



Review Article

THE NEW ADVANCEMENT NANOTECHNOLOGY: PRNOSOMES 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 reduce problems of niosomes associated with physical stability such as aggregation, fusion, leakage problems and provide additional convenience in transportation, 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 niosome 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, reduces serious 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 PRNIOSOMES: 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 and brings 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 are taken in a clean and dry wide mouthed glass vial of 5.0 ml capacity and alcohol is added to it. After warming, all the ingredients were mixed well with a glass rod and the open end of the glass bottle was covered with a glass lid to prevent the loss of solvent from it and warmed over water bath at 60-70°C for about 5 min until the surfactant mixture is dissolved completely. Then the aqueous phase is added and warmed on a water bath till a clear solution was formed which 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. A mixture of cholesterol and surfactants was prepared and poured into round bottom flask on rotary evaporator by sequential spraying of aliquots onto carrier's surface. The evaporator was used to evacuate the vapour and rotating flask can be rotated in water bath under vacuum at 65-70°C for 15 – 20 min. This process is

repeated until all of the surfactant 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 exist 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, and 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 drug untrapped drug	Centrifugation, Cellophane dialysis tubing
Determination of entrapment efficiency	Vesicle Lysis using alcohol and propylene glycol, Dialysis method

<i>In-vitro</i> drug release studies	Franz dialyzing apparatus-1, Spectarpor membrane tubing, diffusion cell, <i>In-vitro</i> skin permeation,	diffusion membrane, USP dissolution apparatus-1, molecular porous	cell, cellophane
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Measurement of Angle of repose

The angle of repose of dry proniosomes powder was measured by a funnel method (Lieberman et al 1990). The proniosomes free flowing powder was poured into a funnel which was fixed at a position so that the 13mm outlet orifice of the funnel is 5cm above a level black surface. The powder flows down from the funnel to form a cone on the surface and the angle of repose was then calculated by measuring the height of the cone and the diameter of its base with the help of a calibrated scale.

Scanning electron microscopy (SEM)

The particle size of proniosomes is a very important characteristic. The surface morphology such as roundness, smoothness, and formation of aggregates and the size distribution of proniosomes were studied by Scanning Electron Microscopy (SEM). Proniosomes were sprinkled onto the double-sided tape that was affixed on aluminum stubs. The aluminum stub was placed in the vacuum chamber of a scanning electron microscope (XL 30 ESEM with EDAX, Philips, Netherlands). The samples were observed for morphological characterization using a gaseous secondary electron detector (working pressure: 0.8 torr, acceleration voltage: 30.00 KV) XL 30, (Philips, Netherlands).

Optical Microscopy

The proniosomes derived niosomes were mounted on glass slides and viewed under a microscope (Medilux-207R II, Kyowa-Getner, and Ambala, India) with a magnification of 1200X for morphological observation after suitable dilution. The photomicrograph of the preparation also obtained from the microscope by using a digital SLR camera.

Measurement of vesicle size

The vesicle dispersions were diluted about 100 times in the same solvent medium used for their preparation. Vesicle size was measured on a particle size analyzer (Laser diffraction particle size analyzer, Sympatec, Germany).

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

Entrapment efficiency

Entrapment efficiency of the proniosomes derived niosomal dispersion can be done by separating the untrapped drug by dialysis, centrifugation or gel filtration as described above and the drug remained entrapped in niosomes is determined by complete vesicle disruption using 50% n-propanol or 0.1% Triton X-100 and analyzing the resultant solution by appropriate assay method for the drug.

In-vitro methods for the assessment of drug release from proniosomes. In-vitro drug release can be done by (Chen DB 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 be hermetically sealed. The dialysis sac is then dialyzed 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 be performed by using Franz diffusion cell. Proniosomes powder was placed in the donor chamber of a Franz diffusion cell fitted with a cellophane membrane. The proniosomes was then dialyzed against a suitable dissolution medium at room temperature; the samples were withdrawn from the medium at suitable intervals of time, and analysed for drug content using suitable method (U.V spectroscopy, HPLC, etc). the maintenance of sink condition is essential.

Drug Release Kinetic Data Analysis:

The release data obtained from the various formulations were studied further for their fitness of data in different kinetic models like Zero order, Higuchi's and Peppas's. In order to understand the kinetic and mechanism of drug release, the result of in-vitro drug release study of Niosome was fitted with various kinetic equation like zero order (Equation 1) as cumulative % release vs. time, Higuchi's model (Equation 2) as cumulative % drug release vs. square root of time. r and k values were calculated for the linear curve obtained by regression analysis of the above plots.

$$C = k_0 t \dots (1)$$

Where k_0 is the zero order rate constant expressed in units of concentration / time and t is time in hours.

$$Q = k_H t^{1/2} \dots (2)$$

Where k_H is Higuchi's square root of time kinetic drug release constant

To understand the release mechanism in-vitro data was analyzed by Peppas's model

(Equation 3) as log cumulative % drug release vs. log time and the exponent n was calculated through the slope of the straightline.

$$M_t / M^\infty = b t^n \dots (3)$$

Where M_t is amount of drug release at time t , M^∞ is the overall amount of the drug, b is constant, and n is the release exponent indicative of the drug release mechanism. If the exponent $n = 0.5$ or near, then the drug release mechanism is Fickian diffusion, and if n have value near 1.0 then it is non-Fickian diffusion.

Osmotic shock:

The change in the vesicle size can be determined by osmotic studies. Niosomal formulations are incubated with hypotonic, isotonic, hypertonic solutions for 3 hours.

Then the changes in the size of vesicles in the formulations are viewed or observed under optical microscopy.

Stability studies:

For determine the stability of proniosomes, the optimized batch was stored in airtight sealed glass vials at different temperatures. Surface characteristics and percentage drug retained in proniosomes and parameters for evaluation of the stability, since instability of the formulation would reflect in drug leakage and a decrease. In the percentage drug retained.

The proniosomes were sample at regular intervals of time (0,1, 2 and 3 months), observed for colour change, surface characteristics and tested for the percentage drug retained after being hydrated to form niosomes and analyzed by suitable analytical methods (UV spectroscopy, HPLC method etc).

Zeta potential analysis:

Zeta potential analysis is usually done for determining the colloidal properties of the prepared formulations. The suitably diluted proniosome derived niosome dispersion was determined using zeta potential analyzer based on electrophoretic light scattering and laser Doppler velocimetry method (Zetaplus™, Brookhaven Instrument Corporation, New York, USA). The temperature was set at 25°C. Charge on vesicles and their mean zeta potential values with standard deviation of 5 measurements which were obtained directly from the measurement.

Some important application of Proniosome are:

Non-Steroidal Anti-Inflammatory 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 significantly improved 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, Span 60, Span 80, Tween 20, Tween 40, and Tween 80 for transdermal drug delivery system of losartan potassium. Proniosome formulation more effective in hypertension control (high blood pressure) (Abd-Elbary A et al., 2008; Thakur R et al., 2009).

Skin disorders:

Developed a proniosomal gel for transdermal drug delivery of chlorpheniramine maleate (CPM). The system was formulated with Span 40 and evaluated for the effect of composition of formulation and having high penetration property. (Thakur R et al., 2009; Varshosaz J, et al 2005).

Hormonal insufficiencies:

A proniosome based transdermal drug delivery system of levonorgestrel (LN) was developed and extensively characterized both in-vitro and in-vivo. The proniosomal structure was liquid crystalline compact niosomes

hybrid which could be converted into niosomes upon hydration. The system was evaluated in-vitro for drug loading, rate of hydration (spontaneity), vesicle size, polydispersity, entrapment efficiency and drug diffusion with high skin permeability across rat skin (Thakur R et al., 2009; Almira I et al., 2001).

Antibacterial therapy:

Amphotericin-b proniosomes could be stored for 9 months without significant changes in distribution of vesicle size and 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 delivering entrapped drug over an extended period of time. 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 (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 liposomes and 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. Proniosomes are convenient to store, transport and for unit dosing because of proniosomes 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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