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Niosomes: A novel drug delivery system

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ABSTRACT: Niosomes are a novel drug delivery system, in which the medication is encapsulated in a vesicle. These are biodegradable, biocompatible non-immunogenic, and exhibit flexibility in their structural characterization. The vesicle is composed of a bilayer of non-ionic surface-active agents and hence they are named niosomes. They are established to provide targeting and controlled release of natural pharmaceutical compounds. The concept of incorporating the drug into niosomes for better targeting of the drug at an appropriate tissue destination is widely accepted by researchers and academicians. The ionic drug carriers are relatively toxic and unsuitable whereas niosomal carriers are safer. Niosomes are very useful and have a bright future in the pharmaceutical industry. The present review discusses the most important features of noisome such as their diverse structures, the different preparation approaches, characterization techniques, factors that affect their stability, their use by various routes of administration, their therapeutic applications in comparison with natural drugs, and especially the brain targeting with niosomes-ligand conjugation. Also, niosomes have great drug delivery potential for targeted delivery of anti-cancer, anti-infective agents.

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INTRODUCTION:

The biological effects of a drug on a patient depend upon the pharmacological properties of the drug. Targeted drug delivery, also known as smart drug delivery, is a method of treatment that involves the increase in medicament in one or few body parts in comparison to others. Drug targeting is a kind of phenomenon in which a drug gets distributed in the body in such a manner that the drug interacts with the target tissue at a cellular or subcellular level to achieve a desired therapeutic response at the desired site without undesirable interactions at other sites. Two strategies are widely used for drug targeting to the desired organ/tissue: passive targeting and active targeting. Drug delivery vehicles transport the drug either within or in the vicinity of the target. The name drug targeting represents the ability to

give the therapeutic effect at the particular site of action. In the niosomes drug delivery system, the medication is encapsulated in a vesicle [1].

The vesicle is composed of a bilayer of non-ionic surface-active agents and hence the name niosomes. Niosome is one of the techniques used to obtain the controlled release of a drug-controlled drug delivery system is another term used to obtain a desirable drug release for a longer period of time.

Noisome have a bilayer structure (same as a cell membrane) which is made up of cholesterol, non-ionic surfactant as well as diethyl ether along with the subsequent hydration in an aqueous media. As we know niosome are microscopic lamellar structures whose sizes range between 10 to 100 nm. They also have the higher chemical stability of surfactant than phospholipids so niosome can be hydrolyzed by ester bond easily. Niosome possesses an infrastructure consisting of hydrophobic and hydrophilic mostly together and so also accommodate the drug molecules with a wide range of solubility (Fig 1) [2].

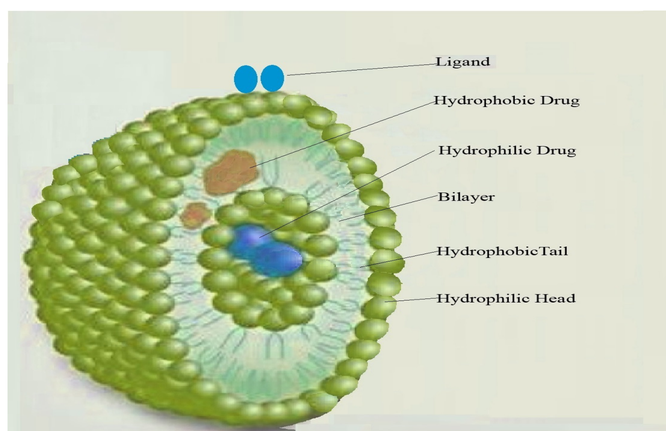

Fig 1. Structure of Niosome.

ADVANTAGES OF NIOSOMES [3-5]:

- They can accommodate a variety of drug moieties such as hydrophilic, lipophilic, and amphiphilic drugs.
- Niosomes exhibit flexibility in their structural characteristics (composition, fluidity, and size) and can be designed according to the desired situation.
- Niosomes can improve the performance of the drug molecules.
- Better availability to the particular site, just by protecting the drug from the biological environment.
- Niosomes surfactants are biodegradable, biocompatible, and non-immunogenic.
- They can enhance the permeation of drugs through the skin.
- They do not require any special method for storage and handling of the final product.
- Niosomes are osmotically active and stable.
- Higher patient compliance in comparison with oily dosage forms.
- The vesicles may act as a depot, releasing the drug in a controlled manner.

DISADVANTAGES [6]:

- Leaking of the entrapped drug may occur.
- Aggregation of the vesicles may occur.
- Hydrolysis of encapsulated drugs limits the shelf life of the dispersion.

TYPES OF NIOSOMES:

- There are various types of niosomes:
- Multi Lamellar Vesicles (MLV)
- Large Unilamellar Vesicles (LUV)
- Small Unilamellar Vesicles (SUV)

Multi Lamellar Vesicles (MLV):

It consists of a number of bilayers surrounding the aqueous lipid compartment separately. The approximate size of these vesicles is 0.5 to 10 µm in diameter. Multilamellar vesicles are the most widely used niosomes. It is simple to make and is mechanically stable upon storage for long periods. These vesicles are highly suited as a drug carrier for lipophilic compounds [7].

Large Unilamellar Vesicles (LUV):

Niosomes of this type have a high aqueous/lipid compartment ratio, so that larger volumes of bio-active materials can be entrapped with the very economical use of membrane lipids.

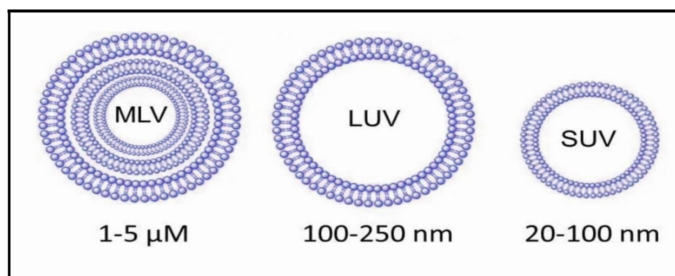

Fig 2. Types of Niosomes.

Small Unilamellar Vesicles (SUV):

These small unilamellar vesicles are mostly prepared from multilamellar vesicles by sonication method, French press extrusion electrostatic stabilization is the inclusion of dicetyl phosphate in 5(6)-carboxyfluorescein (CF) loaded Span 60 based niosomes (Fig 2) [8-10].

METHOD OF PREPARATION [10-16]:

Sonication:

In this technique, the mixture of drug solution is added to the buffer then the surfactant and cholesterol are combined with each other after this it will be sonicated with a titanium probe sonicator at 60 °C temperature for approximately 4 min to yield niosomes.

Ether Injection Method:

In this method the niosome is introduced slowly in a solution of surfactant in diethyl ether into warm water to maintain the temperature at 60 °C, then the mixture in ether is injected through fourteen gauze needles into an aqueous solution of water after this vaporization of ether occur which lead to the formation of single layer vesicles. Then the diameter of the vesicles which have range from 50 to 1000 nm depends upon the condition of use.

Ethanol Injection Method:

In this technique, an ethanol solution containing surfactant is injected rapidly through a fine needle into excess saline or another aqueous medium then the vaporization of ethanol takes place and the vesicles start to form.

Reverse Evaporation Method:

In this method, 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 to 5 °C. A clear gel is formed which is further sonicated after the addition 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 in a water bath at 60 °C for 10 min to yield niosomes.

Multiple membrane extrusion method:

The mixture of surfactant, cholesterol, and dicetyl phosphate in chloroform is made into a thin film by evaporation. Then the film is hydrated with aqueous drug polycarbonate membranes, solution and the resultant suspension extruded through which are placed in series for up to 8 passages. It is a good method for controlling niosome size.

Micro Fluidization:

In this technique, the principle which involves is known as the submerged jet principle in which two fluidized streams interact with each other at ultra-high velocities and in the microchannels within the interaction chamber. Thin liquid sheet impingements along with a common front are arranged such as that the energy supplies remain the same within the area of niosomes formation; it leads to the formation of niosomal vesicles of greater uniformity, smaller size, and better reproducibility.

Handshaking method (thin film hydration technique):

In this method, the surfactant and cholesterol are dissolved in a volatile organic solvent (such as diethyl ether, chloroform, or methanol) in a round bottom flask. The organic solvent is removed at room temperature (20 °C) using a rotary evaporator leaving a thin layer of solid mixture deposited on the wall of the flask. The dried surfactant film can be rehydrated with an aqueous phase at 0 to 60 °C with gentle agitation to yield multilamellar niosomes.

The "Bubble" Method:

It is a technique that has only recently been developed and which allows the preparation of niosomes without the use of organic solvents. The bubbling unit consists of a round bottom flask with three necks, and this is positioned in a water bath to control the temperature. Water-cooled reflux and thermometer are positioned in the first and second neck, while the third neck is used to supply nitrogen. Cholesterol and surfactant are dispersed together in a buffer (pH 7.4) at 70 °C. This dispersion is mixed for a period of 15 s with a high shear homogenizer and immediately afterward, it is bubbled at 70 °C then nitrogen gas is used to get niosomes.

FACTORS AFFECTING NIOSOMES FORMULATION [15-18]:

Nature of encapsulated drug:

The charge and the rigidity of the niosomal bilayer are greatly influenced by the physical-chemical properties of the encapsulated drug. Entrapment of the drug occurs by interacting with the surfactant head groups leading to the increasing charge and creating mutual repulsion of the surfactant bilayer and thus increasing the vesicle size. The HLB of a drug influences the degree of entrapment.

Nature and type of surfactant:

The mean size of niosomes increases proportionally with the increase in the HLB value of the surfactants like Span 85 (HLB 1.8) to Span 20 (HLB 8.6) because the surface free energy decreases with an increase in hydrophobicity of surfactant. A surfactant 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.

Cholesterol content and its charge:

Hydrodynamic diameter and entrapment efficiency of niosomes are increased by cholesterol. It induces membrane stabilizing activity and decreases the leakiness of the membrane.

An increase in the cholesterol content of the bilayers resulted in a decrease in the release rate of encapsulated material and therefore an increase in the rigidity of the bilayers obtained. The presence of charge tends to increase the interlamellar distance between successive bilayers in multilamellar vesicle structure and leads to greater overall entrapped volume.

Resistance to osmotic pressure:

The diameter is reduced by the addition of hypertonic salt solution to the suspension of niosomes. In a hypotonic solution, inhibition of eluting fluid from vesicles results in the slow release initially followed by a faster release due to the mechanical loosening of vesicle structure under osmotic stress.

Temperature of the Hydration:

Hydration temperature influences the shape and size of the niosome. Hydration temperature should be above the gel, liquid phase transition temperature. Change in temperature affects the assembly of surfactants into vesicles and vesicle shape modification. Improper selection of the hydration temperature, time, and hydration medium volume produces fragile niosomes / drug leakage problems may arise.

Charge:

The presence of charge leads to an increase in interlamellar distance between successive bilayers in multilamellar vesicle structure and greater overall entrapped volume.

EVALUATION OF NIOSOMES [17-20]:

Size and Shape:

Various methods are used for the determination of mean diameters like the laser light scattering method it is also determined by electron microscopy, molecular sieve chromatography, photon correlation microscopy, and optical microscopy.

Vesicle diameter:

The niosomes diameter can be determined using light microscopy, photon correlation microscopy, and freeze-fracture electron microscopy. Freeze thawing (keeping vesicles suspended at 20 °C for 24 h and then heating to ambient temperature) of niosomes increases the vesicle diameter, which might be attributed to the fusion of vesicles during the cycle.

Entrapment efficiency:

After preparing niosomal dispersion, the unentrapped 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 assay method for the drug.

EE (%) = (ADE/TAD) × 100 …..(1)

Where, ADE – Amount of drug entrapped TAD – Total amount of drug, and EE – Entrapment efficiency.

Bilayer Rigidity and Homogeneity:

The biodistribution and biodegradation of niosomes are influenced by the rigidity of the bilayer. In homogeneity can occur both within niosome structures themselves and between niosomes in dispersion and could be identified via. NMR, differential scanning calorimetry (DSC), and Fourier transform-infra red spectroscopy (FT-IR) techniques. Recently, fluorescence resonance energy transfer (FRET) was used to obtain deeper insight into the shape, size, and structure of the niosomes.

Osmotic Shock:

The change in the vesicle size can be determined by osmotic studies. Niosomes formulations are incubated with hypotonic, isotonic, and hypertonic solutions for 3 h. Then the changes in the size of vesicles in the formulations are viewed under optical microscopy.

Zeta potential analysis:

Zeta potential analysis is done for determining the colloidal properties of the prepared formulations. The suitably diluted niosomes derived from pro-niosome dispersion were determined using a zeta potential analyzer based on electrophoretic light scattering and laser Doppler velocimetry method (Zeta plus™, Brookhaven Instrument Corporation, New York, USA). The temperature was set at 25 °C. Charge on vesicles and their mean zeta potential values with a standard deviation of measurements were obtained directly from the measurement.

***In-vitro* drug release:**

A method of *in-vitro* release rate study includes the use of dialysis tubing. A dialysis sac is washed and soaked in distilled water. The vesicle suspension is pipetted into

a bag made up of the tubing and sealed. The bag containing the vesicles is placed in 200 ml of buffer solution in a 250 ml beaker with constant shaking at 25 or 37 °C. At various time intervals, the buffer is analyzed for the drug content by an appropriate assay method.

Stability Study:
The niosomal formulations are subject to stability studies by storing at 4, 25, and 37 °C in a thermostatic oven for a period of three months. After one month, the drug content of all the formulations is checked by entrapping efficiency parameter.

APPLICATION OF NIOSOMES [20-24]:

Niosomes as Drug Carriers:
Niosomes have also been used as carriers for iobitridol, a diagnostic agent used for X-ray imaging.

Anti-neoplastic Treatment:
Most anti-neoplastic drugs cause severe side effects. Niosomes can alter the metabolism and prolong the circulation and half-life of the drug, decreasing the side effects of the drugs. Niosomes decrease the rate of proliferation of tumors and higher plasma levels by slower elimination.

Delivery of Peptide Drugs:
The use of niosomes to successfully protect the peptides from gastrointestinal peptide breakdown is being investigated. An *in-vitro* study conducts by oral delivery of vasopressin entrap derivative in niosomes shows that entrapment of the drug increases the stability of the peptide.

Use in Studying Immune Response:
Due to their immune system selection, low toxicity, and greater stability niosomes are used to study the nature of the immune response provoked by antigens. Non-ionic surfactant vesicles have clearly demonstrated their ability to function as adjuvants as parenteral administration with a number of different antigens and peptides.

Cosmetics:
The first report of non-ionic surfactant vesicles came from the cosmetic applications devised by LOreal. Niosomes develop and patent by LOréal in the 1970s and 80s. The first product Niosome introduce in 1987 by Lancome. The niosome advantage in cosmetic and skincare an application includes their ability to increase the stability of entrapped drugs and also improves the bioavailability of poorly absorb ingredients and enhances skin penetration.

Sustained Release:
Sustained-release action of niosomes can be applied to drugs that have a low therapeutic index and have low solubility with water since those could be maintained in the circulation via niosomal encapsulation.

Leishmaniasis:
Leishmaniasis is a disease in which a parasite of the genus Leishmania invades the cells of the liver and spleen. The use of niosomes in tests conducted showed that it was possible to administer higher levels of the drug without triggering the side effects, and thus allowed greater efficacy in treatment.

Niosome Formulation as a Brain Targeted Delivery System for the Vasoactive Intestinal Peptide (VIP):
Radiolabeled (I125) VIP-load glucose-bearing niosomes are injected intravenously into mice. Encapsulate VIP within glucose-bearing niosomes exhibits higher VIP brain uptake as compared to control.

Niosomes as Carriers for Hemoglobin:
Niosomes can be used as a carrier for hemoglobin. Niosomal suspension shows a visible spectrum super-imposable to that of free hemoglobin. Vesicles are permeable to oxygen and the hemoglobin dissociation curve can be modified similarly to non-encapsulated hemoglobin.

CONCLUSION:
The niosomal drug delivery system is one of the best examples of great evolution in drug delivery technologies and nanotechnology. There are a lot of scopes to encapsulate toxic anti-cancer drugs, anti-AIDS drugs, and antiviral drugs. Niosome represents a positive promising drug delivery module. It is obvious that niosome appears to be a well-preferred drug delivery system over another dosage form. Niosome is mostly stable in nature and economic.

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