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An Overview of Niosomes: A Novel Drug Carrier System and Applications

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Abstract

Niosomes are vesicles that are prepared with a mixture of cholesterol and non-ionic surfactants. They can be used as drug delivery systems, so they should designed according to requirements of drug carrier systems. They should carry the amphiphilic and lipophilic drugs with a predetermined rate to the targeted area. They can carry Niosomes have the potential to increase bioavailability and reduce the side effects of drugs, and they are used more than one hundred drugs in the literature. These examples were applied by several routes such as intravenous, oral, transdermal, inhalated, ocular or nasal. This review includes an overview of the niosome compositions, preparation methods, characterization, and their drug delivery applications.

Introduction

Drug delivery is the technique for delivering a pharmaceutical agent to obtain a more effective therapeutic response. Controlled drug delivery is becoming more popular in disease treatment strategies with the aid of their sustained release profiles. There are several drug delivery systems that have been designed, such as liposomes, proliposomes, microspheres, gels, prodrugs, cyclodextrins, micelles, and nanomaterial-based systems[1].

Lipid-based drug delivery systems such as liposomes, proliposomes, niosomes, and proniosomes offer many advantages as biodegradablity non-toxical properties, and can encapsulate a wide range of drugs[2]. Also, they have high stability, high carrier capacity, the feasibility of variable routes of administration, including oral, topical, parenteral, and pulmonary routes[3].

Niosome vesicles are obtained by hydration of microscopic synthetic non-ionic surfactants.
They can include cholesterol or not, and they are structurally similar to liposomes. They are active carrier systems for amphiphilic and lipophilic drugs. While layers in liposomes consist of phospholipids, layers in niosomes consist of non-ionic surfactants. Niosomes are formed by the non-ionic surfactants forming in an aqueous environment by spontaneously forming spherical, single-layer, double-layer, multi-layer systems, polyhedral structures according to the preparation

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method used[4, 5].

The location of the surfactant in the niosome is such that the hydrophilic ends face outwards while the hydrophobic ends face each other to form the double layer of the surfactant [6].

Niosomes are recommended as better carrier systems than liposomes because surfactants are cheaper and have higher chemical stability than phospholipids, which can easily be hydrolyzed due to their ester bonds. The application methods of niosomal formulations vary in intramuscular, intravenous, peroral, and transdermal forms [7]. Niosomes have several advantages as a drug delivery systems. However, they have some disadvantages either. In Table 1, they were listed[8].

Table 1. Advantages and disadvantages of niosomes [8]

Advantages	Disadvantages
The formation of vesicles is varied and can be controlled	Aggregation
Osmotically active and stable	Leakage of encapsulated drug
No special conditions are required for the use and storage of surfactants	Hydrolysis of the encapsulated drug (reducing shelf life)
Surfactants are biodegradable and biocompatible	High energy requirement for size reduction
They can be applied orally, dermally or parenterally	Physicochemical stability problems in industrial level production
Increases oral bioavailability of low absorbed drugs and penetration of drugs through the skin	
It is a cheaper method	
They can be used to transport a wide range of drugs	

Niosomes include cholesterol, surfactants, and other substances. Cholesterol is responsible for providing stability to the vesicles. Surfactants vary as ether-linked surfactants, dialkyl chain surfactants, ester-linked surfactants, sorbitan esters, and polysorbats [7]. Other substances can be used for increasing the surface charge density. They prevent aggregation and coalescence of vesicles. Disethyl phosphate (DCP) and stearyl amine (SA) are examples of such membrane additions that negatively or positively stimulate charge [9].

Niosome Preparation Methods

The preparation method affects the size, size distribution, number of layers, loading efficiency, and membrane permeability of vesicles. The preparation methods used to create the niosomes are as follows;

- Ether injection
- Ethanol injection
- Thin film
- Sonication
- Microfluidization
- Multiple Membrane Spraying
- Reverse Phase Evaporation
- Transmembrane pH Gradient
- Bubble
- Freeze-drying
- Freeze–Thaw
- Niosome from proniosome

Other factors affecting the niosom formulation include surfactant nature, surfactant structure, membrane composition, properties of the drug to be encapsulated, temperature, resistance to osmotic stress, cholesterol amount and load [10, 11].

Characterization of Niosomes

The characterization of the obtained niosome particles depends on certain parameters. These are vesicle diameter and morphology, vesicle load, bilayer formation, lamella number, membrane strength and homogeneity, loading efficiency, in vitro release, and stability studies.

Niosomes are spherical and range in size from 20 nm to 50 µm. Light microscopy, culture counter, photon correlation microscopy, atomic force microscopy, and frozen fraction electron microscopy can be used to determine vesicle size and size distribution. Scanning electron microscopy (SEM), atomic force microscopy (AFM), and cyto transmission microscopy are used to determine the shapes and surface characteristics of niosomes [12].

Vesicle surface charge plays a fundamental role in the stability and behavior of niosomes. Charged niosomes are more stable against aggregation and assembly than uncharged niosomes. The surface potentials of niosomes can be determined according to zeta potential measurement by micro electrophoresis or dynamic light scattering method. pH-sensitive fluorpores can be used as an alternative method [13].

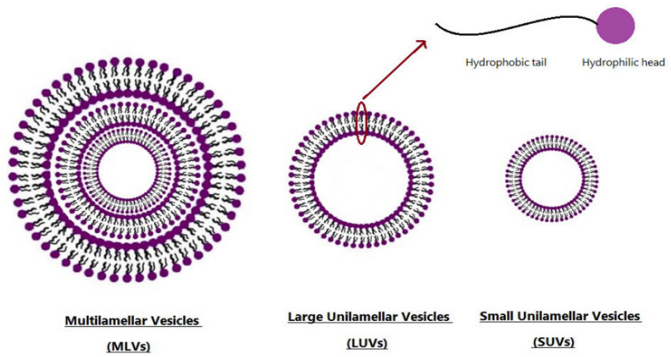
Double layer vesicle formation can be characterized by x-cross formation depending on non-ionic surfactants' distribution under light polarization microscopy [14].

The number of lamella within the vesicles can be characterized by NMR spectroscopy, electron microscopy, and small-angle X-ray scattering [15].

Membrane stability is affected by the biodistribution and biodegradation of niosomes. The bilayer strength of the vesicles can be determined by the movement of the fluorescent probe as a function of temperature. Membrane homogeneity can be determined by P-NMR, differential scanning calorimetry (DSC), fourier transform infrared spectroscopy (FTIR) and fluorescence resonance energy transfer (FRET) [16].

The drug loading and encapsulation efficiency of the niosomal solution can be determined after removal of the unloaded drug. Unloaded drug is separated by dialysis, centrifugation or gel filtration. The in-vitro drug release of niosomes can be characterized by the dialysis, reverse dialysis and Franz diffusion method [17, 18].

The stability of the niosomes is affected by the type and concentration of surfactant and cholesterol. Stability is expressed by constant particle size and amount of drug held constant. For example: sonicated spherical niosomes are stable at room temperature. Sonicated polyhedral niosomes are not stable at room temperature but stable at temperatures above phase transition temperature [19].



Applications of Niosomes in Drug Delivery

Niosomes can be used in several areas such as drug delivery systems, drug targeting, and treatment of diseases. Some examples of niosome drug delivery application in the literature were summarized in the tables below.

Table 2. Niosome applications in anti-leishmaniasis

DRUG	REFERENCES
Itraconazole	Khazaeli et al., 2014[20]
Tioxolone- Benzoxonium Chloride	Parizi et al., 2019[21]
Amphotericin B	Mostafavi et al., 2019[22]

Table 3. Niosome applications in psoriasis

DRUG	REFERENCES
Methotrexate	Lakshmi et al. -2007[23] Abdelbary et al., 2015[24]
Urea	Lakshmi et al. -2011[25]
Dithranol	Aggarwal et al., 2001[26]
Diacerein	Moghddam et al., 2016[27]
Capsaicin	Gupta et al., 2014[28]
Celastrol	Meng et al., 2019[29]

Table 4. Niosome applications in cancer treatment

DRUG	REFERENCES
Doxorubicin	Uchegbu et al. -1995[30] Tavano et al., 2013[31]
doxorubicin, quercetin and siRNA	Hemati et al., 2019[32]
Vincristine Sulfate	Parthasarthi et al. -1994 [33] Mehrabi et al., 2020[34]]
Bleomycin	Naresh et al. -1996[35]
Cytarabine Hydrochloride	Ruckmani et al., 2000[36]
Daunorubicin hydrochloride	Balasubramanian et al. -2002[37]
Withaferin A	Sheena et al. -1998[38] Shah et al., 2020[39]
Curcumin	Xu et al., 2016[40] Wong et al., 2020[41]
Cisplatin	Kanaani et al., 2017[42]
Carboplatin	Davarpanah et al., 2018[43]
Propolis	Ilhan-Ayisigi et al. 2020[44]
Balanocarpol	Obeid et al., 2020[45]

In Table 2, 3 and 4, some examples of niosome applications in anti-leishmaniasis treatment, psoriasis treatment and cancer treatment were listed as respectively. In Table 4, Biological active substances and drugs were used for encapsulating with niosome in order to enhance bioavailability.

Table 5. Niosomes in other drug delivery applications

DRUG	CATEGORY	REFERENCES
Flurbiprofen, Piroxicam	Anti-inflammatory	Reddy et al. -1993[46]
Diclofenac	Anti- inflammatory	Raja naresh et al. -1994[47]
Estradiol	Hormone	Hofland et al. -1994[48] Don et al.-1997[49]
Rifampicin	Antituberculosis	Jain et al.-1995[50] Jain et al., 2006[51] Jatav et al.-2011[52] Khan et al., 2020[53]
Ketoconazole	Anti-fungal	Satturwar et al. -2002[54] Arora and Ajay et al. 2010[55]
Tretoin II	Anti-acne	Manconi et al. -2003[56]
Acetazolamide	Diuretic	Guinedi et al -2005[57] Aggarwal et al. -2007[58]
Primaquine	Anti-malarial	Varghese et al.-2004[59]
Insulin	Hormone	Paradakhty et al. -2007[60]
Cromolyn sodium	Anti asthmatic	Elbary et al. -2008[61]
Fluconazole	Anti-fungal	Kumar sharma et al. -2009[62]
Gliclazide	Anti-diabetic	Tamizharsi et al. -2009[63]

Venlafaxine	Anti-depressant	Negi et al. -2011[64]
Acyclovir	Anti-viral	Kapoor et al. -2011[65]
Rofecoxib	Anti-inflammatory	Das et al. -2011[66]
Nystain	Anti-fungal	El-Ridy et al., 2011[67]
Metformin hydrochlordie	Anti-diabetic	Hasan et al., 2013[68]
Nevirapine	Anti-viral	Mehta and Jindal, 2015[69]
Celecoxib	Anti-inflammatory	Auda et al., 2016[70]
Doxycycline hyclate	Ocular	Gugleva et al., 2019[71]
Brimonidine tartrate	Ocular	Emad Eldeeb et al., 2019[72]

In Table 5, some examples of niosome applications in other drug's delivery such as antifungal, antidiabetic, antiviral, and so on were listed. As can be seen from the tables, niosomes can be used for delivering of a wide range of drugs in the treatment of several diseases. With the aid of controlled drug release, patients' quality of life also be enhanced. Because patients can forget to take their pills in the time such as Alzheimer, cancer, thyroidism and it can be very dangerous. So, drug delivery systems can extend the time of taking and, they can release the active substance controlled.

Niosomes provide a promising and novel carrier system in the delivery of proteins, a wide range of drugs, siRNAs, and other biological molecules. This system solves the poor bioavailability, physical and chemical instability and potentially serious side effects. They can be also be synthesized easily and economically, and there is no special requirement for storage, protection, or industrial manufacturing. Niosomes can be used in several fields such as antivirals, anticancer, antimalarial, antituberculosis, antileishmaniasis drugs, and they can be administered effectively via several routes. However, the technology is still developing, and there are some unknown parameters such as toxicity. This vesicle system is already in use in the commercial cosmetic industry, but it still requires further experiments. Nevertheless, the fact that niosomes are a great candidate as a drug delivery system remains stable, and their literature and commercial applications are increasing day by day.

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