



A PRECISE REVIEW ON PRONIOSOMES: A NOVEL APPROACH TO VESICULAR DRUG DELIVERY SYSTEM

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ABSTRACT:

Delivery of poorly soluble drugs has been a major challenge in drug development and discovery. Many approaches have been made for enhancing solubility of these drugs. In this context vesicular drug delivery had gained a lot of interest in delivering drugs with improved solubility and targeted action, prolonging the release of drug by circulating in blood stream for longer period, reducing toxicity of drug. Lack of stability of vesicular system led to development of proniosomal approach. Proniosomes are free flowing dry formulations upon reconstitution with aqueous media form stable niosomal dispersion within minutes. They overcome many disadvantages associated with liposomes and niosomes. The current review provides idea on overview of niosomes, their preparation methods, characterization, evaluation and applications.

Key words: Liposomes, Niosomes, Proniosomes, Targeted action, Vesicular drug delivery.

1. INTRODUCTION:

The main goal of any drug design is to improve bioavailability, maintain constant level of drug plasma concentration, reduce toxicity, prolong release of drug by providing targeted action. Nano drug delivery systems have been emerging as novel trends overcoming the problems encountered in conventional dosage forms. Conventional dosage forms show faster drug release, rapid rise blood drug concentration and thereby exponentially fall until next dose of drug is administered. In recent years' numerous attempts have been made to overcome the disadvantages of conventional systems one such approach is encapsulating the drug in vesicular systems like Liposomes, Niosomes, Ethosomes, Transferosomes which

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prolong the existence of drug in systemic circulation, enhance permeability of drug into targeted tissues and decrease cellular toxicity [1]. Drug encapsulation protects drugs from premature biodegradation, alter release characteristics, drug distribution, metabolic stability and toxic manifestations.

Among various vesicular carrier systems niosomes due to presence of non-ionic surfactants has shown better intrinsic targeting and better stability [4]. But niosomes possess certain limitations like fusion, aggregation, flocculation making them physically instable. To overcome this disadvantages, they are successfully formulated as Proniosomes. Proniosomes are versatile vesicular carriers which are dry, free flowing in nature. They are

converted to niosomal dispersion by agitation for few minutes in hot aqueous media by hydration just before use [2], [3]. Proniosomes on hydration result in conventional niosomes with uniform size distribution. Since they are dry preparation, they offer more stability during storage and sterilization^{4,6}. Proniosomes are promising systems for entrapping both polar, non-polar or lipophilic and lipophobic drugs [5].

Pro's of Proniosomes:

- Apart from enhancing stability the non-ionic surfactants and phospholipids increase diffusion into tissues [7], [8].
- They offer convenience of dosing, transportation, distribution, and storage [9], [11].
- They avoid problems with conventional niosomes like fusion, aggregation, physical stability and leakage [12].
- They enhance stability of drug by preventing hydrolysis, oxidation etc. [10], [13].
- Enhance drug penetration through skin [11], [13].

Con's of Proniosomes

- Complete entrapment of drug during hydration may not be possible, so the amount of an entrapped drug should be determined [36].
- Complex process [36].

They are mainly of two types:

A) Liquid crystalline Proniosomes [14]: The lipophilic chains of surfactants transform into disordered liquid state when Surfactant molecules meet water forming liquid crystalline Proniosomes. This occurs in three ways: a) Addition of solvents b) Increasing temperature at Kraft's point and c) Using both temperature and solvents

B) Dry granular Proniosomes: These are dry formulations formed by coating of water-soluble carriers like maltodextrin and sorbitol with surfactants in which each water-soluble particle is covered with a thin layer of surfactant. They are further classified as:

Sorbitol based Proniosomes: These systems utilize sorbitol as a carrier. Surfactant mixture prepared in organic solvent is sprayed onto sorbitol powder and then the surfactant is evaporated. The surfactant coats as a thin layer and hydration of this layer allows formation of multilamellar vesicles which is very important when drug is susceptible to hydrolysis [14].

Maltodextrin based Proniosomes: These systems utilize maltodextrin as a carrier. It is used for entrapping hydrophilic and amphiphilic drugs. Maltodextrin is a polysaccharide, forms hollow particle with high surface area resulting in thinner surfactant coating which makes it easy for rehydration [8-10].

2. PREPARATION OF PRONIOSOMES

Proniosomes are prepared by following methods

Slurry method: Maltodextrin is used as a carrier for preparing Proniosomes by slurry method. In this method maltodextrin powder and entire volume of surfactant is added to round bottomed flask. The flask is subjected to evaporation under rotary evaporator to evaporate chloroform at 60-70rpm, a temperature of 43°C to 47 °C and a reduced pressure of 600mmHg until powder becomes dry and free flowing. The flask is subjected to vacuum overnight. This is a simple method and the time required for preparation do not depend on surfactant solution to carrier material. The prepared Proniosomes are stored in sealed containers at 4 °C [16].

Spray coating method: Sorbitol is used as a carrier in this method. Sorbitol, surfactant solution is placed in a round bottom flask and attached to rotary evaporator and aliquots of sorbitol powder is sequentially sprayed. Care should be taken during spraying to prevent over wetting of powder bed. The evaporator is then evacuated, and the rotating flask is lowered into a water bath at 65-70 °C. The flask is rotated in the water bath under vacuum for 15-20 min, until sorbitol becomes dry and add another aliquot of surfactant solution, this process is repeated until all surfactant solution is applied. Dry the material in desiccator overnight at room temperature under vacuum [16], [18].

Coacervation Phase separation method: Add surfactants, carriers, cholesterol, solvent in a 5ml clean and dry mouth glass vial and subjected to heating with

intermittent stirring. Place the mixture in water bath at 60-70°C for 5 mins until surfactant gets dissolved completely cover the open end of glass vial to prevent loss of solvents. Now add aqueous phase to above vial and heated until clear solution is formed which gets converted to proniosomal gel on cooling [17].

Formation of Niosomes From Proniosomes

Niosomes are obtained from proniosomes upon brief agitation with hot aqueous media at 80°C for 2 minutes to get niosomal dispersion. Removal of free untrapped drug: The encapsulation efficiency [24] of formed proniosomes after separation of untrapped drug is determined by using following techniques a) Dialysis: The niosomal dispersion is subjected to dialysis at room temperature with suitable dissolution medium. Samples are withdrawn at suitable time intervals and drug content is analyzed by UV spectroscopy [19].

Gel Filtration: In this technique niosomal dispersion is filtered through Sephadex G50 column and separated with suitable mobile phase and drug content is analyzed with suitable analytical techniques [20].

Centrifugation: The niosomal suspension is centrifuged and surfactant is separated. The residue is washed and resuspended to form niosomal suspension free from untrapped drug [21].

Additives Used in Formulation of Proniosomes

Surfactant: Non-ionic surfactants are commonly used for manufacturing of proniosomes. HLB value of surfactants

plays a major role in selection of surfactant for increased encapsulation of drug. HLB value between 4 and 8 forms vesicles of good size. Commonly used surfactants are alkyl ethers, alkyl esters, alkyl amides, esters of fatty acids [34].

Carrier: Sorbitol, maltodextrin, spray dried lactose, Lactose monohydrate, Mannitol, Sucrose stearate, glucose monohydrate are used as carriers. Carriers provide flexibility to the ratio of surfactant to other additives to be added. They increase the surface area and enhance efficient loading [33].

Cholesterol: It stabilizes the system by preventing aggregation by repulsive steric or electrostatic effects. The presence of cholesterol in membrane shows changes with respect to bilayer stability, fluidity, and permeability. Reports studied showed that increase in cholesterol content showed increase in entrapment efficiency upon a limit and further increase in cholesterol led to decrease in efficiency [33-35].

Lecithin: Phosphatidyl choline is major component of lecithin. Depending on their origin they are of two types soy lecithin and egg lecithin. It has many advantages in vesicular system like acts as a permeation enhancer, prevents drug leakage, increases drug entrapment due to high transition phase temperature. Vesicles from soy lecithin forms larger size than egg lecithin but vesicles from soy lecithin has good penetrability due to presence of unsaturated fatty acids than egg lecithin [12], [13].

Solvents: Alcohols used in preparation has great impact on vesicle size and drug

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permeation rate. The vesicles formed from different alcohols have sizes in the order of: Ethanol > Propanol > Butanol > isopropanol. Vehicles like 7.4 PH Phosphate buffer, 0.1% Glycerol, hot water are used as aqueous phase in preparation of proniosomes [12], [13].

3. EVALUATION OF PRONIOSOMES

Shape and surface morphology: Vesicle shape and surface is determined by scanning electron microscopy (SEM). The prepared proniosomes are placed on metal stubs and coated with conductive gold with sputter coater attached to the instrument. Then photographs are taken to check shape and surface morphology [22].

Particle size: Vesicular size is determined by using optical microscopy under 100X magnification. Niosomal dispersion is prepared by adding saline solution to proniosomes in a small glass vial with occasional stirring for 10 mins. The dispersion is observed under microscope and size of 100 vesicles are measured by using stage micrometer.

Vesicular size is also determined by using Particle size analyser. The niosomes are diluted to 100 times to its initial volume by using solvent used in preparation of niosomes. The apparatus consists of small volume sample holding cell and He-Ne laser beam of 632.8 nm focused with a minimum power of 5Mw using Fourier lens to the centre point of multi-element detector [22].

Drug content Determination: 100 mg equivalent weight of proniosomes are taken and lysed with 50 ml of methanol by shaking for 15 mins. Dilute the solution to 100 ml with methanol. Take 10 ml of this solution and dilute to 100 ml with saline phosphate buffer. Samples are withdrawn

and the amount of drug present is measured by measuring absorbance at specified wavelength of the drug [23].

In vitro diffusion studies: It is determined by using Franz diffusion cell., keshary-Chen diffusion cell, cellophane dialyzing membrane, USP type - I dissolution apparatus, spectrapor molecular porous membrane tubing. Drug release from proniosomes derived niosomes follow following mechanisms: desorption from surface of vesicles or diffusion of drug from bilayered membrane or a combined desorption and diffusion mechanisms [25].

Stability studies: As per ICH guidelines stability for dry proniosome powders is determined by accelerated stability at 40°C/75% relative humidity as per international climatic zones and conditions (WHO 1996). Long term stability studies are determined at temperature 25°C/ 60% relative humidity for the countries in zone I and zone II. For countries in zone III and zone IV the temperature is 30°C/65% relative humidity [25].

4. APPLICATIONS

Proniosomal approach finds better application in treating various disorders, they include

Targeted drug delivery: The reticulo-endothelial system preferentially uptake niosomal vesicles, so niosomes can be used to target reticuloendothelial system. The uptake of niosomes is controlled by circulating serum factors known as opsonins. These opsonins are marked for clearance. Such localization of drugs is used for treating tumors in animals known to metastasize to the liver and spleen. A carrier system such as antibodies can be attached to

niosomes to target them to specific organs [27].

In Diabetes: Furesamide proniosomes prepared from spans, soyalecithin, cholesterol, diacetyl phosphate were studied and showed enhanced skin permeation, proved to be effective for non-invasive delivery of furesamide [26].

Studying Immune response: Due to their exclusive immunological selectivity, low toxicity and greater stability proniosomes and niosomes are used to study immune response provoked by antigens [28].

For Sustained release: Sustained release action of niosomes can be utilized for drugs with low therapeutic index and low water solubility since drug could be maintained in circulation by encapsulating in proniosomes [29].

For Localized action: Due to its size, low penetrability through epithelium and connective tissue keeps the drug localized for longer period of time ensuring localized action at site of administration. This results in improved efficacy and reduce systemic toxic effects [30].

Carrier for Haemoglobin: Proniosomal vesicle is permeable to oxygen so it can be used as a carrier for haemoglobin for treating anaemic patients [31].

For Delivery of Peptide Drugs: The major disadvantage of drugs given through oral route is breakdown of peptides by gastrointestinal enzymes. Entrapment of peptides as proniosomes bypass the gastric enzymes and protect drug from gastric degradation [32].

5. CONCLUSION

Proniosomes are dry preparations upon hydration form niosomal dispersion finds

potential application in drug delivery. They are known to overcome various stability problems associated with niosomes like aggregation, fusion, leakage with decreased manufacturing cost. Their ease of handling, convenience in storage and dosing makes them more promising candidates. Encapsulation of drug makes offers additional benefits by preventing drug degradation and makes the drug to stay for longer period in systemic circulation thereby providing sustained release and enhanced tissue permeability.

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