation & storage.[7]

COMPONENTS OF PRONIOSOMES

Surfactant

The surfactants are the surface active agent usually organic compounds that are amphiphilic in nature. They have a variety of functions including acting as the permeability enhancers, solubilizers, emulsifiers & wetting agents. The alkyl amides, alkyl ethers, alkyl esters & esters of fatty acids are the most common non-ionic surfactants used for the vesicle formation. On the basis of Hydrophilic Lipophilic Balance [HLB] value the selection of the surfactant should be done, which is the good indicator of the vesicle forming ability of any surfactant. The formation of the bilayer vesicles instead of the micelles not only depends upon the Hydrophilic Lipophilic Balance [HLB] values of the surfactant but also on the chemical structure of the component & the critical packing parameter. The Hydrophilic Lipophilic Balance [HLB] value of the surfactant plays the key role in controlling the drug entrapment of the vesicle it forms. As the Hydrophilic Lipophilic Balance is the good

indicator of the vesicle forming ability of any surfactant, the Hydrophilic Lipophilic Balance [HLB] number in between 4 & 8 was found to be compatible with the vesicle formation.[8-9]

Solvent and Aqueous phase

On the drug permeation rate & vesicle size the alcohol has a great effect when used in proniosome. The vesicles formed from the different alcohols are of different size & they follow the order: Ethanol > Propanol > Butanol > Isopropanol. The phosphate buffer 7.4, hot water, 0.1% glycerol, is used as aqueous phase in preparation of proniosomes

Carrier

The carrier permits the flexibility in the ratio of surfactant and other components that incorporated. when it is used in the proniosomes preparation. Along with this also it increases the surface area & hence the efficient loading. The carriers should be non-toxic & safe, free flowing, poor solubility in the loaded mixture solution & good water solubility for the ease of hydration. The commonly used carriers are listed below:

i] Sucrose stearate. ii]) Malodextrin. iii] Spray dried lactose. iv] Sorbitol. v] Glucouse monohydrate. vi] Lactose monohydrate.[10-12]

Lecithin

Depending on their source of origin they are generally named such as egg lecithin from egg yolk & soya lecithin from soya beans. The phosphatidyl choline is the major component of lecithin. In the vesicular system it plays number of important role such as:

i] It enhanced the percent drug entrapment due to high Tc [phase transition temperature]

ii] It prevents the leakage of drug.

iii] It acts as the permeation enhancers.

The soya lecithin forms the vesicles of larger when compared to the egg lecithin whereas when we compared these 2 on the basis of the penetration capability the soya lecithin is the better candidate to select because it contains linoleic acid, unsaturated fatty acid, oleic acid whereas the egg lecithin contain the saturated fatty acid.[13-14]

Cholesterol

Used as the membrane additive the cholesterol is naturally occurring steroid. The steroids are important components of the cell membrane & their presence in the membrane brings about the significance changes with regard to the bilayer stability, permeability & fluidity. It prevents the aggregation by the inclusion of the molecules that stabilize the system against the formation of the aggregate by the repulsive steric or the electrostatic effects. El-Laithy et al. reported that there is a significant increase in entrapment efficiency [%] as the cholesterol content increase, but after the

certain limit further the cholesterol increase result in significant decrease in the entrapment efficiency. The increase in the entrapment efficiency shows that cholesterol which acts as the vesicular cement in the molecular cavities of the surfactant bilayer & abolishes the gel to sol transition thereby forms the less leak vesicles. The increase in the rigidity decrease the permeability of the entrapped drug & hence improves the entrapment efficiency. However, after the certain limit when the cholesterol amount was increased the opposite result occurred. The reason behind this decreased entrapment efficiency may be due to the reason that the cholesterol molecule will compete with the drug for the space within the bilayer it remove the drug from the bilayer & in addition to this will disrupt the structure of vesicular membrane.[15]

TYPES OF PRONIOSOMES

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

A] Dry granular proniosomes

i] Sorbitol based proniosomes

ii] Maltodextrin based proniosomes

The Sorbitol based proniosomes is the dry formulation that involves the sorbitol as a carrier, which is further coated with the non-ionic surfactant & by the addition of the hot water followed by the agitation it is used as the noisome within minutes.

By fast slurry method the maltodextrin based proniosomes are prepared.

B] Liquid crystalline proniosomes

For transdermal delivery of the drug this type of proniosomes are reservoirs. The transdermal patch involves an aluminum foil as the baking material along with the plastic sheet. Followed by covering with the nylon mesh the proniosomal gel is spread evenly on the circular plastic sheet.[1]

METHODS OF PREPARATION OF PRONIOSOMES

Proniosome preparation mainly comprised of nonionic surfactants, coating carriers and membrane stabilizers. The formulation may be prepared by following methods.

Spraying method

In this method the preparation of proniosomes by spraying the surfactant in the organic solvent onto the carrier & then the solvent is evaporated. Until the desired surfactant loading is achieved it is necessary to repeat the process . The coating of surfactant on the carrier is very thin & the hydration of this coating allows the vesicles to form as the carrier dissolves. The resulting niosomes have the uniform size distribution which are similar to those produced by the conventional methods.

Slurry method

By using the different carrier the proniosomes were produced by the slurry method. In this method, in the rotary evaporator the whole volume of surfactant solution is added to the maltodextrin powder & then vacuum is applied until the powder appears to be dry & free flowing product. The drug containing the proniosomes-derived niosomes can be prepared in the manner similar to that used for the conventional niosomes by adding the drug to the surfactant mixture prior to spraying the solution on the carrier [mannitol, sorbitol & maltodextrin] or used to hydrate the proniosomes by the addition of the drug to the aqueous solution.

Coacervation phase separation method

In this Coacervation phase separation method, accurately weighed amount of cholesterol, carrier, drug & surfactant are taken in the clean & dry wide mouthed glass vial [5 ml] and by simple mixing the solvent to be added to it. The open end of the glass vial can enclosed by a lid and heated on water bath at 60-70ºC for 5 min in order to prevent the loss of solvent. The mixture should be allowable to cool at the room temperature & the dispersion gets converted to the proniosomes.[11,16]

METHODS FOR EVALUATION OF PRONIOSOMES

a] Optical microscopy

For the number of vesicles formed after hydration the proniosomal powder was evaluated. With phosphate buffer [Ph 7.4] the proniosomal powder was subjected to hydration & the formed niosomes counted by the optical microscope using the haemocytometer. The niosomes are mounted on the glass slides & viewed under the microscope with the magnification of 1200X for the morphological observation after the suitable dilution. By using the digital SLR camera the photomicrograph of the preparation is also obtained from the microscope.

b] Drug content

In the standard flask the proniosomal formulation equivalent to 250mg of drug was taken & they were mixed with 50mL of the propanol by shaking & 1mL of the mixture was then diluted with the phosphate buffer [Ph 7.4]. By spectroscopically at 281 nm the absorbance was measured & drug content was calculated from calibration curve.

c] Vesicle morphology

It involves the measurement of shape & size of proniosomal vesicles. In 2 conditions the size of the proniosomal vesicles can be measured by the dynamic light scattering method these two conditions are: with agitation & without agitation. The hydration without agitation results in largest vesicle size.

d] Penetration and permeation studies

By CLSM [confocal laser scanning microscopy] the depth of penetration in the proniosomes can be visualized.

e] Transmission electron microscopy

By using TEM [transmission electron microscopy] the morphology of the hydrated niosome dispersion is determined. A drop of the niosome dispersion is diluted 10-fold using the deionized water. To the carbon coated 300 mesh copper grid a drop of the diluted niosome dispersion is applied & is left for 1 minute to allow some of the niosomes to adhere to a carbon substrate. By adsorbing the drop with the corner of the piece of the filter paper the remaining dispersion is removed. A drop of 2% aqueous solution of uranyl acetate is applied for 1 second, after twice rinsing the grid [deionized water for 3-5 seconds]. By absorbing the liquid with the tip of a piece of filter paper the remaining solution is removed & the sample is air dried. At 80 kv the sample is observed.

f] Encapsulation efficiency

After separation of the unentrapped drug the encapsulation efficiency of the proniosomes is determined.

1] By the following techniques the separation of unentrapped drug is done

i] Dialysis

Tubing against the suitable dissolution medium the aqueous niosomal dispersion is dialyzed at room temperature then the samples are withdrawn from the medium at the suitable time interval centrifuged & by using UV spectroscopy analyzed for drug content.

ii] Gel filtration

By gel filtration of niosomal dispersion through a sephadex G50 column the free drug is removed & separated with the suitable mobile phase & with analytical techniques they are analyzed.

iii] Centrifugation

The niosomal suspension is centrifuged & the surfactant is separated. To obtain the niosomal suspension free from unentrapped drug the pellet is washed & then resuspended.

2] Determination of entrapment efficiency of proniosomes

After removal of the unentrapped drug by dialysis the vesicles are obtained which are then resuspended in 30% v/v of the PEG 200 & 1 ml of the 0.1% v/v triton x-100 solution was added to solubilize vesicles. The resulted clear solution is then filtered & analyzed for the drug content. The percentage of the drug entrapped is calculated by using the following formula: Percent Entrapment = Amount of drug entrapped/total × 100

g] Shape and surface morphology

It is studied by SEM [scanning electron microscopy], TEM [transmission electron microscopy] & optical microscopy. The surface morphology means smoothness, roundness & aggregation formation.

h] In-Vitro Methods for Assessment of Drug Release from Proniosomes

i] Dialysis tubing

In this the apparatus has prewashed dialysis tubing which can be sealed hermetically. Against the suitable dissolution medium the dialysis sac is then dialyzed at room temperature; at suitable intervals the samples are withdrawn from the medium then centrifuged and analyzed for the drug content using suitable method [HPLC, UV spectroscopy, etc]. The sink condition's maintenance is essential.

ii] Reverse dialysis

A number of small dialysis tubes containing 1 ml of dissolution medium are placed In this technique. Into the dissolution medium the proniosomes are then displaced. With this method the direct dilution of the proniosomes is possible however by using this method the rapid release cannot be quantified.

iii] Franz diffusion cell

By using Franz diffusion cell the in-vitro studies can be performed. The proniosomes are placed in the donor chamber of a Franz diffusion cell fitted with the cellophane membrane. Against the suitable dissolution medium the proniosomes is then dialyzed at room temperature, At suitable intervals, the samples are withdrawn from the medium & analyzed for the drug content by using suitable method [HPLC, UV spectroscopy etc.]. The sink condition's maintenance is essential.

iv] Zeta potential analysis

For determining the colloidal properties of the prepared formulations the zeta potential analysis is done. By using zeta potential analyzer based on the electrophorectic light scattering & laser Doppler Velocimetery method the suitably diluted proniosomes derived niosome dispersion is determined. At 25$^{\circ C}$ the temperature is set. Directly from the measurement the charge on vesicles & their mean zeta potential values with the standard deviation of 5 measurements are obtained.

i] Scanning electron microscopy

The proniosomes can be easily visualized by using SEM [Scanning Electron Microscopy] , TEM [Transmission Electron Microscopy] & by Optical Microscopy. Onto the double-sided tape that is to be affixed on aluminum stubs, the proniosomes are sprinkled In the vacuum chamber of a scanning electron microscope the aluminum stub is placed. By using a gaseous secondary electron detector [working pressure: 0.8 tor, acceleration voltage: 30.00 KV] XL 30, [Philips, Netherlands], the samples are observed for the morphological characterization.

j] Measurement of angle of repose

i] Cylinder Method

Into the cylinder the proniosomal powder was poured which was fixed at the position 10cm above the leveled surface, the powder is flowed down in the cylinder to form the cone on a surface & by measuring the height of the cone & the diameter of its base the angle of repose was then calculated

ii] Funnel Method

The proniosomal powder was poured into the funnel which was fixed at the position 10cm above the level surface & from funnel the powder is flowed down to form the cone on the surface. By measuring the height of the cone & the diameter of its base the angle of repose was calculated Angle of repose is calculated by the following equation;

Angle of repose=Tan-1 [h/r]

k] Drug Release Kinetics and Data Analysis:

The result of the in-vitro drug release study of noisome are fitted with the various kinetic equations, in order to understand the kinetics & mechanism of drug release:

i] The Zero order, as cumulative % release vs. time,

C = K0t Where, k0 = zero order constant expressed in units of concentration/time t = time in hours.

ii] The Higuchi's model, as cumulative % drug release vs. square root of time.

Q = KHt1/2 Where, KH = higuchi's square root of time kinetic drug release constant.

n = release exponent indicative of the drug release mechanism If the exponent n= 0.5 or near, then the drug release mechanism is Fickian diffusion, & if n have near 1.0 then it is Non Fickian diffusion.

l] Stability Studies

By storing the prepared proniosomes at various temperature conditions like refrigeration [2°-8°^{C}], room temperature [25°± 0.5°^{C}] & elevated temperature [45°^{C} ± 0.5°^{C}] from a period of one month to three months the studies are carried out to determine stability of proniosomes. The drug content & variation in the average vesicle diameter are periodically monitored. The ICH guidelines suggests stability studies for the dry proniosomes powder meant for the reconstitution should be studied for the accelerated stability at 75% relative humidity as per international climatic zones & the climatic conditions.[17]

Advantages of Proniosomes

1. The size, shape, fluidity & composition of the niosomes drug can be controlled as & when required.
2. It can entrap both hydrophobic & hydrophilic drugs.
3. It is biocompatible, biodegradable & non immunogenic to the body.

4. Due to depot formation it shows controlled & sustained release of the drugs.
5. By avoiding hydrolysis of encapsulated drugs which limiting the shelf life of the dispersion.
6. By avoiding the problem of physical stability like aggregation, fusion, sedimentation and leakage on storage.
7. There is no difficulty in sterilization, transportation, distribution, storage uniformity of dose and scale up.
8. It is easy for storage & handling.[18-20]

APPLICATION OF PRONIOSOMES

In Studying Immune Response

Due to their greater stability, immunological selectivity & low toxicity the proniosomes are used to study the immune response. To study the nature of the immune response provoked by antigens the niosomes are being used.

In Delivery of Peptide Drugs

The oral peptide drug delivery has long been faced with the challenge of bypassing a enzymes which breakdown the peptide. The use of proniosomes intended to protect the peptides breakdown successfully from gastrointestinal tract. In the study the oral delivery of the vasopressin derivative entrapped in the proniosomes showed the highest entrapment of a drug & significant increase in the stability of the peptide which are incorporated.[21]

In Anti-neoplastic Treatment

Most of the antineoplastic drugs cause severe side effects. Niosome can alter the metabolism, prolong circulation & half-life of a drug thus decreasing the side effects of the drugs. The niosome entrapment of the doxorubicin & methotrexate [in two separate studies] showed the beneficial effects over the entrapped drugs such as the decreased rate of the proliferation of the tumor & the higher plasma levels accompanied by the slower elimination. The podophyllotoxin- [PPT-DPPC] dipalmitoyl phosphatidyl choline proliposomes [PPT-DPPC-PL] for the improvement of the stability of PPT-DPPC.[22]

In NSAID application

The NSAID [Non-steroidal anti-inflammatory drug] like KT [Ketorolac tromethamine] when administered intramuscularly & orally in divided multiple doses for the short-term management of the postoperative pain. Hence, an alternative noninvasive mode of delivery of the drug is needed, so that the transdermal route of delivery is an unconditionally an attractive route of administration to maintain the drug blood levels of the Ketorolac tromethamine for an extended period of time.

In Hormonal Therapy

The proniosome based transdermal drug delivery system of LN [Levonorgestrel] was developed & widely characterized both in vivo & in vitro. The biological assay for the progestational activity included the inhibition & endometrial assay with the formation of corpora lutea.[23]

The proniosomes as Carriers for Haemoglobin

By using the photo initiator such as eosin & visible light. These hydrogel are constrained to the surgical sites nearby to the light source as they form with difficulty after injection into body. For the number of polymers Ion-mediated gelation has been described for e.g. alginates/calcium ions or chitosan/phosphate ions. For cross-linking of the above mentioned polymers the concentrations of the counter ion available under physiological situations are usually lacking. There are 2 important factors which limit the use of calcium-alginate. Which are as follows:

i] Potential immunogenicity

ii]Longer time in-vivo degradability.[24]

In Drug Targeting

The ability to target the drugs is one of the most useful aspects of the proniosomes. The Proniosomes can be used to target the drugs to the reticule-endothelial system. The RES [reticule-endothelial system] preferentially takes up the proniosomes vesicles. By circulating serum factors called poisonings the uptake of proniosomes is controlled. These poisonings mark the proniosomes for the clearance. Such localization of drugs is utilized to treat the tumors in the animals known to metastasize to the liver & spleen. For treating the parasitic infections of the liver this localization of drugs can also be used. The proniosomes can also be utilized for targeting the drugs to the organs other than the reticule-endothelial system. The carrier system [such as antibodies] can be attached to the proniosomes [as the immunoglobulin binds readily to the lipid surface of the niosome] to target them to the specific organs.[25]

The proniosomes used in Cardiac Disorders

The proniosomal carrier system that is used for the treatment of hypertension, for example captopril which is capable of efficiently delivering the entrapped drug over an extended period of time.

In sustained release drug delivery

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

To achieve localized drug action

To achieve the localized drug action the drug delivery through the proniosomes is one of the approaches. The localized drug action results in the enhancement of efficacy of the drug & at the same time it will reduces its systemic toxic effects.[26]

In Leishmaniasis

The leishmaniasis is an illness which is caused by the parasite of the genus leishmania invades the cells of the liver & spleen. The commonly prescribed drugs that are used for the treatment of leishmaniasis is derivatives of antimony [antimonials] which in higher concentrations can cause the liver, cardiac & kidney damage. The use of proniosome in assessments conducted showed that it was possible to administer higher levels of the drug.[27]

CONCLUSION

For the future the proniosomes are the promising drug carriers, with greater physical & chemical stability & potentially scalable for the commercial viability. Different types of drug deliveries can be possible by using proniosomes based niosomes like targeting, topical, ophthalmic, oral vaccine, parenteral, etc. The proniosomes derived niosomes represent the promising drug delivery module. Mostly they are known to avoid many of the problems associated with either a aqueous niosome dispersion as problems of physical stability such as leakage, aggregation & fusion. They provide additional convenience of dosing, transportation, storage & distribution.

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