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Niosomes: A Novel Drug Delivery System

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Abstract: The design and development of a novel drug delivery system (NDDS) has two prerequisites. First, it should deliver the drug following a predetermined rate and second, it should release a therapeutically effective amount of the drug at the site of action. Conventional dosage forms are unable to meet these requisites. Niosomes are essentially non-ionic surfactant-based multilamellar or unilamellar vesicles in which an aqueous solution of solute is entirely enclosed by a membrane resulting from the organization of surfactant macromolecules as a bilayer. Niosomes are formed on hydration of non-ionic surfactant film which eventually hydrates imbibing or encapsulating the hydrating aqueous solution. The proposed review deals with the composition, methods of preparation, and applications of Niosomes in the pharmaceutical field. The main aim of the development of Niosomes is to control the release of drugs in a sustained way, modify of distribution profile of the drug, and target the drug to the specific body site..

Keywords: NDDS, Niosomes

INTRODUCTION

Paul Ehrlich, in 1909, initiated the development of targeted delivery when he envisaged a drug delivery mechanism that would target directly to diseased cells. The capacity to precisely guide a medicinal agent to the intended site of action with little to no contact with non-target tissue is known as drug targeting. In noisome, the vesicles forming amphiphile is a non8ionic surfactant such as Span860 which is usually stabilized by the addition of cholesterol and a small amount of anionic surfactant such as diacetyl phosphate. The first report of non8ionic surfactant vesicles came from the cosmetic applications devised by L'Oréal. The concept of incorporating the drug into noisome for better targeting of the drug at appropriate tissue destination is widely accepted by researchers and academicians. Niosomes can be used for targeted, ocular, topical, parental, and other kinds of drug delivery.

DEFINITIONS

A liposome based on non-ionic surfactants is called a noisome. Cholesterol is incorporated as an excipient in the majority of niosome formations. You can utilize different excipients as well. Niosomes are more able to penetrate than earlier emulsion formulations. Although niosomes and liposomes have a bilayer structure, niosomes are more stable due to the preparation process, which gives them numerous advantages over liposomes. Niosomes are minuscule particles that are sized on a nonmetric scale. The particle size ranges from 10nm8100nm. [1] Vesicular systems are a unique way of drug administration that can boost the bioavailability of encapsulated pharmaceuticals and provide therapeutic activity in a controlled manner for a prolonged time. Niosomes are non-ionic surfactant vesicles in aqueous media resulting in closed bilayer structures that can be used as carriers of amphiphilic and lipophilic drugs [2]. Niosomes are microscopic lamellar structures formed on an admixture of non-ionic surfactant of the alkyl or diallyl polyglycerol ether class and cholesterol and the enclosed interior usually contains a buffer solution at appropriate pH [3]. Cholesterol with a tiny quantity of an anionic surfactant, such as diacetyl phosphate, stabilize the non-ionic surfactant vesicles that form amphiphile in niosomes [4]. Non-ionic surfactants provide a few advantages over phospholipids because they are more economical and chemically more stable as they are not easily hydrolyzed or oxidized during storage. It is possible to alter the vesicular structure to enable regulated or prolonged medication administration, improving [5].

Advantages [6]

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

High patient compliance because the vesicle suspension is a water-based carrier as opposed to greasy dose formulations.

2. Take into account the diverse spectrum of solubilities of medicinal compounds.

3. The vesicle formulation's properties are changeable and manageable. The properties of the vesicles can be changed by adjusting their concentration, size, lamellarity, surface charge, and composition.

4. The vesicles may operate as a depot, releasing the medicine in a controlled manner.

5. They are osmotically active and stable, and boost the stability of entrapped pharmaceuticals.

6. Surfactants don't need any particular handling or storage conditions.

7. They increase drug penetration via the skin and increase the oral bioavailability of poorly absorbed medications.

8. Oral, parenteral, and topical administration are possible ways to get them to the site of action.

Disadvantages: [6]

1. Inefficient drug loading
2. Special equipment is required
3. Time consuming process
4. Suspension of Niosomes may exhibit fusion, aggregation, leaching, or hydrolysis
5. Sometimes causes reduced shelf-life of Niosomes dispersion.

STRUCTURE OF NIOSOMES

Microscopic lamellar structures are known as niosomes. They are composed of cholesterol and non-ionic surfactants belonging to the alkyl or diallyl polyglycerol ether family, which are then hydrated in aqueous environments. As seen in Fig. 1, the surfactant molecules have a tendency to position themselves so that the hydrophilic ends of the non-ionic surfactant point outward and the hydrophobic ends face one another to create the bilayer. Additionally, Fig.2. The surfactant molecules' lamellar orientation is better understood from this figure.

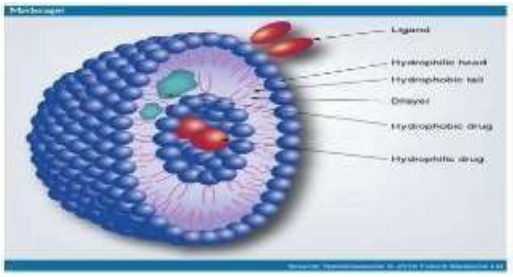

Fig 1.

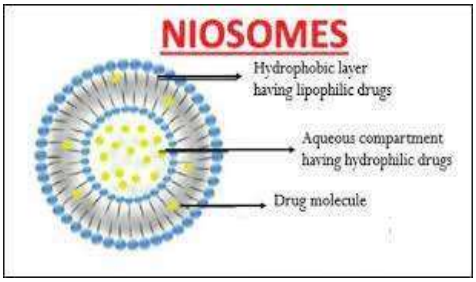

Fig 2.

Because the non-ionic surfactants are amphiphilic, they use energy, such as heat and physical agitation, to form a closed bilayer vesicle in aqueous conditions. While the hydrophilic heads of the bilayer structure stay in touch with the aqueous solvent, the hydrophobic portions of the structure are orientated away from it. By altering the vesicles' composition, size, lamellarity, tapping volume, surface charge, and concentration, one can modify their properties. The vesicle is subject to a variety of forces, including the entropic repulsive forces of the surfactant head groups, short-acting repulsive forces, Vander Waals forces between surfactant molecules, and repulsive forces arising from electrostatic interactions among charged groups of surfactant molecules. These forces are in charge of keeping niosomes' vesicular structure intact. However, the stability of niosomes is affected by the type of surfactant, nature of the encapsulated drug, storage temperature, detergents, use of membrane-spanning lipids, the interfacial polymerization of surfactant monomers in situ, the inclusion of charged molecules [7].

TYPES OF NIOSOMES: [8]

The niosomes are classified as a function of the number of bilayers or as a function of size or as a function of method of preparation. The various types of niosomes are described below.

1. **Multi lamellar vesicles, (MLV, Size=>0.05 µm)**: -It consists of several bilayers surrounding the aqueous lipid compartment separately. The estimated size of these vesicles is 0.5-10 µm diameter. Multilamellar vesicles are the most widely used niosomes. These vesicles are ideal for using as medication carriers for substances that are lipophilic.
2. **Large unilamellar vesicles, (LUV, Size=>0.10 µm)**: - Niosomes of this type have a high aqueous or lipid compartment ratio so that the larger volume of bio-active materials can be captured while making extremely sparing use of membrane lipids..
3. **Small unilamellar vesicles, (SUV, Size=0.025-0.05 µm)**: - 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.

COMPOSITION OF NIOSOMES: [8]

1. Non-ionic Surfactants: Mainly following types of non-ionic surfactants are used for the formation of niosomes.
   - **a)** Alkyl Ethers: For the preparation of niosomes some surfactant-containing chemicals are:
     - i. Surfactant-I: is monoalkyl glycerol ether.
     - ii. Surfactant-II: is diglycerol ether.
     - iii. Surfactant III: is an ester-linked surfactant. Other than alkyl glycerol, alkyl glycosides, alkyl ethers bearing polyhydroxy head groups which are also used in the formulation of noisome
   - **b)** Alkyl Esters: Surbiton esters are the most preferred surfactant used for the preparation of niosomes.
   - **c)** Alkyl Amides: e.g.: galactosides and glycosides.
   - **d)** Fatty Acid and Amino Acid Compounds: Long-chain fatty acids and amino acid moieties have been used in some niosomes formulations.
2. Cholesterol.

   Cholesterol is a steroid derivative, which is mainly used for the formulation of niosomes.
3. Charged Molecule E.g., diacetyl phosphate, phosphatide acid (-ve charge), stearyl amine, and stearyl pyridinium chloride (+ve charge). To prevent aggregation of niosomes these types of charged molecules are used.

- **METHODS OF PREPARATION: [9-14]**

Ether injection method:

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.

Handshaking method (Thin-film hydrating technique):

Surfactant + cholesterol + solvent
↓
Remove organic solvent at Room temperature
↓
The thin layer formed on the Walls of the flask
↓
The film can be rehydrated to form multilamellar Niosomes.

Sonication method:

The drug in buffer + surfactant/cholesterol in 10 ml
↓
The above mixture is sonicated for 3 minutes at 60°C using a titanium probe yielding niosomes.

Micro fluidization method:

Two ultra-high-speed jets inside the interaction chamber
↓
Impingement of a thin layer of Liquid in microchannels
↓
Formation of uniform Niosomes.

Reverse phase evaporation technique (REV):

Cholesterol + surfactant dissolved in ether + chloroform

↓

Sonicated at 5°C and again sonicated after adding PBS

↓

The drug in aqueous phase is added to the above mixture

↓

Viscous niosomes suspension is diluted with PBS

↓

The organic phase is removed at 40°C at low pressure

↓

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

Trams membrane PH gradient (inside acidic) Drug Uptake Process: or Remote Loading Technique:

Surfactant + cholesterol in chloroform

↓

The solvent is evaporated under reduced pressure

↓

Thin film is deposited on the walls of RBF

↓

Hydrated with citric acid by vortex mixing

↓

3 cycles of freezing and thawing then sonication

↓

PH raised to 7.087.2 by 1M disodium phosphate

↓

RBF is a bubbling unit with three necks in a water bath

↓

Reflux, thermometer, and nitrogen supply by three necks

↓

Cholesterol + surfactant dispersed in buffer pH 7.4 at 70°C

↓

The above dispersion is homogenized for 15 seconds and then bubbled with nitrogen gas at 70°C

↓

To get niosomes.

Characterizations of Niosomes: [13]

1. Size, shape and charge the characterization methods of liposome size, shape, and charge are shown in Table

Size, Shape & Charge Characterizing Methods	Methods Used To Determine Character
Vesicle size & surface methodology	Transmission electron microscopy freeze-fracture electron microscopy
Vesicle size & size distribution	Dynamic light scattering, tem, zeta sizer, laser light scattering, gel permeation, gel exclusion
Surface charge	Free-flow electrophoresis
Electric surface potential & surface pH	Zeta potential measurements & pH sensitive probes
Lamellarity phase behavior	Small angle x-ray scattering, NMR differential scanning calorimetry

2. Bilayer Formation

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

3. Number of Lamellae

   Small-angle X-ray scattering, electron microscopy, and nuclear magnetic resonance (NMR) spectroscopy are used to ascertain this.

4. Membrane Rigidity

   Membrane rigidity can be measured using the mobility of the fluorescence probe as a function of temperature.

5. Entrapment Efficiency

   After preparing liposomal dispersion, the entrapped drug is separated by dialysis, centrifugation, or gel filtration as described above and the drug remained entrapped in niosomes is determined by complete vesicle disruption using 50% n-propanol or 0.1% Triton X-100 and analyzing the resultant solution by appropriate drug assay method. Entrapment efficiency = (Amount entrapped / total amount) x 100.

6. Niosomal drug loading and encapsulation efficiency

   To determine drug loading and encapsulation efficiency, the liposomal aqueous suspension was ultra-centrifuged, supernatant was removed and sediment was washed

twice with distilled water to remove the adsorbed drug.

The liposomal recovery was calculated as:

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

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

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

The drug loading was calculated as:

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

7. In-vitro release

Dialysis tubing is a tool used in in-vitro release rate studies. After cleaning, distilled water is used to immerse a dialysis sac. The tubing-filled bag is pipetted with the vesicle suspension and sealed. In a 250 ml beaker, the bag containing the vesicles is submerged in 200 ml of buffer solution and shaken continuously at either 25°C or 37°C. An appropriate assay method is used to evaluate the buffer for drug content at different time periods.

8. Vesicle charge

The behavior of niosomes both in vivo and in vitro can be significantly influenced by the vesicle surface charge. Compared to uncharged vesicles, charged niosomes are often more stable against fusion and aggregation. Microelectrophoresis can be used to determine the zeta potential of individual niosomes in order to estimate their surface potential. Using pH-sensitive fluorophores is an alternate strategy. Recently, the zeta potential of niosomes has been measured using dynamic light scattering.

APPLICATIONS OF NIOSOMES: [9]

The application of niosomes technology is widely varied and can be used to treat several diseases. The following are a few uses of niosomes that are either proven or under research.

- It is used as Drug Targeting.
- It is used as Anti8neoplastic Treatment i.e. Cancer Disease.
- It is used for Leishmaniasis i.e. Dermal and Mucocutaneous infections e.g. Sodium stibogluconate.
- It is used to act as Delivery of Peptide Drugs
- It is used in Studying Immune Response.
- Niosomes as Carriers for Haemoglobin.

➢ **RECENT STUDIES: [15]**

Over the past three decades, niosomes have been successfully used as drug carriers to overcome some major biopharmaceutical problems such as insolubility, side effects, and poor chemical stability of drug molecules. Table 2 summarizes the most recent applications of niosomes as drug delivery systems.

Type of Drug	Name of The Drug	Composition	Experimental Model
Angiotensin receptor blockers	Candesartan cilexetil	Span 60, cholesterol, diacetyl phosphate, maltodextrin	In vitro dissolution test for proniosomal tablets, in vivo evaluation of proniosomal tablets, pharmacokinetic analysis
Anti-inflammatory	Naproxen Dexamethasone	Tween 80, Tween 20, cholesterol, Span 60, cholesterol	In vitro drug release study, Preformulation study Characterization of niosomes, in vitro release studies, stability test
Antibacterial	Moxifloxacin Cefixime	Tween 60, cholesterol C - Glycoside derivative surfactant, cholesterol	In vitro release studies, antimicrobial activity, In vitro release study, biocompatibility and bioavailability studies using experimental animals
Anticancer	Doxorubicin Paclitaxel	Span 60, cholesterol, diacetyl phosphate, N - lauryl glucosamine Span 40, cholesterol, diacetyl phosphate	Optimization studies for formulation, skin irritancy, histopathological investigation of rat skin Formulation studies, Pharmacokinetic and tissue distribution studies

Antiviral	Nevirapine	Tyloxapol, cholesterol	Diffusion kinetics of drug, micro viscosity studies, in vitro release study
H_2 receptor antagonist	Famotidine	Span 60, cholesterol	Kinetic analysis of drug-release profiles, ex vivo permeability study

CONCLUSION:

The concept of incorporating the drug into liposomes or niosomes for better targeting of the drug at appropriate tissue destinations is widely accepted by researchers and academicians. Niosomes represent a promising drug delivery module. They present a structure similar to liposomes and hence they can represent alternative vesicular systems concerning liposomes, due to the noisome ability to encapsulate different types of drugs within their multi- environmental structure. Niosomes are thought to be better candidates for drug delivery as compared to liposomes due to various factors like cost, stability, etc. Niosomes can be used for targeted, ocular, topical, parenteral, and other kinds of drug delivery. Niosomes are a novel drug delivery system that has a wide range of advantages when compared with other conventional and vesicular delivery systems niosomes drug targeting is done, and controlled drug delivery of drug products is formulated. In various formulations the stability of formulation was enhanced when prepared as niosomes, their toxicity was reduced, etc. From the above compilation of work, it can be concluded that niosomes are suitable for encapsulating various types of drugs. Niosomes have been used for many chronic diseases with effective treatment efficiently reduced side effects and better patient compliance. Thus, niosomes can be used with wider applications in the field of disease management.

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