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Review Article

PRONIOSOMES: A RECENT ADVANCEMENT IN NANOTECHNOLOGY AS A DRUG CARRIER

N.Bharti*, S. Loona and M.M.U.Khan
Sri Sai College of Pharmacy, Badhani, Pathankot, Punjab, India.
***Corresponding author's E-mail:** nitanbharti@yahoo.com

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ABSTRACT

Advancement in the nanotechnology brings revolutionary changes and helps in preparing newer formulations. Preparation of proniosomes is one of the new advancement in nanotechnology. Proniosomes are water soluble carrier particles that are coated with surfactant and can be hydrated to form niosomal dispersion immediately before use on brief agitation in hot aqueous media. These proniosomes minimize problems of niosomes physical stability such as aggregation, fusion, leaking and provide additional convenience in transportation, distribution, storage and dosing. This is a new approach to stabilize niosomal drug delivery system without affecting its properties of merits. These proniosomes- derived niosomes are as good as or even better than conventional niosomes. The focus of this review is to bring out different aspects related to proniosomes merits, types, preparation, characterization, entrapment efficiency, *in-vitro* drug release, in-vitro permeation studies, stability studies and applications.

Keywords: Proniosomes, Niosomes, liposomes, Stability, Drug release.

INTRODUCTION

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 gives assurance for higher patient compliance[1]

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[2] or niosomes[3] have specific advantages while avoiding demerits associated with conventional dosage forms. To overcome the disadvantage of vesicular system, Proniosomes are designed.

Liposomes are bilayered lipid vesicles, consisting primarily of phospholipids and cholesterols[4]. Drug encapsulated in lipid vesicles prepared from phospholipids and non-ionic surfactant is known to be transported into and across the skin. Because of their ability to carry variety of drugs, liposomes have been extensively investigated for their potential applications in pharmaceutics; such as drug delivery for drug targeting; for controlled release or for increasing solubility[5, 6].

Niosomes are non-ionic surfactant vesicles obtained on hydration of synthetic non-ionic surfactant, with or without incorporation of cholesterol or other lipids[7]. They are vesicular systems similar to liposomes that can be used as carriers of amphiphilic and lipophilic drugs. One of the reasons for preparing niosomes is the assumed higher chemical stability of the surfactants than that of phospholipids, which are used in the preparation of liposomes. Due to the presence of ester bond, phospholipids are easily hydrolyzed[8]. Niosomes are promising vehicle for drug delivery and being non-ionic. It is less toxic and improves the therapeutic index of drug by restricting its action to target cells. Niosomes or non-ionic surfactants are microscopic lamellar structure formed of the alkyl or dialkyl polyglycerol ether hydration in aqueous media[9]. The advantages of Niosomes are[10, 11, 12]:

1. They are osmotically stable. Drug molecules with a wide range of solubility can be accommodated in niosomes; they are able to entrap hydrophilic drug by partitioning of these molecules into their hydrophobic domain.
2. They can reduce drug toxicity because of their non-ionic nature.
3. Low cost of production as no special condition is required for handling and storage of niosomes.
4. Non-ionic surfactants are biodegradable, biocompatible and non-immunogenic.
5. They can be tailored according to the desired situation by modifying their structural characteristics (composition, fluidity and size).
6. They can enhance performance of drug by improving availability and controlled delivery at a particular site.
7. Niosomal dispersion in an aqueous phase can be emulsified in a non-aqueous phase to regulate the delivery rate of drug and administer normal vesicle in external non-ionic phase.

8. The vesicle suspension is water-based vehicle. This offers high patient compliance in comparison with oily dosage forms.
9. The vesicles may act as a depot, releasing the drug in a controlled manner.
10. They improve oral bioavailability of poorly absorbed drugs and enhance skin penetration of drugs.
11. They can be made to reach the site of action by oral, parenteral as well as topical routes.
12. They improve the therapeutic performance of the drug molecules by delayed clearance from the circulation, protecting the drug from biological environment and restricting effects to target cells.

Proniosomes are recent development in Novel drug delivery system. These are most advanced drug carrier in vesicular system which overcomes demerits of liposomes and niosomes such as[13]:

(1) Demerits of liposomes includes:

- Liposomes require special precautions and conditions for formula tion and preparations.
- Complex method for routine and large scale production.
- Less chemical stability.
- High cost.

(2) Demerits of niosomes includes physical instability such as:

- Aggregation.
- Fusion.
- Leaking of entrapped drug.
- Sedimentation[14].

Above mentioned demerits of physical instability may lead to hydrolysis of the encapsulated drug which affects the shelf life of the dispersion.

PRONIOSOMES

Proniosomes are dry formulation of water-soluble carrier particles that are coated with surfactant and can be measured out as needed and dehydrated to form niosomal dispersion immediately before use on brief agitation in hot aqueous media within minutes. The resulting niosomes are very similar to conventional niosomes and more uniform in size[15].

Advantages of proniosomes over niosomes[16, 17] include:

1. Avoiding problem of physical stability like aggregation, fusion, leaking.
2. Avoiding hydration of encapsulated drugs which is limiting the shelf-life of the dispersion.
3. Proniosomes are water soluble carrier particles that are coated with surfactant and can be hydrated to form niosomal dispersion immediately before use on brief agitation with hot aqueous medium. This has additional convenience of the transportation, distribution; storage and designing would be dry niosomes a promising industrial product.
4. Furthermore, unacceptable solvents are avoided in proniosomal formulations. The systems may be directly formulated into transdermal patches and doesn't require the dispersion of vesicles into polymeric matrix.
5. The storage makes proniosomes a versatile delivery system with potential for use with a wide range of active compounds.

Non-ionic surfactants, coating carriers and membrane stabilizers used for the preparation of proniosomes (as shown in Table 1).

Typically, Proniosomes may contain various non-ionic surfactants like span 20, 40, 60, 80 and 85, tween 20, 40, 80; lecithin, alcohol (ethanol, methanol, isopropyl alcohol) and chloroform. The chemical structure of surfactant influences drug entrapment efficiency [18]. Increasing the alkyl chain length is leading to higher entrapment efficiency. It had also been reported that spans having highest phase transition temperature provides highest entrapment for the drug and vice versa[19].

Table 1: Surfactants, coating carriers and membrane stabilizers used for preparation of proniosomes[16, 20.]

NON-IONIC SURFACTANT	COATING CARRIERS INVESTIGATED	MEMBRANE STABILIZERS
Span 20	Sucrose stearate	Cholesterol
Span 40	Sorbitol	Lecithin
Span 60	Maltodextrin(Maltrin M500)	
Span 80	Maltodextrin(Maltrin M700)	
Span 85	Glucose monohydrate	
Tween 20	Lactose monohydrate	
Tween 60	Spray dried lactose	
Tween 80		

Factors affecting physical nature of proniosomes[16]:

There are some factors such as hydration temperature, choice of surfactant, nature of membrane, nature of drug, etc., can affect significantly the physical nature of proniosomes [16] (as shown in figure 1).

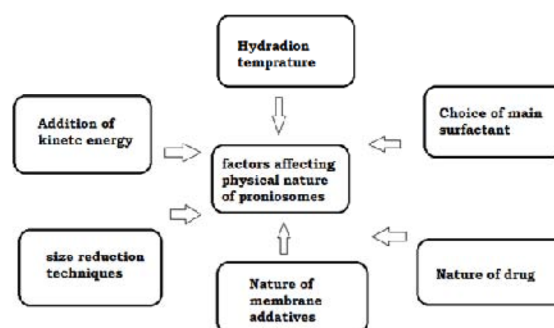

Figure 1: Factors affecting physical nature of proniosomes.

Proniosomes can be categorized in two major divisions such as

- Dry granular type of proniosomes
- Liquid crystalline proniosomes

DRY GRANULAR PRONIOSOMES

Dry granular type of proniosomes involves the coating of water-soluble carrier such as sorbitol and maltodextrin with surfactant. The result of coating process is a dry formulation in which each water-soluble particle is covered with thin film of surfactant. It is essential to prepare vesicles at a temperature above the transition temperature of the non-ionic surfactant being used in the formulation. These are further categorized as follows:

(a) Sorbitol based proniosomes

Sorbitol based proniosomes is a dry formulation that involves sorbitol as the carrier, which is further coated with non-ionic surfactant and is used as niosomes within minutes by addition of hot water followed by agitation. They are normally made by spraying surfactant mixture prepared in organic solvent onto the sorbitol powder and then evaporating the solvent. Since the sorbitol carrier is soluble in organic solvent, the process is required to be repeated till the desired surfactant coating has been achieved. The surfactant coating on the carrier is very thin and hydration of this coating allows multilamellar vesicles to form as the carrier dissolves[15, 21- 23].

(b) Maltodextrin based proniosomes

A proniosome formulation based on maltodextrin was recently developed that has potential application in deliver of hydrophobic or amphiphilic drugs. The better of these formulations used to hollow particle with exceptionally high surface area. The principal advantage with this formulation was the amount of carrier required to support the surfactant could be easily adjusted and proniosomes with very high mass ratios of surfactant to carrier could be prepared[17, 24].

LIQUID CRYSTALLINE PRONIOSOMES

When the surfactant molecules are kept in contact with water, there are three ways through which lipophilic chains of surfactants can be transformed into a disordered, liquid state called lytorophic liquid crystalline state (neat phase). These three ways are increasing temperature at kraft point (Tc), addition of solvent, which dissolves lipids; and use of both temperature and solvent. Neat phase or lamellar phase contains bilayer arranged in sheets over one another within intervening aqueous layer. These types of structures give typical X-ray diffraction and thread like bi-refringent structures under polarized microscope.

The liquid crystalline proniosomes or proniosomal gel acts as a reservoir for transdermal delivery of drug. The transdermal patch involves aluminum foil as the backing material along with plastic sheet (of suitable thickness stuck to the foil by means of adhesive). Proniosomal gel is spread evenly on the circular plastic sheet followed by covering of nylon mesh[25-29].

PRONISOMES AS DRUG CARRIERS

The proniosomes are promising drug carriers (as shown in the table 2) because they possess greater chemical stability and lack of many disadvantages associated with liposomes. It has additional merits with niosomes are low toxicity due to non-ionic nature, no requirement of special precautions and conditions for formulation and preparation. Niosomes have shown advantages as drug carriers. Such as low cost and chemical stability as compared to liposomes but they are associated with problem related to physical stability such as fusion, aggregation, sedimentation and leakage and storage.

Proniosomes are dry formulations of surfactant coated carrier vesicles which can be measured out as needed and rehydrated by brief agitation in hot water the resulting niosomes are very similar to conventional niosomes and more uniform size[30]. This proniosomes are minimizing the problems using dry, free flowing product which is more stable during storage and sterilization and it has additional merits of easy of transfer, distribution, measuring and storage make proniosomes a pronouncing versatile delivery system[15].

PREPARATION OF PRONIOSOMES

Carrier which is selected for proniosomes preparation should have following characteristics like free flow ability, non-toxicity, poor solubility in the loaded mixture solution and good water solubility for ease of hydration. Different carriers and non-ionic surfactants and membrane stabilizers are used for the proniosome preparation[16].

Slurry method: Proniosomes are prepared by developed slurry method using Maltodextrin as a carrier. The time required to produce proniosome by this is independent of the ratio of surfactant to carrier material. In slurry method, the entire volume of surfactant solution is added to Maltodextrin powder in rotary evaporator and vacuum applied the powder appears to be dry and free flowing.

Drug containing proniosomes-derived niosomes can be prepared in manner analogous to that used for the conventional niosomes, by adding drug to the surfactant mixture prior to spraying the solution onto the carrier (Sorbitol, Maltodextrin) or by addition of drug to the aqueous solution used to dissolve hydrate the proniosomes.

The required volume of surfactant and cholesterol stock solution per gram of carrier and drug should be dissolved in the solvent in 100 ml round bottom flask containing the carrier (Maltodextrin) Additional chloroform can be added to form slurry in case of lower surfactant loading. The flask has to be attached to a rotary flash evaporator to evaporator solvent at 50-60 rpm at a temperature of 45±2°C and a reduced pressure of 600mm Hg until the mass in the flask had become container under refrigeration in light[24, 35.]

Table 2: Proniosomes as a carrier of various drug molecules[20, 31-34.]

Drug	Hydrophilic or lipophilic	Category	Result(s)
Aceclofenac	Lipophilic	NSAIDS	The polynomial equation and contour plots developed by central composite design allowed to prepare proniosomes with optimum characteristic.
Alprenolol hydrochloride	Lipophilic	Anti-hypertensive	The use of the maltodextrin in proniosomes helps in enhancement of drug release.
Captopril	Hydrophilic	Anti-Hypertensive	Prolonged release of captopril.
Celecoxib	Lipophillic	Cyclooxygenase inhibitor	Enhanced bioavailability of celecoxib.
Clotrimazole	Lipophillic	Anti-fungal	The effects of different ratios of non-ionic surfactants on permeability profile were assessed
Chlorphenirami-ne maleate	Hydrophilic	Anti-histamine	Span 40 proniosomes showed optimum stability, loading efficiency and particle size and release kinetics suitable for transdermal delivery of drug.
Cromolyn Sodium	Hydrophilic	Anti-asthmatic and anti-allergic	High nebulisation efficiency percentage and good physical stability were observed.
Estradiol	Lipophilic	For symptomatic treatment of the usual symptoms associated with menopause	The non-ionic surfactant in proniosomal formulation helps in enhancement of drug permeation through the skin.
Flurbiprofen	Lipophilic	NSAIDS	The drug release rate from cholesterol free proniosomes was to be high.
Griseofulvin	Lipophilic	Anti-fungal	Enhanced absorption of the drug.
Haloperidol	Hydrophilic	Anti-psychotic effect	The formulation with single surfactant increased the permeation of drug more than those with mixture of surfactants.
Ibuprofen	Lipophilic	NSAIDS	Proniosomes derived niosomes are superior in their ability to release the drug at a constant rate.
Indomethacin	Lipophilic	NSAIDS	The release rate of the drug from the vesicle was in the controlled manner.
Ketoprofen	Lipophilic	NSAIDS	Demonstrated permeation enhancement of ketoprofen compared to plain gel.
Ketorolac	Lipophilic	NSAIDS	The drug entrapment was high within the lipid bilayers of vesicles.
Levovorgestrel	Lipophilic	Anti contraceptive	The study demonstrated the utility of proniosomal transdermal patch bearing levonorgestrel for effective contraception.
Losaratn potassium	Hydrophilic	Anti-hypertensive	Enhanced bioavailability and skin permeation.
Piroxicam	Lipophilic	NSAIDS	Span 60 based lecithin vesicle showed significant decrease in paw swelling. There is a increased drug delivery from lipid vesicles.
Tenoxicam	Lipophilic	NSAIDS	Tenoxicam loaded proniosomal formula proved to be non-irritant, with significantly higher anti-inflammatory and analgesic effects
Valsartan	hydrophobic	Anti-hypertensive	Proniosomes showed the influence of membrane additives on the physicochemical properties and stability.
Vinpocetine	hydrophilic	Dietary suppliment	Proniosomes were prepared to optimize the extent of drug permeation through the skin

Spray coated method: A 100 ml round bottom flask containing desired amount of carrier can be attached to rotary flash evaporator. A mixture of surfactant and cholesterol should be prepared and introduced into round bottom flask 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°C for 15-20 min. This process has to be prepared until all of the surfactant solution had been applied. The evaporation should be continued until the powder becomes completely dry[15, 30, 36.]

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 f 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°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 a Pronisomal gel[29].

FORMATION OF NIOSOMES FROM PRONIOSOMES[17, 24]

The niosomes can be prepared from the proniosomes (as shown in figure 2) by adding the aqueous phase with the drug to the proniosmes with brief agitation at a temperature greater than the mean transition phase temperature of the surfactant.

$$T > Tm$$

Where,

T = Temperature

Tm = Mean phase transition temperature

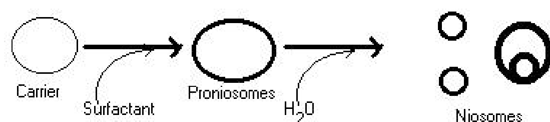

Figure 2: Formation of niosomes from proniossomes

CHARACTERIZATION OF PRONIOSOMES

Vesicle morphology: Vesicle morphology involves the measurement of size and shape of proniosomal vesicles. Size of proniosomal vesicles can be measured by dynamic light scattering method in two conditions: without agitation and with agitation. Hydration without agitation results in largest vesicle size. Scanning electron microscopy (SEM) can also be used for the measurement of vesicle size and shape. Determination of vesicle size is important for the topical application of vesicles. Size of captopril vesicles was found after agitation of dispersion as energy applied in agitation resulted in the breakage of the larger vesicles to small vesicles. The size of captopril vesicles was found 11.38-25.06 mm (without agitation) and 4.14-8.36 mm (with agitation). Hence, it can be concluded that increasing hydrophobicity of the surfactant monomer leads to a smaller size vesicles, since surface energy decreases with increasing the hydrophobicity.

The size distribution of niosomes with tweens was significantly lower than with span surfactants. The vesicle size analysis of Indomethacin niosomes showed that vesicles were discrete and separate with no aggregation or agglomeration. The diameter Indomethacin niosomes was found to be in the rage of 10-15 mm[37].

Haloperidol proniosomes with lower HLB values seemed to be mostly spherical and discrete with sharp boundaries having smooth and rigid surfaces. The main difference between deformable and rigid vesicles was found due to fluidity of the lipid bilayer of the deformable vesicles.

Shape and surface morphology: Surface morphology means roundness, smoothness and formation of aggregation. It was studied by scaning electron microscopy, optical microscopy, transmision electron microscopy[19].

Scanning electron microscopy: The surface morphology and size distribution of 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 tor, acceleration voltage: 30.00 KV) XL 30, (Philips, Netherlands)[17, 24].

Optical microscopy: The Niosomes were mounted on glass slides and viewed under a microscope (Medilux-207RII, Kyowa-Getner, Ambala, India) with 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[38].

Angle of repose: The angle of repose of dry proniosomes powder was measured by a funnel method. The proniosomes 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[15, 23, 24, 35, 39].

Encapsulation efficiency: The encapsulation efficiency of proniosomes is determined after separation of the un-entrapped drug.

(1) Separation of unentraped drug is done by the following techniques:

(a) Dialysis: The aqueous niosomal dispersion is dialyzed tubing against suitable dissolution medium at room temperature then samples are withdrawn from the medium at suitable time interval centrifuged and analyzed for drug content using UV spectroscopy[38].

(b) Gel filtration: The free drug is removed by gel filtration of niosomal dispersion through a sephadex G50 column and separated with suitable mobile phase and analyzed with analytical techniques[40].

(c) Centrifugation: The niosomal suspension is centrifuged and the surfactant is separated. The pellet is washed and then resuspended to obtain a niosomal suspension free from unentrapped drug[15].

(2) **Determination of entrapment efficiency of proniosomes:** The vesicles obtained after removal of unentraped drug by dialysis is then resuspended in 30% v/v of PEG 200 and 1 ml of 0.1% v/v triton x-100 solution was added to solubilize vesicles the resulted clear solution is then filtered and analyzed for drug content. The percentage of drug entrapped is calculated by using the following formula[29]:

Percent Entrapment = Amount of drug entrapped/total amount of drug*100

Drug release kinetics data analysis

The release data obtained from various formulations were studied further fitness of data in different kinetic models like Zero order, Higuchi's and peppa's.

In order to understand the kinetic and mechanism of drug release, the result of in-vitro drug release study of noisome were 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^2 and k values were calculated for the linear curve obtained by regression analysis of the above plots

$$C = K_0 t \quad \text{................ (1)}$$

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

$$Q = K_H t^{1/2} \quad \text{................ (2)}$$

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 peppa's model (equation 3) as log cumulative % drug release vs. log time and the exponent n was calculated through the slope of the straight line.

$$M_t / M_\infty = bt^n \quad \text{................. (3)}$$

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 near 1.0 then it is Non-Fickian diffusion[41].

***In-vitro* methods for the assessment of drug release from proniosomes**

(1) Dialysis tubing: In-vitro drug release could be achieved by using dialysis tubing. The proniosomes is prewashed dialysis tubing, which can be hermetically sealed. The dialysis sac is then dialyzed against a suitable dissolution medium at room temperature; the samples are withdrawn from the medium at suitable intervals, centrifuged and analyzed for drug content using suitable method (UV spectroscopy, HPLC etc.). The maintenance of sink condition is essential[42].

(2) Reverse dialysis: In this technique a number of small dialysis as containing 1 ml of dissolution medium are placed in proniosomes. The proniosomes are then displaced into the dissolution medium. The direct dilution of the proniosomes is possible with this method; however the rapid release cannot be quantified using this method[42].

(3) Franz diffusion cell: The in-vitro studies can be performed by using Franz diffusion cell. Proniosomes are placed in the donor chamber of a Franz diffusion cell fitted with a cellophane membrane. The proniosomes is then dialyzed against suitable dissolution medium at room temperature; the samples are withdrawn from the medium at suitable intervals, and analyzed for drug content using suitable method (UV spectroscopy, HPLC, etc.). The maintenance of sink condition is essential[43].

***In-vitro* permeation study:** The rate of permeation of drugs from proniosomal formulations can be determined by using Franz diffusion cell, Keshary chien diffusion cell and drug content can be determined by suitable analytical method. The interaction between skin and proniosomes may be an important contribution to the improvement of transdermal drug delivery. One of the possible mechanisms for niosomal permeability enhancement is structural modification of stratum corneum. Both phospholipids and non-ionic surfactants used in proniosomes act as penetration enhancers, leading to increase the permeation of the many drugs[44].

The permeation of haloperidol from proniosomal formulations was determined by flow through diffusion cell. Direct contact and adherence of vesicles with skin surface is important for the drug to penetrate and partition between the stratum corneum and formulation.

Zeta potential analysis: Zeta potential analysis is done for determining the colloidal properties of the prepared formulations. The suitably diluted proniosomes derived noisome dispersion was determined using zeta potential analyzer based on Electrophorectic light scattering and laser Doppler Velocimetery 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 were obtained directly from the measurement[45].

Stability studies on proniosomes: Stability studies carried out by storing the prepared proniosomes at various temperature conditions like refrigeration on (2°-8°C) room temperature (25°±0.5°C) and elevated temperature (45° C±-0.5°C) from a period of one month to three months. Drug content and variation in the average vesicle diameter were periodically monitored. ICH guidelines suggests stability studies for dry proniosomes powder meant for reconstitution should be studied foe accelerated stability at 75% relative humidity as per international climatic zones and climatic conditions[35, 37, 46].

Various characterization parameters and instruments /methods used in proniosomes are shown in Table 3.

APPLICATIONS OF PRONIOSOMES

(1) Drug targeting: One of the most useful aspects of proniosomes is their ability to target drugs. Proniosomes can be used to target drugs to the reticulo-endothelial system. The reticulo-endothelium system[47] (RES) preferentially takes up proniosomes vesicles. The uptake of proniosomes is controlled by circulating serum factors called opsonins. These opsonins mark the noisome for clearance. Such localization of drugs is utilized to treat tumors in animals known to metastasize to the liver and spleen[8]. This localization of the drugs can also be used for treating parasitic infections of the liver. Proniosomes can

also be utilized for targeting drugs to organs other than the RES. A carrier system (such as antibodies) can be attached to proniosomes (as immunoglobin bind readily to the lipid surface of the noisome) to target them to specific organs[48]. Many cells also possess carbohydrates determinates, and this can be exploited by niosomes to direct carrier system to particular cells.

Table 3: Characterization parameters and instrument/methods used in proniosomes

PARAMETER	INSTRUMENT/METHOD USED
Vesicle morphology	Scanning electron microscopy, Laser microscopy.
Shape and surface morphology	Optical microscopy, Scanning microscopy, Transmission microscopy.
Angle of repose	Funnel method
Encapsulation efficiency	Diode array spectrophotometer, Centrifugation method, Dialysis method.
Drug release kinetic data analysis	Higuchi's model, Peppa's model.
In-vitro methods for assessment drug release from proniosomes	Dialysis tubing, Reverse dialysis, Franz diffusion cell.
In-vitro permeation study	Franz diffusion cell, Keshary chien diffusion cell
Zeta potential analysis	Zeta potential probe model.

(2) Anti-neoplatic treatment[49, 50]: Most antineoplastic drugs cause severe side effects. Proniosomes can alter the metabolism; prolong circulation and half life of the drug, thus decreasing the side effects of the drugs. Proniosomal entrapment of Doxorubicin and Methotrexate[51, 52] (in two separate studies) showed beneficial effects over the unentraped drugs, such as decreased rate of proliferation of the tumor and higher plasma levels accompanied by slower elimination[53].

(3) Treatment of leishmaniasis[54]: Leishmanasis 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 proniosomes 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.

(4) Delivery of peptide drugs[55]: Oral peptide drug delivery has long been faced with a challenge of bypassing the enzymes which would breakdown the peptide. Use of proniosomes 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 proniosomes showed that entrapment of the drug significantly increased the stability of the peptide.

(5) Uses in studying immune response[56]: Proniosomes are used in studying immune response due to their immunological selectivity, low toxicity and greater stability. Proniosome are being used to study the nature of the immune response provoked by antigens.

(6) Niosomes as carriers for haemoglobin[57]: Proniosomes can be used as carriers for haemoglobin within the blood. The proniosomal vesicle is permeable to oxygen and hence can act as a carrier for haemoglobin in anaemic patients.

(7) Transdermal drug delivery systems[58]: One of the most useful aspects of proniosomes is that they greatly enhance the uptake of drugs through the skin. Transdermal drug delivery utilizing proniosomal technology is widely used in cosmetics; In fact, it was one of the first uses of the niosomes[59]. Topical use of proniosome entrapped antibiotics to treat acne is done. The penetration of the drugs through the skin is greatly increased as compared to un-entrapped drug[60]. Recently, transdermal vaccines utilizing proniosomal technology is also being researched. The proniosome (along with liposomes and transferomes) can be utilized for topical immunization using tetanus toxoid. However, the current technology in proniosomes allows only a weak immune response, and thus more research to be done in this field.

(8) Sustained release[61]: The role of liver as a depot for methotrexate after proniosomes are taken up by the liver cells. Sustained release action of proniosomes can be applied to drugs with low therapeutic index and low water solubility since those could be maintained in the circulation via proniosomal encapsulation.

(9) Localized drug action[35, 51]: Drug delivery through proniosomes 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. Antimonials encapsulated within proniosomes 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 proniosomal drug delivery technology is still at an infancy stage, but this type of drug delivery system has promise in cancer chemotherapy and anti-leishmanial therapy.

CONCLUSION

Proniosomes derived niosomes represent a promising drug delivery module. These systems have been found to be more stable during sterilization and storage than niosomes. Proniosomes are thought to be better candidates of drug delivery as compared to liposomes and niosomes due to various factors like cost, stability etc. Proniosomes have been tested to encapsulate lipophilic as well as hydrophilic drug molecules. The use of proniosomal carrier results in delivery of high concentration of active agent(s), regulated by composition and their physical characteristics. Various types of drug deliveries can be possible using

proniosomes based niosomes like targeting, ophthalmic, topical, parenteral, peroral vaccine etc. More researches are carried out in this field to know the exact potential in this novel drug delivery system.

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About Corresponding Author: Mr. Nitan Bharti

Mr. Nitan is graduated from Guru Nanak Dev University, Amritsar, Punjab, India and post graduated from Rajiv Gandhi University of Health and Sciences, Bangalore, Karnataka, India. He is also pursuing his Ph.D from Shoolini University, Solan, Himachal Pradesh, India. He has a teaching experience of 6 years in Sri Sai College of Pharmacy, Badhani, Pathankot, Punjab. He is also guiding research projects of both B.Pharm and M.Pharm students.