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Review article on Niosomes and their future

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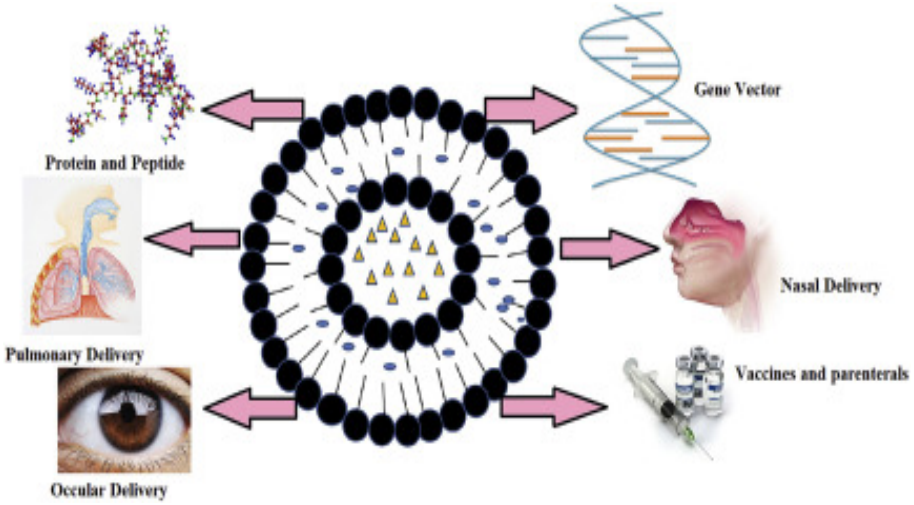
Abstract:

Over the past decade, a significant number of review and research articles have been published on niosomes. This demonstrates the keen interest of researchers in niosomes due to their advantageous characteristics compared to other vesicular carrier systems. Niosomes are formed through the self-assembly of non-ionic surfactant vesicles. Various factors, such as the type of non-ionic surfactant used, method of preparation, and temperature of hydration, influence the formation of niosomes. In this comprehensive review article, we aim to encompass all essential aspects of niosomes, including different preparation methods, types of niosomes, factors influencing their formation, niosome characterization, applications, routes of administration, and recent advancements in niosomal research. Additionally, we provide a literature review of research conducted in the past decade.

INTRODUCTION

Niosomes are vesicular drug delivery systems that can be utilized for sustained, controlled, and targeted drug delivery. While liposomes were the initial vesicular drug delivery systems, they have various disadvantages such as toxicity, high cost, and stability issues at different pH levels. Due to these drawbacks, research interest has shifted towards niosomes. Niosomes can be unilamellar, oligolamellar, or multilamellar. They are composed of non-ionic surfactants, which gives them the name "niosomes" and makes them non-toxic. Additionally, niosomes may contain cholesterol or its derivatives and charged molecules.

Cholesterol provides rigidity to the structure, while the charged molecule keeps the preparation stable. Niosomes form when non-ionic surface-active agents assemble themselves. Due to their structure, they can be used for loading and delivering both hydrophilic and hydrophobic drugs.



Structure of Niosomes

Niosomes are the bi-layered structure of non-ionic surface-active agents. These thermodynamically stable bilayered structures are formed only when surfactants and cholesterol are mixed in a proper proportion, and the temperature is above the gel liquid transition temperature. This bi-layered structure contains a hollow space in the center. Because of their special geometry niosomes can encapsulate hydrophilic as well as a hydrophobic drug in their structure.

Components of Niosomes

Niosomes are prepared using lipid compounds, such as cholesterol or L-α-soya phosphatidylcholine, and nonionic surfactants. Lipid compounds give niosomes their rigidity, shape, and adaptability. Nonionic surfactants are crucial in niosome development. Spans (spans 60, 40, 20, 85, and 80), tweens (tweens 20, 40, 60, and 80), and Brij (30, 35, 52, 58, 72, and 76) are commonly used nonionic surfactants for niosome formulation. Niosomes are nonionic surfactant-based vesicles that effectively carry drugs. They have a bilayer structure consisting of nonionic surfactants and lipid compounds (cholesterol or L-α-soya phosphatidylcholine) in an aqueou sphase.

Nonionic Surfactant

Niosomes are multilamellar vesicles created using synthetic nonionic surfactants. The entrapment efficiency of the drug depends on the hydrophilic head group and hydrophobic tail of the surfactants. The size of the niosomes increases with higher HLB values of the surfactant and longer alkyl chain lengths. Therefore, an HLB value of 14-17 is not suitable for niosome formulation. In addition to the amount of surfactant, the surfactant's structure significantly affects the stability and prevention of niosome aggregation through steric or electrostatic force repulsion. The critical packing parameter (CPP) explains how the surfactant's structure influences niosome formation. It is calculated using the following equation:

CPP = VIc×Ao

where CPP is the critical packing parameter, V is the hydrophobic group volume, Ic is the critical hydrophobic group length, and Ao is the area of the hydrophilic head group. The predicted micellar structure is determined based on the value of the critical packing parameter:

- If CPP < 1/2, spherical micelles are formed.
- If 1/2 < CPP < 1, bilayer micelles are formed.
- If CPP > 1, inverted micelles are formed.

Table 1: The materials used in niosome preparation.

Nonionic surfactants	Examples	References
Alkyl ethers		
(i) Alkyl glycerol ethers	Hexadecyl diglycerol ether (C16G2)	[9]
(ii) Polyoxyethylene glycol alkyl ethers (Brij)	Brij 30, Brij 52, Brij 72, Brij 76, Brij 78	[10–12]
Crown ethers	Bola	[13, 14]
Alkyl esters		
(i) Sorbitan fatty acid esters (Spans)	Span 20, Span 40, Span 60, Span 80, Span 65, Span 85	[15–18]
(ii) Polyoxyethylene sorbitan fatty acid esters (Tweens)	Tween 20, Tween 40, Tween 60, Tween 80, Tween 65, Tween 85	[7, 19, 20]
Alkyl amides		
(i) Glycosides	C-Glycoside derivative surfactant (BRM-BG)	[21]
(ii) Alkyl polyglucosides	Octyl-decyl polyglucoside (OrCG110), decyl polyglucoside (OrNS10)	[22]
Fatty alcohols or fatty acids		
(i) Fatty alcohols	Stearyl alcohol, cetyl alcohol, myristyl alcohol	[23]
(ii) Fatty acids	Stearic acid, palmitic acid, myristic acid	[23]
Block copolymer		
(i) Pluronic	Pluronic L64, Pluronic 105	[24, 25]
Lipidic components		
Cholesterol		[26]
l-α-Soya phosphatidyl choline		[27]
Charged molecule		
Negative charge	Diacetyl phosphate, phosphatidic acid, lipoamino acid, dihexadecyl phosphate	[28, 29]
Positive charge	Stearylamine, stearyl pyridinium chloride, cetyl pyridinium chloride	[29]

Comparison of Liposomes and Niosomes

Although liposomes and niosomes are practically the same, both can be employed as part of a focused and managed drug delivery system. The properties of both depend on the structure of the bilayer and the methods used in their preparation. Both liposomes and niosomes enhance bioavailability and prevent drug clearance from the body. Niosomes are composed of uncharged single-chain surfactant and cholesterol, while liposomes are composed of double-chain phospholipids. There are major differences in features that exist between liposomes and niosomes.

Niosomes behave in vivo similarly to liposomes, extending the circulation of the encapsulated drug and affecting its distribution in organs and metabolic stability. Similar to liposomes, the properties of niosomes are influenced by the composition of the bilayer and the production method. It has been reported that the inclusion of cholesterol in the bilayers reduces the volume of drug entrapment during formulation, thereby affecting the entrapment efficiency.

Niosomes are prepared from uncharged single-chain surfactant and cholesterol, while liposomes are prepared from double-chain phospholipids, which can be neutral or charged. The concentration of cholesterol in liposomes is much higher than that in niosomes, resulting in lower drug entrapment efficiency for liposomes compared to niosomes.

Moreover, liposomes are expensive and their ingredients, such as phospholipids, are chemically unstable due to their susceptibility to oxidative degradation.

Strengths and Limitations of Niosomes in Drug Delivery

Niosomes have several strengths compared to liposomes. One significant advantage is their chemical stability. Niosomes are more resistant to chemical degradation or oxidation and can be stored for longer periods of time. The surfactants used in niosome preparation are biodegradable, biocompatible, and nonimmunogenic .

Additionally, the composition, size, lamellarity, stability, and surface charge of niosomes can be controlled by factors such as the preparation method, surfactant type, cholesterol content, surface charge additives, and suspension concentration. However, niosomes also have some limitations. Physical stability can be a problem as niosomes are prone to aggregation, fusion, drug leakage, or hydrolysis of encapsulated drugs during storage. Furthermore, sterilizing niosomes requires significant effort, as heat sterilization and membrane filtration are not suitable methods. Therefore, further research is needed in these areas to develop commercially viable niosomal preparations.

Niosomes as Drug Carrier

Niosomes have shown great promise as carriers for delivering pharmacological and diagnostic agents. Many studies have discussed the preparation, characterization, and use of niosomes in drug delivery. Their nonionic nature makes them highly biocompatible and low in toxicity.

Anticancer Drug Delivery

Chemotherapy is currently the main treatment for cancer. However, the therapeutic effectiveness of many anticancer drugs is limited by their inability to penetrate tumor tissue and their harmful effects on healthy cells. To address these issues, researchers have explored the use of niosomes as a new drug delivery system. They encapsulated 5-Fluorouracil (5-FU), a commonly used drug for treating different types of skin cancers, in an innovative bola-niosomal system composed of α,ω-hexadecyl-bis-(1-aza-18-crown-6) (bola-surfactant), Span 80, and cholesterol. The researchers evaluated the percutaneous permeation of 5-FU-loaded bola-niosomes using human stratum corneum and epidermis membranes. The results showed that the bola-niosomes increased drug penetration by 8- and 4-fold compared to the free drug aqueous solution [13]. Cisplatin, another commonly used drug, is limited by its severe toxic effects. However, their findings suggest that niosomal encapsulation of cisplatin significantly reduces toxicity and retains antimetastatic activity when compared to free cisplatin.

Breast Cancer

Cosco et al. prepared and tested 5-FU-loaded polyethylene glycol-coated (PEG-coated) and uncoated bola-niosomes on breast cancer cell lines (MCF7 and T47D). Both formulations of bola-niosomes showed increased cytotoxic effects compared to the free drug. In vivo experiments using MCF-7 xenograft tumor SCID mice models demonstrated that the PEGylated niosomal 5-FU at a concentration ten times lower (8 mg/kg) had more effective antitumor activity than the free drug solution (80 mg/kg) after 30 days of treatment.

Codrug Delivery:

Nanoparticles have become a promising carrier for co-delivery of multiple drugs in combination therapy. Combination therapies enhance therapeutic efficacy and reduce dosage, while maintaining equal or greater levels of effectiveness and reducing drug resistance. Anticancer drugs often have severe side effects. Pasut et al. achieved higher anticancer activity for carcinoma cells using a multidrug delivery system. Interestingly, the multidrug delivery system decreased cytotoxicity against endothelial cells and cardiomyocytes compared to free drug treatment. Their system involved the covalent conjugation of epirubicin and nitric oxide to both terminals of PEG, enabling simultaneous delivery of these two agents.

CONCLUSION

In conclusion, niosomes are innovative nano drug carriers that can be utilized in the design of effective drug delivery systems. They offer opportunities for loading both hydrophilic and lipophilic drugs and have been studied extensively for the delivery of

anticancer agents, anti-inflammatory agents, anti-infective agents, and more. These studies have shown that niosomes improve the stability of the enclosed drug, reduce dosage requirements, and enable targeted delivery to specific tissues. By employing novel preparation, loading, and modification methods for specific routes of administration, the structural properties and characteristics of niosomes can be further enhanced. Therefore, niosomes hold great promise as tools in commercially available therapeutics.

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