V R Varsha et al /J. Pharm. Sci. & Res. Vol. 11(7), 2019, 2594-2597

ISSN:0975-1459
Journal of Pharmaceutical Sciences and Research
www.jpsr.pharmainfo.in

Proniosomes: As a potential drug delivery system

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Abstract

Vesicular drug delivery systems have gained wide attention in the field of nanotechnology. Sustained and controlled release drug products are often formulated maintain the drug concentration at site of action for longer interval of time such as liposomes, niosomes, ethosomes, transferosomes, etc. Among them proniosomes become the superior over other vesicular carriers. Proniosomes are dry formulations of water soluble nonionic surfactant coated carrier system which immediately forms niosomes upon hydration. They have the capability to overcome the instability problems associated with niosomes and liposomes and have the potential to improve solubility, bioavailability, and absorption of various drugs. Also, they offer versatile drug delivery concept for number of both hydrophilic and hydrophobic drugs. This new emerging concept has demonstrated the potential in improving the oral bioavailability, targeting drugs to the specific site and also permeation of drugs across the stratum corneum to achieve controlled release action and reduce toxic effects associated with drugs. This review mainly focus on different aspects of proniosome such as preparation, components, merits, characterization applications, and future trends.

Key words: Nanotechnology, Proniosomes, Bioavailability, Solubility, Liposomes

INTRODUCTION

In the current arena, no single drug delivery system fulfills all the criteria, but attempts have been made through novel approaches. Many novel techniques developed for various routes of administration, to achieve either controlled or targeted delivery. The aim of novel drug delivery is to maintain the constant and effective drug level in the body and minimizing the side-effects and it also localizes the drug action by targeting the drug delivery by using drug carriers[1].

Vesicular systems have been receiving a lot of interest as a carrier for advanced drug delivery. Encapsulation of the drug in vesicular structures is one such system, which can be expected to prolong the duration of the drug in systemic circulation, and to reduce the toxicity by selective up taking[2]. Over other conventional dosage forms liposomes and noisome have many advantages especially their particulate nature, also they act as a drug reservoir. Proniosome technology offers novel solution for poorly soluble drugs. Proniosome is a dry free flowing, granular product that could be hydrated immediately before use and would avoid many of the problems associated with aqueous niosome dispersions and problem of physical stability. Proniosomes are a versatile delivery system because of the ease of distribution, measuring, transfer, and storage[3].

ADVANTAGES OF PRONIOSOMES OVER NIOSOMES[4]

- Avoiding problem of physical stability like aggregation, fusion, leaking.
- Avoiding hydration of encapsulated drugs which is limiting the shelf-life of the dispersion.
- Proniosomes are water soluble carrier particles. This has additional convenience of the transportation, distribution; storage.
- Unacceptable solvents are avoided in proniosomal formulations. The systems may be directly formulated into transdermal patches and doesn't require the dispersion of vesicles into polymeric matrix.
- The storage makes proniosomes a versatile delivery system with potential for use with a wide range of active compounds.

COMPONENTS OF PRONIOSOME

Surfactants:

Surfactants are the surface active agent usually organic compounds which have both hydrophobic and hydrophilic groups. Therefore, a surfactant molecule contains both a water insoluble (lipophilic) and a water soluble (hydrophilic) component. They have variety of functions including acting as solubilizers, wetting agents, emulsifiers and permeability enhancers. Alkyl ethers, alkyl esters, alkyl amides and esters of fatty acids are the most commonly used non-ionic amphiphiles for the vesicle formation[5].

Carrier materials:

The carrier when used in the proniosomes preparation gives the flexibility in the ratio of surfactant and other components that incorporated. In addition to this, it increases the surface area and hence efficient loading. The carriers should be safe,effective and non-toxic, free flowing, poor solubility in the loaded mixture solution and good water solubility for ease of hydration[6].

Membrane stabilizer:

Cholesterol and lecithin are mainly used as membrane stabilizer. Steroids are important components of cell membrane and their presence in membrane and their presence in membrane brings about significance changes with regard to bilayer stability, fluidity and permeability. Cholesterol is a naturally occurring steroid used as 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 low solubility in water and can form liposomes, bilayer sheets, micelles or lamellar structures depending on hydration and temperature[7].

Solvent and Aqueous phase:
Alcohol used in Proniosome has a great effect on vesicle size and drug permeation rate. Vesicles formed from different alcohols are of different size and they follow the order: Ethanol > Propanol > Butanol > Isopropanol. Ethanol has greater solubility in water hence leads to formation of highest size of vesicles instead of isopropanol which forms smallest size of vesicle due to branched chain present. Phosphate buffer pH 7.4, 0.1% glycerol, hot water is used as aqueous phase in preparation or formulation of proniosomes[8].

Drug:
The drug selection criteria could be based on the following assumptions[9].

- Low aqueous solubility of drugs.
- High dosage frequency of drugs.
- Controlled drug delivery suitable drugs
- Short half life.
- Higher adverse drug reaction drugs.

TYPES OF PRONIOSOMES

i. Dry granular proniosomes
ii. Liquid crystalline proniosomes

i. Dry Granular Proniososmes :
Dry granular proniosomes involves the coating of water-soluble carrier such as sorbitol and malt dextrin with surfactant. The result of coating process is a dry formulation in which water water-soluble particle is covered with thin film of surfactant. It is essential to prepare vesicles at a temperature above the transition temperature of the non-ionic surfactant being used in the formulation. These are further categorized as follows:

a) Sorbitol based Proniosomes :
Sorbitol based proniosomes is a dry formulation that involved sorbitol as the carrier, which is further coated with non-ionic surfactant and is used as niosomes within minutes by addition of hat water followed by agitation. These are normally made by spraying surfactant mixture prepared in organic solvent on to the sorbitol powder and then evaporating the solvent. Since the sorbital carrier is soluble in organic solvent, the process is required to be repeated till the desired surfactant coating 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 [10].

b) Maltodextrin based proniosomes :
A proniosome formulation based on maltodextrin was recently developed that has potential application in deliver of hydrophobic or amphiphilic drugs. The better of this formulation used to hollow particle with exceptionally high surface area. The principal with this formulation was the amount of carrier required to support the surfactant could be easily adjusted and proniosomes with very high mass ratios of surfactant to carrier could be prepared [9,10]

ii. Liquid Crystalline Proniosomes :
When the surfactant molecules are kept in contact with water, there are three ways through which lipophilic chains of surfactants can be transformed into a disordered, liquid state called lytorophic liquid crystalline state (neat phase). These three ways are –

- Increasing temperature at kraft point (Tc)
- Addition of solvent, which dissolves lipids
- Using both temperature and solvent.

Neat phase or lamellar phase contains bilayer arranged in sheets over one another within intervening aqueous layer. These types of structures give typical X-ray diffraction and thread like bi-refringent structures under polarized microscope.

METHOD OF PREPARATION

Proniosome preparation mainly comprised of non-ionic surfactants, coating carriers and membrane stabilizers. The formulation may be prepared by following methods.

Slurry method:
Proniosomes can be prepared by addition of the carrier and the entire surfactant solution in a round bottomed flask which is fitted to rotary flash evaporator and vacuum was applied to form a dry and free flowing powder. Finally, the formulation should be stored in tightly closed container under refrigeration in light. This method is advantageous because due to uniform coating on carrier it protects the active ingredients and surfactants from hydrolysis and oxidation. Along with that the higher surface area results in a thinner surfactant coating, which makes the rehydration process more efficient[11].

Slow spray coating method:
A 100 ml round bottom flask containing desired amount of carrier can be attached to rotary evaporator. The evaporator has to be evacuated and rotating flask can be rotated in a 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[12].

Co-acervation phase separation method:
This is the most used method to prepare proniosmal gel. Weighed quantities of drug, lipid and surfactants are taken in a dry wide-mouthed glass beaker followed by the addition of solvent. The ingredients are mixed well and warmed over water bath at 60–70°C until the surfactant mixture dissolves completely. During the process care must be taken to prevent loss of any solvent due to evaporation. Finally, the aqueous phase is added to the mixture and warmed on water bath. The resultant solution is cooled overnight to obtain proniosomal gel[13].

FORMATION OF NIOSOMES FROM PRONIOSOMES

The niosomes can be prepared from the proniosomes by adding the aqueous phase with the drug to the proniosmes with brief agitation at a temperature greater than the mean transition phase temperature of the surfactant[7]. Formation of noisome from proniosome figure (i).

$T > Tm$

Where,
T = Temperature
Tm = Mean phase transition temperature

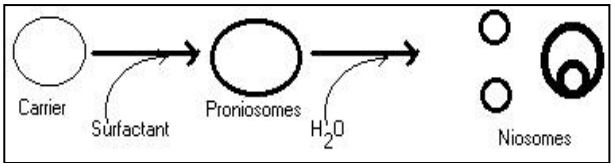

Fig (i): Formation of niosomes from proniosomes

CHARACTERIZATION OF PRONIOSOME

Evaluation studies are further carried out for the prepared proniosomes in order to find out the

- Measurement of angle of repose
- Scanning electron microscopy (SEM)
- Optical microscopy
- Measurement of vesicle size
- Drug content
- Entrapment efficiency
- *In-vivo* release studies
- Stability studies

Measurement of angle of repose:

Funnel method

The funnel, which was fixed at a position and the proniosomal powder was poured into it so that the outlet orifice of the funnel is 10 cm above the level of surface. The powder flowed down from the funnel to form a cone on the surface and then angle of repose was further calculated by measuring the height of the cone and the diameter of its base[14].

SEM:

Particle size of proniosomes is a factor of prime importance. The surface morphology and size distribution of proniosomes were studied by SEM. A double-sided tape that was affixed on aluminum stubs and the proniosomal powder was spread on it. The aluminum stub was placed in a vacuum chamber of scanning electron microscope (XL 30 ESEM with EDAX, Philips, Netherlands). The morphological characterization of the samples was observed using a gaseous secondary electron detector (working pressure of 0.8 torr, acceleration voltage-30.00 KV) XL 30, (Philips, Netherlands)[14,15].

Optical microscopy:

The niosomes were mounted on glass slides and viewed under a microscope (Medilux-207RII, Kyowa-G etner, Ambala, India). The microscope has a magnification of ×1200 used for morphological observation after sufficient dilution. The photomicrograph of the preparation was obtained from the microscope by using a digital Single lens reflex (SLR) camera[16].

Measurement of vesicle size:

The vesicle dispersions were diluted about 100 times in the same medium, which was used for their preparation. Vesicle size was measured on a particle size analyzer. The apparatus consist of a He-Ne laser beam of 632.8 nm focused with a minimum power of 5Mw using a Fourier lens (R-5) to a point at the center of multi-element detector and a small volume sample holding cell. The samples were stirred with a stirrer before determining the vesicle size[11].

Drug content:

Proniosomes equivalent to 100 mg were taken in a standard volumetric flask. They were lysed with 50 ml methanol by shaking for 15 min. The solution was diluted to 100 ml with methanol. Then 10 ml of this solution was diluted to 100 ml with saline phosphate buffer at certain pH. Aliquots were withdrawn and absorbance was measured at a certain wavelength and drug content was further calculated from the calibration curve.

Entrapment efficiency:

Separation of unentrapped drug from the niosomal suspension was carried out by exhaustive dialysis method and centrifugation method. Theniosomal suspension was taken into a dialysis tube to which osmotic cellulose membrane was securely attached to one side, the dialysis tube was suspended in 100 ml saline buffer at certain pH, which was stirred on a magnetic stirrer. The niosomal suspension and the unentrapped drug were seperated into the medium through osmotic cellulose membrane. After 6 h of exhaustive dialysis, optical density values were noted and the estimation of the entrapped drug was carried out by UV spectrophotometric method. Entrapment Efficiency was calculated using the formula[17].

***In vivo* release studies:**

The release of the drug from the proniosomal formulations was determined using different techniques such as Franz diffusion cell, Keshary-Chien diffusion cell, Cellophane dialyzing membrane, United states pharmacopeia (USP) dissolution apparatus Type-1, spectrapor molecular porous membrane tubing. Drug release from proniosomes derived niosomal vesicles can follow any one or more of the following mechanisms; desorption from the surface of vesicles or diffusion of drug from bilayered membrane or a combined desorption and diffusion mechanisms[18].

Stability studies:

Stability studies were carried out by storing the prepared proniosomes at various temperature conditions such as refrigeration temperature (2°-8°C), room temperature (25° ± 0.5°C) and elevated temperature (45° ± 0.5°C) from a period of 1 month to 3 months. Drug content and variation in the average vesicle diameter were periodically monitored[19,20].

CLINICAL APPLICATIONS

Application in cardiology:

Proniosomes are used as carriers for the transdermal delivery of captopril for the treatment of hypertension. Proniosomal system causes extended release of the drug in the body. Encapsulation of the drug is carried out using Sorbitan esters, Cholesterol and lecithin[21].

Application in diabetes:

Skin permeation mechanism of furesamide proniosomes is performed in which span, soya, lecithin, diacetyl phosphate, and cholesterol were used. Over all findings suggest that the proniosomes serve as non-invasive delivery of furesamide[22].

Delivery of peptide drugs:

Oral peptide drug delivery has a drawback of bypassing the enzymes, which would breakdown the peptide and protein bonds. Niosomes were used to successfully protect the peptides from gastrointestinal peptide breakdown. Oral

delivery of vasopressin derivative entrapped in niosomes showed that entrapment of the drug significantly increased the stability of the peptide[23].

Niosomes as carriers for hemoglobin:

Blood has many carrier proteins present in it. Niosomes can be used as carriers for hemoglobin within the blood. The niosomal or the proniosomal vesicle is permeable to oxygen and hence it acts as a carrier for hemoglobin in patients.

Hormonal therapy:

Work had been performed on proniosome based transdermal delivery of levonorgestrel the emergency contraceptive. The structure of the niosome was liquid crystalline compact hybrid. The system was tested for particle size, encapsulation efficiency, stability study, *in vivo* and *in vitro* study. Bioassay for progestational activity was also performed. It included endometrial assay and blockade of development of corpora lutea[17].

CONCLUSION

Proniosomes are promising drug carriers for the future. These systems have been found to be more stable during sterilization and storage than niosomes. Proniosomes are thought to be better candidates of drug delivery as compared to liposomes and niosomes due to various factors like cost, stability etc. The use of proniosomal carrier results in delivery of high concentration of active agent(s), regulated by composition and their physical characteristics. Dry powder form of proniosomes makes them suitable for preparing unit dosage forms such as tablets, capsules and beads. There is lot of scope to investigate new carrier material for preparation of proniosomes and their potential remains to be investigated to full extent.

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