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Niosomes – An Overview

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Abstract
Non-ionic surfactant vesicles (or niosomes) are now widely studied as alternates to liposomes. An increasing number of non-ionic surfactant has been found to form vesicles, capable of entrapping hydrophilic and hydrophobic molecules. The drug disposition by niosomal drug delivery proved that the drug accumulated in visceral organs (lung, kidney, liver, spleen) was lower than free drug. Niosomes are uni or multilamellar vesicles formed from synthetic, non-ionic surfactant of alkyl or dialkyl poly glycerol ether class, offering an alternative to liposomes as drug carriers. Niosomes can entrap solutes in a manner analogous to liposomes, are relatively more stable in vitro and can improve the stability of entrapped drug as compared with stability in conventional dosage forms.
Keywords: Non-ionic surfactant, liposomes, visceral organs, multilamellar vesicles, niosomes, entrapped drug.

1) Introduction

Niosomes are a novel drug delivery system, in which the medication is encapsulated in a vesicle. The vesicle is composed of a bilayer of non-ionic surface active agents and hence the name niosomes. The niosomes are very small, and microscopic in size. Their size lies in the nanometric scale. Although structurally similar to liposomes, they offer several advantages over them. Niosomes have recently been shown to greatly increase transdermal drug delivery and also can be used in targeted drug delivery, and thus increased study in these structures can provide new methods for drug delivery. Niosomes are formed mostly by cholesterol incorporation as an excipient. Other excipients can also be used. Niosomes have more penetrating capability than the previous preparations of emulsions. They are structurally similar to liposomes in having a bilayer, however, the materials used to prepare niosomes make them more stable and thus niosomes offer many more advantages over liposomes.

1.1) Structure of niosomes:

Niosomes are microscopic lamellar structures, which are formed on the admixture of non-ionic surfactant of the alkyl or dialkyl polyglycerol ether class and cholesterol with subsequent hydration in aqueous media. Structurally, niosomes are similar to liposomes, in that they are also made up of a bilayer. However, the bilayer in the case of niosomes is made up of non-ionic surface active agents rather than phospholipids as seen in the case of liposomes. Most surface active agents when immersed in water yield micellar structures, however some surfactants can yield bilayer vesicles which are niosomes. Niosomes may be unilamellar or multilamellar depending on the method used to prepare them.The niosome is made of a surfactant bilayer with its hydrophilic ends exposed on the outside and inside of the vesicle, while the hydrophobic chains face each other within the bilayer. Hence, the vesicle holds hydrophilic drugs within the space enclosed in the vesicle, while hydrophobic drugs are embedded within the bilayer itself. The figure below will give a better idea of what a niosome looks like and where the drug is located within the vesicle.

A typical niosome vesicle would consist of a vesicle forming ampiphile i.e. a non-ionic surfactant such as Span-60, which is usually stabilized by the addition of cholesterol and a small amount of anionic surfactant such as diacetyl phosphate, which also helps in stabilizing the vesicle.

2) Comparison Of Niosome V/S Liposome

Niosomes are different from liposomes in that they offer certain advantages over liposomes. Liposomes face problems such as –they are expensive, their ingredients like phospholipids are chemically unstable because of their predisposition to oxidative degradation, they require special storage and handling and purity of natural phospholipids is variable. Niosomes do not have any of these problems. Also since niosomes are made of uncharged single-chain surfactant molecules as compared to the liposomes which are made from neutral or charged double chained phospholipids, the structure of niosomes is different from that of liposomes. However Niosomes are similar to liposomes in functionality. Niosomes also increase the bioavailability of the drug and reduce the clearance like liposomes. Niosomes can also be used for targeted drug delivery, similar to liposomes. As with liposomes, the properties of the niosomes depend both- on the composition of the bilayer, and the method of production used.

3) Types of Niosomes

The niosomes are classified as a function of the number of bilayer (e.g. MLV, SUV) or as a function of size. (e.g. LUV, SUV) or as a function of the method of preparation (e.g. REV, DRV). The various types of niosomes

(Weiner *et al*., 1989) are described below.
3.1) Multi lamellar vesicles (MLV)
3.2) Large unilamellar vesicles (LUV)
3.3) Small unilamellar vesicles (SUV)
3.1) Multi lamellar vesicles (MLV)
It consists of a number of bilayer surrounding the aqueous lipid compartment separately. The approximate size of these vesicles is 0.5-10 μm diameter. Multilamellar vesicles are the most widely used niosomes (Bangham *et al*., in 1974). It is simple to make and are mechanically stable upon storage for long periods. These vesicles are highly suited as drug carrier for lipophilic compounds.
3.2) 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 a very economical use of membrane lipids.

These provide a number of advantages as compared to multilamellar vesicles, including high encapsulation of water-soluble drugs, economy of lipid and reproducible drug release rates.

The term 'large unilamellar' usually means any unilamellar structure larger than 100 μcm. Because of the large size of the vesicles, a high percentage drug capture can be achieved. A number of techniques are used for the preparation of large unilamellar vesicles including freeze-thaw cycling (Shew and Deamer,1985), Reverse phase evaporation method, ether injection method and calcium induced fusion method.
3.3) Small unilamellar vesicles (SUV)
These small unilamellar vesicles are mostly prepared from multilamellar vesicles by sonication method, French press extrusion method or, homogenization method. The approximate sizes of small unilamellar vesicles are 0.025-0.05 μcm diameter. They are thermodynamically unstable and are susceptible to aggregation and fusion. Their entrapped volume is small and percentage entrapment of aqueous solute is correspondingly low.

4) Specific Methods Of Preparation For Niosomes
The methodology for niosome preparation has been evolved rapidly during the last few years as a response to prepare well defined niosomes for specific applications.

4.1) Multi lamellar vesicles (MLV)
Bangosomes popularly known as multilamellar vesicles are prepared as per the method described by Bangham *et al*., 1974. In this method the lipids are dissolved in an organic solvent in a round bottom flask. A thin lipid layer is formed on the inside wall of the flask after removal of the organic solvent by rotatory evaporation at reduced pressure.

Multilamellar vesicles are formed spontaneously when an excess volume of aqueous buffer is added to the dry lipid. After shaking (by hand or vortex mixer), it results in formation of dispersion of multilamellar vesicles. Duration and intensity of shaking, the presence of charge inducing agents in the bilayer, ionic strength of the aqueous medium and lipid concentration are the important parameters influencing the size and the encapsulating efficiency of multilamellar vesicles. The lipids formed are quite heterogeneous both in size and in the number of lamella.

4.2) Small unilamellar vesicles (SUV)
4.2.1) Sonication: In this method, the preparation of small lamellar vesicles has been reviewed by Bangham (Bangham *et al*., 1974). The usual multilamellar vesicles and large unilamellar vesicles are sonicated either with a bath type sonicator or a probe sonicator, under an inert atmosphere (usually nitrogen or argon) to get the small unilamellar vesicles. During sonication, the multilamellar vesicles are broken down and small unilamellar vesicles with high radius of curvatures are formed.
4.2.2) French press method: Dispersions of MLV's can be converted to small unilamellar vesicles by passage through a small orifice under high pressure (Berenholz *et al*., 1977). A French pressure cell was used by Hamilton and Guo in 1984. Multilamellar vesicles dispersion is placed in the French press and extruded at about 20000 psi at 4°C(Hamilton and Guo, 1984): On passing through the cell, a heterogeneous population of vesicles are formed ranging from several micrometers in diameter to small unilamellar vesicles size. Multiple extrusions results in a progressive decrease in the mean particle diameter (30-80nm) depending upon the pressure used. These niosomes are more stable than sonicated ones and can be used advantageously as drug delivery carriers.
4.2.3) Ethanol injection method: An alternative method for producing small niosomes that avoids both sonication and high pressure is the ethanol injection method, first described by Batzri and Korn in 1973. In this method, the lipid is dissolved in ethanol and is rapidly injected into an excess of buffer solution or other aqueous medium though a needle. The force of the injection is usually sufficient to achieve complete mixing, so that the ethanol is diluted almost instantaneously in water and the phospholipids molecules are dispersed evenly throughout the medium.

This procedure can yield a high proportion of small unilamellar vesicles. This method has the advantage of extreme simplicity and a very low risk of bringing about degradative changes in sensitive lipids. Its major short comings are the limitation of solubility of lipids in ethanol and the volume of ethanol that is introduced into the medium (7.5% V/V maximum). The percentage of encapsulation is low if the materials (to be entrapped) are dissolved in the aqueous phase. Another drawback is the difficulty of removing ethanol from phospholipid membrane.

4.2.4) Ether injection method: This method is very similar to the ethanol injection method and was introduced by Deamer and Bangham in 1976. This method provides a means of making small lamellar vesicles by slowly introducing a solution of lipids dissolved in diethyl ether into a warm aqueous medium. The lipid mixture is injected into an aqueous solution of the material to be encapsulated (using a syringe-type infusion pump) at 55-65°C or under reduced pressure. The subsequent removal of residual ether under vacuum leads to the formation of single layer vesicles.

Ether injection is a method which treats sensitive lipids very gently and has very little risk of causing oxidative degradation. Since the solvent is removed at the same rate as that of its introduction rate. There is no limit to the final concentration of lipid which is achieved. The process can be run continuously for a long period of time, giving rise to a high percentage of the aqueous medium encapsulated within the vesicles. The disadvantages of this technique include the long time taken to produce a batch of niosomes, a careful control for the introduction of lipid solution and requirement of a mechanically operated infusion pump.

4.2.5) Homogenization: The homogenization of multilamellar vesicles or other lipid dispersions by commercially available high sheer homogenizer like micro fluidizer produces unilamellar vesicles. The small unilamellar vesicles formed are longer than the minimal size formed by sonication alongwith significant amounts of large particles. The size of the vesicles produced by micro fluidizer depends on the pressure used the number of passes of the preparation through this device and the niosomal lipid composition.

4.2.6) Dried reconstituted vesicles: In this method (Kirby and Gregoriadis, 1984, Tohsawa *et al*., 1984) the solid lipid is dispersed into a finely divided form before contact with the aqueous fluid, which forms the medium for the final suspension. Freeze drying is used instead of drying the lipids from the organic solution and subsequently the suspension of empty small unilamellar vesicles are frozen and lyophilized. The small unilamellar vesicles dried lipid is already very highly organized into membrane structures which on addition of water can be rehydrated, fused and resealed to form vesicles with high capture efficiency.

4.3) Large unilamellar vesicles (LUV)

Large unilamellar vesicles provide a number of important advantages as compared to the multilamellar vesicles including high encapsulation of water soluble drugs with economy of lipid and reproducible drug release rates. However, large unilamellar vesicles are perhaps the most difficult type of niosomes to produce.

4.3.1) Reverse phase evaporation method: Large Unilamellar vesicles can be prepared by forming water in oil emulsion of phospholipids and buffer in the excess organic phase followed by removal of the organic phase under reduced pressure. The two phases are usually emulsified by sonication. Removal of the organic solvent under vacuum causes phospholipid coated water droplets to cool and eventually form a viscous gel. The next step is to bring about the collapse of certain proportion of water droplets.

In these circumstances, the lipid monolayer which encloses the collapsed vesicle contributes to adjacent intact vesicles to form the outer leaflet of the bilayer of a large unilamellar niosomes. The aqueous content of the collapsed droplet provides the medium required for the suspension of these newly formed niosomes. After conversion of the gel to a homogeneous free flowing fluid, the suspension is dialyzed in order to remove the last traces of solvent. This method has gained widespread use for applications where high encapsulation of water soluble drug is required (Szoka and Papahadjopoulos, 1978). Entrapment efficiency up to 65% can be obtained with this method and can be used to encapsulate both small and large molecules. The biologically active macromolecules such as RNA and various enzymes have been encapsulated without loss of activity. The disadvantage of this method is the exposure of the material (to be encapsulated) to organic solvents and mechanical agitation which lead to the denaturation of some proteins or breakage of DNA strands.

*4.3.2) Calcium induced method***:** This method is used to produce unilamellar vesicles and it is of high interest for the present investigation as it has the advantage of aggregation of small vesicles in the presence of calcium followed by subsequently fusion.

In this method (Papahadjopoulos *et al*., 1975) the drug encapsulation depends on the lipid concentration and approximately 30% of encapsulation of the drug is expected. The vesicles are obtained in the size range of 0.2-1 µcm diameter.

The flocculent precipitate is formed as a result of aggregation of the negatively charged vesicles by calcium cations. After incubation, the membranes are fused to give extended sheets of phospholipid lamella which are said to roll up into long cochleate cylinders with a swill-roll cross section, presumably again with calcium ions as a driving force, in different parts of the same membrane sheet, together being pulled upon itself.

On addition of EDTA these lamella get unravelled and released subsequently forming large unilamellar vesicles. This technique has the advantage that it does not expose lipids or entrapped materials to the deleterious chemicals or physical condition.

4.3.3) Dehydration/rehydration of small unilamellar vesicles: In this method (Shew and Deamer,1985) sonicated vesicles are mixed in an aqueous solutions with the solute desired to be encapsulated and the mixture is dried under a stream of nitrogen. As the sample is dehydrated, the small vesicles fuse to form a multilamellar film that effectively sandwich's the solute molecules between successive layers. Upon rehydration, large vesicles are produced encapsulating a significant proportion of the solute. The optimal mass ratio of lipid to solute is approximately 1:2 to 1:3. This method has the potential application to large scale production, since it depends only on controlled drying and rehydration processes and does not require extensive use of organic solvents, detergents or dialysis system.

4.3.4) Detergent removal method: Removal of detergent from the mixed micelles formed by solubilization of dried lipid mixtures or preformed niosomes with a detergent containing aqueous phase results in the formation of unilamellar vesicles.

This is a gentle method where no strong mechanical forces and no high temperature are applied. The procedure should include a step to minimize the residual detergent level after niosomes formation. The techniques reported for the removal of detergents include dialysis (Kagawa and Racker, 1971), column chromatography (Enoch and Strittmatter, 1979), and biobeads method (Gerristen *et al*., 1978).

5) In Vivo Behaviour Of Niosomes

In vivo niosomes have been found equiactive to liposomes in improving the therapeutic performance of the drug (Hunter *et al*., 1988) and their distribution in body follows the pattern of their colloidal drug delivery systems. Although, tissues of extravasation: liver, lung, spleen and bone marrow are responsible for disposition of a major part of niosomes, yet their level in liver is always higher due to the natural vectoring process (Hunter *et al*., 1988, Azmin *et al*., 1985). Variation in size also influences the pattern of niosomal disposal from the blood. The large size niosomes may reside in lung due to alveolar and effect of alveolar phagocytic cells, whereas, the small sized vesicles, can pass through fenestrations in liver sinusoidal epithelium and thus, have better access to spleen (Carter *et al*., 1989, Rogerson *et al*., 1988)

It appears that, like liposomes, niosomes are also taken up intact by the liver and substantial of the niosomes results in the release of the free drug which eventually re-enters the circulation and maintains the plasma drug level (Azmin *et al*., 1985). The effect of two doses of niosomal sodium stibogluconate given on successive days was additive, indicating that liver might act as a depot of drugs.

Parthasarathi *et al*., 1994 found that niosomes are stable in plasma. However, non-ionic surfactants in higher concentration delipidize the low density lipoproteins (Tucker and Florence, 1983).

6) Conclusion

The success of liposomal system has stimulated the search for other vesicle forming amphiphiles. Non-ionic surfactant vesicles (niosomes) are among the first alternative materials studied for the drug delivery. Niosomes, the multilamellar vesicles made up of non-ionic surfactant with or without cholesterol surrounding aqueous compartments are one of those carriers.

Niosomes are efficient carriers for controlled drug delivery, to entrap hydrophilic drugs in the larger interior aqueous layer , whereas, lipophilic drugs in the outer lipid bilayer. Since, the niosomes, are biodegradable and non toxic and hence, a good carrier for targeting of therapeutic agents at the site of interest with reduced systemic toxicity.

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The process of preparation of niosomes has been shown in the flow diagram.

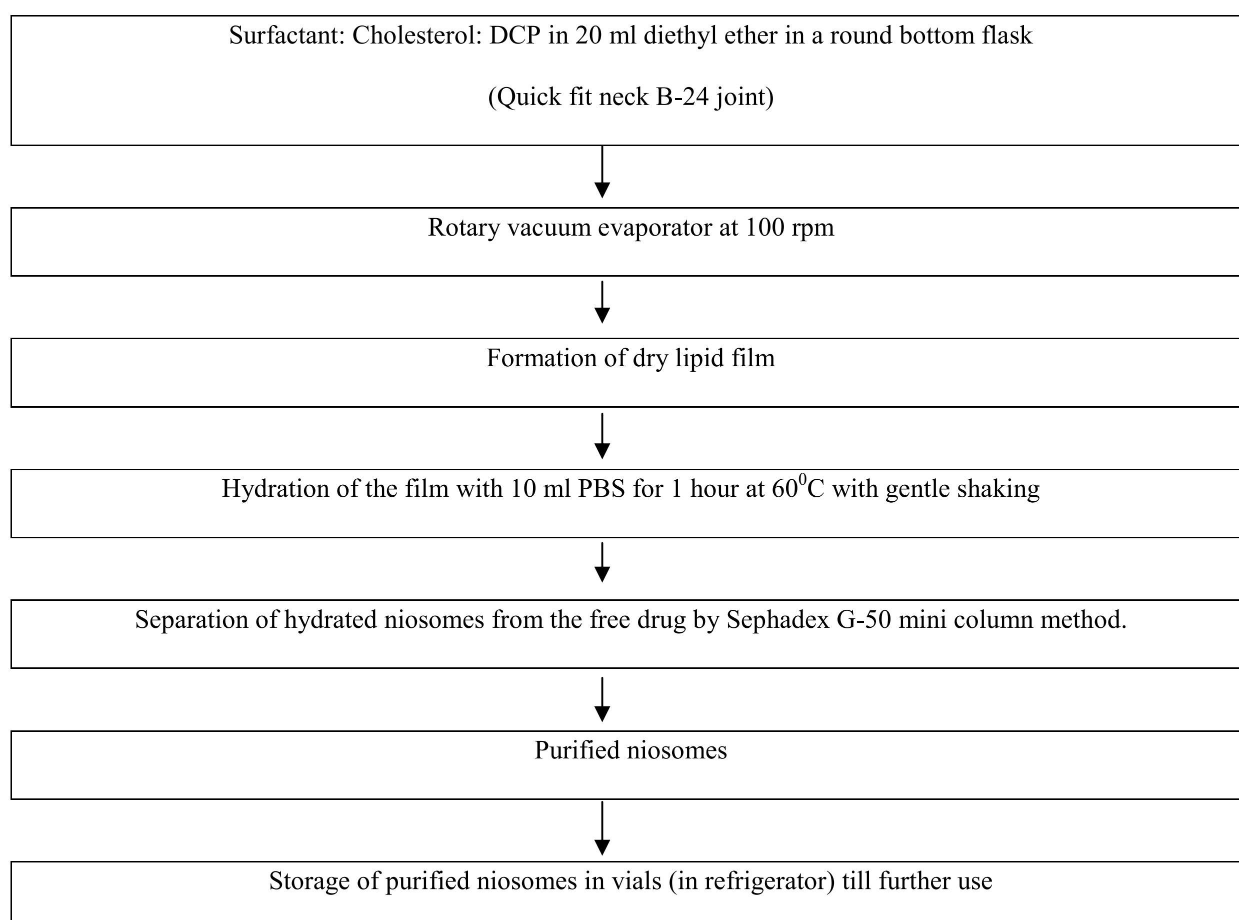

Fig. 1 : Flow Diagram Showing Preparation Of Niosomes

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