International Journal of Pharmacy
Journal Homepage: http://www.pharmascholars.com

Review Article **CODEN: IJPNL6**

NIOSOMES – VESICULAR DRUG DELIVERY SYSTEM

V. Lokeswara Babu [*], Sam T. Mathew [1], K.N. Jayaveera [2] and V.V. Prasanth [3]

*Dept. of Pharmaceutics, Bhaskar Pharmacy College, Hyderabad – 500 075, Andhra Pradesh
[1]Asst. Manager, Accenture Pharmaceutical Service, Bangalore, Karnataka
[2]Dept. of Chemistry, JNTUA, Anantapur – 515001, Andhra Pradesh
[3] Dept. of Pharmaceutics, Gautham College of Pharmacy, Bangalore, Karnataka

***Corresponding author e-mail: lokshv83@gmail.com**

ABSTRACT

At present days drugs are formulated by using different novel drug delivery system (NDDS) which are used for targeting drugs to different organ systems and for controlled /sustained release of drug from the dosage forms. The NDDS can be used to overcome many disadvantages of conventional dosage forms like poor bioavailability, first pass effect, systemic toxicity, degradation of drug in stomach etc. which results in decreased biological activity of the drugs. Vesicular system is one of the important NDDS studied since a lot of time, of which main importance was given to liposomes. Due to the unstability of phospholipids (used for the formulation of liposomes) on storage was replaced with non ionic surfactants. Niosomal vesicles were prepared by using non ionic surfactants and were first reported in cosmetic industry. Niosomes are used as carrier systems for the delivery of most of the drugs, biologically active agents, hormones and antigens for the better treatment. The present review involves a detailed description about the drug delivery through niosomal formulation.

Keywords: Liposomes, NDDS, Niosomes, Non – ionic surfactants, Phospholipids and Vesicular drug delivery system.

INTRODUCTION

The novel drug delivery system (NDDS) maintains a relatively constant and effective drug level in the body for controlled or sustained drug action at a predetermined rate. Different novel approaches includes incorporation of drug in carrier system such as colloidal carrier system, microspheres, nanoparticles and vesicular system such as liposomes, niosomes, virosomes etc. or by altering drug structure at molecular level.

The vesicular systems are consisting of one or several lipid bilayer membrane vesicles which are formed by using diverse range of amphiphilic building blocks. These vesicles were first reported in cosmetic industry by Bingham [1] in 1965. This article includes definition, advantages, formulation of niosomes, methods of preparation, characterization and applications of Niosomes as vesicular drug delivery system.

Definition

Niosomes are the highly ordered vesicular bilayer membrane made up of non – ionic surfactant with or without incorporation of cholesterol and dicetyl phosphate. The closed bilayer vesicular structure of niosome formed by the self assembling of non – ionic surfactants in the presence of aqueous media [2].

The niosomes are categorized in to 3 types and their size and the method of preparation is given in *Table No.1*

Advantages

The various advantages of niosomes as drug delivery system include:

1. Niosomes can improve oral bioavailability of poorly absorbed drugs.
2. Niosomes can enhance the skin penetration of drugs.
3. Niosomes act as a depot for short acting peptide drugs [3] and releases the drug in a controlled rate and increases the stability of entrapped drug.
4. Niosomes prolong the circulation of entrapped drug and altering its organ distribution and metabolic stability [4].
5. Niosomes can entrap hydrophilic, amphiphilic and lipophilic drugs and the entrapment efficiency drug increases by increasing the concentration and lipophilicity of surfactant [5].
6. Surfactants used in the preparation of niosomes are nontoxic, biodegradable, biocompatible and non-immunogenic and they don't require special conditions for handling and storage [6].
7. Niosomes are chemically stable as compare to liposomes.
8. Niosomes acts as carriers for enhanced delivery of drugs to specific cells and improves their therapeutic index by restricting drug effects to target cells [7] only.
9. The release of drug from the reservoir is slow which may reduces the systemic toxicity of the drug.

FORMULATION OF NIOSOMES

The main constituents required for the formation of niosomes are non – ionic surfactant, cholesterol and membrane stabilizers. The different non – ionic surfactants include poly glycerol alkyl ether, glucosyl dialkyl ethers, crown ethers, ester linked surfactants, polyoxyethylene alkyl ether or Brij and series of spans and tweens. Cholesterol is added to provide rigidity to the bilayer membrane and also to produce non leaky or less leaky niosomes. Dicetyl phosphate is added to increase the size of the vesicles, to provide charge on the vesicles to maintain electrostatic stabilization and to increase the drug entrapment efficiency. Stearylamine and diacyl glycerol are also used to maintain electrostatic stabilization of vesicles.

METHODS OF PREPARATION

Niosomes can be prepared by any one of the following methods

Injection Method

In this method, add a solution of surfactant dissolved in diethyl ether slowly into warm water maintained at 60°C. The surfactant mixture in ether is injected through 14-gauge needle into an aqueous solution of material [7]. The vaporization of ether results in the formation of single layered vesicles.

Hand Shaking Method (Thin Film Hydration Technique) [8]**:** The surfactant and cholesterol mixture is dissolved in a volatile organic solvent like diethyl ether, chloroform or methanol in a round bottom flask. Remove the organic solvent by using rotary flash evaporator at room temperature which results in the formation of a thin layer of solid mixture deposited on the wall of the flask. The dried surfactant film can be rehydrated by using aqueous phase at 0 – 60 °C with gentle agitation results in formation of multilamellar niosomes.

Thermosensitive niosomes were prepared by Raja Naresh *et al* [9] by evaporating the organic solvent at a temperature of 60 °C and leaving a thin film of lipid on the wall of rotary flash evaporator. The aqueous phase containing drug was added slowly with intermittent shaking of flask at room temperature followed by sonication. Methotrexate and Doxorubicin loaded by using this method.

Sonication: The preparation of niosomal vesicles by Sonication is described by Cable [10]. In this method an aliquot of drug solution in buffer is added to the surfactant/cholesterol mixture in a 10ml glass vial. The mixture is sonicated at 60 °C for 3 minutes using a sonicator with a titanium probe to yield niosomes. The drugs loaded by using this method are 8 – Arginine, 9-desglycinamide, Vasopressin and Oestradiol.

Multiple Membrane Extrusion Method: The mixture of surfactant, cholesterol and dicetyl phosphate in chloroform is converted into a thin film by evaporation of organic solvent. The film is hydrated with aqueous drug solution and it results in the formation of multilamellar vesicles which are then extruded through a series of filters of various pore sizes under moderate pressures to produce small unilamellar vesicles. It is a good method for controlling the size of the niosomes.

Reverse Phase Evaporation Technique: Cholesterol and surfactant in the ratio of 1:1 are dissolved in a mixture of ether and chloroform. An aqueous phase containing drug is added to this organic mixture and the resulting two phases are sonicated at 4 – 5 °C which results in the formation of a clear gel. Then it is further sonicated after the addition of a small amount of phosphate buffered saline (PBS). The organic phase is removed at 40 °C under low pressure. The resulting viscous niosomal suspension is diluted with PBS and heated on a water bath at 60

°C for 10 min to form vesicles [11]. Raja Naresh *et al* [8] have reported the preparation of Diclofenac Sodium niosomes using Tween 85 as surfactant by using this method.

Formation of Niosomes from Proniosomes : Proniosomes [12] are dry formulations of surfactant – coated carrier and these are rehydrated by gentle agitation in hot water. Proniosomes are prepared by spraying surfactant in organic solvent onto sorbitol powder and then evaporating the solvent. The sorbitol acts as a carrier which is soluble in organic solvent so it is necessary to repeat the process until the desired surfactant loading has been achieved. The surfactant coating on the carrier is very thin and hydration of this coating allows the formation of multilamellar vesicles. The resulting niosomes are very similar to those produced by conventional methods and the size distribution is more uniform. This method is suitable for formulation of hydrophobic drugs in a lipid suspension by minimizing problems of niosome physical stability such as aggregation, fusion and leaking and provides additional convenience in transportation, distribution, storage and dosing. The schematic representation of formation of proniosomes and niosomes is given in *fig. 1*

Separation of Unentrapped Drug

The methods used for the separation of unentrapped drug from the aqueous dispersion of niosomal drug system include:

1. The aqueous niosomal dispersion is exhaustively dialyzed using cellophane tubing against phosphate saline buffer (PBS) of pH 7.4 or saline [13].
2. The column chromatographic method also used for separation of free drug from niosomal suspension by using Sephadex G – 50. The free drug is retained by Sephadex G – 50 while vesicles percolate down along with elute. This method is called as gel filtration [14].
3. Another method is by the centrifugation of niosomal suspension. The incorporation of cholesterol in the preparation increases the density and the suspended vesicles in water, phosphate saline buffer (PBS) or saline are expected to sediment under the high gravitational effect [15].

CHARACTERIZATION OF NIOSOMES

The niosomal vesicle are evaluated for the following characteristics

Size, Shape and Morphology: The niosomal vesicular structure has been visualized by using freeze fracture electron microscopy. Mean diameter of the vesicles determined by using photon correlation spectroscopy. Electron microscopy is used for the morphological studies of vesicles

Entrapment efficiency & Drug release Rate: Entrapment efficiency of niosomes was determined by exhaustive dialysis method. The measured quantity of niosomal suspension was taken into a dialysis tube to which osmosis cellulose membrane was securely attached on one side. The dialysis tube was suspended in 100ml phosphate saline buffer (pH 7.4), which was stirred on a magnetic stirrer. The unentrapped drug was separated from the niosomal suspension into the medium through osmosis cellulose membrane. At every hour entire medium (100ml) was replaced with fresh medium (for about 9-12h) till the absorbance reached a constant reading indicating no drug is available in unentrapped form. The niosomal suspension in the dialysis tube was further lyzed with propane-1-ol and estimated the entrapped drug by UV spectrophotometric method at 210nm.

Vesicle Surface Charge

The presence of surface charge on vesicular dispersion is critical. The aggregation of vesicles in isotonic saline solution occurs when the vesicles are prepared without the inclusion of a charged molecule in the bilayer. The aggregation of vesicles is attributed to the shielding of the vesicle surface charge by ions in the solution which reduces the electrostatic repulsion. A reduction in the formation of aggregates was observed when a charged molecule like dicetylphosphate was incorporated in bilayer vesicle.

Vesicle surface charge can be estimated by measuring particle electrophoretic mobility and expressed as the zeta potential which is calculated by using Henry's equation.

$$\zeta = \frac{\mu E \, 4\pi \eta}{\varepsilon}$$

Where, ζ is Zeta potential, μE is Electrophoretic mobility, η is Viscosity of the medium and ε is Dielectric constant.

APPLICATIONS OF NIOSOMES

Niosomal drug delivery system is potentially applicable to many pharmacological agents for their therapeutic action against various diseased conditions. The following are different therapeutic applications of niosomes,

Niosomes in the treatment of Leishmaniasis

Leishmaniasis is a disease in which parasite invades cells of liver and spleen. The commonly prescribed drugs in the treatment of Leishmaniasis are antimonials, which are related to arsenic and at high concentration they damage the heart, liver and kidney. The administration of these drugs in the form of niosomes can prevent organ damage [17].

Niosomes in Oncology

Drug delivery to the tumor can be more effective for Methotrexate and Doxorubicin when administered in the form of niosomes.

Doxorubicin is an anthracyclic antibiotic with broad spectrum antineoplastic activity, shows a dose dependant cardiomyopathy and myelosuppression. The vesicles with polyoxyethylene surface were rapidly taken up by the liver and accumulated to a lesser extent in tumor. Intravenous administration of Methotrexate entrapped in niosomes to S-180 tumor bearing mice resulted in total regression of tumor and also higher plasma level and slower elimination of the drug [18].

Niosomes as Immunological Adjuvant

Niosomes have been used for studying the nature of the immune response provoked by antigens. Brewer and Alexander [19] have reported niosomes as potent adjuvant in terms of immunological selectivity, low toxicity and stability by comparing the enhanced antibody production in response to bovine serum albumin with Freund's complete adjuvant.

Moser *et al* [20] carried out study on niosomal hemoglobin for its compatibility and interaction with blood. The study mainly involves the agglutination phenomenon with ABO blood group components as plasma extenders and erythrocyte phenotypes.

Vyas SP *et al* [21] carried studies on non – invasive topical genetic immunization against Hepatitis B in the form of niosomes.

Niosomes for Oral Drug Delivery

Yoshida *et al* [22] investigated oral delivery of peptide drugs such as 9-desglycinamide–8-arginine vasopressin entrapped in polyoxyethylene-3 or 7-stearyl ether niosomes in an *in vitro* intestinal loop model which results in significant increased stability of peptide drugs.

The oral bioavailability of celecoxib [23] and griseofulvin [24] can be enhanced by formulating in the form proniosomes and niosomes respectively. Pardakhty A [25] developed Insulin niosomes as sustained release oral dosage form using Brij as non ionic surfactant by film hydration method.

Niosomes for Transdermal Delivery

Slow penetration rate of drug through skin is the major drawback of transdermal drug delivery systems. An increase in the penetration rate has been achieved by transdermal delivery of drug incorporated in the form of niosomes. Jayaraman *et al* [26] has studied the topical delivery of erythromycin from various formulations including niosomes on hairless mouse. Balakrishnan P *et al* [27] studied enhanced skin delivery and bioavailability of minoxidil niosomes in hair loss treatment prepared by using Brij/Span with cholesterol using film hydration method.

Niosomes as Diagnostic Agents

Niosomes can also be used for diagnostic purposes. Korkmaz *et al* [28] formulated DTPA carrying niosomes (hexadecyl triglycerol ether: cholesterol: DTPA) to study the *in vitro* release, radiolabelling, *in vivo* distribution and to perform scintigraphic imaging studies. They found that niosomes can act as good carrier for radiopharmaceuticals and site specific vesicle for spleen and liver imaging.

Niosomes as Ophthalmic Carriers

Acetazolamide in the form of niosomes can improve the low corneal penetration and bioavailability characteristics in rabbit. Abdelkader H [29] successfully developed and characterized naltrexone HCl niosomes using reverse phase evaporation and thin film hydration method as ocular delivery system.

CONCLUSION

As compared with the conventional dosage forms niosomal drug delivery system is suitable for encapsulating toxic anticancer drugs, anti-infective drugs, anti AIDS drugs, anti-inflammatory drugs, antiviral agents, hormones, antigens, peptide drugs etc. and are better drug carriers to achieve better bioavailability and targeting properties and also to reduce toxicity and side effects of the drugs by encapsulation. Vesicular drug carriers (niosomes) can be transported by macrophages which are infiltrate tumor cells and possible to deliver antitumor agents within vesicles by activated macrophage system to tumor sites. Till now only animal experiments for targeted drug delivery system is reported but further clinical investigations in human volunteers, pharmacological and toxicological investigations in animals and human volunteers may help to exploit niosomes as prosperous drug carriers for targeting drugs more efficiently for treating cancer, infection and AIDS etc.

Figure 1: Schematic representation of formation of niosomes from Proniosomes

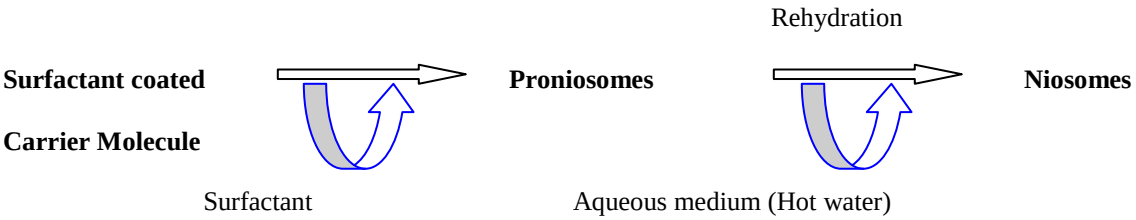

Table 1: Different types of Niosomes

	Multilamellar Vesicles	Small Unilamellar Vesicles	Large Unilamellar Vesicles
Vesicle Size	Greater than 0.05µm	0.025 – 0.05µm	Greater than 0.10µm
Method of Preparation	Hand Shaking Method	Sonication	Reverse Phase evaporation Method
		Extrusion Method	
		Solvent Dilution Technique	

REFERENCES

1. Bangham AD, Standish MM, Watkins JC. J Mol Biol. 1965 Aug;13(1):238–252.
2. Lasic DD. J Colloid Interface Science 1990; 140: 302 – 304.
3. Arunothayanum P, Turton JA, Uchegbu IF and Florence AT. J Pharm Sci. 1999 Jan;88(1):34-8.
4. Azmin MN, Florence AT, Handjani-Vila RM, Stuart JFB, Vanlerberghe G, and Whittaker JS. J. Pharm. Pharmacol. 1985; 37: 237–242.
5. Chandraprakash KS, Udupa N, Umadevi P and Pillai GK. Int J Pharmaceutics **1990**;61:R1-R3.
6. Florence AT. Non-ionic surfactant vesicles preparation and characterization. In: Gregoriadis G, editor. Liposome Technology, Vo. 2. CRC Press, Beca Raten, FL 1993:157-176.
7. Baillie AJ, Florence AT, Hume LR, Rogerson A and Muirhead G.T. J. Pharm Pharmacology. 1985; 37(12):863–868.
8. Kunitake T, Okata Y. J. Amer. Chem. Soc. 1976, 99: 3860.
9. Raja Naresh RA, Chandrashekhar G, Pillai GK and Udupa N. Ind.J.Pharmacol. 1994; 26:46-48.
10. Cable C. An examination of the effects of surface modifications on the physicochemical and biological properties of non-ionic surfactant vesicles [PhD thesis]. In: Glasgow: University of Strathclyde, 1989.
11. Jausma H, Joosten JGH and Junginger HE (1988) Coll.Polym.Sci. 266, 640.
12. Blazek-Walsh AI and Rhodes DG. Pharm. Res. 2001; 18: 656-661.
13. Baillie AJ, Coombs GH, Dolan TF and Laurie J. J. Pharm. Pharmacology 1986, 38, 502.
14. Azmin MN, Florence AT, Handjani – Vila RM, Stuart JFB, Vanlerberghe Gand Whittaker JS. J.Pharm.Pharmacology. 1985, 37, 237.
15. Newman GC and Huang C. (1975) Biochemistry *1975* Jul 29;*14*(15):*3363*-70.
16. Hunter CA, Dolan TF, Coombs GH and Baillie AJ. J.Pharm. Pharmacol. 1988; 40(3): 161-165.
17. Chandraprakash KS, Udupa N, Umadevi P and Pillai GK. *Ind. J. Pharm. Sci.* 1992; 54 (5): 197.
18. Brewer JM and Alexander JA.. Immunology. 1992; 75 (4):570-575.
19. Moser P, Arvier MM, Labrude P, Vignerson C, Pharm Acta Helv. (1990) 65 (3): 82.
20. Vyas SP, Singh RP, Jain S, Mishra V, Mahor S, Singh P, Gupta PN, Rawat A, Dubey P. Int J Pharm. 2005 May 30; 296(1-2):80-6.
21. Yoshioka T, Sternberg B, Moody M and Florence AT. J. Pharm. Pharmcol. Supp. 1992; 44: 1044.
22. Nasr M. AAPS PharmSciTech. 2010 Mar; 11(1):85-9.
23. Jadon PS, Gajbhiye V, Jadon RS, Gajbhiye KR, Ganesh N. AAPS PharmSciTech. 2009;10(4):1186-92.
24. Pardakhty A, Varshosaz J, Rouholamini A. Int J Pharm. 2007 Jan 10;328(2):130-41.
25. Jayaraman CS, Ramachandran C and Weiner N. J. Pharm. Sci. 1996; 85 (10): 1082-1084.

26. Balakrishnan P, Shanmugam S, Lee WS, Lee WM, Kim JO, Oh DH, Kim DD, Kim JS, Yoo BK, Choi HG, Woo JS, Yong CS. Int J Pharm. 2009 Jul 30;377(1-2):1-8.
27. Korkaz M, Ozer AY and Hincal AA. In: Synthetic Surfacnt vesicles, niosomes and other non-phospholipid vesicular systems, Uchegbu I.F. (Ed.) Harwood Academic Press, Netherland, 2000; 83.
28. Abdelkader H, Ismail S, Kamal A, Alany RG. Pharmazie. 2010 Nov;65(11):811-7.