NIOSOME DRUG DELIVERY SYSTEM: ADVANCES AND MEDICAL APPLICATIONS – AN OVERVIEW

V. Sankar *, K. Ruckmani [1] , S. Jailani [1] , K.Siva ganesan [1] , S.P.Sharavanan [1]

[*] *Department of Pharmaceutics, P.S.G. College of Pharmacy , Coimbatore – 641004*
[1] *Department of Pharmaceutical Engineering and Technology, Anna University, Trichirapppalli-620024.*

[*]*E-mail: sansunv@yahoo.co.in*
Phone: 0422-2570170 Extn. 5841
Fax: 0422-2594400

Summary

Niosomes, vesicular systems made of nonionic surfactants, have several advantages over conventional non-vesicle formulations. In recent years, Niosomes have become the vesicles of choice in drug delivery. Niosome vesicles are found to be of value in immunology, membrane biology and diagnostic techniques. The focus of this review is to bring out different aspects related to Niosome preparation, characterization, entrapment efficiency, *in vitro* drug release, applications and merits.

Key words; Niosomes, Characterization, Medicinal Applications.

Introduction

Different types of pharmaceutical carriers are present. They are particulate, polymeric, macromolecular and cellular carrier. Particulate type carrier also known as colloidal carrier system includes lipid particles (low and high density lipoprotein-LDL and HDL, respectively), microspheres, nanoparticles, polymeric micelles and vesicular systems like liposomes, niosomes. Niosomes are formed from the self-assembly of nonionic amphiphiles in aqueous media resulting in closed bilayer (unilamellar or multilamellar) structures [(1)].

Span surfactants are used widely in foodstuffs paves the way for the use of niosomal vesicles in pharmaceutical formulations. Niosomes were first reported by Vanlerberghe et al.1972 and latter by Handjani-Vila et al.1979 for their use in cosmetic industries[(2, 3)]. From early 1980s, niosomes have gained wide attention by researchers for their use as drug targeting agents, drug carriers to have variety of merits with avoidance of demerits associated with the conventional form of drugs. These vesicles are widely used not only as the models for cell membranes, but also as drug carriers to deliver the drug into the targets of tumors and viruses[(4)].

Encapsulation of a drug in vesicular structures can be predicted to prolong the existence of drug in systemic circulation and perhaps, reduces the toxicity if selective uptake can be achieved. The phagocytic uptake of the systemic delivery of the drug-loaded vesicular delivery system provides an efficient method for delivery of drug directly to the site of infection, leading to reduction of drug toxicity with no adverse effects.Niosomal delivery systems delay drug elimination of rapidly metabolizable drugs, and function as sustained release systems. This system solves the problems of drug insolubility, instability, and rapid degradation.

Niosomes are preferred over other vesicular systems as they offer the following advantages[(5)]. Niosomes are chemically stable as compared to liposomes, can entrap both lipophilic and hydrophilic drugs, have low toxicity because of their non-ionic nature, no special precautions and conditions are required, exhibit flexibility in their structural characterization, improve the performance of the drug via better availability and controlled delivery at a particular site, biodegradable, biocompatible, and non immunogenic, good stabity, low cost and lesser storage problems.

Methods

Preparation Of Niosome

There are number components present in niosomes with non ionic surfactants and cholesterol being the main ingredients. Methods of preparation of Niosomes involve dissolution of cholesterol, non ionic surfactant and drug in organic solvent followed by drying it to a thin film, and then dispersion of film in an aqueous medium to obtain niosome suspension at a critical hydrating temperature. The hydrating temperature used to prepare niosomes should be above the phase transition temperature of the non ionic surfactant used i.e. temperature at which there is transition from gel to liquid phase. Different non ionic surfactants and membrane stabilizers used for the niosome preparation are shown in table No.1

Table No.1: Non Ionic Surfactants and membrane Stabilizers used for the preparation of Niosomes

S.No	Non ionic surfactants used
1	Span20
2	Span40
3	Span60
4	Span80
5	Span85
6	Tween20
7	Tween40
8	Tween60
9	Tween80
10	Tween61
11	Combination of Span20:Tween80
12	Combination of Span60:Tween80

13	Brij30
14	Brij52
15	Brij72
16	Brij76
17	Brij92
18	Brij97
19	Wasag7
20	Wasag15
21	Palmitoyl muramic acid(PMA)
22	N-Hexadecanoyl-2-aminoethyl-15- crown-5.(PCE)
23	Hexa substituted cyclophosphazenic acid derivatives
24	O-14 maltoside
25	Decylpolyglucoside (Oramix R NS 5)
26	Decylpolyglucoside (Oramix R NS 10)
27	N-palmitoyl glucosamine
28	Mono palmitoyl-rac-glycerol
S.No	Membrane Stabilizers used (Fatty alcohols)
1	Myristyl alcohol
2	Lauryl alcohol
3	Cetyl alcohol
4	Stearyl alcohol
5	Cetostearyl alcohol
6	Cholesterol

Different laboratory methods (Hydration techniques) are used for the formulation of niosomal vesicles (NSVs).

Ether Injection Method: The injection of an organic solution of surfactants: lipids through a 14 gauze needle at a rate approximately 0.25 ml/m in to a preheated 4.0 ml aqueous solution of the drug maintained at 60^{o}[6, 7, 8].

Hand Shaking Method :(Thin film hydration) surfactant: lipid is dissolved in 10 ml of organic solvent in a round bottomed flask .The organic solvent is evaporated under vaccum at room temperature in a rotary evaporator to form a thin film of surfactant: lipid. This film is then hydrated with a solution of the drug [6, 8].

Reverse Phase Evaporation: The formation of an oil in water (o/w) emulsion from an organic solution of surfactants: lipids and an aqueous solution of the drug. The organic solvent is then evaporated to leave niosomes dispersed in the aqueous phase. In some cases, a gel results which must be further hydrated to yield niosomes[8].

Sonication: Surfactant: Lipid mixture in organic solvent is mixed with aqueous phase in a vial. Then the dispersion is probe or bath sonicated for 3 min at $60^{o.}$

Aqueous Dispersion Method: The homogenization of a surfactant: lipid mixture followed by the bubbling of nitrogen gas through this mixture

Size Reduction Of Niosomes

Niosomes prepared are usually in the micron size range. Some formulation methods produce niosomes in the sub-micron (300 nm) size range. Size reduction step must be considered in the niosome formulation, subsequent to the initial hydration step as vesicle size is important for biodistribution.

Reduction in vesicle size may be achieved by a number of methods (i.e.)Probe sonication , Extrusion through 100 nm Nucleopore filters , Combination of sonication and filtration (220 nm Millipore® filter), Microfluidizer, High-pressure homogenization.

Characterization Of Niosomes

Niosomes are characterized for vesicle size, size distribution, shape, surface charge, lamellarity, membrane microstructure are enlisted in Table No.2 **.**

Table No.2 : Methods for the characterization of Niosomal vesicles (NSVs).

S. No.	Parameter	Instrument / Method Employed
1	Vesicle size Determination and size distribution	1.Malvern Mastersizer 2.Photon correlation spectroscopy(PCS) 3.Optical microscopy 4.Scanning electron microscopy(SEM) 5.Salad-1100 laser diffraction particle size analyzer 6.Coulter submicron particle size analyzer 7.Klotz® particle sizer 8.Anderson cascade impactor
2	Shape and morphological characterization	1.Optical microscopy 2.Polarized light microscopy 3.Transmission electron microscopy 4.Freez fracture microscopy(FF-TEM) 5.Multiple tau digital correlator 6.Small angle X-ray diffraction (SA-XRD) 7.Phase Contrast microscopy 8.Quasi elastic light scattering
3	Zetapotential / Surface charge	1.Microelectrophoresismeter 2.High performance capillary electrophoresis 3.Malvern Zetasizer (zetameter)

4	Lamellarity	1.Optical microscopy 2.Transmission electron microscopy
5	Membrane microstructure	Negative staining TEM
6	Bilayer fluidity	Differential polarized phase flourometry
7	Bilayer spacing and thickness	X-ray scattering
8	Thermal behavior and shape transition	1.Differential thermal analysis (DTA) 2.Differential scanning calorimetry (DSC) 3.Hot stage microscopy
9	Rheological properties	1.Oswalt-U-tube 2.Low shear rheoanalyser
10	Conductivity	Conductometer

Determination Of Encapsulation Efficiency

The encapsulation efficiency is determined after separation of the unentrapped drug from entrapped drug using different techniques like Ultracentrifugation, Minicolumn centrifugation, Centrifugation, Gradient centrifugation, Gel filtration, Gel chromatography , Cellophane dialysis tubing D-9777, Dialysis bag, Size exclusion chromatography(SEC), Ficoll floatation technique' (to remove unentraped plasmid/DNA from NSVs), Cobra auto gamma counting system.

Entrapment efficiency of hydrophilic and lipophilic drugs depend on preparation method. Based on this the drug is actively or passively entrapped in vesicles. The percentage of drug entrapped is calculated using the following formula.

$$\% \text{ Entrapment efficiency} = \frac{\text{Amount of drug entrapped}}{\text{Total amount of drug}} \times 100.$$

***In Vitro* Drug Release From Niosomal Vesicles**

In Vitro drug release and skin permeation studies from niosomes are determined by different techniques like Side-by-side diffusion cell, Franz diffusion cell, Synthetic silicone membrane, K-C diffusion cell, Membrane diffusion technique, Cellophane dialyzing membrane, Sigma dialysis tubing, Dissolution dialysis apparatus. *In Vitro* skin permeation studies have been carried out using Hamster flank skin, Wister rat skin(7-9 weeks old), Newborn pig skin.

Drug release from Niosome can follow any one or more of the following mechanisms, Desorption from surface of vesicles or diffusion of drug from bilayered membrane or a combined desorption and diffusion mechanism.

Different studies carried out on Niosomes and their medicinal applications/purpose are summarized in Table No.3

Table No.3 : Studies on Niosomes and their medicinal applications

S.No	Purpose / Application	Drugs studied
1	Cancer chemothraphy and targeted drug delivery	Doxorubicin, Danorubicin Hcl Methotrexate, 5-flurouracil, Adriamycin, Vincristine, Cytarabine Hcl.
2	Transdermal drug delivery	Nimesulide, Lidocaine, Cyclosporin, Estradiol, Erythromycin, Alpha-Interferon, Indomethacin, Plasmid DNA for the human Interleukin1 receptor, Finasteride, Enoxacin, Trentinoin, Dithranol.
3	Enhancement of bioavailabity	Diclofenac, Flurbiprofen, Bleomycin, Vincristin, Acetazolamide, Doxorubicin.
4	Ocular drug delivery	Timolol maleate, Acetazolamide, Cyclopentolate.
5	Pulmonary drug delivery	All trans retinoic acid (ATRA).
6	Brain targeted drug delivery	Vasoactive intestinal peptide loaded glucose bearing NSVs.
7	Protein/Peptide and Harmone delivery	LHRH, Insulin (oral), 9-desglycinamide-8-arginine vasopressin(DGAVP).
8	Local/ Intra articular drug delivery	Radiolabelled Diclofenac sodium niosomal vesicles.
9	Enhancement of stability	9-desglycinamide-8-arginine vasopressin(DGAVP). Heamoglobin, Dithranol, Beta Carotene.
10	Improved photostability	Beta Carotene.
11	Improved thermal and oxidative stability	Propranolol hydrochloride, Doxorubicin.
12	Prolonged release	Sodium stibogluconate, Rifampicin, Bacopasaponin-C.

13	For improved anti infective therapy	Haemagglutinin,Ovalbumin,Hepatitis B DNA vaccine NSVs, Plasmid DNA encoding proteins of Hepatitis B virus, Influenza DNA vaccine NSVs, Tetanus toxoid NSVs.
14	Immunostimulatory NSVs(antigenic)	Urokinase
15	Diagnosis Radiopharmaceutical carrier and Imaging study	Iobitridol (X ray imaging studies) Iopromide (kidney imaging studies)

Conclusion

Researchers all over the world continue to put in their efforts in improving the vesicular systems by making them free from aggregation, fusion, leaching or hydrolysis of entrapped drugs and their uptake by natural defense mechanisms. The innovative methods are under development to enhance the shelf life of Niosome dispersions. Although there are still many hurdles to overcome, there is great promise that Niosomal formulations will greatly benefit the delivery of vaccines, proteins and DNA. Clinical relevance is the most important criteria for any novel drug delivery system hence deeper *in vivo* studies are to be explored for Niosomal vesicles to pass the benefits to human lives.

References

1.Schreier H, Bouwstra J. Liposome's and niosomes as topical drug carriers-dermal and transdermal drug-delivery. J. Control Rel. 1994; 30:1–15.

2.Jain CP, Vyas SP. Preparation and characterization of niosomes containing rifampicin for lung targeting. J.Microencap. 1995;12: 401–407.

3.Handjani-Vila RM, Rlbier A, Rondot B.et al. Dispersion of lamellar phases of non-ionic lipids in cosmetic products. Int. J. Cosmetic Sci. 1979;1:303–314.

4.Jae-Ho Lee, John P Gustin, Tianhong Chen.et al. Vesicle-Biopolymer Gels: Networks of Surfactant Vesicles Connected by Associating Biopolymers. Langmuir 2005; 21:26.33.

5.Carafa M,SantucciE,LucaniaG.Lidocaine-loaded non ionic surfactant vesicles: characterization and in vitro permeation studies. Int. J. Pharm. 2002; 231:21–32.

6.Niemec SM, Hu Z, Ramachandran C.et al. The effect of dosing volume on the disposition of cyclosporine A in hairless mouse skin after topical application of a non-ionic liposomal formulation.An in vitro diffusion study. STP Pharm. Sci. 1994;2:145–149.

7.Vanhal D, Vanrensen A, Devringer T.et al. Diffusion of estradiol from non-ionic surfactant vesicles through human stratum-corneum in vitro.STP Pharm. Sci. 1996;6: 72–78.

8 .Jia-You Fang, Chi-Tzong Hong, Wen-Ta Chiu.et al. Effect of liposomes and niosomes on skin permeation of Enoxacin. Int. J. Pharm. 2001;219: 61–72.