PRONIOSOMES AS DRUG CARRIERS

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ABSTRACT
Approaches to stabilize niosomal drug delivery system without affecting its properties of merits have resulted in the development of the promising drug carrier, proniosomes. Proniosomes is dry formulation using suitable carrier coated with non ionic surfactants and can be converted into niosomes immediately before use by hydration. These proniosome-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 preparation, characterization, entrapment efficiency, *in vitro* drug release, applications and merits.

Keywords: Proniosomes, characterization, medical applications.

INTRODUCTION

From early 1980s, niosomes (Schreier and Bouwstra, 1994, Baillie *et al.,* 1985) have gained wide attention by researchers for their use as drug targeting agents, drug carriers to have variety of merits while avoiding demerits associated with the conventional form of drugs. Niosomes were studied as better alternatives to liposomes for entrapping both hydrophilic and hydrophobic drugs (Yosika *et al*., 1994, Uchegbu *et al.,* 1995 and Uchegbu and Vyas, 1998). From a technical point of view, niosomes are promising drug carriers as they possess greater chemical stability and lack of many disadvantages associated with liposomes (Hunt and Tsang, 1981, Wong and Thompson, 1982, Frfkjaer *et al.,* 1984, Gregoriadis, 1984, Niven *et al.,* 1992 and Muller *et al.,* 2002) such as high cost and the variable purity problems of phospholipids (Vora, *et al.,* 1998). The additional merits with niosomes are low toxicity due to non ionic nature, no requirement of special precautions and conditions for formulation and preparation (Carafa *et al.,* 2002.) Moreover it is the simple method for the routine and large-scale production of niosomes without the use of unacceptable solvents (Alsarra *et al.,* 2004). However, stability is a prime concern in the development of any formulation and even though, niosomes have shown advantages as drug carriers, such as being low cost and chemically stable as compared to liposomes (Namdeo and Jain, 1999). They too, are associated with problems related to physical stability, such as fusion, aggregation, sedimentation, and leakage on storage (Solanki *et al*., 2007).

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 (Solanki *et al*., 2007). The resulting niosomes are very similar to conventional niosomes and more uniform in size (Hu and Rhodes, 1999). The proniosome approach (Hu and Rhodes, 1999; Blazek-Welsh and Rhodes, 2001a and b) minimizes these problems by using dry, free-flowing product, which is more stable during sterilization and storage. Ease of transfer, distribution, measuring, and storage make proniosomes a versatile delivery system with potential for use with a wide range of active compounds (Solanki *et al*., 2007).

In general a limited number of studies are available which deal with the preparation and evaluation of proniosomes (Vora, *et al.,* 1998, Hu and Rhodes, 1999; Blazek-Welsh and Rhodes, 2001a, b; Fang, *et al.,* 2001, Alsarra, *et al.,* 2004, Solanki *et al*., 2007, Ankur Gupta *et al*., 2007, Azeem *et al*., 2008 and Abd-Elbary *et al*., 2008). These studies mostly focused on the utilization of proniosomes in transdermal drug delivery. This article briefly reviews the trends and the future perspective in the development of proniosomal drug delivery systems.

Preparation of proniosomes
here are number of components present in proniosomes with non ionic surfactants and cholesterol, lecithin being the main ingredient. Desirable characteristics of the selected carrier that could be used in the preparation of proniosomes were addressed by Payne *et al*. (2008). These include; safety and non-toxicity, free flowability, poor solubility in the loaded mixture solution and good water solubility for ease of hydration (Abd-Elbary *et al*., 2008). Different carriers and non ionic surfactants and membrane stabilizers used for the proniosome preparation are shown in table 1. Three different methods were reported for the preparation of proniosomes.

Slurry method: Maltodextrin powder 10 g as carrier is added to a 250-mL round-bottom flask and the entire

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Table 1: Non-ionic surfactants and coating carriers used for the preparation of proniosomes

S. No.	Non ionic surfactants used
1	Span 20 (Vora *et al.*, 1998 and Alsarra, *et al.*, 2004)
2	Span 40 (Vora *et al.*, 1998 and Fang *et al.*, 2001)
3	Span 60 (Vora *et al.*, 1998 and Blazek-Welsh and Rhodes, 2001a, b)
4	Span 80 (Vora *et al.*, 1998 and Ankur Gupta *et al*., 2007)
5	Span 85 (Fang *et al.*, 2001)
6	Tween 20 (Fang *et al.*, 2001 and Alsarra, *et al.*, 2004)
7	Tween 60 (Fang *et al.*, 2001)
8	Tween 80 (Fang *et al.*, 2001)
	Coating materials investigated
1	Sucrose stearate (Abd-Elbary et *al*., 2008)
2	Sorbitol (Hu and David G. Rhodes, 1999 and Ankur Gupta *et al*., 2007)
3	Maltodextrin (Maltrin M500) (Blazek-Welsh and Rhodes, 2001a and b)
4	Maltodextrin (Maltrin M700) (Blazek-Welsh and Rhodes, 2001a and b)
5	Glucose monohydrate (Abd-Elbary et *al*., 2008)
6	Lactose monohydrate (Abd-Elbary et *al*., 2008)
7	Spray dried lactose (Abd-Elbary et *al*., 2008)
	Membrane stabilizers used
1	Cholesterol (Solanki *et al*., 2007 and Abd-Elbary et *al*., 2008)
2	Lecithin (Fang *et al.*, 2001, Alsarra, *et al.*, 2004 and Ankur Gupta *et al*., 2007)

volume of surfactant solution (14.5 mL) 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 and free flowing. The flask was removed from the evaporator and kept under vacuum overnight. Proniosome powder was stored in sealed containers at 4°C. The time required to produce proniosomes is independent of the ratio of surfactant solution to carrier material and appears to be scalable (Blazek-Welsh and Rhodes, 2001a and b; Solanki *et al*., 2007 and Perrett *et al.*, 1991).

Coacervation phase separation method: This method is widely adopted to prepare proniosomal gel. Precisely 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 (0.5 ml) is added to it. After warming, all the ingredients are mixed well with a glass rod; the open end of the glass bottle is covered with a 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 (0.1% glycerol solution) is added and warmed on a water bath till a clear solution was formed which is then converted into proniosomal gel on cooling (Vora *et al.*, 1998 and Gupta *et al*., 2007).

Slow spray-coating method: This method involves preparation of proniosomes by spraying surfactant in organic solvent onto sorbitol powder and then evaporating the solvent. Because the sorbitol carrier is soluble in the organic solvent, it is necessary to repeat the process until the desired surfactant loading 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 (Bangham *et al.*, 1965 and Yoshioka *et al.*, 1994). The resulting niosomes are very similar to those produced by conventional methods and the size distribution is more uniform. It is suggested that this formulation could provide a suitable method for formulating hydrophobic drugs in a lipid suspension without concerns over instability of the suspension or susceptibility of the active ingredient to hydrolysis (Hu and David G.Rhodes, 1999). This method was reported to be tedious since the sorbitol carrier for formulating proniosomes is soluble in the solvent used to deposit the surfactant. Sorbitol is also found to interfere with the encapsulation of certain drugs.

Preparation of niosomes from proniosomes by hydration

Prepared proniosome powder is weighed and filled in screw cap vials. Water or saline at 80°C is added and the vials capped. The vials are attached to a vortex mixer and agitated for 2 minutes to get niosomal suspension (Blazek-Welsh and Rhodes, 2001a).

Characterization of proniosomes

Proniosomes are characterized for vesicle size, size distribution, shape, surface morphology, aerodynamic behavior, spontaneity are enlisted in table 2.

Separation free (unentrapped) drug

The encapsulation efficiency of proniosomes is determined after separation of the unentrapped drug from

Table 2: Methods for the characterization of proniosomes

S. No.	Parameter	Instrument/Method Employed
1	Vesicle size determination and size distribution	1. Malvern Mastersizer (Abd-Elbary *et al*., 2008) 2. Optical microscopy (Ankur Gupta *et al*., 2007) 3. Laser diffraction particle size analyzer (Hu and Rhodes, 1999 and Solanki *et al*., 2007) 4. Coulter submicron size analyzer (Fang *et al.,* 2001)
2	Shape and surface morphological characterization	1. Optical microscopy (Ankur Gupta *et al*., 2007) 2. Transmission electron microscopy (Abd-Elbary *et al.,* 2008) 3. Scanning electron microscopy (Alsarra, *et al.,* 2004)
3	Aerodynamic behavior	Twin-Stage Impinger (Abd-Elbary *et al.,* 2008)
4	Angle of repose	Funnel method (Hu and David G.Rhodes, 1999 and Lieberman *et al.,* 1990)
5	Spontaneity (Rate of hydration)	Using Neubaur's chamber (Vora *et al.,* 1998)

Table 3: Studies on proniosomes and their medical applications

S. No.	Purpose/Application	Drugs studied
1	Transdermal drug delivery	Ketorolac (Alsarra, *et al.,* 2004) Estradiol (Fang *et al.,* 2001) Captopril (Ankur Gupta *et al*., 2007) Levonorgestrel (Vora *et al.,* 1998) Frusemide (Adnan Azeem *et al*., 2008)
2	Inhalation therapy (Nebulisable drug delivery)	Cromolyn sodium (Abd-Elbary et *al*., 2008)
3	Enhancement of solubility	Piroxicam (Solanki *et al*., 2007)
4	Improved permeability (Partitioning behavior) of highly hydrophilic drug	Alprenolol hydrochloride (Blazek and Rhodes, 2001a)
5	Prolonged release for improved anti-inflammatory activity	Ibuprofen (Hu and Rhodes, 1999)

entrapped drug using techniques like centrifugation (Hu and Rhodes, 1999, Fang *et al.,* 2001, Blazek-Welsh and Rhodes, 2001a, Alsarra, *et al.,* 2004, Gupta *et al*., 2007 and Abd-Elbary *et al*., 2008) and by using cellophane dialysis tubing D-9777 and dialyzing exhaustively against 400 mL saline at 4°C for 24 hours (Vora *et al.,* 1998 and Solanki *et al*., 2007).

Determination of entrapment efficiency (measurement of partitioning)

The vesicles obtained after removal of drug by centrifugation, the pellet was collected and resuspended in 0.9% saline followed by addition of 1:1 ratio of absolute alcohol: propylene glycol mixture to lyse the vesicles (Vora *et al.,* 1998).

The vesicles obtained after removal of unentrapped drug by dialysis is then resuspended in 30% v/v of PEG-200 and 1ml of 0.1% v/v Triton X-100 solution was added to solubilize vesicles (Abd-Elbary *et al.,* 2008). The resulting clear solution is then filtered and analysed for drug content.

The percentage of drug entrapped is calculated using the following formula (Hao *et al*., 2002 and Abd-Elbary *et al*., 2008).

$$EE\ \% = \frac{ED}{TD} \times 100$$

Where EE% is the entrapment efficiency percent, ED is the entrapped drug concentration and TD is the theoretical drug concentration.

In vitro drug release from proniosomal vesicles

In vitro drug release and skin permeation studies for proniosomes were determined by different techniques like Franz diffusion cell (Fang *et al.,* 2001b), Keshary-Chien diffusion cell (Vora *et al.,* 1998), Cellophane dialyzing membrane (Alsarra, *et al.,* 2004 and Ankur Gupta *et al*., 2007), USP Dissolution apparatus Type I (Abd-Elbary *et al*., 2008), Spectrapor© molecular porous membrane tubing (Abd-Elbary *et al*., 2008).

In vitro skin permeation studies have been carried out using dorsal skin of albino rabbit (Alsarra *et al.,* 2004),

female albino rat (Sprauge-Dawley strain), flank skin (Vora *et al.,* 1998) and Wister rat skin (7-9 weeks old) (Fang *et al.,* 2001). Drug release from proniosome-derived niosomal vesicles can follow any one or more of the following mechanisms; desorption from surface of vesicles or diffusion of drug from bilayered membrane or a combined desorption and diffusion mechanism.

Stability studies on proniosomes

Stability studies were carried out by storing the prepared proniosomes at various temperature conditions like refrigeration temperature (2°-8°C), room temperature (25° ± 0.5°C) and elevated temperature (45° ± 0.5°C) from a period of one month to three months. Drug content and variation in the average vesicle diameter were periodically monitored (Vora *et al.,* 1998, Gupta *et al*., 2007 and Abd-Elbary *et al*., 2008).

ICH guidelines suggests stability studies for the dry proniosome powders meant for reconstitution should be studied for accelerated stability at 40°C/75% relative humidity as per international climatic zones and climatic conditions (WHO, 1996). For long term stability studies the temperature is 25°C/60% RH for the countries in zone I & II and for the countries in Zone III & IV the temperature is 30°C/65% RH. Product should be evaluated for appearance, colour, assay, pH, preservative content, particulate matter, sterility and pyrogenicity

Different studies carried out on proniosomes and their medical applications/purpose are summarized in table 3.

CONCLUSION

Proniosomes are promising drug carriers for the future with greater physical and chemical stability and potentially scalable for commercial viability. The delivery system holds promise for the effective drug delivery for amphiphilic drugs. Proniosomes has attracted a great deal of attention for the delivery of drugs through transdermal route because of the advantages like non-toxicity and penetration enhancing effect of surfactants and effective modification of drug release properties. Proniosomes in dry powder form makes the possibility of convenient unit dosing as the proniosome powder can further be processed to make beads, tablets or capsules. The findings of the studies on proniosomes till date, opens the door for the future use of different carrier materials with biocompatibility and suitability for the preparation of proniosomes. However, future experiments should explore the suitability of proniosomes with more drugs having defined drawbacks for improved and effective intended therapy. Studies should be explored to assess the ability of different carrier materials to formulate proniosomes and the ability of proniosomes to deliver the drugs meant for administration through various routes.

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