



Niosomes in Ocular Drug Delivery System: A Review of Magic Targeted Drug Delivery

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ABSTRACT

Targeting of drug is the skill to express a therapeutic agent exclusively to favored site of action with no interface between non target tissues. At the moment there is no drug delivery system achieves specific site targeted delivery with the controlled release kinetics. Niosomes has achieved remarkable popularity as best carriers for drug targeting in ocular therapeutics. Ocular dosage form has very poor bioavailability which is due to the production of tear, poor absorption, very short resident time. Conventional ophthalmic drops, suspension and semisolid dosage forms are even though they are still acceptable nowadays to achieve desired therapeutic concentration of drug to treat ocular disorders but they are inefficient to fight against numerous ocular diseases. Hence the application of niosomes is gaining attention at present. This review exhibits the importance of vesicular drug delivery as one of the future targeted ocular delivery system. Furthermore it depicts the advantages, formulation and its characterization studies in detail. Henceforth it meets the expectations and providing the vesicular delivery system for effective therapy.

Keywords: Niosomes, controlled release kinetics, Bioavailability, Transient residence time, corneal epithelium.

INTRODUCTION

The Ideal drug delivery system delivers drug to the location of action throughout the period of treatment. The concept of targeted delivery is fabricated for delivery of drug in tissues by decreasing the level of medication in other parts of tissues. As a result of this, drug is localized on targeted site resulting to achieve maximum efficacy of the drug. There are several carriers such as liposome's, immunoglobulin, microspheres, serum proteins and certain synthetic polymers and niosomes. Niosomes are one amongst this carriers.¹

Niosomes (non toxic surfactant vesicles) are microscopic lamellar structure. They are formed on addition of non toxic surfactant of the alkyl or dialkyl polyglycerol ether class and cholesterol followed by the subsequent hydration in aqueous media.

Niosomes can be SUV (small unilamellar vesicles), MLV (Multi lamellar vesicles) or LUV (large unilamellar vesicles). They can be formulated by thin film hydration, Hand shaking, Ether Injection, Reverse phase evaporation, Sonication, microfluidisation and Trans membrane pH gradient. Niosomes vary widely by their properties depending both on procedure used for their production and composition of bilayer. But the principle is same (i.e.) formation of lipid phase followed by subsequent hydration on aqueous medium leads to the formation of niosomes.

The formulated niosomes were characterized by vesicle diameter, entrapment efficiency, *in-vitro* drug release, zeta potential analysis and stability studies. Niosomes are gifted as an efficient carrier of drug which has possibility

to lessen the side effects and enhanced therapeutic efficacy in different ailments. Niosomes act as storehouse releasing drug in prolonged and sustained manner and also provide improved drug concentration at the location of action administered by oral, parenteral, ocular, nasal, and topical routes. The growth of niosomal drug delivery has shown promising approaches in ocular therapeutics.²

NIOSOMES IN OCULAR DRUG DELIVERY

The most attractive and very difficult task ever faced by pharma scientist to develop ocular dosage forms because of significant and pharmacokinetically specific environment that exist in eye. The challenge is to get around the shielding barrier of the eye without affecting any permanent tissue damage. The majority of existing ocular drug delivery system is still in primitive and inefficient. It is very difficult task to achieve effective concentration of drug in eye because of complex mechanisms that exist in the eye.³

Considering these points the development of a drug delivery is belonging important in treatment of various ocular diseases. Ocular drug targeting has major goals.

1. Enhancing drug permeation,
2. Improving bioavailability
3. To control the release of drug
4. To target drugs at active site

However the use of Niosomes would be a promising approach in targeting drug for ocular therapeutics.⁴



NIOSOMES STRUCTURE

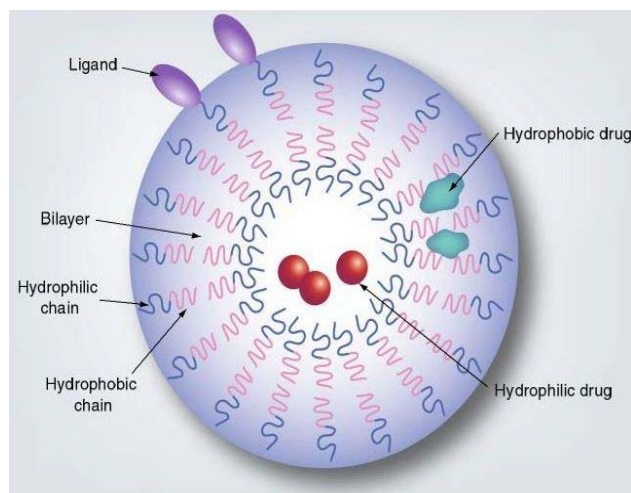


Figure 1: Structure of the Niosome

Advantage of Niosomes in ocular drug delivery

The purpose of vesicular (lipid vesicles and non-ionic surfactant vesicles) systems for therapeutic principle may offer several advantages:⁵

1. Niosomes can entrap both hydrophilic and lipophilic drug.
2. Enhance skin penetration therapy improving bioavailability of drug
3. Niosomes are depository for releasing drug in sustained or prolonged manner.
4. They have greater bio availability when compared to conventional formulations.
5. Bio degradable, bio compatible and non immunogenic to the body.
6. More stable than liposomes.
7. Better patient compatibility better therapeutic effect than conventional.
8. Provide accommodation of drug molecules through a broad range of solubility's.
9. Vesicles may act as a storehouse, releasing the drug in a controlled manner.
10. They are osmotically active and stable as well as they increase the stability of entrapped drug.
11. Handling and storage of surfactants requires no extraordinary conditions.

NIOSOME FORMATION

Theoretically, it requires the need of a particular amphiphile and aqueous solvent to form niosomes. Association between the amphiphile and aqueous phase leads in high interfacial tension and at the same time the static hydrophilic and ionic repulsion between the head groups ensure that these groups are in contact with water and these two opposite forces lead to a supramolecular

assembly. Membrane additives such as cholesterol, surfactants of non ionic groups and charge inducers are needed in the preparation of niosomes.⁶

COMPOSITION OF NIOSOMES

It comprises of two essential components like cholesterol and non ionic surfactants. Cholesterol provides firmness and appropriate shape. The surfactants take part in a very important function in the formation of niosomes. Surfactants of non ionic groups like spans have different grades as span 20, span 40, span 60, span 80 and span 85. Similarly the surfactant of Tweens also has different grades such as Tween 20, Tween 40, Tween 60 and tween 80. Moreover the surfactant brij also has variety of grades such as brij 30, brij 35, brij 52, brij 58, brij 72 and brij 76. These surfactants are generally used for the preparation of niosomes. Other surfactants that are reported to form niosomes are as follows⁷

1. Ether linked surfactant
2. Di-alkyl chain surfactant
3. Ester linked
4. Sorbitan Esters
5. Poly-sorbates

Other additives

Membrane additives like charge inducers play vital role in niosome formulation. Their roles are to increase surface charge density, prevent vesicles flocculation, aggregation and fusion. To induce charges there are negatively and positively charged molecules as reported by number of scientists. Examples of charge inducers are;

1. Dicyetyl phosphate (DCP) – negative charge
2. Stearyl amine (SA) - positive charge.⁸

METHODS OF PREPARATION

The general method of preparation of niosomes involves organic solvents on evaporation leads to production of a lipid film followed by subsequent hydration with the aqueous medium. However there are various methods that are described in elaborate.⁹⁻¹¹

Formulation of Small Unilamellar Vesicles (SUV)

Sonication

Sonication is a usual technique for the preparation of niosome vesicles. 10-ml glass vial containing drug, surfactants and cholesterol is taken and is mixed with buffer. After that the mixture is probe sonicated for about 3 minutes by a sonicator with titanium probe to produce niosomes. The resulting product contains small and unilamellar vesicles. This technique is most widely used in preparation of small vesicles. Sonication process comprises of two types and they are of probe and bath type sonicators, depending upon the requirement either of which can be used.

Micro fluidization

Micro fluidization is modern systems based on submerge jet principle. Throughout the system the two fluidized streams act together at elevated velocities and proceed throughout exactly distinct micro channel surrounded by the interface chamber at right angles thus affecting a very efficient transfer of energy. Arrangement of common front where the impingement of thin liquid occur results in the production of niosomes formation. This method produces uniform and small size vesicles thus shows better reproducibility.

Formulation of Multi Lamellar Vesicles**Hand shaking method (Thin film hydration technique)**

In round bottom flask ether, chloroform or methanol is taken to which the surfactant and cholesterol are blended. The temperature is maintained around (60°C) when this process is carried out volatile solvent gets evaporated leading to the deposition of lipid film on the sides of the flask followed by which the addition of aqueous phase at 45°C results in production of multilamellar vesicles.

Trans-membrane pH gradient (inside acidic) drug uptake process (Remote Loading)

The organic solvent chloroform is taken in round bottom flask to which the surfactant and cholesterol is added. Organic solvent on evaporation leads to production of lipid film on the side walls of the flask. Furthermore, the formulated thin film is undergone to hydration process by vortex mixing with 300 mM citric acid (pH 4.0). The formed multi lamellar niosomes are frozen and thawed three times followed by the sonication process for few minutes. To this niosomal suspension aqueous solution containing 10 mg/ml of drug is added and later vortexed. Adding up of the disodium phosphate (1M) gradually raises pH from 7.0-7.2. At last, the solution should be mixed properly and heated at 60°C for 10 minutes to produce the desired multi lamellar vesicles.

Formulation of Large Unilamellar Vesicles**Reverse phase evaporation technique (REV)**

Novelty in this system is the removal of volatile organic solvent by the process of evaporation. Mixture of ether and chloroform is taken; disperse cholesterol and surfactant in equal ratio i.e (1:1) to the above solvent. Aqueous phase containing drug is added to the above solution and the resulting two phases are sonicated for few minutes. Clear gel is formed which is further sonicated for few minutes by the addition of small amount of phosphate buffer saline. Underneath at low pressure, the organic phase is removed by evaporation. The resulting suspension is further diluted with PBS solution and heated on water bath at optimum temperature (45°C) for 10 min to yield niosomes.

Ether injection method

The non- ionic surfactants and cholesterol taken in a beaker followed by the introduction of warm water maintained at the temperature of 60°C. Further, the ether containing mixture of drug solution is added slowly into aqueous solution (Phosphate Buffer) with the help 14-gauge needle. Only one layered niosomes vesicle are produced by the vaporization of ether. The diameter of niosomes varies from size range of 50 - 1000 nm which is obtained depending upon the procedure used. Major disadvantage in this process is the existence of small quantity of ether in the vesicle suspension which is difficult to remove.

Miscellaneous**Multiple membrane extrusion method**

The combination of non-ionic surfactant, cholesterol, and di-acetyl phosphate are dissolved in chloroform and evaporated. As a result it develops thin film followed by the hydration of aqueous phase; the suspension of niosomes is passed through the polycarbonate membranes which are arranged in a series of eight passages. Hence this technique opts for controlling the size of niosomes.

The "Bubble" Method

This method is suitable for preparation of niosomes and liposomes without the use of volatile organic solvents. Bubbling unit comprises of 3 necked round bottomed flasks which is kept in water bath for controlling the temperature. To the 1st neck of the flask water cooled reflux and 2nd neck thermometer is placed, and nitrogen supply through the 3rd neck. By the side heat the flask to 70°C temperature. Membrane additives like cholesterol and surfactant are added together in the buffer (pH 7.4) and miscellaneous with elevated shear homogenizer for 15 seconds and immediately afterwards "bubbled" at 70°C using nitrogen gas.

CHARACTERISATION OF NIOSOMES**Size**

The formulated niosomes are assumed to be sphere-shaped and also different techniques can be utilized to resolve their mean diameter. Laser light scattering method, electron microscopy, molecular sieve chromatography, ultracentrifugation, photon correlation microscopy, optical microscopy and freeze fracture electron microscopy. Bilayer vesicle formation by combination of non-ionic surfactants is characterized by "X-cross formation under light polarization microscopy and membrane rigidity" can be measured by means of mobility of fluorescence probe as function of temperature. "NMR spectroscopy, small angle X-ray scattering and Electron microscopy" are used to determine the number of lamellae.¹²⁻¹⁴



Entrapment efficiency

The prepared niosomal dispersion is subjected to dialysis, centrifugation or gel filtration. In order to disrupt vesicles 50% n-propanol or 0.1% Triton X-100 are used to find out entrapped drug in niosomes. Analysis is done by suitable assay method. Where, Entrapment efficiency (EE) can be defined by:

% Entrapment efficiency (EE) = (Amount entrapped/ total amount) x100.

In-vitro Release Study by using Dialysis

In-vitro release can be studied with the help of dialysis tubing. The sac was washed and soaked in water. The solution/ suspension are pipette into a bag made up of the tubing and then sealed. It is then placed in a 250 ml beaker containing phosphate buffer of 200 ml with constant shaking at 37°C provided with magnetic stirrer. The buffers are withdrawn at various time intervals and replaced with fresh buffers. Drug content is analyzed by an appropriate assay method.

Reverse dialysis

Reverse dialysis system (i.e.) niosomal dispersion are taken in small dialysis tubes containing few ml of dissolution medium and the niosomes are then displaced from the dissolution medium.

Franz diffusion cell

Franz diffusion cell (FDC) consists of donor and receptor compartment which is partitioned by the membrane called cellophane membrane. The prepared formulation is taken in the donor compartment and the dissolution medium in the receptor compartment. Dialysis process is done using dialysis membrane against suitable dissolution medium maintained at room temperature. The samples are withdrawn at suitable time intervals and analyzed for drug content by using UV spectrophotometer.

EVALUATION OF NIOSOMES IN OCULAR DRUG DELIVERY

Particle size analysis

Scanning electron microscopy (SEM) is used to analyze the surface morphology of the particle present in niosomes. Pictures of niosomes are taken by random scanning of the stub and count. The diameters for about 30 niosomes are measured from the photomicrographs of each batch. Finally, the average mean diameters are taken into consideration.

Stability studies

Stability studies for the formulated niosomal dispersion are carried out by storing at 4°±2°C, 25°±2°C and 40°±2°C in for the period of three months. Drug content and *in-vitro* release studies has been carried out on the selected formulations after one month and periodically thereafter for three months.

Rheological properties

The most significant parameter in ophthalmic preparations is viscosity. Generally the fact is resident time of drug in cul-de-sac is improved by increased viscosity. Ostwald- U- tube is used to study the rheological parameter of niosomes by diluting the product with water to required concentration and allowed it to equilibrate for 1 hr at 25°C. Relative viscosity can be calculated by comparing efflux time with that of water.

Ocular irritancy of niosomes

Ocular irritancy of the formulation could be evaluated by observing them for any redness, swelling or increased tear secretion. Study involves well fit rabbits weighing 2.5-3 kg are selected. Left and right eyes are instilled with the test and control samples respectively for a period of 40 days by instilling once. Separated eyes are fixed and cut vertically, dehydrate, clear, impregnate in soft and hard paraffin, section at 8µm thickness with the microtone and stain with haemotoxylin and eosin. Stained sections are photographed for corneal histological examinations by using optical microscopy.¹⁷⁻¹⁹

Intraocular pressure

Study involves adult male normotensive rabbits weighing 1.5 – 2 kg are used. Tonometer is used to determine the change in intraocular pressure. Before instillation of drug in both the eyes IOP can be measured after instilling a drop of a local anesthetic. Difference in IOP (ΔIOP) for each eye is calculated as follows,

$$\Delta IOP = IOP_{\text{dosed eye}} - IOP_{\text{control eye}}$$

Aqueous humor analysis

Study involves selection of albino rabbits weighing 2.5 kg. Rabbits are set aside under anesthesia all through the experiment by intramuscularly injecting 50/50 mixture of ketamine hydrochloride (30 mg/kg) and xylazine hydrochloride (10 mg/kg). To diminish further suffering anaesthetizes the eyes using one to two drops of oxybuprocaine. Needle of 25 G is inserted above the corneoscleral limbus just across the cornea. Samples are collected and stored at - 20°C for analyzing the sample. Amount of drug in the aqueous humor samples could be analyzed by using HPLC with UV detector.

FUTURE PROSPECTS

Available ophthalmic dosage forms of conventional type give rise to 1-3 % of drug absorption to through the cornea. Henceforth vesicular drug delivery system has the advantage of drug to be instilled in the form of a drop, which increases patient convenient also improves the permeation of drug across cornea thereby improving the bioavailability as well as prolongation of resident time of drug. There is very good perception for this delivery system in future.



DRUGS USED IN NIOSOMAL DELIVERY

Routes of Drug Administration	Examples of Drugs
Intravenous Route	Doxorubicin, methotrexate, tretinoin, vincristine
Peroral route	DNA vaccines, proteins, peptides, insulin
Ocular route	Timolo maleate, cyclopentolate
Nasal route	Sumatriptan, influenza viral vaccine
Inhalation	All transretinoic acid
Transdermal route	Fluriprofen, piroxicam, ketrolac
Vaginal	Insulin
Topical	Clobetasol propionate, Rofecoxib, Minoxidil, Propyl thiouracil

CONCLUSION

The perceptions of encapsulating drug in to niosomes have suitability of targeting the drug at appropriate tissue target is generally accepted phenomenon. Encapsulation of active principles in niosomal vesicles seems to be a novel approach and other novel concepts like proniosomes, discomes and aquasomes are also in recent trends to improve the drug delivery potential. From the above collected works it can be stated that niosomes are gifted formulation for targeted delivery. Niosomes have evolved for treatment of many dreadful diseases effectively with reduced side effects and better patient compliance. Thus niosomes present itself as a promising delivery system in therapeutics.

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