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Proniosomes: A Review

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Abstract: Proniosomes are promising drug carriers and are more advantageous than the conventional niosomes and liposomes. Proniosomes is dry formulation non ionic surfactants coated carriers and can be converted into niosome immediately before use by hydration. Approaches to stabilize niosomal drug delivery system without affecting its properties of merits have resulted in the development of the promising drug carrier proniosomes. These proniosome-derived niosomes are as good as or even better than conventional niosomes. This review article is focusing on different aspects related to proniosomes such as advantages, preparation, characterization, applications and merits of proniosome.

Key words: Proniosomes, niosomes, preparation, characterization, applications

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1. Introduction

From early 1980s, niosomes¹⁻² have gained wide attention by researchers for their use as drug targeting agents. Proniosomes are dry formulations of non ionic surfactant coated carrier and rehydrated using hot water by agitation method. Proniosomes minimize problems of niosomes such as aggregation, fusion and leaking and sedimentation and easy of transfer, distribution, measuring and storage makes proniosomes a versatile delivery system. Stability of dry proniosomes is expected to be more stable than pre-manufactured niosomal formulation. Proniosomes are dry powder, which makes further processing and packaging possible. The dry powder form provides optimal flexibility and unit dosing. Drug delivery systems having a vesicular carrier such as liposome and niosomes have distinct advantages over conventional dosage forms. They may serve as a solubilisation matrix, as local depot, as permeation enhancer or as a rate limiting membrane barrier for the modulation of systemic absorption of drugs via the skin³. In recent years, non-ionic surfactants vesicle also referred to as niosomes, have been studied as alternative to conventional liposomes in drug delivery⁴. Compared to liposomes (phospholipids vesicle), they offer greater choice of surfactants lower cost and higher chemical stability. 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 minutes¹⁴. The proniosomal approach minimizes the above mentioned problems, as it involves a dry product or a liquid crystalline gel that can be hydrated immediately before use^{6,7}. Proniosomes are water soluble carrier particulates that are coated with surfactants and can be hydrated to form niosomal dispersion immediately before use in hot aqueous media⁸. Proniosomes offer a versatile drug delivery concept with potential for delivery of drugs via transdermal route. This would be possible if proniosome form niosomes upon hydration with water from skin following topical application under occlusive conditions⁹.

Advantages of Proniosomes:

- Proniosomes minimizes the problems of niosomes such as physical stability like leaking, fusion, aggregation, sedimentation.
- It Avoid hydrolysis of encapsulated drugs.
- Liposomes and niosomes require special storage and handling while proniosomes not required.

Method of preparations:

Various methods are used for preparation of proniosomes such as:

Slurry method:

Powdered drug is poured into a 250-mL round-bottom flask and the specific volume of surfactant solution is 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 is removed from the evaporator and kept under vacuum overnight. Proniosome dry powder was stored in sealed containers at 4°C⁵.

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 are mixed well with a glass rod and 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 is added and warmed on a water bath till a clear solution was formed which is then converted into proniosomal on cooling^{9, 11}.

Slow spray coating method:

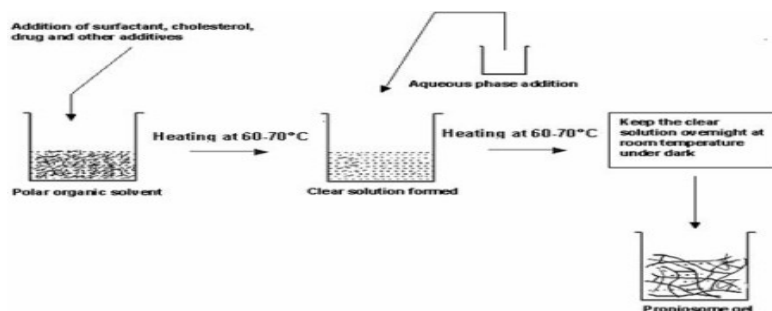
A 100 ml round bottom flask containing desired amount of carrier can be attached to rotary flash evaporator. A mixture of cholesterol and surfactants is prepared and poured into round bottom flask on rotary evaporator by sequential spraying of aliquots onto carrier's surface. The evaporator is used to 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.

Factors affecting the formulation of Proniosomes:

- Surface chain length
- Drug concentration
- Cholesterol content
- Charge of the lipid
- Total lipid concentration
- pH of the medium

Formulation 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 are capped. The vials are attached to a vortex mixer and agitated for 2 minutes to get niosomal suspension¹².



Characterization of Proniosomes:

Proniosomes are characterized for particle size, size distribution, shape, surface morphology and spontaneity.

Table 1: Methods /equipments used for the characterization of proniosomes

Sr. No.	Parameter	Analytical method/equipment used for characterization of parameter
1.	Particle size and size distribution	Laser diffraction particle size analyser Photon correlation spectroscopy ^{14,15}
2.	Shape and surface morphological characterization	Scanning electron microscopy Transmission electron microscopy, Optical microscopy ^{16,17,18}
3.	Angle of repose	Funnel method ¹⁶
4.	Spontaneity (Rate of hydration)	Neubaur's chamber ¹⁷

Separation of free (unentrapped) drug:

The encapsulation efficiency of proniosomes is determined after separation of the unentrapped drug from entrapped drug using techniques like centrifugation^{8,12} and by using cellophane dialysis tubing D-9777 and dialyzing exhaustively against 400 mL saline at 4°C for 24 hours^{11,5}.

Entrapment efficiency (measurement of partitioning):

The vesicles obtained after removal of drug by centrifugation, the pellet was collected and re suspended in 0.9% saline followed by addition of 1:1 ratio of absolute alcohol: propylene glycol mixture to lyse the vesicles¹¹. 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 vesicles¹⁹. The resulting clear solution is then filtered and analysed for drug content. The percentage of drug entrapped is calculated using the following formula.

$$\text{Entrapment efficiency\%} = \frac{\text{Entrapment efficiency}}{\text{Theoretical drug concentration}} \times 100$$

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, Keshary-Chien diffusion cell¹¹, Cellophane dialyzing membrane, USP Dissolution apparatus Type I¹⁰, Spectrapor© molecular porous membrane tubing¹⁰.

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^{9,10,11}.

Particle size determination:

The vesicle size of each niosomal (formulae N1–N6) and proniosome-derived niosomal formulations (formulae PN (D18-11 and D18-16) was determined using Master sizer S laser different meter (Malvern instruments, Malvern, Worcestershire, UK) at 25±0.5°C. or size measurements, the preparation was appropriately diluted with purified water and measured using a lens (with a laser range of 300 mm that measure particle size range from 0.5 to 900m, and a beam length of 2.4 mm was attached to a measuring cell). The obscuration level was kept at 10% at a stable count rate Three replicates were taken for each sample and polystyrene beads was used as a standard to check instrument performance.

Scanning electron microscopy:

Proniosomes, prepared as described above, were sprinkled on double-sided conductive carbon tape on an aluminum stub. Excess sample was blown off with compressed air. The specimen was then coated with Au: Pd (60:40) using a Ladd Sputter Coater at 2.5 KV and 20 mA for 45 s. The coated specimen was observed using a Philips 515 Scanning Electron Microscope at 50KV and recorded on Polaroid PIN 55 film.

Statistical analysis:

Statistical analysis was done by means of one way anova followed by Tukey's post-hoc test, p value <0.05 was considered statistically significant.

Table 2: Studies on proniosome and their medical applications

S. no.	Purpose and Application	Drug Studied
1.	Transdermal drug delivery	Ketorolac ²⁵ Estradiol; Captopril; Levonorgestrel ¹¹ Frusemide
2.	Inhalation therapy	Cromolyn sodium ¹⁰
3.	Improved permeability	Alprenolol hydrochloride ¹²
4.	Prolonged release for improved anti-inflammatory activity	Ibuprofen ⁸

Application of Proniosome:

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.^{12,20}

Hypertension:

Fabricated proniosomes using different non-ionic surfactants, such as Span 20, Span 40, Span60, Span 80, Tween 20, Tween 40, and Tween 80 fortransdermal drug delivery system of losartanpotassium. proniosomal formulation.^{19,20}

Skin disorders

Developed a proniosomal gel fortransdermal drug delivery of chlorpheniraminemaleate (CPM). The system was formulated withSpan 40 and evaluated for the effect of compositionof formulation.^{20,21}

Hormonal insufficiencies

A proniosome based transdermal drug deliverysystem of levonorgestrel (LN) was developed andextensively characterized both in vitro and in vivo.The proniosomal structure was liquid crystallinecompactniosomes hybrid which could beconverted into niosomes upon hydration. Thesystem was evaluated in vitro for drug loading, rate of hydration (spontaneity), vesicle size,polydispersity, entrapment efficiency and drugdiffusion across rat skin.^{20,22}

Antibacterial therapy:

Amphotericin-b proliposomes could be stored for 9 months without significant changes in distribution of vesicle size and for 6 months without loss of pharmacological activity.^{20,23}

Carriers for Haemoglobin:

Niosomes can be used as carriers for haemoglobin within the blood.

Used in Cardiac disorders:

Proniosomal carrier system for captopril for the treatment of hypertension 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.^{20, 24}

2. Conclusion

Proniosomes are very effective drug carrier rather than liposome or niosome. Proniosomes are novel drug carriers with greater physical and chemical stability and potentially scalable for commercial viability. Proniosomes are better drug carrier as compared to liposomes and niosomes due to storage, transport and unit dosing convenience. More researches have to be made in this field to come out with all the potential in this novel drug delivery system.

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