RESEARCH ARTICLE

Niosomes: Potential Nanocarriers for Drug Delivery

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ABSTRACT

Niosomes are novel vesicular drug delivery systems, where the solution is surrounded by non-ionic surfactant vesicles. The niosomes offer different benefits over the traditional drug delivery system. Niosomes are structurally similar to liposomes, as they also consist of a bilayer. In the case of niosomes, the bilayer consists of non-ionic surface-active agents instead of phospholipids, as seen in liposomes. Niosomes are much more stable during the process of formulation and storage, as compared to liposomes. Niosomes may resolve the issues of insolubility, volatility, poor bioavailability, and rapid drug degradation. It has been discovered in recent years that, these vesicles can enhance drug bioavailability and can act as a new strategy to deliver many conventional therapeutic agents, such as, protein drugs, and gene materials. It is also easy to prepare and scale up this novel delivery system with low production costs. The delivery of drugs via niosomal formulations may be relevant to several pharmacological agents for their activity against different diseases. The present review provides an overview about the advantages and disadvantages, fabrication techniques, types, characterization technique, and different applications of niosomes.

Keywords: Application of niosomes, Drug delivery, Fabrication techniques, Niosomes.

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INTRODUCTION

The current research and development approach relies on developing drug delivery systems that make clinically proven drugs perform their best in treatment instead of searching for new drugs. The goal of any drug delivery system should always be to achieve the highest therapeutic action with minimal side effects. Non-ionic surfactants can form vesicular delivery, like phospholipids, and when dispersed in water, called niosomes.[1]

Non-ionic surfactant based vesicles that are uni/multilamellar in structures enclosing lipophilic components and an aqueous solution of solutes are called niosomes. These vesicles are produced by the self-assembly of hydrated surfactant monomers. Compared to liposomes, niosomes overcomes the stability associated problems, which includes oxidation, high economy, a purity that influences on size and shape. Both hydrophilic and lipophilic drugs can be entrapped in niosomes (Figure 1). The bilayers of niosomes have sandwiched lipophilic areas in between the hydrophilic inner and outer surfaces of the bilayers. Hence, drugs can be delivered extensively along with other required materials using niosomes.

In recent years, these were extensively studied for their modified potential of the biodistribution and activity profile of the drug. It acts as a carrier in the release of medicaments, hormones, antigens, and bioactive molecules. Moreover, niosome also acts as an alternate version to unravel the problem of insolubility, unsteadiness, and rapid deprivation of drugs.[2,3]

COMPOSITION OF NIOSOMES

A normal niosomal vesicle consists of an amphiphilic-forming vesicle, i.e., a non-ionic surfactant such as Span-60, which is normally balanced by the introduction of cholesterol and a small amount of anionic surfactant such as dicetyl phosphate, which also tends to stabilize the vesicle.[4] The two key

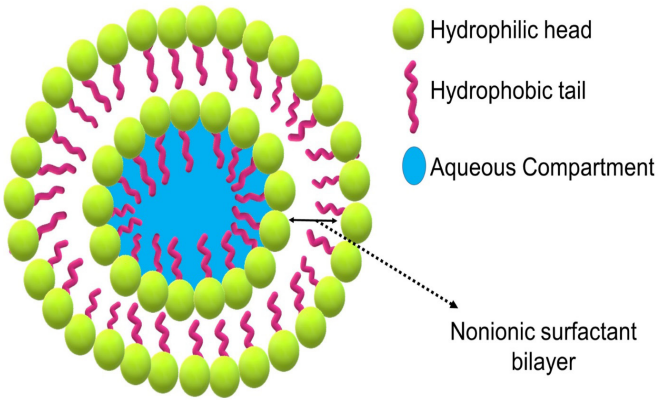

Figure 1:. A typical structure of niosome

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components used to produce niosomes are cholesterol and non-ionic surfactants. Cholesterol is a steroid intermediate used in the preparation of niosomes to provide rigidity and proper form. Non-ionic surfactants such as Brijs (Brij 30, 35, 52, 58, 72, and 76), Spans (Span 20, 40, 60, 80, and 85), and Tweens (Tween 20, 40, 60, and 80) are commonly used for the preparation of the niosomes.[4,5]

MERITS AND DEMERITS OF NIOSOMES

Niosomes show numerous meritorious features. Niosomes are chemically stable, osmotically active, and have long storage time compared to liposomes. These are non-immunogenic and biodegradable in nature. Surface development and alteration are very simple because of the hydrophilic head functional groups. Due to their non-ionic nature, niosomes exhibit low toxicity and high compatibility with biological systems. It may entrap lipophilic drugs in vesicular bilayer membranes and hydrophilic drugs in aqueous compartments. Exposure to raw material is easy. They show high patient compliance because of the water-based suspension of niosomes.[6-10] However, fusion, aggregation, physical instability, leaking of entrapped drug, and hydrolysis of encapsulated drugs that reduce dispersion shelf-life and time-consuming process of multilamellar vesicle fabrication are some of the limitations associated with niosomes.[11,12]

DISTINCTION OF NIOSOMES FROM LIPOSOMES

The niosomes are distinct drug delivery systems as compared to liposomes (Table 1).

CATEGORIES OF NIOSOMES

Categories of niosomes are distinguished by three factors: first, based on niosome size structure, second, fabrication process, and third, based on vesicle size (Figure 2).[13]

Multilamellar Vesicles (MLVs)

The MLVs are produced collectively from some bilayers adjacent to the section of the aqueous lipid. Such vesicles are estimated to have a diameter of between 100 and 1,000 nm.[14]

Large Unilamellar Vesicles (LUVs)

The LUV has a high proportion of aqueous parts to the lipid segment, so that bioactive resources can be captured by membrane lipids.[15] Such vesicles are around 100-250 nm in diameter.

Small Unilamellar Vesicles (SUVs)

The SUVs are approximately 10 to 100 nm in size and can be prepared from LUVs via several processes, such as, sonication, high-pressure homogenization, and extrusion.[15]

Discomes

Discomes have low concentrations of cholesterol and serve as potential carriers of drugs showing sustained release mechanism.

Apsasome

Apsasome contains ascorbyl palmitate, cholesterol, and highly charged lipid-like, dihexadecyl phosphate (DCP). To obtain the final product, it should be hydrated and sonicated by a water solvent. Apsasome may strengthen the transdermal drug delivery systems and reduce the disorders caused by reactive oxygen species.[16]

Proniosomes

Proniosomes are the aggregation of niosomes consisting of carriers and surfactants, which are water-soluble. The proniosomes are constructions of dehydrated niosomes that would be hydrated to be used earlier. Proniosomes can reduce problems with niosomes, such as aggregation, fusion, and drug leakage for a while.

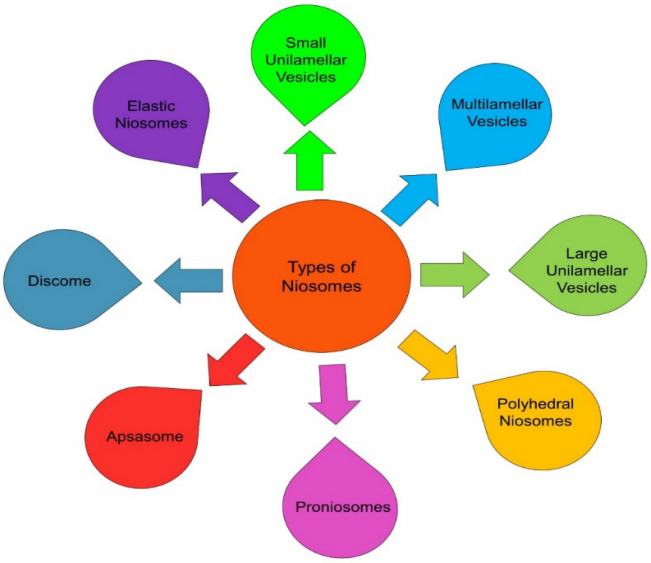

Figure 2: Different categories of niosomes

Table 1: Comparative features of niosomes and liposomes

Features	*Niosomes*	*Liposomes*
Composition	Vesicles composed of surfactants with or without cholesterol incorporation	Vesicles composed of concentric phospholipid bilayer
Toxicity	Less toxic	Comparatively more toxic
Stability	Non-ionic surfactants are stable	Used phospholipids are unstable
Storage conditions	No special storage conditions are needed	Special storage conditions are required
Size	The size varies between 10 to 100 nm	The size varies between 10 to 3,000 nm
Fabrication techniques	There is no need for special methods for such formulations	A special method for phospholipid handling and purification is needed

Polyhedral Niosomes

This form of niosomes is formed by hexadecyl diglycerol ether replacing cholesterol with any of the non-ionic surfactants and polyoxyethylene 24 cholesteryl ether without cholesterol. Such vesicles have unusual structures that may contain water-soluble particles.

Elastic Niosomes

This kind of niosome may be smooth and lack destructive structure, so they have the ability to allow smaller pores from side to side.

FABRICATION TECHNIQUES

There are several methods for niosome preparation. These consist of the lipid injection process, bubble method, thin-film hydration (handshaking) method, microfluidization method, trans-membrane pH gradient drug uptake process, emulsion method, micelle solution, enzyme method, ether injection technique, the formation of niosomes from proniosomes, supercritical reverse-phase evaporation method, and reverse-phase evaporation method.[17,18-31] Benefits and drawbacks of various fabrication techniques are represented in Table 2. Some new techniques have been grown over the past decade, for example, Manosroi and colleagues using supercritical carbon dioxide fluid defined the supercritical reverse-phase evaporation method.[18]

CHARACTERIZATION OF NIOSOMES

Niosomes are typically evaluated during the formulation process and storage according to their size, drug loading efficiency, surface morphology, and stability. Such characteristics are very important for niosomes as they affect not only the encapsulation rate and the stability of the niosomes, but also their *in vivo* efficiency.[32]

Microscopy

Atomic force microscopy (AFM), scanning electron microscopy (SEM), and transmission electron microscopy (TEM) techniques are used to assess the morphology of the niosomes in order to better identify the sharp niosomes.[28,33] Niosomes are rarely self-assembled and require energy as a driving force, such as, heating or mechanical stirring.[34] It is possible to use confocal laser scanning microscopy (CLSM) to identify the difference between niosomes and discomes. The sizes of the niosomes were stated to vary widely, from about 20 nm to 50 μm.[35]

Sizes and Zeta Potential

A laser scattering particle size analyzer is used to determine the polydispersity index (PDI) and size distribution. Dynamic light scattering, zeta-sizer, and microelectrophoresis are used to determine zeta potential, which is required to check the stability of niosomes in solution.

Encapsulation Efficiency

The encapsulation efficacy is the ability of vesicles to load therapeutic agents. It focuses mostly on the type of non-ionic surfactant, the method of synthesis, and other agents used in the process of formulation, such as cholesterol. It is estimated that the encapsulation rate could exceed 75% to about 90%, but it is typically within the 10 to 40% range.[36]

Stability

Niosomal stability plays an important role in the development of its formulation. The method of preparation, loaded drugs, and varieties of membrane-forming materials influence it. The variations in particle size, zeta potential, morphology, and loaded product leak risk can be calculated to determine the stability for their packaging. In order to determine the safety of niosomes during circulation, these drug-charged vesicles can be incubated at 37°C and in serum (or even under harsh conditions) to replicate *in vivo* conditions.[37]

Bilayer Formation

Bilayer vesicle formation due to the assembly of non-ionic surfactants under light polarization microscopy can be characterized by x-cross formation.[38]

Table 2: Benefits and drawbacks of various fabrication techniques of niosomes

Fabrication techniques	*Benefits*	*Drawbacks*	*References*
Supercritical reverse-phase evaporation method	No use of organic solvents	Need of special equipment	18
Trans-membrane pH gradient process	High drug entrapment efficiency	Use of organic solvents	25
Lipid injection method	No use of organic solvents	Not ideal for heat-labile drugs	26
Ether injection method	A simple laboratory technique	Not ideal for heat-labile drugs	22
Preparation using micelle solution and enzymes	No use of organic solvents	Enzymatic degradation of the active ingredient	27
Reverse phase evaporation method	High drug entrapment efficiency	Use of organic solvents	23, 24
Emulsion method	A simple laboratory technique	Use of organic solvents	25
Formation of niosomes from proniosomes	No use of organic solvents, better physical stability	Total drug retention during hydration is not possible	30
Microfluidization	No use of organic solvents	Not ideal for heat-labile drugs	28, 29
Bubble method	No use of organic solvents	Not ideal for heat-labile drugs	30
Thin-film hydration (handshaking) method	A simple laboratory technique	Use of organic solvents	19, 20, 21

Number of Lamellae

Small-angle X-ray scattering, NMR spectroscopy, and electron microscopy are used to characterize the number of lamella in vesicles.[39]

In vitro Drug Release

Drug release may be controlled by dialyzing niosomal suspension against the buffer at a certain temperature and by assessing the product content of dialysate.[40]

BIOMEDICAL APPLICATIONS OF NIOSOMES

Niosomes as Drug Carriers

Niosomes were also used as iobitridol carriers, a screening agent for X-ray imaging. Topical niosomes can serve as a solubility matrix or local reservoir for the sustained release of dermally active ingredients, as penetration modulators, and as a rate-limiting membrane barrier in the regulation of the systemic drug absorption.

Niosomes as Carriers for Hemoglobin

Niosomes may be used as a hemoglobin carrier. Niosomal suspension reveals a superimposable visible spectrum that is known to be or on the free hemoglobin range. Vesicles are oxygen-permeable, and the curve of hemoglobin dissociation can be changed similarly to hemoglobin, which is not encapsulated. Antineoplastic therapy severe side effects are induced by most antineoplastic treatments. Niosomes improve the metabolism; increase the release and half-life of the drug, thus, reducing the side effects of the drugs. Niosomes have lower tumor proliferation frequency and higher plasma volumes, but slower elimination.[4,41]

Immune Response

Low toxicity and greater stability owing to their immunological selectivity; niosomes are used to research the existence of antigens induced immune response. Non-ionic surfactant vesicles showed clearly their ability to function as antimicrobial agents with a variety of different antigens and peptides during parenteral administration.[42]

Ophthalmic Drug Delivery

Gentamicin sulphate, a water-soluble antibiotic, shows an extensive alteration in the release rate during its experimental studies. Moreover, in contrast to the regular drug sample solution, niosomal formulation of drug exhibit sluggish release.[2] Timolol maleate (0.25%) niosomes, formulated via coating with chitosan shows more effect on intraocular tension with fewer side effects as compared to the marketed products.[43]

Neoplasia

The side effects and poor therapeutic efficacy are growing disadvantages of cancer chemotherapy. A dose-dependent irreversible cardiotoxic effect has been shown by doxorubicin, a broad-spectrum anthracycline used for antitumor function. Niosomal delivery of this drug to mice containing the S-180 tumor also showed a longer lifespan and reduced sarcoma proliferation. This could arise from the high effectiveness of niosomes in drug encapsulation, which in addition to drug metabolism, induces a prolonged circulation.[44]

Leishmaniasis

Leishmaniasis is one of the diseases that attack the liver and spleen cells by the protozoan parasites. It is treated using antimonials. Such drugs are not capable of developing plasma levels as free drugs. Niosomes may be used in reticuloendothelial system disease treatment. Niosomal formulation of anit-monials by sodium stibogluconate can permeate through the cells and target the specific cells.[44,45]

Transdermal Drug Delivery

The benefit of drug delivery through skin is that it does not require the first-pass metabolism. The limitation of this delivery is that drugs are absorbed through the skin slowly.[46]

Gene Delivery

In recent years, gene therapy has been a powerful tool for the treatment of diseases, but delivery remains a problem for clinical applications. Non-viral gene carriers, based on lipids and polymers, are being used as two methods for gene material delivery.[47] Niosomes were commonly used as carriers of oligonucleotides in reported studies for the treatment of many types of diseases. These can be used for the transfer of gene materials due to certain benefits, such as, comparatively small sizes, strong physical, and chemical characteristics, etc.[48]

In Cosmetics

The first study on non-ionic surfactant vesicles derived from cosmetic products produced by L'Oreal. In the 1970s and 1980s, niosomes are formulated and copyrighted by L'Oreal. The first niosome product was launched by Lancôme in 1987. Niosomes can be used to increase the stability of trapped products, improve the bio-availability of poorly absorbed ingredients, and enhance skin penetration in cosmetic and skin care applications.[49,50]

CONCLUSION

Currently, focus on vesicular drug delivery systems such as liposomes and niosomes have been attracted. Niosome is clearly a preferred drug delivery system over liposomes. Niosomes offer an effective, prolonged, convenient, and targeted drug delivery system with both hydrophilic and lipophilic drug loading abilities. Niosome ability can be improved through the use of new methods of fabrication, loading, and alteration. Such areas, therefore, require further investigation and study, in order to produce marketed niosomal preparations.

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