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NIOSOME AS A NOVEL DRUG DELIVERY SYSTEM-REVIEW

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ABSTRACT

Design and development of novel drug delivery system (NDDS) has two rudiments. It should deliver the drug at a rate directed by the needs of the body during the period of treatment and second it should release therapeutically effective amount of drug at the target site. The concept of drug targeting or site specific drug delivery was introduced first time by Paul Ehrlich in 1909.Conventional dosage forms are unable to meet these requisites. Niosomes are microscopic in size, unilamellar or multilamellar structure, essentially non-ionic surfactant-based vesicles in which an aqueous solution of solute is entirely enclosed by a membrane resulting from the organization of surfactant macromolecules as bilayer. Niosomes are now widely utilized as an alternative to liposome and serve as a better option for drug delivery as compared to liposome due to several factor like stability, cost etc. They improve the therapeutic performance of the drug molecules by delayed clearance from the circulation, defending the drug from biological environment and restricting effects to target cells. This review article focuses on the recent advances in niosomal drug delivery, potential advantages over other delivery systems, preparation methods, methods of characterization, applications and the current research in the field of niosomes.

Keywords:Niosome, vesicles, non-ionic surfactants, structure.

INTRODUCTION

The main goal of a site specific drug delivery system is not only to increase the selectivity and drug therapeutic index, but also to reduce the toxicity of the drug. Paul Ehrlich, in 1909, initiated the era of development for targeted delivery when he envisaged a drug delivery mechanism that would target directly to diseased cell. Since then, numbers of carriers were utilized to carry drug at the target organ/tissue, which include immunoglobulins, serum proteins, synthetic polymers, liposomes, microspheres, erythrocytes, niosomes etc. Among different carriers liposomes and niosomes are well documented drug delivery. In general, Vesicular systems are a novel means of drug delivery that can enhance bioavailability of encapsulated drug and provide therapeutic activity in a controlled manner for a prolonged period of time. Niosomes are non-ionic surfactant vesicles in aqueous media resulting in closed bilayer structures that can be used as carriers of amphiphillic and lipophilic drugs. The bilayer is multilamellar or unilamellar which enclose aqueous solution of solutes and lipophilic components are in the bilayer itself. Niosomes are formed by hydration of non-ionic surfactant dried film resulting in imbibing or encapsulating the hydrating solution. Major component of niosomes is non-ionic surfactant which give it an advantage of being more stable whencompared to liposomes thus overcoming the problems associated with liposomes i.e. susceptibility to oxidation, high price and the difficulty in procuring high purity levels which influence size, shape and stability[1]. Niosomes can entrap both hydrophilic and lipophilic drugs in aqueous layer and vesicular membrane respectively. The bilayers of niosomes have both inner and outer surfaces to be hydrophilic with sandwiched lipophilic area in between. Thus a large number of drugs and other materials can be delivered using niosomes. Niosomal drug delivery has been studied using various methods of administration including intramuscular, intravenous, peroral and transdermal. In addition, as drug delivery vesicles, niosomes have been shown to enhance absorption of some drugs across cell membranes, to localize in targeted organs and tissues and to elude the reticula endothelial

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system. Surfactant forming niosomes are biodegradable, non-immunogenic and biocompatible. Incorporating drugs into niosomes enhances the efficacy of drug, such as nimesulide, flurbiprofen, piroxicam, ketoconazole and bleomycin exhibit more bioavailability than the free drug.

Structural components of niosomes:

1. Surfactants: A wide range of surfactants and their combinations in different molar ratios have been used to entrap many drugs in niosomes of varying features such as size.

2. Ether linked surfactants: These are polyoxyethylene alkyl ethers which have hydrophilic and hydrophobic moieties are linked with ether. The general formula of this group is C nEO m, where n can be 12-18 and m can be 3-7. Surfactants with polyhydroxyl head and ethylene oxide units are also reported to be used in niosomes formation. Single alkyl chain surfactant C16 mono alkyl glycerol ether with an average of three glycerol units is one of the examples of this class of surfactants used for the preparation of niosomes. Polyoxyethelene 4- lauryl ether (Brij30) has an HLB value of 9.7, phase transition temperature <10 0C and cannot be used to formulate some drugs and iodides, mercury salts, phenolic substances, salicylates, sulfonamides and tannins as it cause oxidation leading to discoloration of product. Polyoxyethylenecetyl ethers (Brij58) and Polyoxyethylenestearyl ethers (Brij72and76) are also used in preparation of niosomes.

3. Ester linked surfactants: These surfactants have ester linkage between hydrophilic and hydrophobic groups and have been studied for its use in the preparation and delivery of sodium stibogluconate to the experimental marine visceral leishmaniasis.

4. Sorbitan Esters: These are most widely used ester linked surfactants especially in food industry. The commercial sorbitan esters are mixtures of the partial esters of sorbital and its mono and di-anhydrides with oleic acid. These have been used to entrap wide range of drugs viz doxorubicin.

5. Alkyl Amides: These are alkyl galactosides and glucosides which have incorporated amino acid spacers. The alkyl groups are fully or partially saturated C12 to C22 hydrocarbons and some novel amide compounds have fluorocarbon chains.

6. Fatty Acids and Amino Acid Compounds: These are amino acids which are made amphiphilic by addition of hydrophobic alkyl side chains and long chain fatty acids which form “Ufasomes” vesicles formed from fatty acid bilayers.

7. Cholesterol: Steroids bring about changes in fluidity and permeability of the bilayer and are thus important components. Cholesterol a waxy steroid metabolite is usually added to the non-ionic surfactants to provide rigidity and orientational order. It does not form the bilayer itself and can be incorporated in large molar ratios. Cholesterol is an amphiphilic molecule; it orients its -OH group towards aqueous phase and aliphatic chain towards surfactant’s hydrocarbon chain. Rigidization is provided by alternative positioning of rigid steroidal skeleton with surfactant molecules in the bilayer by restricting the movement of carbons of hydrocarbon. Cholesterol is also known to prevent leakage by abolishing gel to liquid phase transition.

8. Charge Inducers: Charge inducers increase the stability of the vesicles by induction of charge on the surface of the prepared vesicles. It act by preventing the fusion of vesicles due to repulsive forces of the same charge and provide higher values of zeta potential. The commonly used negative charge inducers are diacetyl phosphate, dihexadecyl phosphate and lipoamine acid and positive charge inducers are sterylamine and cetylpyridinium chloride.

Methods of preparation of niosomes:

Various methods are reported for the preparation of niosomes such as:

1. Ether injection method
2. Thin film hydration technique
3. Sonication method
4. Reverse phase evaporation technique (REV)
5. Microfluidization
6. Multiple membrane extrusion method
7. Trans membrane pH gradient (inside acidic) drug uptake process (remote loading)
8. Bubble method
9. Formation of niosomes from proniosomes

1. Ether injection method: This method provides a means of making niosomes by slowly introducing a solution of surfactant dissolved in diethyl ether (volatile organic solvent) 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 (volatile organic solvent) leads to formation of single layered vesicles. Depending upon the conditions used the diameter of the vesicle range from 50 to 1000 nm.

2. Thin Film Hydration: All vesicles forming Components i.e. surfactant, cholesterol and charge inducers are dissolved in a volatile organic solvent in a round bottom flask. Using rotary evaporator the organic solvent is evaporated at room temperature forming a thin dry film of dissolved components. The dried thin film is hydrated with aqueous phase with gentle agitation which

leads to formation of niosomes. The drug can be added to the aqueous phase if hydrophilic and can be dissolved in organic solvent with other components if hydrophobic.

3. Sonication method: In this method at first the surfactant-cholesterol mixture is dispersed in the aqueous phase. This dispersion is then probe sonicated for 10 minute at 60 oC, which leads to the formation of multilameller vesicles (MLV). These MLVs are further ultrasonicated either by probe sonicator or bath sonicator, which in turn leads to the formation of unilameller vesicles.

4. Reverse phase evaporation technique: 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.

5. Microfludisation: This is a recent technique to prepare small multi lamellar vesicles. A microfluidizer is used to pump the fluid at a very high pressure (10,000 psi) through a 5 pm screen. Thereafter; it is forced along defined micro channels, which direct two streams of fluid to collide together at right angles, thereby affecting a very efficient transfer of energy. The lipids can be introduced into the fluidizer. The fluid collected can be recycled through the pump until vesicles of spherical dimensions are obtained. This method resulted in niosomes with greater uniformity and small size which shows better reproducibility.

6. Multiple membrane extrusion method: In membrane extrusion method, the size of niosomes is reduced by passing them through membrane filter. This method can be used for production of multi lamellar vesicles as well as large unilamellar vesicles. It is found as a good method for controlling niosomal size.

7. TransmembranepH gradient (inside acidic) drug uptake process (remote loading): 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.

8. The "Bubble" Method: 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.

9. Formation of niosomes from proniosomes: 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 preparation is termed "Proniosomes".

Types of niosomes:

1. Bola surfactant containing niosomes: Bola surfactant containing niosomes are the surfactants that are made of omegahexadecylbis-(1-aza-18 crown-6) (bola surfactant): span- 80/cholesterol in 2:3:1molar ratio.

2. Proniosomes: Proniosomes are the niosomal formulation containing carrier and surfactant, which requires to be hydrated before being used. The hydration results in the formation of aqueous noisome dispersion. Proniosomes decreases the aggregation, leaking and fusion problem associated with niosomal formulation.

3. Aspasomes: Combination of acorbylpalmitate, cholesterol and highly charged lipid diacetyl phosphate leads to the formation of vesicles called aspasomes. Aspasomes are first hydrated with water/aqueous solution and then sonicated to obtain the niosomes. Aspasomes can be used to increase the transdermal permeation of drugs. Aspasomes have also been used to decrease disorder caused by reactive oxygen species as it has inherent antioxidant property.

4. Niosomes in carbopolgel: Niosomes were prepared using drug, spans and cholesterol. The niosomes thus obtained were then incorporated in carbopol-934 gel (1%w/w) base containing propylene glycol (10% w/w) and glycerol (30% w/w). Using human cadaver skin, in vitro diffusion studies of such niosomal gel, plain drug gel and marketed gel were carried out in diffusion cell. It was observed that the mean flux value and diffusion co-efficient were 5 to 7 times lower for niosomal gel as compared to plain drug gels.

5. Vesicles in water and oil system (v/w/o): It has been reported that the emulsification of an aqueous niosomes into an oil phase form vesicle in water in oil emulsion (v/w/o). This can be prepared by addition of niosomes

suspension formulated from mixture of sorbitol monostearate, cholesterol and solulan C24 (Poly- 24-Oxyethylene cholesterylether) to oil phase at 60 0C. This result in the formation of vesicle in water in oil (v/w/o) emulsion which by cooling to room temperature forms vesicle in water in oil gel (v/w/o gel). The v/w/o gel thus obtained can entrap proteins/ proteinous drugs and also protect it from enzymatic degradation after oral administration and controlled release.

6. Niosomes of hydroxyl propyl methyl cellulose: In this type, a base containing 10% glycerin of hydroxy propyl methyl cellulose was first prepared and then niosomes were incorporated in it.The bioavailability and reduction of paw edema induced by carrageenan was found to be higher by this niosomal system than the plain formulation of drugs.

Factors affecting the physicochemical properties of niosomes:

1. Nature of surfactants: A surfactant used for preparation of niosomes must have a hydrophilic head and hydrophobic tail. The hydrophobic tail may consist of one or two alkyl or perfluoroalkyl groups or in some cases a single steroidal group. The ether type surfactants with single chain alkyl as hydrophobic tail is more toxic than corresponding dialkylether chain .The ester type surfactants are chemically less stable than ether type surfactants and the former is less toxic than the latter due to ester-linked surfactant degraded by esterases to triglycerides and fatty acid *in vivo*. The surfactants with alkyl chain length from C12-C18 are suitable for preparation of noisome.

2. Membrane additives: Stability of niosomes can be increased by the number of additives into niosomal formulation along with surfactant and drugs. The membrane stability, morphology and permeability of vesicles are affected by numbers of additives e.g. addition of cholesterol in niosomal system increases the rigidity and decreases the drugs permeability through the membrane. Niosomes prepared by C16G2 /cholesterol/MPEG- Chol show spherical vesicles with diameters ranging from 20 nm to 200 nm.

3. Resistance to osmotic stress: Addition of a hypertonic salt solution to a suspension of niosomes brings about reduction in diameter. In hypotonic salt solution, there is initial slow release with slight swelling of vesicles probably due to inhibition of eluting fluid from vesicles, followed by faster release, which may be due to mechanical loosening of vesicles structure under osmotic stress.

4. Drug: Entrapment of drug in niosomes increases vesicle size, probably by interaction of solute with surfactant head groups, increasing the charge and mutual repulsion of the surfactant bilayers, thereby increasing vesicle size. The hydrophilic lipophilic balance of the drug affects degree of entrapment.

5. Cholesterol contents: The incorporation of cholesterol into bilayer composition of niosome induces membrane stabilizing activity and decreases the leakiness of membrane.Hence, incorporation of cholesterol into bilayer increases entrapment efficiency. The permeability of vesicle bilayer to 5, 6-carboxy flourescein (CF) is reduced by 10 times due to incorporation of cholesterol.

6. Method of preparation: Method of preparations can also affect the niosomal properties. Different type of methods like ether injection, hand shaking; sonication etc. has been reviewed by Khandare et al., 1994. The average size of acyclovir niosomes prepared by hand-shaking process was larger (2.7 µm) as compared to the average size of niosomes 1.5 µm prepared by ether injection method which may be attributed to the passage of cholesterol and span-80 solution through an orifice into the drug solution . Reverse phase evaporation can be used to produce smaller size vesicles. Vesicles with smaller size and greater stability can be produced by microfluidization method. Niosomes obtained by transmembrane pH gradient (inside acidic) drug uptake process showed greater entrapment efficiency and better retention of drug.

Advantages of niosomes:

The application of niosomes for therapeutic purpose may offer several advantages

1. High patient compliance in comparison with oily dosage forms as the vesicle suspension is a water–based vehicle.
2. Accommodate drug molecules with a wide range of solubilities.
3. The characteristics of the vesicle formulation are variable and controllable. Altering vesicle composition, size, lamellarity, surface charge and concentration can control the vesicle characteristics.
4. The vesicles may act as a depot, releasing the drug in a controlled manner.
5. They are osmotically active and stable, as well as they increase the stability of entrapped drug.
6. Handling and storage of surfactants requires no special conditions.
7. They improve oral bioavailability of poorly absorbed drugs and enhance skin penetration of drugs. [36-40]

EVALUATION:

Entrapment efficiency

After preparing niosomal dispersion, unentrapped drug is separated by dialysis centrifugation and gel filtration. The drug remain entrapped in niosomes

is determined by complete vesicle disruption using 50% n-propanol or 0.1% Triton X-100 and analyzed resultant solution by appropriate assay method using following equation**.**

Particle size analysis

Particle size analysis was done by scanning electronic microscopy (SEM) using JEOL JSM-T330A scanning microscope brass stab. The stabs were placed briefly in a drier and then coated with gold in an ion sputter. Pictures of niosomes were taken by random scanning of the stub and count. The diameter is about 30 niosomes was measured from the photomicrographs of each batch. Finally, average mean diameters were taken into consideration.

***In-vitro* release study**

Human cadaver skin (HCS) was obtained from ventral part of forearm of 35 years old male corpse and was stored at 4°C. HCS membrane was spread and punches it at approximately 3 cm2 area. Trimmed away the excessfat and sliced to 500 □m thickness using a Daw's derma tone. These slices were hydrated in pH 7.4 PBS for 24 hrs prior to use. The HCS were attached to Khesary cell (K.C filled with 100 ml of PBS) and add 10 mg niosomal suspension on it. Finally, cell was immersed into the receptor compartment. The dermal surface was just flush to the surface of permeation fluid (PBS), which was maintain at 37°C □□ 0.50°C and stirred magnetically at 50 rpm, aliquots were withdraw and replaced with the same volume of fresh buffer, at every sampling points and analyzed by U. V. Spectrophotometer method at 294 nm.

Stability study

Stability studies are performed by storing niosome at two different conditions, usually 4±1°C and 25±2°C. Formulation size, shape and number of vesicles per cubic mm can be measured before and after storing for 30 days. After 15 and 30 days, residual drug can also be measured. Light microscope is used for determination of size of vesicles and the numbers of vesicles per cubic mm is measured by haemocytometer. Number of niosomes per cubic mm = Total number of niosomes x dilution factor x 400/Total number of small squares counted.

CONCLUSION

The concept of drug targeting at specific tissue site by incorporating drug into niosomes is widely accepted by researchers and academicians. Niosomes is a well preferred drug delivery system, so it can be used as alternative drug delivery system and also having various advantages over liposomes like cost, stability etc. Niosomes have ability to encapsulate different type of drugs within their multi environmental structure like antiinfective, anticancer drug. And various types of drug deliveries can bepossible using niosomes like targeting, ophthalmic, topical, parenteral, etc.

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