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Review Article

NIOSOMES : A NOVEL TREND IN DRUG DELIVERY

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ABSTRACT

Niosomes are a novel drug delivery system, in which the medication is encapsulated in a vesicle. Niosomes are formations of vesicles by hydrating mixture of cholesterol and nonionic surfactants. Different novel approaches used for delivering these drugs include liposomes,microspheres, nanotechnology, micro emulsions, antibody loaded drug delivery, magnetic microcapsules, implantable pumps and niosomes. Niosomes and liposomes are equiactive in drug delivery potential and both increase drug efficacy as compared with that of free drug. Niosomes are now widely studied as an alternative to liposomes . They improve the therapeutic performance of the drug molecules by delayed clearance from the circulation, protecting the drug from biological environment and restricting effects to target cells. The application of niosomal technology is widely used to treat a number of diseases.

Keywords: niosomes , vesicles , target cells , biological environment.

INTRODUCTION

Paul Ehrlich, in 1909, initiated the era ofdevelopment for targeted delivery when heenvisaged a drug delivery mechanism that would target directly to diseased cell. Sincethen, numbers of carriers were utilized tocarry drug at the target organ/tissue, whichinclude immunoglobulins, serum proteins,synthetic polymers, liposomes, microspheres,erythrocytes, niosomes etc[1].

Drug targeting can be defined as the ability todirect a therapeutic agent specifically todesired site of action with little or nointeraction with nontarget tissue26

The concept of targeted drug delivery is designed forattempting to concentrate the drug in the tissues of interestwhile reducing the relative concentration of the medicationin the remaining tissues. As a result, drug is localised onthe targeted site. Hence, surrounding tissues are notaffected by the drug. In addition, loss of drug does nothappen due to localisation of drug, leading to get maximumefficacy of the medication.[2]

Niosomes are one of the best among these carriers.Structurally, niosomes are similar to liposomes and also areequiactive in drug delivery potential but high chemicalstability and economy makes niosomes superior thanliposomes. Both consist of bilayer, which is made up ofnon-ionic surfactant in the case of niosomes andphospholipids in case of liposomes. Niosomes aremicroscopic lamellar structures of size range between 10 to1000 nm and consists of biodegradable, non-immunogenicand biocompatible surfactsnts[3].

The niosomes areampiphillic in nature, which allows entrapment ofhydrophilic drug in the core cavity and hydrophobic drugsin the non-polar region present within the bilayer henceboth hydrophilic and hydrophobic drugs can be incorporated into niosomes.4Niosomes or non-ionic surfactant vesicles are microscopic lamellar structures formed onadmixture of non-ionic surfactant of the alkyl ordialkyl polyglycerol ether class and cholesterolwith subsequent hydration in aqueous media. In Niosomes, the vesicles

forming amphiphile is anon-ionic surfactant such as Span – 60 which is usually stabilized by addition of cholesterol andsmall amount of anionic surfactant such as dicetyl-phosphate.[5]

Schematic representation of a drug targeting through its linkage to niosome via antibody is shown in figure 1.

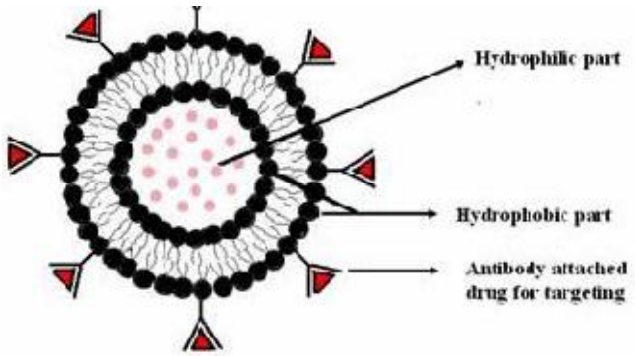

Figure 1 showing structure of niosomes [6]

ADVANTAGES OF NIOSOMES[7]:

1. The vesicles may act as a depot, releasing the drug in a controlled manner.
2. They are osmotically active and stable, and also they increase the stability of entrapped drug.
3. They improve the therapeutic performance of the drug molecules by delayed clearance from the circulation, protecting the drug from biological environment and restricting effects to target cells.
4. The surfactants used are biodegradable, biocompatible and non-immunogenic.
5. They improve oral bioavailability of poorly absorbed drugs and enhance skin penetration of drugs.
6. They can be made to reach the site of action by oral, parenteral as well as topical routes.
7. The vesicles may act as a depot, releasing the drug in a controlled manner.
8. Handling and storage of surfactants requires no special conditions.
9. Due to the unique infrastructure consisting of hydrophilic, amphiphilic and lipophilic moieties together they, as a result can accommodate drug molecules with a wide range of solubilities.
10. Niosomal dispersion in an aqueous phase can be emulsified in a non-aqueous phase to regulate the delivery rate of drug and administer normal vesicle in external non-aqueous phase.5

Types of niosomes[8]

The niosomes are classified as a function of the number of bilayer (e.g. MLV, SUV) or as a function of size. (e.g. LUV, SUV) or as a function of the method of preparation (e.g.REV, DRV). The various types of niosomes are described below:

i) Multi lamellar vesicles (MLV)(MLV, Size=>0.05 µm)

ii) Large unilamellar vesicles (LUV),(LUV, Size=>0.10 µm).

iii) Small unilamellar vesicles (SUV).(SUV, Size=0.025-0.05 µm)

1. Multilamellar vesicles (mlv):

It consists of a number of bilayer surrounding the aqueous lipid compartment separately. The approximate size of these vesicles is 0.5-10 µm diameter. Multilamellar vesicles are the most widely used niosomes.these vesicles are highly suited as drug carrier for lipophilic compounds.

2. Large unilamellar vesicles (luv):

Niosomes of this type have a high aqueous/lipid compartment ratio, so that larger volumes of bio-active materials can be entrapped with a very economical use of membrane lipids.

3. Small unilamellar vesicles (suv):

These small unilamellar vesicles are mostly prepared from multilamellar vesicles by sonication method, French press extrusion electrostatic stabilization is the inclusion of dicetyl phosphate in 5(6)-carboxyfluorescein (CF) loaded Span 60 based niosomes.

Niosomes in comparison with liposomes [27,11]

Niosomes are now widely studied as an alternative to liposomes, which exhibit certain disadvantages 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 are prepared from uncharged single-chain surfactant and cholesterol whereas liposomes are prepared from doublechain phospholipids (neutral or charged).

Niosomes behave in-vivo like liposomes, prolonging the circulation of entrapped drug and altering its organ distribution and metabolic stability. Encapsulation of various anti neoplastic agents in these carrier vesicles has been shown to decrease drug induced toxic side effects, while

maintaining, or in some instances, increasing the anti-tumor efficacy. Such vesicular drug carrier systems alter the plasma clearance kinetics, tissue distribution, metabolism and cellular interaction of the drug. They can be expected to target the drug to its desired site of action and/or to control its release.

.Components of niosomes:[9]

Niosomes mainly contains following types of components:

Non-ionic surfactants:

Selection of surfactant should be done on the basis of HLB value. As Hydrophilic Lipophilic Balance (HLB) is a good indicator of the vesicle forming ability of any surfactant, HLB number in between 4 and 8 was found to be compatible with vesicle formation. It is also reported that the hydrophilic surfactant owing to high aqueous solubility. on hydration do not reach a state of concentrated systems in order to allow free hydrated units to exist aggregates and coalesced to form lamellar structure.

a) Alkyl ethers: some surfactants[4] for the preparation of niosomes containing drugs/chemicals as:

1) Surfactant-I (Mol.Wt.473) is C16 monoalkyl glycerol ether with average of three glycerol units.

2) Surfactant-II (Mol.Wt.972) is diglycerol ether with average of the seven glycerol units.

3) Surfactant III (Mol.Wt.393) is ester linked surfactant.

b) Alkyl esters:Sorbitan esters are most preferred surfactant used for the preparation of niosomes amongst this category of surfactants. Vesicles prepared by the polyoxyethylene sorbitan monolaurate are relatively soluble than other surfactant vesicles]. For example polyoxyethylene (polysorbate 60) has been utilized for encapsulation of diclofenac sodium.

c) Alkyl amides:Alkyl amide (e.g. galactosides and glucosides) have been utilized to produce niosomal vesicles

d) Fatty acid and amino acid compounds: Long chain fatty acids and amino acid moieties have also been used in some niosomes preparation.

Cholesterol: Steroids are important components of the cell membrane and their presence in membrane affect the bilayer fluidity and permeability. Cholesterol is a steroid derivative, which is mainly used for the formulation of niosomes. Although it may not show any role in the formation of bilayer, its importance in formation of niosomes and manipulation of layer characteristics can not be discarded. In general, incorporation of cholesterol affect properties of niosomes like membrane permeability, rigidity, encapsulation efficiency, ease of rehydration of freeze dried niosomes and their toxicity.As a result of this, the niosome become less leaky in nature.

Charged molecule: Some charged molecules are added to niosomes to increase stability of niosomes by electrostatic repulsion which prevents coalescence. The negatively charged molecules used are diacetyl phosphate (DCP) and phosphotidic acid. Similarly, stearylamine (STR) and stearyl pyridinium chloride are the well known positively charged molecules used in niosomal preparations.These charged moleculesare used mainly to prevent aggregation of niosomes.Maltodextrin is a polysaccharide. It has minimal solubility in organic solvent. Thus it is possible to coat maltodextrin particles by simply adding surfactant in organic solvent.

METHOD OF PREPRATION

Ether injection method[10, 11]

This method provides a means of makingNiosomes by slowly introducing a solution ofsurfactant dissolved in diethyl ether into warmwater maintained at 60°C. The surfactant mixturein ether is injected through 14-gauge needle into anaqueous solution of material. Vaporization of ether leads to formation of single layered vesicles.Depending upon the conditions used the diameterof the vesicle range from 50 to 1000 nm.

Hand shaking method (Thin film hydration technique)[11]

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.

Sonication [11]

A typical method of production of the vesicles is bySonication of solution was introduced. 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 at60°C for 3 minutes using a sonicator with atitanium probe to yield Niosomes.

Micro fluidization[12]:

Micro fluidization is a recent technique 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.

The "Bubble" Method[13]

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) at70°C, the dispersion mixed for 15 seconds with high shear homogenizer and immediately afterwards "bubbled" at 70°C using nitrogen gas.

Reverse Phase Evaporation Technique (REV) [14]

Cholesterol and surfactant (1:1) are dissolved in amixture of ether and chloroform. An aqueous phase containing drug is added to this and the resultingtwo phases are sonicated at 4-5°C. The clear gel formed is further sonicated after the addition of asmall amount of phosphate buffered saline (PBS).

The organic phase is removed at 40°C under lowpressure. The resulting viscous niosome suspension is diluted with PBS and heated on a water bath at60°C for 10 min to yield Niosomes.It was reported that the preparation of DiclofenacSodium Niosomes using Tween 85 by this method

Applications

Niosomal drug delivery is potentially applicable to many pharmacological agents for their action against various diseases. Few of their therapeutic applications are as follows:

Targeting of bioactive agents

1. To reticulo-endothelial system (RES)15

The vesicles occupy preferentially to the cells of RES. It is due to circulating serum factors known as opsonins, which mark them for clearance. Such localized drug accumulation has, however, been exploited in treatment of animal tumors known to metastasize to the liver and spleen and in parasitic infestation of liver.

To organs other than reticulo-endothelial system(RES)[16,17]

By use of antibodies, carrier system can be directed tospecific sites in the body. Immunoglobulins seem to haveaffection to the lipid surface, thus providing a convenientmeans for targeting of drug carrier. Many cells have theintrinsic ability to recognize and bind particularcarbohydrate determinants and this property can be used todirect carriers system to particular cells.

Delivery of peptide drugs

Niosomal entrapped oral delivery of 9-desglycinamide, 8-arginine vasopressin was examined in an in-vitro intestinalloop model and reported that stability of peptide increasedsignificantly18. Immunological applications of niosomesFor studying the nature of the immune response provoked by antigens niosomes have been used. Niosomes have beenreported as potent adjuvant in terms of immunologicalselectivity, low toxicity and stability[19]

Niosome as a carrier for Hemoglobin

Niosomal suspension shows a visible spectrumsuperimposable onto that of free hemoglobin so can be used as a carrier for hemoglobin. Vesicles are alsopermeable to oxygen and hemoglobin dissociation curvecan be modified similarly to non-encapsulatedhemoglobin[20]

Transdermal delivery of drugs by niosomes

An increase in the penetration rate has been achieved by transdermal delivery of drug incorporated in niosomes as slow penetration of drug through skin is the major drawback of transdermal route of delivery for other dosage forms. The topical delivery of erythromycin from various formulations including niosomes has studied on hair less mouse and from the studies, and confocal microscopy, it was found that non-ionic vesicles could be formulated to target pilosebaceous glands[21]

Diagnostic imaging with niosomes

Niosomal system can be used as diagnostic agents. Conjugated niosomal formulation of gadobenatedimeglcemine with [N-palmitoylglucosamine (NPG)], PEG4400, and both PEG and NPG exhibit

significantly improved tumor targeting of an encapsulated paramagnetic agent assessed with MR imaging[22]

Ophthalmic drug delivery

From ocular dosage form like ophthalmic solution, suspension and ointment it is difficult to achieve excellent bioavailability of drug due to the tear production, impermeability of corneal epithelium, non-productive absorption and transient residence time. But niosomal and liposomal delivery systems can be used to achieve good bioavailability of drug. Bio adhesive-coated niosomal formulation of acetazolamide prepared from span 60, cholesterol stearylamine or dicetyl phosphate exhibits moretendencies for reduction of intraocular pressure as compared to marketed formulation (Dorzolamide)[23]

Localized Drug Action

Drug delivery through Niosomes is one of the approaches to achieve localized drug action, since their size and low penetrability through epithelium and connective tissue keeps the drug localized at the site of administration. Localized drug action results in enhancement of efficacy of potency of the drug and at the same time reduces its systemic toxic effects e.g. Antimonials encapsulated within niosomes are taken up by mononuclear cells resulting inlocalization of drug, increase in potency and hence decrease both in dose and toxicity24.

The evolution of niosomal drug delivery technology is still at an infancy stage, but this type of drug delivery system has shown promise in cancer chemotherapy and anti-leishmanial therapy.25

CONCLUSION:

Neosomal drug delivery system is one of the examples of great evolution in drug delivery technologies.

Niosomes have great drug delivery potential for targeted delivery of anti-cancer, antiinfective agents. Drug delivery potential of niosome can enhance by using novel concepts like proniosomes. Niosomes also serve better aid in diagnostic imaging and as a vaccine adjuvant.

The concept of incorporating the drug into niosomes for a better targeting of the drug at appropriate tissue destination is widely accepted by researchers. Niosomes represent a promising drug delivery module. They present a structure similar toliposome. Various type of drug deliveries can be possible using niosomes like targeting, ophthalmic, topical, parenteral.

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