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Proniosome: Present Scenario and Future Trends

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ABSTRACT

In recent years considerable attention has been focused on the vesicular based drug delivery system. Vesicular systems are a novel means of drug delivery that can enhance the bioavailability of encapsulated drugs and provide therapeutic effectivity in a controlled manner for a prolonged period. The drug delivery using colloidal particulate carriers such as liposomes, niosomes are occurring but these systems have some chemical problems associated with degradation by hydrolysis or oxidation as well as physical problems such as sedimentation, aggregation, or fusion during storage. So, a novel approach was adopted in dealing with these problems is, proniosomes which are converted to niosomes upon hydration. Proniosomes are dry formulation or semisolid formulation of water-soluble carrier particles that are coated with a surfactant. This review focuses on different aspects of proniosome such as scope, merits, preparation, characterization, drug release, present scenario, and future trends.

INTRODUCTION:

Scope: Proniosome has found to be more stable during sterilization and storage than niosomes. It can entrap both hydrophilic and hydrophobic drug. Proniosome are better candidate for drug delivery as compared to liposome, niosomes, transfersome due to various factors like cost, stability etc. Dry powder form of proniosomes makes them suitable for preparing unit dosage forms such as tablets, capsule and beads. Higher stability of peptides can be achieved by proniosomal technology. There is a lot to scope to investigate new carrier material for preparation of proniosomes and their potential remains to be investigated to full extent.

Present Scenario: Proniosomes are non hydrated niosomes, which upon hydration formed niosomes. The stability and shelf life of proniosomes especially have been found to be much better and prolonged in comparison to other vesicular systems. Now a day's researcher focus is shifted to formulation of proniosomes by using herbal drugs because of having minimum side effects. They are more convenient for the delivery of vaccine and antigens.

The vesicular system is a novel means of drug delivery that can enhance the bioavailability of encapsulated drugs, targeted and controlled drug delivery, and helps in prolonging drug duration in the systemic circulation, and decrease toxicity (1). Vesicles are colloidal particles in which a concentric bilayer is made up of amphiphilic molecules surrounded by an aqueous compartment. Based on this technique, several vesicular drug delivery systems are evolved such as liposomes, niosomes, and proniosomes (2).

Proniosomes are one of the provesicular approaches which overcome the limitation of other vesicular drug delivery system (3). Proniosomes are vesicular systems, in which the vesicles are made up of non-ionic based surfactants, cholesterol, and other additives which may be hydrated immediately before use to yield aqueous niosomes dispersions(4).

Proniosomes exists in two forms depending on the type of carrier and method of preparation:

a.) Dry granular proniosomes:

Sorbitol based proniosomes: Proniosomal powders are dry formulation containing water-soluble carrier particles imbibed with surfactants which can be measured as needed and

dehydrated to form niosomal dispersions immediately before use on brief agitation in hot aqueous media within minutes (5).

Maltodextrin based proniosomes are prepared by the fast slurry method. Maltodextrin is a mixture of glucose, disaccharides, and polysaccharides, obtained by the partial hydrolysis of starch (6).

b.) Semisolid liquid proniosomes: Proniosomes are prepared by the coacervation phase separation method. It is easily formed by dissolving the surfactant in a minimal amount of acceptable solvent and the least amount of aqueous phase (7).

Several studies have been reported which prove the utility of oral proniosomal powder in providing enhanced solubility and bioavailability for poorly soluble drugs.

Merits:

Liposomes and niosomes are well known drug delivery systems. But these delivery systems have many disadvantages in terms of preparation, storage, and sterilization, etc. The disadvantages of liposomes and niosomes are overcome by proniosome:-

1. Liposomes and niosomes are dispersed aqueous systems and have a problem of degradation by hydrolysis or oxidation (8).

2. Proniosmes do not require special storage and handling but liposomes and niosomes require it (8).

3. Poniosomes are easy to transfer, distribute, measuring and storage.

4. Proniosomes exhibit better purity than liposomes (9).

5. It should provide drug delivery with improved bioavailability and reduced side effects (9).

6. It shows a controlled and sustained release of drugs due to depot formation (9).

7. It exhibits better purity than liposomes (10).

8. Avoiding hydrolysis of encapsulated drugs which limits the shelf life of the dispersion (10).

Niosomes formation from proniosomes by hydration:

The niosomes can be prepared by hydration of proniosomes, where the aqueous phase containing the drug should be added to the proniosomes with brief agitation at a temperature greater than the mean transition phase temperature of the surfactant (11).

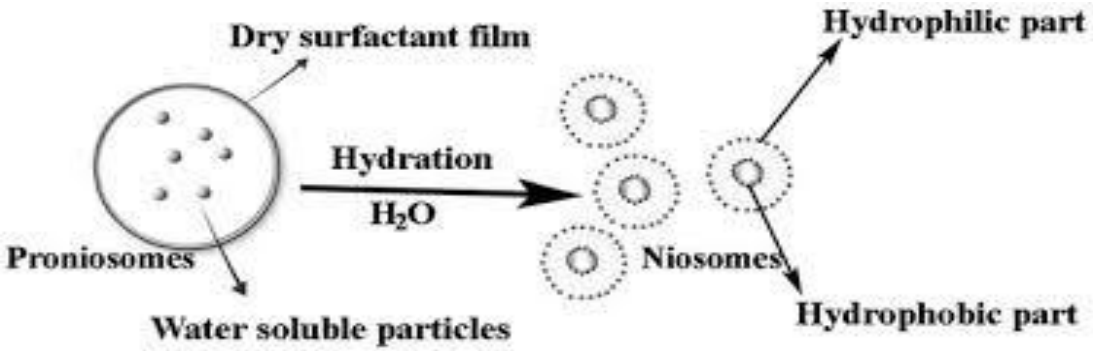

Figure No. 1: Formation of niosomes from proniosome.

The material used for preparation of proniosomes:

Surfactants: Selection of surfactant should be done based on HLB value which is a good indicator of the vesicle forming ability of any surfactant. HLB number in between 4 and 8 was found to be compatible with vesicle formation (12).

Carrier material: The carrier when used in the proniosomes preparation gives flexibility in the ratio of surfactant and other components that are incorporated. In addition to this, it increases the surface area and hence efficient loading. The carrier should be safe, effective, and non-toxic, free-flowing, poorly soluble in the loaded mixture solution, and should have good water solubility for ease of hydration (13).

Membrane stabilizer: Cholesterol and lecithin are mainly used as membrane stabilizer. Cholesterol is a naturally occurring steroid used as a membrane additive. It prevents aggregation by the inclusion of molecules that stabilize the system against the formation of aggregate by repulsive steric or electrostatic effects. Phosphatidylcholine is a major component of lecithin. It has a solubility in water and can form liposomes, bilayer sheets, micelles, or lamellar structures depending on hydration and temperature (14).

Solvent and Aqueous phase: Alcohol used in the proniosome has a great effect on vesicle size and drug permeation rate. Vesicles formed from different alcohols are of different sizes

and they follow the order: Ethanol > Propanol > Butanol > Isopropanol. Phosphate buffer, 0.1 % glycerol, hot water is used as an aqueous phase in the preparation of proniosomes (15).

Table No. 1: Various materials used for the preparation of proniosomes[15].

Specification	Materials	Actions
Non-ionic Surfactants	**Fatty alcohol:** Cetyl alcohol, stearyl alcohol, Cetostearyl alcohol, oleyl alcohol **Ethers:** Brij, Decyl glucoside, Lauryl glucoside, Octyl glucoside, Triton X-100 **Esters:** Glyceryl laurate, Polysorbates, Spans **Block copolymers:** Poloxamers	Maintain HLB level
Membrane stabilizers	Cholesterol & lecithin	**Cholesterol:** it influences the stability & permeability of vesicles. **Lecithin:** It acts as a Penetration enhancer
Carriers	Maltodextrin, lactose, sorbitol, mannitol	Efficient loading
Organic solvents	Methanol, chloroform, ethyl alcohol	Influence on vesicle size and permeability of drug

METHOD OF PREPARATION:

Proniosomes consist of several ingredients such as a non-ionic surfactant, carriers, cholesterol, lecithin, and solvent. Proniosomes are prepared by three methods:-Coacervation phase separation method, the spray coating method, and the slurry method.

1. **Coacervation phase separation method:** Proniosomal gels can be prepared by this method which comprises surfactant, lipid, and drug in a wide-mouthed glass vial along with a small amount of alcohol in it. The mixture is warmed over a water bath at 60-70ºC for 5 min until the surfactant mixture is dissolved completely. Then the aqueous phase is added to the above vial and warmed still a clear solution is formed which is then converted into proniosomal gel on cooling. After hydration of proniosomes, they are converted to uniformly sized niosomes (16).

2. The slurry method:-Proniosomes can be prepared from a stock solution of surfactant and cholesterol in a suitable solvent. The required volume of surfactant and cholesterol stock solution per gram of carrier and drug should be dissolved in the solvent in a 100 ml round bottom flask containing the carrier (maltodextrin or lecithin). Additional chloroform can be added to form the slurry in case of lower surfactant loading. The flask has to be attached to a rotary flash evaporator to evaporate solvent at 50-60 rpm at a temperature of 45±2˚C and a reduced pressure of 600 mm hg until the mass in the flask becomes a dry, free-flowing product. Finally, the formulation should be stored in a tightly closed container under refrigeration in light (17).

3. The slow spray coating method:-This method involves the preparation of proniosomes by spraying surfactant onto the carrier and then evaporating the solvent. It is necessary to repeat the process until the desired surfactant loading has been achieved because the carrier is soluble in the organic solvent. The surfactant coating on the carrier is very thin and hydration of this coating allows multilamellar vesicles to form as the carrier dissolves. The resulting niosomes have uniform size distribution similar to those produced by conventional methods. The main advantage of this method is to provide a means to formulate hydrophobic drugs in lipid suspension with or without problem with the instability of the suspension or susceptibility of active ingredients to hydrolysis (17,18).

Characterization of Proniosomal Gel:

Vesicle formation: The proniosomal gel containing the drug was spread as thin layers on a glass slide with one drop of saline solution and examined under a triangular research microscope with a Fujifilm digital camera for niosomal vesicles formation (19).

Vesicle size analysis: Vesicle size was analyzed by a Malvern particle size analyzer (20).

Viscosity:

The viscosity of the proniosomal gel was determined using a Brookfield viscometer. Spindle No.7 was attached to the viscometer and dipped into a flask containing proniosomal gel, parameters such as rpm and spindle No. was set (20 rpm, spindle No. 7) and viscosity was recorded (21).

pH Measurement:

The pH of the gel was determined by a digital pH meter. A sample of 0.1 g of the gel was dissolved in 10 ml of distilled water and the electrode was then dipped into gel formulation and constant reading was noted. The readings were taken for an average of three times (22).

Spreadability: Spreadaility is expressed in terms of time in seconds taken by two slides to slip off from the gel and placed in between the slides under the direction of a certain load. The lesser time taken for the separation of two slides, the better will be the spreadability. It is calculated by using the formula:

$$S = M\times L/T$$

Where M is the weight tied to the upper slide and T is the time taken to separate the slides (23).

Extrudability:

In this method, the formulation is filled in a standard cap collapsible aluminum tube and sealed by crimping to the end. The weights of the tube were recorded. The tubes were placed between two slides and were clamped. 500 g was placed over the slides and then the cap was removed. The amount of extruding gel was collected and weighed. The percentage of extruding gel was calculated (24).

Separation of the free (unentrapped) drug: The free drug can be separated from the entrapped drug using techniques such as:

Dialysis: Using a suitable dissolution medium, the aqueous niosomal dispersion has to be dialyzed in dialysis tubing at room temperature. At appropriate time intervals, the samples should be withdrawn from the medium, centrifuged, and analyzed for drug content using suitable methods as UV spectroscopy, HPLC, etc (25).

Gel filtration: Gel filtration is another method used for the separation of unentrapped drug from niosomal dispersion using a Sephadex-G-50 column, eluted with suitable mobile phase and analyzed with suitable analytical technique (26).

Centrifugation: By centrifugation of niosomal suspension, the pellets and supernatant are separated. The obtained pellets are washed and then resuspended to obtain a niosomal suspension free from the unentrapped drug (27, 28).

Percent entrapment efficiency:

Proniosomes (0.1 g) was diluted with 10 ml of phosphate buffer. The aqueous dispersion was sonicated in a sonicator bath for 10 min, followed by centrifugation at 6,000 rpm at 20ºC for 1 h. The supernatant was collected and assayed by UV spectrophotometer for the un-entrapped drug (29). The percentage of drug encapsulation (% EE) was calculated by the following equation:

% Entrapment efficiency = (1 - Unentrapped drug/Total amount of drug) × 100

***In-vitro* drug release study:**

In-vitro drug release study was performed using Franz diffusion cell. In these studies, two different membranes were used, such as cellophane membrane for *in vitro* drug release study and fresh mice skin for permeation study. The cellophane membrane was soaked for 24 h before diffusion study in phosphate buffer pH 6.8. The proniosomal gel (300 mg) containing 5 mg drug was placed in the donor compartment consisted of phosphate buffer pH 6.8 at a temperature of 37±2ºC under constant magnetic stirring for 3 h. Aliquots of 1 ml were withdrawn every half hour from the receptor compartment and replaced with an equal volume of diffusion media to maintain constant receptor phase volume. The samples were suitably diluted and assayed for drug content using a UV spectrophotometer. From the total drug content cumulative %, drug release in 3 h, and permeation coefficient was calculated (30).

Stability study:

The stability study is performed as per ICH guidelines. The optimized formulations are evaluated for physical stability testing to investigate the leaching of the drug from the vesicles. It is assessed by keeping the proniosomal gel at three different temperature conditions, i.e., refrigeration temperature (4º±8ºC), room temperature (25º±2ºC), and oven (45º±2ºC). Throughout the study, proniosomal formulations are stored in aluminum foil sealed glass vials. The samples were withdrawn at different time intervals for one month and drug leakage from the formulations was analyzed for drug content spectrophotometrically (31).

Table No. 2: Some of the research works carried out on proniosomes

Drug	Category	Result	References
Chlor-pheniramine maleate	Anti-histamine	It was concluded that lecithin produced more stable and larger vesicles with higher loading efficiency but lower dissolution efficiency than cholesterol and dimethyl phosphate. The stability studies were performed at 4˚C and room temperature. The proniosomes that contained span 40/lecithin/cholesterol prepared by ethanol showed optimum stability, loading efficiency, and particle size and release kinetics suitable for transdermal delivery of chlorpheniramine. [64]	32
Captopril	Anti-hypertensive	It investigated the potential of proniosomes as a transdermal drug delivery system for captopril and concluded that proniosomes are promising for prolonged delivery of captopril and have reasonably good stability characteristics. The drug was encapsulated in various formulations of proniosomal gel composed of different ratios of fatty acid esters, cholesterol, and lecithin. Moreover, the use of a transdermal drug delivery system can reduce the side effects associated with captopril. [66]	33
Losartan potassium	Anti-hypertensive	HPMC and carbopol 940 were used and HPMC gel was selected as a suitable base for the incorporation of optimized PNG. The best *in-vitro* skin permeation profile was obtained with proniosomal formulation prepared using span 40 in 24 hr. [69]	34
Carvedilol	Anti-hypertensive	Different non-ionic surfactants like polyoxyethylene alkyl ethers, namely brij 78, brij 92, and brij 72; and sorbitan fatty acid esters (span 60) were evaluated for their applicability in the preparation of carvedilol proniosomal gels. In span 60 proniosomes, an increasing percent of cholesterol, a decreased in release rate was observed on the increasing amount of	35

		carvedilol added. Permeation experiments showed that skin permeation was mainly affected by the weight of proniosomes and that span 60 proniosomal gel showed higher permeation enhancing effect than brij 72. [71]	
Glipizide	Oral rapid and short-acting anti-diabetic	Glipizide will be successfully entrapped within the biolayer of the vesicles with high entrapment efficiency and is a promising approach to sustain the drug release for an extended period an dby that reducing the side effects related to gastric irritation.	36
Valsartan	Angiotensin II inhibitor	Most of the vesicles are well identified, spherical, and discreet with sharp boundaries having large internal aqueous space. The encapsulation efficiency of proniosomes prepared with Span 60 was superior to that prepared with Span 40.	37
Haloperidol	Antipsychotic	The formulation with a single surfactant increased the permeation of the drug more than those with a mixture of surfactant	38

FUTURE TRENDS: Novel drug delivery systems have emerged embracing various routes of administration, to attain targeted delivery. Drug encapsulation in the vesicles is one of the systems which helps to prolong drug duration in systemic circulation and decreases the toxicity by selective uptake. Proniosomal formulations are becoming a useful dosage form for the delivery of drugs such as anti-inflammatory drugs, anti-viral drugs, anti-infective drugs, anti-hypertensive drugs, anti-cancer drugs, etc. But still, there is a need for discovering the new delivery systems using proniosomes in the field of cosmetics, nutraceuticals, herbal actives, and other synthetic formulations. Nowadays herbal medicine is also used in the preparation of proniosomes to reduce the side effects.

Table No. 3: Patents

Patent publication number	Inventors	Title	Reference
US 6051250	Ribier, A.Simonnet, Jean-thierry	Proniosomes for the stabilization of vesicles of amphiphilic lipid and composition for topical application containing the said stabilized vesicles	38
US 06576625B2	A.Singh, R.Jain	Targeted vesicular constructs for cytoprotection and treatment of *H.pylori* infections	39
06951655B2	Y.Cho, K, H. Lee	Pro-micelle pharmaceutical compositions	40

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