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Review Article

THE NEW ADVANCEMENT NANOTECHNOLOGY: PRONIOSOMES AS A PROMISING AND POTENTIAL DRUG CARRIER

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ABSTRACT

The advance in nanotechnology (NDDS) which helps in preparing newer formulations.One of the advancement in nanotechnology is the preparation of 'Proniosome derived' niosomes. Approaches to stabilize niosomal drug delivery system without affecting its properties of merits have resulted in the development of the promising drug carrier, proniosome.These proniosomes minimize or reduces problems of niosomes associated with physical stability such as aggregation,fusion,leakage problems and provide additional convenience intransportation, distribution, storage and dosing.The review article provides an insight about these approaches along with a novel vesicular approach known as proniosomes. This new emerging concept has demonstrated the potential in improving the oral bioavailability, targeting drugs to the specific target site and also permeation of drugs across the stratum corneum(skin). It prolongs the existence of the drug in systemic circulation(blood circulation) and finally reduces the toxicity. The goal of this study is to introduce and explore proniosomes as a carrier system for various pharmaceutical and cosmeceutical applications.

Keywords: Nanotechnology, Proniosomes, Niosomes, promising drug carrier, targeting drugs.

INTRODUCTION

The vesicular systems have been receiving a lot of interest as a carrier for advanced drug delivery. Encapsulation of the drug in vesicular structures is one such system, which can be expected to prolong the duration of the drug in systemic circulation as drug controlled or sustain release drugs and to reduce the toxicity by selective up taking. In the ensuing years, great strides were made toward understanding the way in which vesicular systems interact with the biological membrane at the molecular and cellular level(Sudhamani T et al.,2010). No doubt that drug delivery systems using colloidal particulate carriers such as proniosomes, liposomes or niosomes have proved to possess distinct advantages over conventional dosage forms because the particles can act as drug reservoirs, can carry both hydrophilic drugs by encapsulation or hydrophobic drugs by partitioning of these drugs into hydrophobic domains and modification of the particle composition or surface can adjust the drug release rate and or the affinity for the target site. The vesicles in a dispersed aqueous system may suffer from some chemical problems associated with degradation by hydrolysis or oxidation as well as physical problems such as sedimentation, aggregation, or fusion of carrier such as liposomes, niosomes during storage(Hanan M et al.,2011). Two novel approaches were adopted in dealing with these problems to develop the proliposomes and to develop Niosomes using non-ionic surfactants alternatives to phospholipids in preparing vesicles. Even though proliposomal formulations are an

improvement over conventional liposome dispersions in terms of the physical stability of the preparation, chemical instability is still present and therefore a vacuum or nitrogen atmosphere is recommended during preparation and storage to prevent the oxidation of phospholipids. In the later approach niosomes exhibit good chemical stability during storage but aqueous suspension of niosomes may exhibit problems of physical stability such as aggregation, fusion, leaking of entrapped drugs, or hydrolysis of encapsulated drugs, thus limiting their shelf life(Hanan M et al.,2011). The latest approach in the field of vesicular delivery is to combine the two previously mentioned techniques by extending the pro-vesicular approach to niosomes through the formation of proniosomes which are converted to niosomes upon hydration(Hanan M et al.,2011).There are a number of formulation approaches to resolve the problems of low solubility and low bioavailability. Proniosome technology offers novel solution for poorly soluble drugs. Proniosome is a dry free flowing, granular product that could be hydrated immediately before use and would avoid many of the problems associated with aqueous noisome dispersions and problem of physical stability (Rao R et al.,2010).Composed of soya lecithin are of larger size than vesicle composed of egg lecithin probably due to the difference in the intrinsic composition(Kumar K et al.,2011,Yadav K et al., 2010).In the past few decades, considerable attention has been focused on the development of new drug delivery system named Controlled Drug Delivery System. It has prolonged action formulations which gives continues release of their active ingredients at a predetermined rate and predetermined time. The vital objective for the development of controlled release dosage forms is to prolong the duration of action, increased safety margin of high potency drugs due to better control of plasma levels, reduces fluctuations in plasma concentration, reducesserious side effects and toxicity and gives assurance for higher patient compliance(Thejaswi et al.,2011). Recently, different carrier systems and technologies have been extensively studied with aim of controlling the drug release and improving the efficacy and selectivity of formulation. Now-a-days, the vesicular systems like liposomes (Ijeoma F et al.,1998)or niosomes(Schereie H et al.,1994)have specific advantages while avoiding demerits associated with conventional dosage forms. To overcome the disadvantage of vesicular system,proniosomes are designed.

COMPONENTS OF PRONIOSOMES: The essential and most common components for the delivery system are as follows.

1.1. Surfactants:

Surfactants are the surface active agents which are usually organic compounds that are amphiphilic in nature (having both hydrophobic and hydrophilic groups). Therefore, a surfactant molecule contains both a water insoluble (lipophilic) and a water soluble (hydrophilic) component. They have variety of functions including acting as solubilizers, wetting agents, emulsifiers and permeability enhancers (Sudhamani T et al.,2010). The most common non-ionic amphiphiles used for vesicle formation are alkyl ethers, alkyl esters, alkyl amides and esters of fatty acids.

1.2. Carrier materials:

The carrier when used in the proniosomes preparation or formulation permits the flexibility in the ratio of surfactant and other components that incorporated. In addition to this, it increases the surface area and hence efficient loading. The carriers should be safe,effective and non-toxic, free flowing, poor solubility in the loaded mixture solution and good water solubility for ease of hydration(Akhilesh D et al.,2012,Pandey N et al.,2011).

Commonly used carriers are listed below (Table 1).

Table 1: Drug carriers materials

Sr. No.	Carrier materials investigated
1	Maltodextrin
2	Mannitol
3	Sorbitol
4	Spray dried lactose
5	Lactose monohydrate
6	Sucrose stearate
7	Glucose monohydrate

1.3. Membrane stabilizer: Carriers such as Cholesterol and lecithin components are mainly used as membrane stabilizer. Steroids are important components of cell membrane and their presence in membrane andbrings about significance changes with regard to bilayer stability, fluidity and

permeability. Cholesterol is a naturally occurring steroid used as membrane additive. It prevents aggregation,diffusion by the inclusion of molecules that stabilize the system against the formation of aggregate by repulsive steric or electrostatic effects. It leads transition from the gel state to liquid phase in niosome system. Phosphatidylcholine is a major component of lecithin. It has low solubility in water and can form liposomes, bilayer sheets, micelles or lamellar structures depending on hydration and temperature. Depending upon the source from which they are obtained they are as named as egg lecithin and soya lecithin. It acts as stabilising as well as penetration enhancer(skin,transdermal patches as drug delivery system). It is found those vesicles composed of soya lecithin are of larger size than vesicle composed of egg lecithin probably due to the difference in the intrinsic composition (Kumar K et al., 2011, Yadav K et al., 2010).

1.4. Solvent and Aqueous phase:

Alcohol used in Proniosome has a great effect on vesicle size and drug permeation rate. Vesicles formed from different alcohols are of different size and they follow the order: Ethanol > Propanol > Butanol > Isopropanol. Ethanol has greater solubility in water hence leads to formation of highest size of vesicles instead of isopropanol which forms smallest size of vesicle due to branched chain present. Phosphate buffer pH 7.4, 0.1% glycerol, hot water is used as aqueous phase in preparation or formulation of proniosomes (Yadav K et al., 2010).

1.5. Drug:

The drug selection criteria could be based on the following assumptions (Kumar K et al., 2011).

1. Low aqueous solubility of drugs.
2. High dosage frequency of drugs.
3. Controlled drug delivery suitable drugs
4. Short half life.
5. Higher adverse drug reaction drugs.

Chief advantages of Proniosomal Drug Delivery

In comparison to other drug delivery systems(Goud BA et al.,2012;Alsura IA et al.,2005).

1. The Proniosomal system is passive, non-invasive and is available for immediate commercialization.
2. Proniosomes are platform for the delivery of large and diverse group of drugs as a promising carrier (peptides, protein molecules).
3. Proniosome composition is safe,effective and the components are approved for pharmaceutical and cosmetic uses .
4. Low risk profile- The technology has no large-scale drug development risk since the toxicological profiles of the Proniosomal components are well documented in the scientific literature.

Method of preparations:

Various methods are used for preparation of proniosomes such as:

Slurry method:

Powdered drug was poured into a 250-mL round-bottom flask and the specific 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. The flask was removed from the evaporator and kept under vacuum overnight. Proniosome dry powder was stored in sealed containers at 4°C(Srivastava AR et al.,2009).

Coacervation phase separation method:

This method is ideally used to prepare proniosomal accurately weighed amounts of surfactant, lipid and drug aretaken in a clean and dry wide mouthed glass vial of 5.0 ml capacity and alcohol is added to it. After warming, all theingredients were mixed well with a glass rod and the open end of the glass bottle was covered with a glass lid to prevent theloss of solvent from it and warmed over water bath at 60-70°C for about 5 min until the surfactant mixture isdissolved completely. Then the aqueous phase is added and warmed on a water bath till a clear solution was formedwhich is then converted into proniosomal on cooling (Abd-Elbary A et al., 2008;Vora B et al.,1998).

Slow spray coating method:

Taken a 100 ml round bottom flask (RBF) containing desired amount of carrier can be attached to rotary flash evaporator. Amixture of cholesterol and surfactants was prepared and poured into round bottom flask on rotary evaporator bysequential spraying of aliquots onto carrier's surface. The evaporator was used to evacuate the vapour and rotatingflask can be rotated in water bath under vacuum at 65-70oC for 15 – 20 min. This process is

repeated until all of thesurfactant solution has been applied. The evaporation should be continued until the powder becomes completely dry as a granulated form..

TYPES OF PRONIOSOMES:

Depending on the method of preparation, the proniosomes exists in two forms

A. Dry granular proniosome: According to the type of carrier these are again divided as a) Sorbitol based proniosomes (Kishore N et al.,2010;Ruckmani K et al.,2010).

B. Maltodextrin based proniosomes Sorbitol based proniosomes is a dry formulation that involves sorbitol as a carrier. These are made by spraying surfactants mixture prepared in organic solvent onto the sorbitol powder and then evaporating the solvent. It is useful in case where the active ingredient is susceptible to hydrolysis(Prakash SG et al.,2011;Gupta A et al.,2007;Akhilesh D et al.,2012)

Characterization of proniosomes (Thejaswi C et al.,2005)

Table 2: Shows methods for the characterization of proniosomes

Parameter	**Method/Instruments/Devices**
Particles size and size distribution	Lazer diffraction particle size analyser, Photo correlation spectroscopy(PCS)
Shape and surface morphology	Scanning electron microscopy(SEM), Transmission electron microscopy(TEM) and Optical microscopy.
Vesicle size	Lazer diffraction particle size analyser
Sieve Fractionation	Fritsch analysette sieve shaker
Angle of repose	Funnel method
Aerodynamic behaviour	Twin–stage impinger
Spontaneity(Rate of hydration)	Neubaur's chamber
Separation of unentrapment drug	Centrifugation,Cellophane dialysis tubing
Determination of entrapment efficiency	Vesicle Lysis using alcohol and propylene glycol,Dialysis method
In-vitro drug release studies	Franz diffusion cell,cellophane dialyzing membrane,USP dissolution apparatus-1, Spectarpor molecular porous membrane tubing, Keshary-chein diffusion cell, *In-vitro* skin permeation,

Measurement of Angle of repose

The angle of repose of dry proniosomespowder was measured by a funnel method(Liebermanet al 1990). The proniosomes free flowingpowder was poured into a funnel which wasfixed at a position so that the 13mm outletorifice of the funnel is 5cm above a level blacksurface. The powder flows down from thefunnel to form a cone on the surface and theangle of repose was then calculated bymeasuring the height of the cone and thediameter of its base with the help of caliberated scale.

Scanning electron microscopy (SEM)

The particle size of proniosomes is a very importantcharacteristic. The surface morphologysuch as roundness, smoothness, and formation ofaggregates and the size distribution ofproniosomes were studied by ScanningElectron Microscopy (SEM).Proniosomeswere sprinkled onto the double- sided tapethat was affixed on aluminum stubs. Thealuminum stub was placed in the vacuumchamber of a scanning electron microscope(XL 30 ESEM with EDAX, Philips,Netherlands). The samples were observed formorphological characterization using agaseous secondary electron detector(working pressure: 0.8 torr, accelerationvoltage: 30.00 KV) XL 30, (Philips,Netherlands).

Optical Microscopy

The proniosomes derived niosomes were mounted on glass slidesand viewed under a microscope (Medilux-207RII, Kyowa-Getner, and Ambala, India)with a magnification of 1200X formorphological observation after suitabledilution. The photomicrograph of thepreparation also obtained from themicroscope by using a digital SLR camera.

Measurement of vesicle size

The vesicle dispersions were diluted about100 times in the same solvent medium used for theirpreparation.Vesicle size was measured on aparticle size analyzer (Laser diffractionparticle size analyzer, Sympatec, Germany).

The apparatus consists of a He-Ne laserbeam of 632.8 nm focused with a minimumpower of 5 mW using a Fourier lens [R-5] to apoint at the centre of multielement detectorand a small volume sample holding cell (Sucell). The samples were stirred using a stirrerbefore determining the vesicle size. Hu C.and Rhodes 7 in 1999 reported that theaverage particle size of proniosomes derivedniosomes is approximately 6µm while that ofconventional niosomes is about 14µm.

Entrapment efficiency

Entrapment efficiency of the proniosomes derived niosomaldispersion can be done by separating theunentrapped drug by dialysis, centrifugationor gel filtration as described above and thedrug remained entrapped in niosomes isdetermined by complete vesicle disruptionusing 50% n-propanol or 0.1% Triton X-100and analyzing the resultant solution byappropriate assay method for the drug.

In-vitro methods for the assessment ofdrug release from proniosomes.In -vitro drug release can be done by (ChenDB et al, 2001)

- Dialysis tubing
- Reverse dialysis
- Franz diffusion cell

Dialysis tubing:

According to Muller et al 35 in 2002 studied in- vitro drug release could be achieved by using dialysis tubing method. The proniosomes is placed in prewashed dialysis tubing which can behermetically sealed. The dialysis sac is thendialyzed against a suitable dissolution medium at room temperature; the samples were withdrawn from the medium at suitable intervals, centrifuged and analysed for drug content using suitable method (U.V.spectroscopy, HPLC etc). The maintenance of sink condition is essential.

Franz diffusion cell:

The in-vitro diffusion studies can beperformed by using Franz diffusion cell.Proniosomes powder was placed in the donor chamberof a Franz diffusion cell fitted with acellophane membrane. The proniosomes wasthen dialyzed against a suitable dissolutionmedium at room temperature; the sampleswere withdrawn from the medium at suitableintervals of time, and analysed for drug content usingsuitable method (U.V spectroscopy,HPLC,etc). the maintenance of sink condition isessential.

Drug Release Kinetic Data Analysis:

The release data obtained from the variousformulations were studied further for theirfitness of data in different kinetic models likeZero order, Higuchi's and peppa's. In order tounderstand the kinetic and mechanism ofdrug release, the result of in-vitro drugrelease study of Niosome was fitted withvarious kinetic equation like zero order(Equation 1) as cumulative % release vs.time, higuchi's model (Equation 2) ascumulative % drug release vs. square root oftime. r and k values were calculated for thelinear curve obtained by regression analysisof the above plots.

$C = k0t$ …..(1)

Where k0 is the zero order rate constantexpressed in units of concentration / time andt is time in hours.

$Q = kHt1/2$ …..(2)

Where kH is higuchi's square root of timekinetic drug release constant

To understand the release mechanism in-vitrodata was analyzed by peppa's model

(Equation 3) as log cumulative % drugrelease vs. log time and the exponent n was

calculated through the slope of the straightline.

$Mt / M\infty = btn$ …..(3)

Where Mt is amount of drug release at time t,$M\infty$ is the overall amount of the drug, b isconstant, and n is the release exponentindicative of the drug release mechanism. Ifthe exponent n = 0.5 or near, then the drugrelease mechanism is Fickian diffusion, and ifn have value near 1.0 then it is non-Fickian diffusion.

Osmotic shock:

The change in the vesicle size can bedetermined by osmotic studies. Niosomalformulations are incubated with hypotonic,isotonic, hypertonic solutions for 3 hours.

Then the changes in the size of vesicles inthe formulations are viewed or observed under opticalmicroscopy.

Stability studies:

For determine the stability of proniosomes, theoptimized batch was stored in airtight sealed glass vials at different temperatures. Surfacecharacteristics and percentage drug retainedin proniosomes and parameters for evaluationof the stability, since instability of theformulation would reflect in drug leakage anda decrease. In the percentage drug retained.

The proniosomes were sample at regularintervals of time (0,1, 2 and 3months),observed for colour change, surfacecharacteristics and tested for the percentagedrug retained after being hydrated to formniosomes and analyzed by suitable analyticalmethods(UV spectroscopy, HPLC methodsetc).

Zeta potential analysis:

Zeta potential analysis is usually done for determiningthe colloidal properties of the preparedformulations. The suitably diluted proniosomederived niosome dispersion was determinedusing zeta potential analyzer based onelectrophoretic light scattering and laserDoppler velocimetry method (Zetaplus™,Brookhaven Instrument Corporation, NewYork, USA). The temperature was set at25°C. Charge on vesicles and their meanzeta potential values with standard deviationof 5 measurements which were obtained directlyfrom the measurement.

Some important application of Proniosome are:

Non-Steroidal Anti-Inflamatory drug:

Ketorolac, a potent non-steroidal anti-inflammatory drug, is formulated as a proniosome gel using spans, tweens,lecithin and cholesterol with ethanol as a solvent. Each of prepared proniosomes formulation shows significantlyimproved drug permeation in case of transdermal drug delivery system.(Alsara IA et al.,2005;Thakur R et al.,2009).

Hypertension:

Fabricated proniosomes using different non-ionic surfactants, such as Span 20, Span 40, Span60, Span 80, Tween20, Tween 40, and Tween 80 fortransdermal drug delivery system of losartanpotassium. Proniosomalformulation more effective in hypertention control.(high blood pressure)(Abd-Elbary A et al.,2008;Thakur R et al.,2009).

Skin disorders:

Developed a proniosomal gel fortransdermal drug delivery of chlorpheniraminemaleate (CPM). The system wasformulated withSpan 40 and evaluated for the effect of compositionof formulation and having high penetration property.(Thakur R et al.,2009,Varshosaz J,et al 2005).

Hormonal insufficiencies:

A proniosome based transdermal drug deliverysystem of levonorgestrel (LN) was developed andextensivelycharacterized both in-vitro and in -vivo.The proniosomal structure was liquid crystallinecompactniosomes hybridwhich could beconverted into niosomes upon hydration. Thesystem was evaluated in-vitro for drug loading, rate ofhydration (spontaneity), vesicle size,polydispersity, entrapment efficiency and drugdiffusion with high skin permeabiity across rat skin(Thakur R et al.,2009;Almira I et al., 2001).

Antibacterial therapy:

Amphotericin-b proliposomes could be stored for 9 months without significant changes in distribution of vesicle sizeand for 6 months without loss of pharmacological activity(Kumar S et al.,2007).

Carriers for Haemoglobin:

Proniosomes derived niosomes can be used as carriers for haemoglobin within the blood(systemic circulation).

Used in Cardiac disorders:

Proniosomal carrier system for captopril for the treatment of hypertension(high blood pressure) that is capable of efficiently deliveringentrapped drug over an extended period of time. The roles of liver as a depot for methotrexate after niosomes aretaken up by the liver cells. Sustained release action of niosomes can be applied to drugs with low therapeutic indexand low water solubility(Solanki AB et al., 2007).

CONCLUSION:

The development of proniosomes formulation represents a significant advance over the conventional vesicular systems. This concept of incorporating the drug into proniosomes for a better targeting at the specific site or at appropriate tissue destination and for controlled delivery is widely accepted by the researchers. As a drug delivery device, proniosomes are osmotically active and more stable than niosomes or liposomes.Proniosomes are thought to be better candidates of drug delivery as compared to liposomesand niosomes due to various factors like cost, stability etc. Compared to liposome or niosomes, proniosomes are very promising as drug carriers and 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 time storage. Proniosome are convenient to store, transport and for unit dosing because of 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 and drug toxicity. The slurry method was found to be simple and suitable for laboratory scale preparation of proniosomes.

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