A Review On Proniosomes: Formulation, Characterization and Applications

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ABSTRACT
Nanotechnology is the advancing technology which is based on the study of manipulating the matter on a Nano scale range, and it refers to the constructing and engineering of the functional systems at atomic level. Nanotechnology lead to the development of various types of novel drug delivery systems like liposomes, microparticles, niosomes and proniosomes. Liposomes and niosomes has some demerits like leaking, fusion, aggregation, distribution, transportation and storage. To overcome the demerits of both liposomes and niosomes, proniosomes are developed with enhanced physical stability during storage and transport as they are dry formulation of water soluble carrier encoated with the surfactant and drug encapsulated in the proniosomal vesicles, which helps in prolongation of duration of retention of drug in systemic circulation and by reaching the target tissue shows its action which results in reduced toxicity. This review mainly focusses on demerits of liposomes and niosomes, methods of preparation, characterization and applications of Proniosomes.

Keywords: Liposomes, Niosomes, Proniosomes, Stability, Surfactant, Cholesterol, Characterization, Applications.

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INTRODUCTION

In the field of pharmaceutical sciences, great efforts are being conducted for the research and development of the various novel drug delivery system with the aim to achieve targeted and controlled drug delivery with reduced or minimal side effects when compared to the conventional system. Drug encapsulation in any of the vesicular system should prolong the duration of drug in the systemic circulation leading to enhanced therapeutic efficacy and bioavailability.

Vesicular forms:

Liposomes- These are developed as a colloidal, vesicular structures with concentric phospholipid bilayers. It contains an aqueous core inside to encapsulate the hydrophilic drug and due to the presence of phospholipid bilayer, lipophilic drug can be entrapped[1]. It can encapsulate both hydrophilic and lipophilic drugs.

![Structure of Liposomes](image)

Figure 1: Structure of Liposomes

Demerits -

- When given by oral route, limited success is seen.
- Physicochemical stability problems (sedimentation, aggregation, fusion).
- Difficulty in sterilization and high cost.
- Hydrolysis/oxidation of phospholipids. (i.e., phospholipid purity)[2].

To overcome the stability problems of liposomes, proliposomal approach has been provided.

Proniosomes - Dry, free-flowing powdered formulations containing hydrophilic carrier particles which are coated with the phospholipids. On addition of water, it produces multi-lamellar liposomal suspension [3].

Demerit -
Technical difficulties such as usage of vacuum (or) nitrogen gas during preparation and storage for the prevention of oxidation of phospholipids[4, 5].

To overcome the limitations of the proliposomes and liposomes, niosomes are developed as drug carriers and drug targeting agents [6, 7].

**Niosomes**

These non-ionic surfactant vesicles which are capable of entrapping (or) encapsulating both hydrophilic and lipophilic drug as similar to that of liposomes.

- They are less toxic due to their non-ionic nature.
- The large-scale production of niosomes does not require any special conditions [8, 9].

![Figure 2: Structure of Niosomes](image)

**Comparison between niosomes and liposomes:**

- Niosomes are less expensive than liposomes.
- Niosomes does not require any special conditions or methods for storage and handling of the formulation when compared to liposomes [10, 11].
- Niosomes contain non-ionic surfactants, whereas liposomes contain phospholipids which are neutral or charged.

**Demerits** -
- Aggregation.
- Physical instability.
- Leaking of entrapped drug on storage.
- Time consuming for traditional method of preparation.
- Involves specialized equipment.
- Hydrolysis of encapsulated drugs which reduces the shelf life of the niosomal suspension[12].
To overcome the demerits of niosomes, proniosomes are prepared and reconstituted to produce niosomes.

**PRONIOSOMES**

Proniosomes are dry free-flowing formulations of surfactant-coated carrier, which on rehydration by agitation in hot water, produces a multi-lamellar niosomal suspension suitable for administration[13, 14].

Since these proniosomes are available in dry form of powders, they have a benefit in transportation, distribution, processing, packaging and storage. It can provide optimal flexibility, metered unit dosing in capsule and stability [15]. These versatile drug delivery system has the potential to be used as the carriers for many of the active pharmaceutical components [13, 16]. It minimizes the demerits of the niosomes in stability issues as these proniosomes are more stable when compared to pre-niosomal formulations.

![Figure 3: Structure of Proniosomes](image-url)
Comparison of proniosomes with niosomes-
- Niosomes are microscopic lamellar vesicles formed by the mixture of non-ionic surfactants and cholesterol in the aqueous media, where as the proniosomes are dry formulations of surfactant coated carrier vesicles which are capable to get hydrated to produce niosomes immediately before use.
- Niosomes can be degraded by hydrolysis while proniosomes are dry formulation and can not be degraded by hydrolysis.
- Use of unacceptable solvents in the preparation of niosomes.
- Incomplete hydration of lipid or surfactant film during hydration process for niosomal formulations[17].

Ideal properties for the drug in proniosomal formulations -
- Low aqueous solubility of drugs.
- High dosage frequency of drugs.
- Short half life.
- Controlled drug delivery suitable drugs.
- Higher adverse effects of drugs [18].

Composition of proniosomes
- Phosphotidyl choline - eg. Soya/egg lecithin.
- Drug.
- Non-ionic surfactants
  i) Fatty alcohol - cetyl alcohol, stearyl alcohol, cetostearyl alcohol, oleylalcohol.
  ii) Ethers- decyl glucoside, lauryl glucoside, octyl glucoside, triton X-100.
iii) Esters- glyceryl laureate, polysorbates, spans.
  • Solvents - eg. Ethanol, butanol, iso-propanol.
  • Cholesterol
  • Aqueous phase - eg. Water, glycerol, phosphate buffer [18].

METHODS OF PREPARATION

Slurry Method -
Firstly stock solution of surfactants and cholesterol was prepared by using a suitable solvent. The required volume of above prepared stock solution per gram of carrier and drug should be dissolved in the solvent in the 100ml RBF containing the carrier (i.e. maltodextrin/lecithin). Then add the chloroform which results in the formation of the slurry. This RBF was attached to a rotary flash evaporator to evaporate the solvent at 50-60 rotations per minute, at the temperature of 45± 2 °C and at a pressure of 600 mm Hg, till the content present in the flask is dried and free flowing. Finally, the niosomal formulation should be stored at 4 °C temperature (i.e., refrigeration temperature) in a tightly closed container[12].

Spray coating Method -
Required amount of carrier has to be taken in a 100ml of RBF. Then surfactant and cholesterol mixture was prepared and this mixture was sprayed on to the carrier in RBF which is connected to the evaporator. By sequential spraying of the surfactant and cholesterol mixture on to the carrier until the aliquot coats the carrier and by the evaporation of the solvent, it becomes dry and free flowing powder, which was stored in a tightly closed container at 4°C[19].

Coacervation phase separation method -
This method is used for the preparation of proniosomal gel.
Desired amount of surfactant, carrier, cholesterol and drug should be weighed and taken in a clean wide mouthed glass vial. Then the solvent is added to the above mixture. All the ingredients in the mixture has to be heated and then after mixed with the help of the glass rod. To avoid the loss of solvent, the vial is closed at the open end with the help of the lid. This mixture is warmed on the water bath at the temperature of 60-70°C for 5 min until the surfactant dissolves completely and then it is allowed to cool down at a room temperature until the dispersion is converted to proniosomal gel[20].
Figure 5: Different methods of proniosomal preparations

A. Slurry Method

B. Spray Coating Method

C. Coacervation Phase Separation Method

Hand shaking method -
Required amount of vesicle forming ingredients such as cholesterol and surfactants are dissolved in the suitable solvent (i.e. either ether, methanol or chloroform) in a RBF which is placed in a rotary evaporator. The organic solvent evaporates at a room temperature (i.e. 20-25°C) leaving a thin film which is deposited on the walls of the container. On rehydration with the aqueous phase with little agitation, results in the formation of multilamellar niosomes[15].

Conversion of proniosomes to niosomes-
On addition of surfactant to the carrier surface, it forms a dry surfactant film on carrier surface which is able to enclose water soluble particles. On further addition of the water or the hydration of the proniosomes leads to the formation of niosomal vesicle which is capable of entrapping hydrophilic and hydrophobic drug particles (Fig).
Material used and their action in the proniosomal preparation-

Table 1: [25]

| Components                  | Category          | Action                                         |
|-----------------------------|-------------------|------------------------------------------------|
| Span and Tween              | Surfactants       | Maintenance of HLB level                       |
| Methanol, ether, chloroform | Organic solvents  | Influence on vesicle size and permeability of  |
| and ethanol                 |                   | drug                                           |
| Cholesterol and lecithin    | Membrane stabilizers | Cholesterol influence the stability and permeability of vesicles. Lecithin - penetration enhancer. |
| Maltodextrin, lactose,      | Carriers          | Holds the drug                                 |
| sorbitol, mannitol          |                   |                                                |

Table 2: Parameters for characterization and used instruments

| S No. | Parameters                  | Instruments used                                      |
|-------|-----------------------------|-------------------------------------------------------|
| 1.    | Visualization               | Malvern Mastersizer [23]                              |
|       | Vesicle size                | Laser diffraction particle size analyzer[13,12]       |
|       | Size Distribution           | Coulter submicron size analyzer[24]                  |
|       |                             | Optical microscopy[25]                                |
| 2.    | Morphological characterization | Optical microscopy[25]                              |
|       | Surface                     | Transmission electron microscopy[23]                 |
|       | Shape                       | Scanning electron microscopy[11]                     |
| 3.    | Angle of repose             | Funnel method[13, 26]                                 |
4. Rate of hydration Using Neubaur’s chamber\[2\]
5. Drug content Modified HPLC method\[2\]
6. Aerodynamic behavior Twin-stage impinger\[2\]
7. Entrapment efficiency Vesicle lysis using alcohol and propylene glycol\[9\]
                        Dialysis method\[2\]
8. Determination of colloidal properties Zeta potential analysis\[2\]
9. Penetration and permeation Studies Franz diffusion cells\[2\]
                        Cellophane dialyzing membrane\[1\]
                        USP dissolution apparatus-I\[2\]
                        In vitro skin permeation studies\[2, 2\]

CHARACTERIZATION OF PRONIOSOMES

1. Measurement of angle of repose:
The angle of repose can be measured by two methods.

**Funnel Method** - Funnel is fixed at height of 2 cm above the level of the surface. The proniosomal powder was poured into the funnel and passed down through the funnel outlet orifice of 12 cm to from a cone on the surface. Then the angle of repose was calculated by measuring the height (h) of the cone and the diameter (r/2) of the base\[2\].

**Cylinder Method** - Similar to the funnel method, the proniosomal powder was poured into the cylinder containing outlet orifice which is fixed at a position above the level of surface. The powder flows down through outlet orifice to from a cone. The angle of repose was further calculated by measuring the height (h) of the cone and the diameter (r/2) of the base\[2\].

\[
\text{Angle of repose (}\theta\text{)} = \tan^{-1}\left(\frac{h}{r/2}\right)
\]

2. Scanning electron microscopy (SEM):
Particle size of the proniosomes has primary importance. The surface morphology (i.e., roundness, smoothness, and formation of aggregates) and size distribution of proniosomes was studied by SEM. The proniosomal powder was sprinkled and spreader on a double-sided tape that was affixed on an aluminium stubs and then placed in a vacuum chamber of SEM (XL 30 ESEM with EDAX, Philips, Netherlands). The morphological characterization of the samples was observed by using a gaseous secondary electron detector (Working pressure of 0.8 torr, acceleration volage-30kv)\[2\].

3. Optical microscopy:
The niosomes were mounted on a glass slide and observed under a optical microscope (Medilux - 207 RII, Kyowa- E1 etner, Ambala, India). The microscope with magnification of X 1200 used for the morphological observation. The photomicrograph of the preparation was obtained from the microscope by using digital single lens reflex (SLR) camera\[2\].
4. Measurement of vesicle size:
Niosomal dispersions are diluted about 100 times in the same medium used for their preparation. The sample was stirred well before determining the vesicle size. Vesicle size was measured by using Laser diffraction particle size Analyzer, Sympatec, Germany. The apparatus contains He-Ne laser beam of 632.8 nm focused with a minimum power of 5 mW using a Fourier lens (R-5) to a point at the center of multielement detector and a small volume sample holding cell (Su cell). The average particle size of proniosome derived niosomes was approximately $6 \times 10^{-6}$ m while the conventional niosomes contain about $14 \times 10^{-6}$ m [21].

5. Entrapment efficiency:
Separation of unentrapped drug can be done by various techniques [2, 12].

![Figure 8: Separation of unentrapped drug](image)

**Dialysis** - The niosomal dispersion is dialyzed in dialysis tubing against the suitable dissolution medium at room temperature. The samples are withdrawn at regular time intervals, centrifuged and analyzed for drug content.

**Centrifugation** - The proniosomes derived niosomal suspension is centrifuged and supernatant is separated. The resultant pellet is washed and resuspended for obtaining the unentrapped drug free vesicles.

**Gel Filtration** - The free drug is separated by gel filtration from the niosomal dispersion through a sephadex G-50 column and eluted with suitable mobile phase and analyzed.

Separation of entrapped drug can be done by complete vesicle disruption using 50% n-propanol (or) 0.1% Triton X-100 and analyzing the resultant solution by appropriate method.

$$\text{Percent Drug entrapment} = \frac{\text{Total drug} - \text{Diffused drug}}{\text{Total drug}} \times 100$$

6. In vitro Drug Release:
Proniosomal drug release was determined by using distinct techniques such as Franz cell diffusion, dialysis, reverse dialysis, USP dissolution apparatus Type-1 and molecular porous membrane tubing. Drug release from the suspension can follow any of the mechanism such as desorption from the surface of vesicles (or) diffusion of drug from Bilayered membrane (or) both desorption and diffusion mechanism [2, 11, 22].

7. Rate of Hydration:
Spontaneity of niosomal formation is determined by the no. of niosomes formed after hydration of proniosomes for about 15 mins. Proniosomes are taken in a small stoppered glass tube and spread uniformly. 1ml of saline (0.154M Nacl) was added and kept aside without shaking. After 15 - 20min, Small amount was withdrawn and placed on Neubaur’s chamber. The no. of niosomes formed from proniosomes was counted [18].

STABILITY STUDIES:
To determine the stability of proniosomes, the prepared proniosomes are stored at various temperature conditions like refrigeration temperature (i.e., 2-8°C), room temperature (25 ± 0.5°C) and elevated temperature (45 ± 0.5°C) for a period of 1- 3 months. Drug content and difference in the average vesicle diameter was monitored periodically. As per ICH guidelines stability studies for dry proniosomes powders which are meant for reconstitution should be studied for accelerated stability at 40°C/75% RH as per international climatic zones and climatic conditions. After storing for particular period, the product should be evaluated for appearance, color, assay, pH, particulate matter, sterility, preservative content and pyrogenicity [2, 23, 25].

APPLICATIONS OF PRONIOSOMES
Proniosomes as drug carriers :
Proniosomes act as Drug carriers for above mentioned drugs, which are only few examples. Drug delivery has been studied by different methods of administration which includes IV, peroral, transdermal, aerosoles and intramuscular. In vivo behavior of proniosomes will be similar to liposomes[27].

Clinical applications:
In cardiology – Proniosomes as carriers for captopril drug for treatment of hypertension in the form of transdermal delivery which results in an extended release of the drug in the body. Encapsulation of drug is carried out using sorbitan esters, cholesterol and lecithin [21].
In diabetes- Furosemide proniosomes are injected transdermally which reduces the glucose levels[21].
Hormonal therapy – Levonorgestrel proniosomes was given in transdermal drug delivery system. Bioassay for progestational activity was performed including endometrial assay and blockage of development of corpora lutea [21].

Immune response - Niosomes and proniosomes are being used to study the nature of the immune response due to their immunological selectivity, low toxicity and greater stability [21].

Peptide drugs- Oral peptide drug delivery has a limitation of bypassing the enzymes, which leads to breakdown of peptide and protein bonds [21].

Anti-neoplastic Treatment - Niosomes have the ability to alter the metabolism, prolong circulation and half-life of the drug leading to minimal side effects. Doxorubicin and methotrexate niosomes shows an advantageous effects over the unentrapped drugs in decreasing the rate of proliferation of the tumor [21].

Table 3: List of Drugs used in different proniosomal formulations

| Category         | Drug                          | Application          |
|------------------|-------------------------------|----------------------|
| NSAID            | Indomethacin, piroxicam, ketorolac, flurbiprofen, Aceclofenac | Oral [21]            |
|                  |                               | Gel & Patch [21, 27] |
| Anticancer       | Doxorubicin                   | IV [27]              |
|                  | Exemestane                    | Oral [27]            |
| Diuretic         | Furasemide                    | Gel & Patch [21, 27] |
| Anti-hypertensive| Losartan Potassium, Valsartan, captopril, alprenolol HCL | Gel & Patch [21, 27] |
| Anti-asthmatic   | Cromolyn Sodium               | Nebulisable [21]     |
| Anti-histamatic  | Chlorpheniramine Maleate      | Gel & Patch [21]     |
| Anti-infectives  | Hexadecyl triglycerol Ether   | IV [21]              |
| Diagnostic imaging | Gadolinium                  | IV [21]              |

CONCLUSION:

Proniosomes represent a promising drug delivery technologies and represent the structure similar to the liposomes. Hence, they can represent an alternative vesicular systems. Proniosomes derived niosomes are known to avoid many problems such as physical stability problems like aggregation, fusion and leakage. They also provide an additional benefits of transportation, distribution, storage and dosing. From the above article, it is concluded that the concept of entrapment or incorporating the drug into proniosomes for the better targeting of the appropriate tissue target is widely accepted by researchers and academicians.

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