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Niosomes: A Novel Drug Delivery System

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Abstract: The development for the targeted delivery when it was investigated a drug delivery mechanism that would target directly to the diseased cell. In noisome, the vesicles forming amphiphile is a non-ionic surfactant which is usually stabilized by addition of cholesterol and small amount of anionic surfactant. Nonionic surfactant vesicles have been seen lot of advantage in the area of novel drug delivery systems due to their salient features such as biodegradable, biocompatible, chemical stable, less production cost, easy to store, easy to handle and low toxicity. The niosomes are classified as a function of the number of bilayers or as a function of size or as a function of the method of preparation. We discuss the method of preparation and also the evaluation parameters of the niosomal preparation. The application of niosomes technology is widely varied and it can be used to treat a number of diseases.

Keywords: Niosomes, non-ionic surfactant, novel drug delivery system, vesicles etc.

INTRODUCTION

The Paul Ehrlich, in 1909, initiated the development for targeted delivery when he investigated a drug delivery mechanism that would target directly to the diseased cell. Drug targeting can be defined as the ability to direct a therapeutic agent specifically to desired site of action with little / no interaction with non-target tissue[1]. In noisome, the vesicles forming amphiphile is a non-ionic surfactant such as Span-60/80 which is usually stabilized by addition of the cholesterol and small amount of anionic surfactant such as dicetyl phosphate or phosphatidic acid. The first report of non-ionic surfactant vesicles came from the cosmetic applications devised by the L'Oreal. The concept of incorporating the drug into niosome for a better targeting of the drug at the appropriate tissue destination is mostly accepted by researchers and academicians. Various types of drug deliveries can be possible using niosomes like ophthalmic, parental, topical, targeting etc[2,3].

A niosome is a non-ionic surfactant based liposome. Niosomes are formed mostly by the cholesterol incorporation as an excipient and other excipients can also be used. Niosomes have more penetrating capability than previous preparations of emulsions. They are similar to liposomes in structurally and

having a bilayer, however, the materials used to preparation of niosomes make them more active and stable, so niosomes offer many more advantages than the liposomes. The sizes of niosomes are microscopic and dissemble in nanometric scale. The particle size ranges from 10nm to 100nm[4,5].

Salient Features of Niosomes:[6,7]

- Niosomes are osmotically active and stable.
- It gives better availability to the particular site just by protecting the drug from biological environment.
- Niosomes consist of non-ionic surfactants are biocompatible, biodegradable, non-immunogenic and non carciogenic.
- Niosomes are less toxic and improves the therapeutic index of drug by restricting its action to the targeted cells.
- Niosomes prolonging the circulation of entrapped drug and altering its organ distribution and metabolic stability.

Advantages:[8]

- They are osmotically active and stable, and also they increase the stability of the entrapped drug.
- They improve the oral bioavailability of poorly absorbed drugs and enhance skin penetration of drugs.
- Niosome can encapsulate a large number of materials in a small vesicular volume.
- Surfactants used to prepare niosome are biodegradable, biocompatible, and not immunogenic.
- Handling and storage of surfactants does not require any special condition.
- Their surface formation and modification are easy.
- They have high compatibility with biological systems and low toxicity.
- Niosomes are having better patient compliance and better therapeutic effect as well.

Disadvantages:[9]

- Inefficient drug loading
- Special equipment's are required
- Time consuming process
- Suspension of Niosomes may exhibit fusion, aggregation, leaching or hydrolysis
- Sometimes causes reduced shelf-life of Niosomes dispersion.

Structure of Niosome:[10,11]

Niosomes are microscopic and lamellar structures consisting following components

a. Non-ionic surfactants,
b. Cholesterols
c. Charge inducing molecules

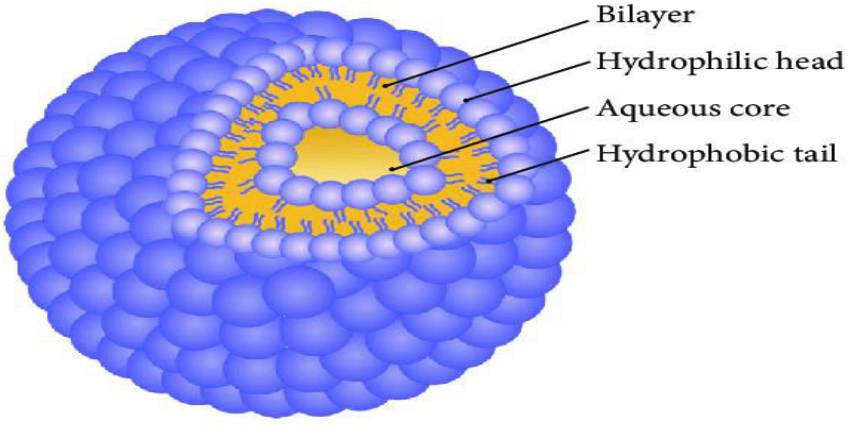

Figure 1: Structure of noisome.

Types of Niosomes:

The niosomes are classified as a function of the number of bilayers or as a function of size or as a function of the method of preparation. The various types of niosomes are, Multi lamellar vesicles, (MLV, Size=>0.05 µm), Large unilamellar vesicles, (LUV, Size=>0.10 µm), Small unilamellar vesicles, (SUV, Size=0.025-0.05 µm).[12]

Multilamellar vesicles (MLV)

It consists of several bilayers surrounding the aqueous lipid compartment separately. The estimated sizes of these vesicles is 0.5-10 µm diameter. Multilamellar vesicles are the mostly used niosomes. These vesicles are highly suited as a drug carrier for lipophilic compounds.[13]

Large unilamellar vesicles (LUV)

Niosomes of this type have a high aqueous or lipid compartment ratio, so that the larger volume of bio-active materials can be entrapped with very economical use of membrane lipids. The sizes of large unilamellar vesicles are in the range of 100-3000 nm in length.[14]

Small unilamellar vesicles (SUV)

The small uni-lamellar vesicles are mostly prepared from multilamellar vesicles by sonication method, French press extrusion electrostatic stabilization is the inclusion of diacetyl phosphate in 5,6 - carboxyfluorescein loaded Span 60 based niosomes. The sizes of the small unilamellar vesicles are in the range of 10-100 nm.[14,15]

Methods of Preparations:

A. Ether injection method:

This method provides a means of making niosome by slowly introducing a solution of surfactant dissolved in diethyl ether into warm water maintained the temperature at 60°C. The surfactant mixture in ether is injected through a 14-gauge needle into an aqueous solution of material. Vaporization of ether shows the formation of single-layered vesicles. Depending upon the conditions used the diameter of the vesicle range from 50-1000 nm.[2]

Surfactant is dissolved in diethyl ether

↓

Then injected in warm water maintained at 60°C through a 14 gauze needle

↓

Ether is vaporized to form single layered niosomes.

B. Handshaking method (Thin-film hydrating technique):

The mixture of vesicles forming an ingredients like surfactant and cholesterol are dissolved in a volatile organic solvent (diethyl either, chloroform or methanol) in a round bottom flask. The organic solvent is removed at room temperature (24°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 to 60°C with gentle agitation. This process forms typical multilamellar niosomes.[2,16]

Surfactant + cholesterol + solvent

↓

Remove organic solvent at Room temperature

↓

Thin layer formed on the walls of flask

↓

Film can be rehydrated to form multilamellar Niosomes.

C. Sonication method:

A typical method of production of the vesicles is by sonication of solution as described by the Cable. In this method an aliquot of drug solution in buffer is added to the surfactant/cholesterol mixture in a 108ml glass vial. The mixture is probe sonicated at 60°C for 3 minutes using a sonicator with a titanium probe to yield a niosomes.[2,17]

Drug in buffer + surfactant/cholesterol in 10 ml

↓

Above mixture is sonicated for 3 mints at 60°C using titanium probe yielding niosomes.

D. Micro fluidization method:

Micro fluidization is a recently develop technique which is used to prepare unilamellar vesicles of defined size distribution. This method is based on submerged jet principle in which the 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 so, that the energy supplied to the system remains within the area of niosomes formation is occur. The result is a greater uniformity, smaller in size and better reproducibility of niosomes formed.[18,19]

Two ultra-high speed jets are inside interaction chamber

↓

Impingement of a thin layer of Liquid in micro channels

↓

Formation of uniform Niosomes.

E. Reverse phase evaporation technique (REV):

In REV the Cholesterol and surfactant (1:1) are dissolved in a mixture of ether and chloroform. An aqueous phase containing drug is added to this mixture and the resulting two phases are sonicated at 4-5°C. The clear gel formed is further sonicated after the addition of small amount of phosphate buffered saline (PBS). The organic phase is removed at 40°C under at low pressure. The resulting viscous noisome suspension is diluted with PBS and heated on a water bath for 10 minat 60°C to yield niosomes.[20]

Cholesterol + surfactant dissolved in ether + chloroform

↓

Sonicated at 50°C and again sonicated after adding PBS

↓

Drug in aqueous phase is added to the above mixture

↓

Viscous niosomes suspension is diluted with PBS

↓

Organic phase is removed at 40°C at low pressure

↓

Heated on a water bath at 60°C for 10 mints to yield niosomes.

F. Trans membrane PH gradient Drug Uptake Process (Remote Loading Technique):

Surfactant and cholesterol are dissolved in chloroform. The solvent is evaporated under reduced pressure to get a thin film on the wall of the RBF. The firm is hydrated with 300mM citric acid (PH 4.00 by vertexes mixing). The multilamellar vesicles are frozen and shared three times and later sonicated to this niosomal suspension. An aqueous solution containing 10 mg/ml of drug is added and vortexes. The PH of

sample is raised to 7.0-7.2 with 1M disodium phosphate. This mixture is later heated at 60°C for 10 minutes so give niosomes.[21,22]

Surfactant + cholesterol in chloroform
↓
Solvent is evaporated under reduced pressure
↓
The thin film is deposited on the walls of RBF
↓
Hydrated with citric acid by vortex mixing
↓
3 cycles of freezing and thawing and then sonication
↓
Addition of aqueous drug solution and vortoxing
↓
pH raised to 7.087.2 by 1M disodium phosphate
↓
RBF as bubbling with three necks in water bath
↓
In RBF Supply the Reflux, thermometer and nitrogen
↓
Cholesterol + surfactant dispersed in buffer pH 7.4 at 70°C
↓
Above dispersion is homogenized for 15sec and then bubbled with nitrogen gas at 70°C temp.
↓
To get the niosomes.

Separation of Unentrapped Drug:

The removal of unentrapped solute from the vesicles can be occur by various techniques, which include Dialysis (The aqueous niosomal dispersion is dialyzed in a dialysis tube against the phosphate buffer or normal saline or glucose solution), Gel Filtration (The un entrapped drug is removed by the gel filtration of niosomal dispersion through a Sephadex-G-50 column and elution with the phosphate buffered saline or normal saline), Centrifugation (The niosomal suspension is centrifuged and the supernatant sample is separated. The pellet is washed and then re suspended to obtain a niosomal suspension free from the un entrapped drug) [23]

Characterizations of Niosomes:

1. Size, shape and charge

The size, shape and charges of niosomes may determined as shown in the following table [24,25]

2. Bilayer Formation

Assembly of non-ionic surfactants to form a bilayer vesicle is characterized by X cross formation under light polarization microscopy.

3. Number of Lamellae

This is determined by using the nuclear magnetic resonance (NMR) spectroscopy, small angle X-ray scattering and electron microscopy.

Table 1: Determination of Size, shape and charge of Niosome

Parameter	Characterization Methods
Vesicle charge and Surface Methodology	TEM, Freeze Fracture Electron Microscopy
Vesicle Size and Size Distribution	Dynamic light Scattering, TEM, Zeta Sizer, Laser Light Scattering, Gel Permeation, Gel Exclusion
Surface Charge	Free-Flow Electrophoresis
Electric Surface Potential and Surface PH	Zeta Potential Measurements and PH Sensitive Probes
Lamellarity Phase Behaviour	Small Angle X-Ray Scattering, PNMR DSC

4. Membrane Rigidity

Membrane rigidity can be measured by means of mobility of fluorescence probe as a function of a temperature.

5. Niosomal drug loading and encapsulation efficiency

To determine drug loading and encapsulation efficiency, the niosomal aqueous suspension was ultracentrifuged and the supernatant was removed after that sediment was washed twice with distilled water in order to remove the adsorbed drug and different parameters calculated by following formulas.[26]

a. The niosomal recovery was calculated as:

$$\text{Niosome recovery (\%)} = \frac{\text{Amount of niosomes recovered}}{\text{Amount of polymer + Drug + Excipient}} \times 100$$

b. The entrapment efficiency (EE) was then calculated using formula:

$$\text{Entrapment efficiency (\%)} = \frac{\text{Amount of drug in niosomes}}{\text{Amount of Drug used}} \times 100$$

c. The drug loading was calculated as:

$$\text{Drug loading (\%)} = \frac{\text{Amount of drug in niosomes}}{\text{Amount of niosomes recovered}} \times 100$$

6. In-vitro release

A method of in-vitro release rate study includes with the use of dialysis tubing. A dialysis sac is washed and soaked in the distilled water. The vesicle suspension is pipetted into a bag made up of tubing and sealed. The bag containing the vesicles is placed in the 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 assay method.[27]

Applications of Niosomes:[6,2829]

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

- It is used as Drug Targeting.
- It is used as Anti-neoplastic Treatment i.e. Cancer Disease.
- It is used as Leishmaniasis i.e. Dermal and Mucocutaneous infections e.g. Sodium stibogluconate.
- It is used as Delivery of Peptide Drugs.
- It is used in Studying the Immune Response.

- Niosomes as Carriers for Heamoglobin.
- Transdermal Drug Delivery Systems Utilizing Niosome.
- It is used in the Ophthalmic drug delivery.

Other Applications:

Niosomes can also be utilized for the 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 the niosomal encapsulation.

Future Prospects:

Niosome is a promising drug delivery system. Noisome can be used to encapsulate toxic drugs like anti-cancer, antiviral, anti-AIDs etc and can increase their bioavailability and targeting properties. Special storage and handling conditions are not required for the prepation of niosomes.

Conclusion:

Niosomes are novel drug delivery system that has a wide range of advantages when it compared with other conventional and vesicular delivery systems, like with niosomes drug targeting is done; controlled and sustained drug delivery of drug products is formulated. In various formulations the stability of niosome formulation was enhanced when prepared, their toxicity is reduced etc. From the above compilation of work it can be concluded that niosomes have suitability for encapsulating various types of drugs. Niosomes have been used for many chronic diseases with effective treatment and reduced the side effects and better patient compliance. Thus, niosomes can be used with number of applications in the field of disease management.

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