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NIOSOMES: AN STUDY ON NOVEL DRUG DELIVERY SYSTEM-A REVIEW

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ABSTRACT

Niosomes are a novel drug delivery system (NDDS), in which the medication is encapsulated in a vesicle. The vesicle is composed of a bilayer of non-ionic surface active agents and hence the name niosomes. The niosomes are very small, and microscopic in size. Their size lies in the nanometric scale. Although structurally similar to liposomes, they offer several advantages over them. It has been an study interest in the development of a NDDS. NDDS has an object to deliver the drug at a rate directed by the needs of the body during the period of treatment of a disease, and reach the active ingredient to the site of action. A number of NDDS have been reported through various routes of administration, to achieve controlled and targeted drug delivery. Encapsulation of the drug in vesicular structures is one of the most important system, which can be predicted to prolong the existence of the drug in systemic circulation and reduce the toxicity, if prescribed uptake can be achieved. Consequently a number of vesicular drug delivery systems such as liposomes, niosomes, transfersomes, and pharmacosomes were developed. Advances have since been made in the area of vesicular drug delivery, leading to the development of systems that allow drug targeting and the sustained or controlled release of conventional medicines. The focus of this review is to the various method of prepration, characterization of niosomes, advantages and brings out the application vesicular systems.

KEYWORDS:- Niosomes, NDDS, Vesicles, Systemic circulation, Controlled drug release etc.

INTRODUCTION

Niosomes are non-ionic surfactant vesicles obtained on hydration of synthetic nonionic surfactants, with or without incorporation of Available online on www.ijprd.com

cholesterol or other lipids [1]. They are vesicular systems similar to liposomes that can be used as carriers of amphiphilic and lipophilic drugs. One of the reasons for preparing niosomes is the assumed

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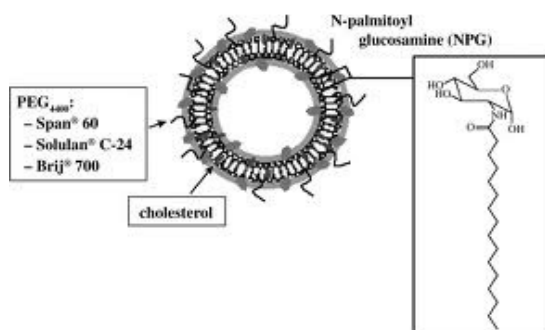


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higher chemical stability of the surfactants than that of phospholipids, which are used in the preparation of liposomes. Due to the presence of ester bond, phospholipids are easily hydrolysed [2]. Unreliable reproducibility arising from the use of lecithins in liposomes leads to additional problems and has led scientist to search for vesicles prepared from other material, such as nonionic surfactants. Niosomes are promising vehicle for drug delivery and being non-ionic, it is less toxic and improves the therapeutic index of drug by restricting its action to target cells. Niosomes or non-ionic surfactant vesicles are microscopic lamellar structures formed on admixture of non-ionic surfactant of the alkyl or dialkyl polyglycerol ether class and cholesterol with subsequent hydration in aqueous media [3]. In niosomes, the vesicles forming amphiphile is a non-ionic surfactant such as Span – 60 which is usually stabilized by addition of cholesterol and small amount of anionic surfactant such as dicetyl phosphate.



Salient Features of Niosomes;

Niosomes can entrap solute in a manner analogous to Liposome.

Niosomes osmotically active and stable.

Niosomes possess an infra structure consisting of hydrophobic and hydrophilic mostly together and so also accommodate the drug molecule with a wide range of solubility.

Niosomes exhibit flexibility in their structural characteristics (composition, fluidity and size) and can be designed according to their desired situation.

Niosomes can improve the performance of drug molecule.

Better availability to the particular site, just by protecting the drug from biological environment. Niosomes surfactants are biodegradable, biocompatible and nonimmunogenic [1].

Advantages of Niosomes

Use of niosomes in cosmetics was first done by L’Oreal as they offered the following advantages [4]:

The vesicle suspension being water based offers greater patient compliance over oil based systems. Since the structure of the niosome offers place to accommodate hydrophilic, lipophilic as well as amphiphilic drug moieties, they can be used for a variety of drugs.

The characteristics such as size, lamellarity etc. of the vesicle can be varied depending on the requirement.

The vesicles can act as a depot to release the drug slowly and offer a controlled release.

They increase the stability of the entrapped drug. Handling and storage of surfactants do not require any special conditions.

Can increase the oral bioavailability of drugs.

Can enhance the skin penetration of drugs.

They can be used for oral, parenteral as well topical use.

Improve the therapeutic performance of the drug by protecting it from the biological environment and restricting effects to target cells, thereby reducing the clearance of the drug.

The niosomal dispersions in an aqueous phase can be emulsified in a non-aqueous phase to control the release rate of the drug and administer normal vesicles in external non-aqueous phase.

METHOD OF PREPARATION

Ether injection method [5, 6]

This method provides a means of making niosomes by slowly introducing a solution of surfactant dissolved in diethyl ether into warm water maintained at 60°C. The surfactant mixture in ether is injected through 14-gauge needle into an aqueous solution of material. Vaporization of ether leads to formation of single layered vesicles. Depending upon the conditions used the diameter of the vesicle range from 50 to 1000 nm.

Hand shaking method (Thin film hydration technique) [6]

The mixture of vesicles forming ingredients like surfactant and cholesterol are dissolved in a volatile organic solvent (diethyl ether, chloroform or methanol) in a round bottom flask. The organic solvent is removed at room temperature (20°C) using rotary evaporator leaving a thin layer of solid mixture deposited on the wall of the flask. The dried surfactant film can be rehydrated with aqueous phase at 0-60°C with gentle agitation. This process forms typical multilamellar niosomes. Thermosensitive niosomes were prepared by evaporating the organic solvent at 60°C and leaving a thin film of lipid on the wall of rotary flash evaporator [7]. The aqueous phase containing drug was added slowly with intermittent shaking of flask at room temperature followed by sonication.

Sonication [6]

A typical method of production of the vesicles is by sonication of solution as described by Cable [8]. In this method an aliquot of drug solution in buffer is added to the surfactant/cholesterol mixture in a 10-ml glass vial. The mixture is probe sonicated at 60°C for 3 minutes using a sonicator with a titanium probe to yield niosomes.

Micro fluidization [9]

Micro fluidization is a recent technique used to prepare unilamellar vesicles of defined size distribution. This method is based on submerged jet principle in which two fluidized streams interact at ultra high velocities, in precisely defined micro channels within the interaction chamber. The impingement of thin liquid sheet along a common front is arranged such that the energy supplied to the system remains within the area of niosomes formation. The result is a greater uniformity, smaller size and better reproducibility of niosomes formed.

5. Multiple membrane extrusion method [9]

polycarbonate membranes, which are placed in series for upto 8 passages. It is a good method for controlling niosome size. Mixture of surfactant, cholesterol and dicetyl phosphate in chloroform is made into thin film by evaporation. The film is hydrated with aqueous drug solution and the

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resultant suspension extruded through which are placed in series for upto 8 passages. It is a good method for controlling niosome size.

Reverse Phase Evaporation Technique (REV) [7]

Cholesterol and surfactant (1:1) are dissolved in a mixture of ether and chloroform. An aqueous phase containing drug is added to this and the resulting two phases are sonicated at 4-5°C. The clear gel formed 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 niosome suspension is diluted with PBS and heated on a water bath at 60°C for 10 min to yield niosomes. It also have been reported the preparation of Diclofenac Sodium niosomes using Tween 85 by this method.

Trans membrane pH gradient (inside acidic) Drug Uptake Process (remote Loading) [10]

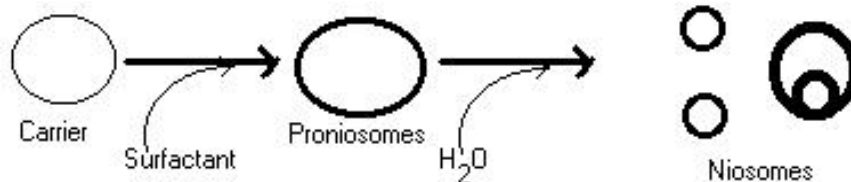
Surfactant and cholesterol are dissolved in chloroform. The solvent is then evaporated under reduced pressure to get a thin film on the wall of the round bottom flask. The film is hydrated with 300 mM citric acid (pH 4.0) by vortex mixing. The multilamellar vesicles are frozen and thawed 3 times and later sonicated. To this niosomal suspension, aqueous solution containing 10 mg/ml of drug is added and vortexed. The pH of the sample is then raised to 7.0-7.2 with 1M disodium phosphate. This mixture is later heated at 60°C for 10 minutes to give niosomes.

The “Bubble” Method [11]

It is novel technique for the one step preparation of liposomes and niosomes without the use of organic solvents. The bubbling unit consists of round-bottomed flask with three necks positioned in water bath to control the temperature. Water-cooled reflux and thermometer is positioned in the first and second neck and nitrogen supply through the third neck. Cholesterol and surfactant are dispersed together in this buffer (pH 7.4) at 70°C, the dispersion mixed for 15 seconds with high shear homogenizer and immediately afterwards “bubbled” at 70°C using nitrogen gas.

Formation of niosomes from proniosomes [12]

Another method of producing niosomes is to coat a water-soluble carrier such as sorbitol with surfactant. The result of the coating process is a dry formulation. In which each water-soluble particle is covered with a thin film of dry surfactant. This



It has been reported the formulation of niosomes from maltodextrin based proniosomes. This provides rapid reconstitution of niosomes with minimal residual carrier. Slurry of maltodextrin and surfactant was dried to form a free flowing powder, which could be rehydrated by addition of warm water.

CHARACTERIZATION OF NIOSOMES

Entrapment Efficiency:

After preparing niosomal dispersion, untrapped drug is separated by dialysis,[13] centrifugation,[13,14] or gel filtration[15] and the drug remained entrapped in niosomes is determined by complete vesicle disruption using 50% n-propanol or 0.1% Triton X-100 and analysing the resultant solution by appropriate assay method for the drug. Where, Entrapment efficiency (EF) = (Amount entrapped / total amount) x 100. Entrapment efficiencies of hydrophilic and lipophilic compounds depend on the preparation method. It has been concluded that niosomes prepared by ether injection method resulted in entrapment efficiencies of carboxy fluorescein that were significantly higher than those of vesicles prepared by hand shaking. Glycerol has been used as a surfactants and reported that the entrapment efficacy decreased as the amount of cholesterol added in the nonionic surfactant vesicle increased [16, 17].

Vesicle Diameter:

Niosomes, similar to liposomes, assume spherical shape and so their diameter can be determined using light microscopy, photon correlation microscopy and freeze fracture electron microscopy. Freeze thawing [9] (keeping vesicles

preparation is termed "Proniosomes". The niosomes are recognized by the addition of aqueous phase at $T > T_m$ and brief agitation.

T = Temperature.

T_m = mean phase transition temperature.

suspension at -20°C for 24 hrs and then heating to ambient temperature) of niosomes increases the vesicle diameter, which might be attributed to fusion of vesicles during the cycle.

In-Vitro Release:

A method of in-vitro release rate study includes the use of dialysis tubing. A dialysis sac is washed and soaked in distilled water. The vesicle suspension is pipetted into a bag made up of the tubing and sealed. The bag containing the vesicles is placed in 200 ml of buffer solution in a 250 ml beaker with constant shaking at 25°C or 37°C . At various time intervals, the buffer is analyzed for the drug content by an appropriate assay method [13].

Stability and Toxicity Studies

Compared to liposomes, niosomes are relatively stable structures some concern has been expressed regarding the stability of niosomes in vitro and their toxicity in vivo. Surfactants are used in the preparation of niosomes, which may be a cause of toxicity. However, there are virtually no reports available on the in vivo toxicity of niosomes linked with the concentration of ether or esters surfactants used in the preparation of vesicles. Hofland et al. studied the toxicity of CnEOM surfactants with two models. These include 1. The ciliary beat frequency (CNF) of trachea, which is important for intranasal administration and 2. The cell proliferation of keratinocytes which is important for the transdermal application of vesicles. A decrease in CBF was considered to be a measure for the toxicity of the formulation. Azmin et al performed first in vivo experiment on drug delivery by means of synthetic non-ionic surfactant vesicles and reported that no adverse effects were

observed in the experiment carried out [18]. Rogerson et al performed in vivo experiment over 70 male BALB/C mice and reported that no fatalities were encountered that could be attributed to the preparation. The toxic or side effects directly related to drug are reduced [19].

APPLICATION OF NIOSOMES

The application of niosomal technology is widely varied and can be used to treat a number of diseases. The following are a few uses of niosomes which are either proven or under research.

Drug Targetting:

One of the most useful aspects of niosomes is their ability to target drugs. Niosomes can be used to target drugs to the reticulo-endothelial system. The reticulo-endothelial system (RES) preferentially takes up niosome vesicles. The uptake of niosomes is controlled by circulating serum factors called opsonins. These opsonins mark the niosome for clearance. Such localization of drugs is utilized to treat tumors in animals known to metastasize to the liver and spleen. This localization of drugs can also be used for treating parasitic infections of the liver [3].

Niosomes can also be utilized for targeting drugs to organs other than the RES. A carrier system (such as antibodies) can be attached to niosomes (as immunoglobulin bind readily to the lipid surface of the niosome) to target them to specific organs. Many cells also possess the intrinsic ability recognize and bind specific carbohydrate determinants, and this can be exploited by niosomes to direct carrier system to particular cells.

Anti-neoplastic Treatment:

Most antineoplastic drugs cause severe side effects. Niosomes can alter the metabolism; prolong circulation and half life of the drug, thus decreasing the side effects of the drugs. Niosomal entrapment of Doxorubicin and Methotrexate (in two separate studies) showed beneficial effects over the untrapped drugs, such as decreased rate of proliferation of the tumor and higher plasma levels accompanied by slower elimination [21].

Leishmaniasis:

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Leishmaniasis is a disease in which a parasite of the genus *Leishmania* invades the cells of the liver and spleen. Commonly prescribed drugs for the treatment are derivatives of antimony (antimonials), which in higher concentrations can cause cardiac, liver and kidney damage. Use of niosomes in tests conducted showed that it was possible to administer higher levels of the drug without the triggering of the side effects, and thus allowed greater efficacy in treatment [22].

Delivery of Peptide Drugs:

Oral peptide drug delivery has long been faced with a challenge of bypassing the enzymes which would breakdown the peptide. Use of niosomes to successfully protect the peptides from gastrointestinal peptide breakdown is being investigated. In an invitro study conducted by Yoshida et al, oral delivery of a vasopressin derivative entrapped in niosomes showed that entrapment of the drug significantly increased the stability of the peptide [23].

Use in Studying Immune Response:

Due to their immunological selectivity, low toxicity and greater stability; niosomes are being used to study the nature of the immune response provoked by antigens [24].

Niosomes as Carriers for Haemoglobin:

Niosomes can be used as carriers for haemoglobin within the blood. The niosomal vesicle is permeable to oxygen and hence can act as a carrier for haemoglobin in anemic patients [25].

Transdermal Drug Delivery Systems Utilizing Niosomes:

One of the most useful aspects of niosomes is that they greatly enhance the uptake of drugs through the skin. Transdermal drug delivery utilizing niosomal technology is widely used in cosmetics; in fact, it was one of the first uses of the niosomes. Topical use of niosome entrapped antibiotics to treat acne is done. The penetration of the drugs through the skin is greatly increased as compared to un-entrapped drug [26]. Recently, transdermal vaccines utilizing niosomal technology is also being researched. A study conducted by P. N. Gupta et al has shown that niosomes (along with liposomes and

transfersomes) can be utilized for topical immunization using tetanus toxoid. However, the current technology in niosomes allows only a weak immune response, and thus more research needs to be done in this field.

Other Applications:

Niosomes can also be utilized for sustained drug release and localized drug action to greatly increase the safety and efficacy of many drugs. Toxic drugs which need higher doses can possibly be delivered safely using niosomal encapsulation.

MARKETED PRODUCT;

Lancome has come out with a variety of anti-ageing products which are based on niosome formulations. L'Oreal is also conducting research on anti-ageing cosmetic products.

COMPARISON BETWEEN NIOSOMES V/S LIPOSOMES

Niosomes are different from liposomes in that they offer certain advantages over liposomes. Liposomes face problems such as –they are expensive, their ingredients like phospholipids are chemically unstable because of their predisposition to oxidative degradation, they require special storage and handling and purity of natural phospholipids is variable. Niosomes do not have any of these problems. Also since niosomes are made of uncharged single-chain surfactant molecules as compared to the liposomes which are made from neutral or charged double chained phospholipids, the structure of niosomes is different from that of liposomes. However Niosomes are similar to liposomes in functionality. Niosomes also increase the bioavailability of the drug and reduce the clearance like liposomes. Niosomes can also be used for targeted drug delivery, similar to liposomes. As with liposomes, the properties of the niosomes depend both- on the composition of the bilayer, and the method of production used.

CONCLUSION

The incorporation of the drug into niosomes for a better targeting of the drug at appropriate tissue destination is widely accepted by research scientist. Niosomes represent a better targeted

drug delivery module. They are the best alternative of liposome and hence they can represent alternative vesicular systems with respect to liposomes, due to the niosome ability to encapsulate different type of drugs within their multienvironmental structure. Niosomes are thoughts to be better candidates drug delivery as compared to liposomes due to various factors like cost, stability etc. Various types of drug deliveries can be possible using niosomes like targeting, ophthalmic, topical, parenteral, transdermal etc. Niosomes have recently been shown to greatly increase transdermal drug delivery and also can be used in targeted drug delivery, and thus increased study in these structures can provide new methods for drug delivery. Niosomes are prepared by different methodology and easily characterized by the different parameters also.

REFERENCES

1. Handjani Vila et al., Dispersions of lamellar phases of non ionic lipids in cosmetic products. *Int. J. Cos. Sci.* 1: 1979; 303-314.
2. Kemps J. and Crommelin D.A. Hydrolyse van fosfolipiden in watering milieu. *Pharm Weekbl.* 123: 1988; 355-363.
3. Malhotra M. and Jain N.K. Niosomes as Drug Carriers. *Indian Drugs*, 31(3): 1994; 81-86.
4. Buckton G., Harwood, *Interfacial phenomena in Drug Delivery and Targeting* Academic Publishers, Switzerland. 1995; p.154-155.
5. Rogerson A., Cummings J., Willmott N. and Florence A.T. The distribution of doxorubicin in mice following administration in niosomes. *J Pharm Pharmacol.* 1988; 40(5): 337–342.
6. Baillie A.J., Coombs G.H. and Dolan T.F. Non-ionic surfactant vesicles, niosomes, as delivery system for the anti-leishmanial drug, sodium stribogluconate *J.Pharm.Pharmacol.* 1986; 38: 502-505.
7. Raja Naresh R.A., Chandrashekhar G., Pillai G.K. and Udupa N. Antiinflammatory activity of Niosome encapsulated diclofenac

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- sodium with Tween -85 in Arthritic rats. *Ind.J.Pharmacol.* 1994; 26:46-48.
8. Cable C. An examination of the effects of surface modifications on the physicochemical and biological properties of non-ionic surfactant vesicles [PhD thesis]. Glasgow: University of Strathclyde, 1989.
 9. Khandare J.N., Madhavi G. and Tamhankar B.M. Niosomes novel drug delivery system. *The Eastern Pharmacist.* 1994; 37: 61-64.
 10. Maver L.D. Bally M.B. Hope. M.J. Cullis P.R. *Biochem Biophys. Acta* (1985), 816:294-302.
 11. Chauhan S. and Luorence M.J. The preparation of polyoxyethylene containing non-ionic surfactant. Vesicles. *J. Pharm. Pharmacol.* 1989; 41: 6p.
 12. Blazek-Walsh A.I. and Rhodes D.G. *Pharm. Res.* SEM imaging predicts quality of niosomes from maltodextrin-based proniosomes. 2001; 18: 656-661.
 13. Yoshioka T., Stermberg B. and Florence A.T. Preparation and properties of vesicles (niosomes) of sobitan monoesters (Span 20, 40, 60, and 80) and a sorbitan triester (Span 85). *Int J Pharm.* 105:1994; 1-6.
 14. Gayatri Devi S., Venkatesh P. and Udupa N. Niosomal sumatriptan succinate for nasal administration. *Int. J. Pharm. Sci.* 62(6), 2000; 479-481.
 15. Szoka F.Jr. and Papahadyopoulos D. Comparative properties and methods of preparation of lipid vesicles (liposomes). *Ann. Rev. Biophys-Bioeng.* 9: 1980; 467-508.
 16. Baillie A.J. et al, The preparation and properties of niosomes- Non-ionic surfactant vesicles. *J.Pharm. Pharmacol.* 1985, 37: 863-868.
 17. Hunter J. A., et al. Vasicular systems (niosomes and liposomes) in experimental murine visceral leishmaniasis for delivery of sodium stibogluconate. *J. Pharm. Pharmacol.* 40: 1988, 161- 165.
 18. Azmin M.N. et al, the effect of non-ionic surfactant vesicle (niosome) entrapment on the absorption and distribution of methotrexate in mice. *J. Pharm. Pharmacol.* 37, 1985, 237–242.
 19. Rogerson A. et al. Adriamycin-loaded niosomes –drug entrapment, stability and release. *J.Microencap.* 4, 1987,321.
 20. Gregoriadis G. Targeting of drugs: implications in medicine. *Lancet.* 1981; 2(8240): 241-246
 21. Cummings J., Staurt J.F. and Calman K.C. Determination of Adriamycin, adriamycinol and their 7-deoxyaglycones in human serum by high-performance liquid chromatography. *J. Chromatogr.* 1984; 311: 125-133.
 22. Hunter C.A., Dolan T.F., Coombs G.H. and Baillie A.J. Vesicular systems (niosomes and liposomes) for delivery of sodium stibogluconate in experimental murine visceral leishmaniasis. *J.Pharm. Pharmacol.* 1988; 40(3): 161-165.
 23. Yoshioka T., Sternberg B., Moody M. and Florence A.T. Niosomes from Span surfactants: Relations between structure and form. *J. Pharm. Pharmcol. Supp.* 1992; 44: 1044.
 24. Brewer J.M. and Alexander J.A. The adjuvant activity of non-ionic surfactant vesicles (niosomes) on the BALB/c humoral response to bovine serum albumin. *Immunology.* 1992; 75 (4):570-575.
 25. Moser P., Marchand-Arvier M., Labrude P., Handjani Vila. R.M. and Vignerson C. Niosomes d'hémoglobine. I. Preparation, proprietes physicochimiques et oxyphoriques, stabilite. *Pharma. Acta.Helv.* 1989; 64 (7): 192-202.
 26. Jayaraman C.S., Ramachandran C. and Weiner N. Topical delivery of erythromycin from various formulations: an in vivo hairless mouse study. *J. Pharm. Sci.* 1996; 85 (10): 1082-1084.
