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REVIEW ARTICLE ON NIOSOMES: A FUTURE OF TARGETED DRUG DELIVERY SYSTEM

Kunturwar Kedar*, Biradar Pratiksha, Suryawanshi Suchita, Suryawanshi Shivraj V.

Shivlingeshwar college of pharmacy, Almala, Tq. Ausa, dist. Latur, Ausa-413520

Department of Pharmaceutical Chemistry

ABSTRACT

Treatment of infectious diseases and immunization has undergone a transformation recent years. With the progress in biotechnology and genetic engineering, not only a great number of disease-specific biological have been developed, but also emphasis has been made to successfully deliver these biologicals. Niosomes are vesicles made up of non-ionic surfactants, which are biodegradable, nontoxic, more stable and inexpensive and have ability to substitute the liposomes. A overall research done on the niosome as a drug carrier. Various drugs are used and tried in niosome surfactant vesicles. Niosomes proved to be a promising drug carrier and has ability to reduce the side effects of drugs and increased therapeutic effectiveness in various diseases.

Key Words: Bilayer, Drug entrapment, Non-ionic-surfactant, Niosomes, Surfactants.

INTRODUCTION

In 1909, Paul Ehrlich started the period of development for target drug delivery, when he forecasted the drug delivery method that would target directly to diseased cell. There are many drug carriers present which have ability carry a drug at target organ\ tissue which include immunoglobulin, serum proteins, microspheres, liposome, synthetic polymer, niosomes etc.[1]

Niosomes are novel drug delivery system, in which the hydrophilic drug is captured in the core cavity and hydrophobic drug present in the bilayer of niosomes in the non-polar region. Therefor both hydrophilic and hydrophobic drugs can be included into niosomes.

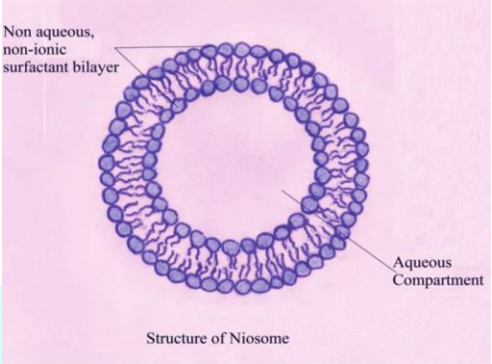
The concept of targeted drug delivery is made to concentrate the drug in the desired tissues to reduce the relative concentration of the medication in the other tissues. As a result, drug targets on the targeted site. Hence, Other surrounding tissues are not affected by the drug. Also, loss of drug decreases due to localization of drug, leading to get maximum efficacy of the medication.[2] Niosomes are one of the best among all the carriers. Structurally, niosomes are nearly similar to liposomes and also are similar in drug delivery potential and also have high chemical stability than liposomes. Both consist of bilayer, which in the case of niosomes is made up of non-ionic surfactant and phospholipids in case of liposomes. Niosomes are microscopic lamellar structures. Having size range between 10 to 1000 nm and consists of biodegradable, non-immunogenic and biocompatible surfactants. The niosomes are amphiphilic in nature, which allows envelopment of hydrophilic drug in the core cavity and hydrophobic drugs in the non-polar region present within the bilayer hence both hydrophilic and hydrophobic drugs can be given by help of niosomes.[3]

Niosomes act in vivo like liposomes, extending the circulation of entrapped drug and changing its organ distribution and metabolic stability.[4] As like liposomes, the properties of niosomes also depend on the composition of the bilayer as well as method of their production. It is described that the insertion of cholesterol in the bilayers decreases the entrapment volume during formulation, and thus entrapment efficiency.[5] However, differences in characteristics in-between liposomes and niosomes, especially since niosomes are prepared from un-ionized single-chain surfactant and cholesterol, whereas liposomes are made from double-chain phospholipids ie. neutral or charged. The concentration of cholesterol in liposomes is more than that in niosomes. As a result, drug entrapment capacity of liposomes becomes lesser than niosomes. Apart from that, liposomes are expensive, and its ingredients, such as phospholipids are chemically unstable because of their tendency to oxidative degradation; moreover, these require special storage and handling and purity of natural phospholipids is variable. Niosomal drug delivery is practically applicable to many pharmacological agents for their action against various diseases. It can also be used as vehicle for less absorbable drugs to design the novel drug delivery system. It increases the bioavailability by crossing the anatomical barrier of gastrointestinal tract via transcytosis of M cells of Peyer's patches in the intestinal lymphatic tissues.[6]

Drug delivery through niosomes is one of the the point of view to get localized drug action within respect to their size and low penetrability through epitheliomas well as the connective tissue. They keep the drug localized at the site of administration. Localized drug action increases efficacy of the drug and, at the same time reduces its systemic toxic effects, eg, antimonial encapsulated within niosomes are absorbed by mononuclear cells, resulting in localization of drug, increase in potency, and hence decrease in dose and toxicity.[7]

COMPOSITION OF NIOSOMES

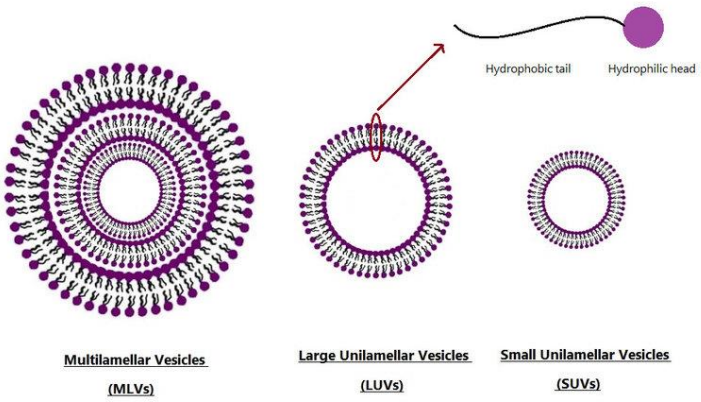
For the preparation of niosomes, cholesterol and Non-ionic surfactants are used as two major components. Cholesterol is a steroid derivative, which provides the rigidity as well as proper shape to the niosomes formation. The surfactants plays a major role in the preparation of niosomes. non-ionic surfactants such as spans(span 20,40,60,85,80), tweens (tween 20,40,60,80) and (brij 30,35,52,58,72,76) are generally used for the preparation of niosomes.[8]



TYPES OF NIOSOME

Based on the vesicle size, niosomes can be divided into three groups. These are

1. Small unilamellar vesicles (SUV, size=0.025-0.05 μm)
2. Multilamellar vesicles (MLV, size=>0.05 μm)
3. Large unilamellar vesicles (LUV, size=>0.10 μm).



Methods of Preparation

Niosomes are prepared by different methods based on following characteristics

1. the sizes of the vesicles and their distribution.
2. number of double layers.
3. entanglement efficiency of the aqueous phase and permeability of vesicle membrane.

Preparation of small unilamellar

vesicles Sonication: It is a classic method of preparation of the vesicles in which a 10-ml glass vial drug solution in buffer is added to the surfactant/cholesterol mixture. Then the mixture is probe sonicated at 60°C for 3 minutes by using a sonicator with titanium probe to get niosomes. The prepared vesicles are small and unilamellar.[9]

Micro fluidization: It is a new technique based on submerged jet principle. In this technique two fluidized streams interconnect at ultrahigh velocities and move forward through accurately defined micro channel within the interaction chamber. The impact of thin liquid sheet along a common front is arranged as the energy supplied to the system remains within the area of niosomes formation that results in a more uniformity, smaller size and better reproducibility of niosomes prepared.[10]

Preparation of multilamellar vesicles

Hand shaking method (Thin film hydration technique): In this method, surfactant and cholesterol are dissolved in a volatile organic solvent which are diethyl ether, chloroform or methanol in a rotary evaporator, leaving a thin layer of solid mixture deposited on the wall of the flask.[9] The dried layer is hydrated with liquid phase containing drug at normal temperature with gentle stirring.

Trans-membrane pH gradient (inside acidic) drug uptake process (remote Loading): Surfactant and cholesterol are dissolved in chloroform.[11] Then the solvent is evaporated under reduced pressure to get a thin film on the wall of the round-bottom flask. The film is moisturized with 300 mM citric acid (pH 4.0) by vortex mixing. The multilamellar vesicles are frozen and melted three times and later sonicated. In this niosomal suspension, aqueous solution containing 10 mg/ml of drug is added and swirled. Then the pH of the sample is raised to 7.0-7.2 with 1M disodium phosphate. Later this mixture is heated at 60°C for 10 minutes to prepare the desired multilamellar vesicles.

Preparation of large Unilamellar Vesicles

Reverse phase evaporation technique (REV):

In this method, cholesterol and surfactant are added in a mixture of ether and chloroform. The liquid phase having drug in it is added to this and the resulting two phases are sonicated at 4-5°C. Then a small amount of phosphate buffer saline is added to the clear gel formed and is then sonicated at low pressure and the organic phase is removed at 40°C. [12]

Ether injection method

The ether injection method is basically based on slow injection of niosomal ingredients in ether through a 14-gauge needle at the rate of approximately 0.25 ml/min into a preheated aqueous phase maintained at 60°C. [9] Firstly a solution of surfactant mixture is prepared and then slowly introduced into warm water which is maintained at 60°C. Tether containing a surfactant mixture is injected through 14-gauge needle into an aqueous solution of material. Single layered vesicles are made by the vaporization of ether. Depending upon the conditions used the vesicles are obtained having diameter range from 50 to 1000 nm. The major disadvantage of this method is, the small amount of ether is frequently present in the vesicle suspension which is difficult to remove. [13]

Miscellaneous

Multiple membrane extrusion method:

A mixture of surfactant, cholesterol, and di acetyl phosphate is dissolved in chloroform and the solvent is evaporated resulting in formation of thin film. The film is hydrated and the resultant suspension ejected through polycarbonate membranes using aqueous drug solution, these are then put in a series for up to eight passages. This is a best method for controlling niosome size.[13]

The "Bubble" Method:

In this technique one by one step is involved by which liposomes and niosomes are prepared without the use of organic solvents. In this, the round bottomed flask is used as bubbling unit with its three necks placed towards water bath to control the temperature. Water cooled reflux and thermometer is placed in the first and second neck and nitrogen supply through the third neck. At 70°C Cholesterol and surfactant are spread together in the buffer (pH 7.4) and mixed with high shear homogenizer for 15 seconds and later immediately "bubbled" at 70°C using nitrogen gas.[14]

Emulsion method

The oil in water emulsion is prepared from an organic solution of surfactant, cholesterol, and also with the help of aqueous solution of the drug.[15] This organic solvent is then evaporated and leaving niosomes dispersed in the aqueous phase.

Lipid injection method:

In this method, mixture of lipids and surfactant is first melted and then injected into a highly blended, heated aqueous phase containing dissolved drug, or the drug can be dissolved in the molten lipid and that mixture will be injected into agitated, heated aqueous phase containing surfactant. This process does not require expensive organic phase.[16]

Niosome preparation using Micelle:

Niosomes may also be prepared by the use of enzymes in a mixed micellar solution. A mixed micellar solution of C16 G2, dicalcium hydrogen phosphate (DCP), polyoxyethylene cholesteryl subacetate di ester (PCSD) when set with esterase converts to a noisome dispersion. PCSD is adhered by the esterase action to yield polyoxyethylene, sebacic acid and cholesterol and then cholesterol in combination with C16 G2 and DCP and then yields C16 G2 niosomes.[16]

Routes of administration with Example

Route of administration	**Examples**
Inhalation	All-trans retinoic acid
Nasal route	Sumatriptan, Influenza viral vaccine
Ocular route	Timolol maleate, cyclopentolate
Intravenous route	Doxorubicin, Methotraxate, etc.
Peroral route	Proteins, Peptides, etc
Transdermal route	Piroxicam, Ketorolac, etc.

Factors Affecting Physico-Chemical Properties of Niosomes

Various factors that affect the physico-chemical properties of niosomes are listed as follows:

1.Composition of niosome: Theoretically for the niosome preparation, the presence of a particular class of amphiphile and aqueous solvent is needed but in some definite cases cholesterol is required in the preparation to provide rigidity, proper shape and conformation to the niosomes. Cholesterol also stabilizes the system by inhibiting the preparation of aggregates by repulsive steric or electrostatic effects. The inclusion of Soudan C24 (a cholesteryl poly-24-oxyethylene ether) in doxorubicin (DOX) orbiton monostearate (Span 60) niosome formulations is an example of steric stabilization. An example of electrostatic stabilization is the insertion of dicetyl phosphate in 5(6)- carboxyfluorescein (CF) loaded Span 60 based niosomes.[14]

2.Nature of encapsulated drug: The physico-chemical properties of encapsulated drug controls charge and rigidity of the niosome bilayer. The drug connects with surfactant head groups and develops the charge that creates mutual repulsion between surfactant bilayers, and hence increases vesicle size.[17] The aggregation of vesicles is prevented due to the charge development on bilayer.

3.Amount and type of surfactant: With increase in the hydrophilic-lipophilic balance (HLB) of surfactants such as Span 85 (HLB 1.8) to Span 20 (HLB 8.6) that mean size of niosomes increases proportionally, because with an increase in hydrophobicity of surfactants the surface free energy decreases. Depending on the temperature, the type of lipid or surfactant and the presence of other components such as cholesterol the bilayers of the vesicles are either in the liquid state or in gel state. When the structure of the bilayers is dis-ordered it will be in liquid state and if alkyl chains are present in a well ordered structure it will be in the gel state. Entrapment efficiency is also affected by phase transition temperature of surfactants, for example Span 60 having higher phase transition temperature provides better entrapment.[10]

4. Effect of molecular weight of surfactant on entrapment:

It was observed from the research studies for many years that with the equivalent increase in molecular weight ,entrapment efficiency increases for niosomes prepared using saturated surfactants like sp an 20, span 40 span 60, in case of span sand tween 20, tween 40 and tween 60 in case of tweens. In comparison to span 60, niosomes prepared with unsaturated spans like span 80 and span 65 showed the less entrapment cause of effect of unsaturation as explained previously.[29]

5. Zeta potential: The Z.P value of span niosomal formulations increases with the hydrophilicity of the surfactants increased. This could be due to the fact that the surface free energy of the Span surfactants increases with increased HLB value.[30]

6. Effect of hydration time: For ideal conditions, the hydration time should be above the gel to liquid phase transition temperature of system, because it has impact on the shape and size of the noisome. The volume of hydration medium and time of hydration of niosomes these both are also critical factors. Inappropriate selection of these factors may result in the formation of brittle niosomes or creation of drug leakage problems. Temperature change in the niosomal system affects construction of surfactants into vesicles and also induces vesicle shape transformation.[31]

7. Resistance to osmotic stress: Addition of a hypertonic salt solution to a suspension of niosomes shows reduction in diameter. In hypotonic salt solution, there is initial slow release with little 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.

Advantages : (4-5)

1. Niosomes increase the bioavailability of drug by protecting the drug from acidic and enzymatic degradation in GIT due to this it increases the bioavailability of drug.
2. We can incorporate variety of drug moieties and used for many drugs because of its amphiphilic nature.
3. We can also improve skin permeation by using niosomes.
4. By slowing down the clearance from the circulation, the therapeutic efficiency of drug molecules is improved.
5. Surfactant can be handled and doesn't need a specific-conditions to store.
6. The vesicles act as a depot and drug can be release in controlled manner.
7. Patience compliance is more in oily dosage from.[18][19]

Disadvantages : (6)

1. There is more drug aggregation in it.
2. It somewhat cause physical instability.
3. The drug contained in niosome can leak.
4. Hydrolysis of niosomes can decrease the shelf life of encapsulated drug.
5. It consumes more time to prepare. [20]

Applications:

Because of their action against various diseases, niosomal drug delivery is practically relevant to many pharmacological agents. Their therapeutic applications as follows:

1. Niosomes as a carrier to hemoglobin

Niosomal suspension shows a visible spectrum which is superimposable onto that of free hemoglobin hence it can be used as a carrier for hemoglobin. Vesicles are also absorptive to oxygen and hemoglobin dissociation curve can be alter closely to non-encapsulated hemoglobin.[21]

2. Neoplasia

The antibiotic Doxorubicin having broad spectrum which shows anti-tumor activity and a dose dependent irreversible cardio toxic effect. By its niosomal entrapment of the drug the half-life of the drug is increased and also extend its circulation and modified its metabolism.[22]

3. Delivery of peptide drug

Niosomal entrapped oral delivery of 9-desglycinamide, 8- arginine vasopressin was tested in an in-vitro intestinal loop model and reported that stability of peptide increased remarkably.[23]

4. Diagnostic imaging with niosomes

Niosomes can be used as diagnostic agents. Conjugated niosomal formulation of gadobenate dimeglcemine with [N-palmitoyl glucosamine (NPG)], PEG 4400, and both PEG and NPG exhibit remarkably better tumor targeting of an encapsulated paramagnetic agents analyzed with MRI.[24]

5. The application of niosomal technology is widely diversed and can be used to treat a number of diseases.

6. Niosomes as Drug Carriers

Niosomes have also been used as carriers for iobitridol, it is a diagnostic-agent used for X-ray imaging. Topical niosomes may work as solubilization matrix, as a local depot for sustained release of dermally active compounds, as penetration enhancers, as rate-limiting membrane barrier for the modulation of systemic absorption of drugs.

7. Drug Targeting

One of the most useful side of niosomes is their ability to target drugs. Niosomes are used to target drugs to the reticuloendothelial system. The reticulo-endothelial system (RES) specially takes up niosome vesicles. The uptake of niosomes is controlled by circulating serum factors called opsonin. These opsonin mark the niosome for clearance. Such localization of drugs is used to treat tumors in animals known to metastasize to the liver and spleen. This localization of drugs can also used for treating parasitic infections of the liver. Niosomes can also used for targeting drugs to organs other than the RES. A carrier system such as antibodies can be attached to niosomes as immunoglobulin's bind willingly to the lipid surface of the niosome to target them to specific organs.

8. Anti-neoplastic Treatment

Many antineoplastic drugs cause severe side effects. Niosomes can alter the metabolism; prolong circulation and half-life of the drug for decreasing the side effects of the drugs. Niosomes are decreased rate of expansion of tumor and higher plasma levels accompanied by slower elimination. [25-28]

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