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A Comprehensive review on Niosome: a prominent carrier in advance drug delivery

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Abstract

Niosomes are vesicular nacarriers that can be used for both amphiphilic and lipophilic drugs. Niosomes are budding vehicles in advanced drug delivery systems. Niosomes are nionic surfactants vesicles that can be formed with or without the addition of cholesterol. Niosomes can be the best choice for nacarriers because of their specific characters like biodegradability, biocompatibility, and immugenic nature. Niosomes can easily trap the hydrophilic and lipophilic drugs and extend the period of the drug in the systemic circulation. Niosomes are the nacarrier that can enhance penetration of drugs into the specific target tissues hence resulting in reduced toxicity. The main aim of this review article is to provide a detailed description of Niosomes.

Keywords: Niosomes; Surfactant; Hydrophilic; lipophilic drugs

1. Introduction

Targeted drug delivery systems are the systems in which drug molecules are directly targeted at the expected site of action without interacting with other tissues. Niosomes are the controlled drug delivery system used to deliver the desired drug release pattern for an extended time period. Niosomes are nionicsurfactants vesicles with lamellar bilayers[1, 2]. With the addition of nionic surfactants (Diethyl ether and cholesterol followed by hydration in aqueous media), Microscopic multilamellar and unilamellar structures of Niosomes are formed. Niosomes size ranges from 10-1000nm.

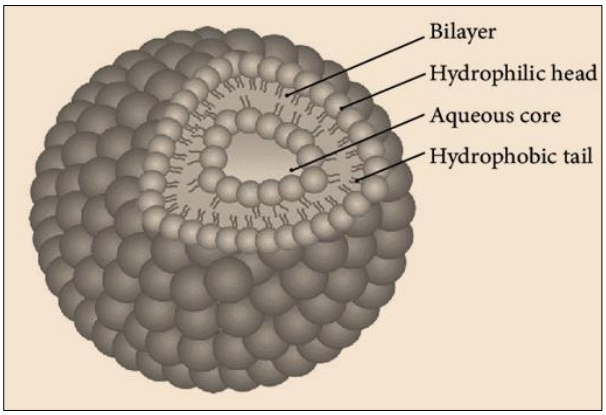

Figure 1 Niosome

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Niosomes are formed mainlywithnionic surfactants, lipids as like cholesterol, and hydration medium. In the process of isome formation, nionic surfactants assembled in a specific way to form a closed bilayer structure. As the interfacial tension work in the formation of niosomes results in the association of hydrophobic tails towards inside and hydrophilic points outside in contact with water[3,4].

Niosomes are categorized into 3 different types' ss per the size and layers.

Table 1 Types of Niosomes

S.	Types of vesicles	Vesicle's size
1	Multi lamellar Vesicles	Greater than 3000nm
2	Large Unilamellar Vesicles	100-3000nm
3	Small Unilamellar Vesicles	10-100 nm

2. Main constituents in the formation of Niosomes

Two main constituents are used in the formation of Niosomes

2.1. N-ionic surfactants

Mainly Spans(Span 80,85,20,40,60) Tweens(Tween80,60,40,20) and Brij's (52,58,76,72,35,30) are used[5].

Other examples of nionic surfactants-

- Ethers- Lauryl glucoside, Decylglucoside, Octylglucoside, xyl-9, Triton X-100
- Esters-Polysorbates,Glyceryllaurate
- Fatty Alcohols - cetostearylalcohol,Cetylalcohol, oleylalcoholstearyl alcohol[6].

2.2. Cholesterol

Cholesterol is used to provide strength, adequate shape, and geometryto Niosomes[7].

2.3. Advantages of niosomes[8-10]

- They are osmotically active and stable.
- They increase the stability of the entrapped drug.
- Handling and storage of surfactants do t require any special conditions.
- Can increase the oral bioavailability of drugs.
- Can enhance the skin penetration of drugs.
- They can be used for oral, parenteral as well topical.
- The surfactants are biodegradable, biocompatible, and n-immugenic.
- Improve the therapeutic performance of the drug by protecting it from the biological environment and restricting effects to target cells, thereby reducing the clearance of the drug.
- The niosomal dispersions in an aqueous phase can be emulsified in a n-aqueous phase to control the release rate of the drug and administer rmal vesicles in external n-aqueous phase.

2.4. Disadvantages of niosomes[11-13]

- Physical instability
- Aggregation
- Fusion
- Leaking of entrapped drug
- Hydrolysis of encapsulated drugs which limiting the shelf life of the dispersion[5-8].

3. Method of preparation for Niosomes

Different methods are used in the formation of Niosomes

3.1. Thin-Film Hydration Method (TFH)

Thin-film hydration method is a simple and well-kwn preparation method. In this method, the surfactants, cholesterol, and some additives such as charged molecules are dissolved in an organic solvent in a round bottomed flask. Then the organic solvent is removed using a rotary vacuum evaporator to obtain thin film on the inside wall of the flask. An aqueous solution of drug is added and the dry film is hydrated above the transition temperatureof the surfactant for specified time with constant shaking. Multilamellarniosomes are formed by this method[174-16].

3.2. Ether Injection Method (EIM)

In ether injection method, the surfactants with additives are dissolved in diethyl ether and injected slowly through a needle in an aqueous drug solution maintained at a constant temperature, which is above the boiling point of the organic solvent. The organic solvent is evaporated using a rotary evaporator. During the vaporization the formation of single layered vesicles occurs[17,19].

3.3. Reverse Phase Evaporation Method (REV)

In this method, niosomal ingredients are dissolved in a mixture of ether and chloroform and added to aqueous phase containing the drug. The resulting mixture is sonicated in order to form an emulsion and the organic phase is evaporated. Large unilamellar vesicles are formed during the evaporation of the organic solvent[20].

3.4. Microfluidization Method

The microfluidization method is based on submerged jet principle. In this method, the drug and the surfactant fluidized streams interact at ultrahigh velocities, in precisely defined micro channels within the interaction chamber. The high speed impingement and the energy involved leads to formation of niosomes. This method offers greater uniformity, smaller size**,** unilamellar vesicles, and high reproducibility in the formulation of niosomes[21].

3.5. Proniosome

Proniosome technique includes the coating of a water-soluble carrier such as sorbitol and mannitol with surfactant. The coating process results in the formation of a dry formulation. This preparation is termed “Proniosomes” which requires to be hydrated before being used. The niosomes are formed by the addition of the aqueous phase. This method helps in reducing physical stability problems such as the aggregation, leaking, and fusion problem and provides convenience in dosing, distribution, transportation, and storage showing improved results compared to conventional niosomes[22].

3.6. Heating Method

This is a patented method which was created by Mozafari et al. [72, 73]. Surfactants and cholesterol are separately hydrated in buffer and the solution is heated to 120°C with stirring to dissolve cholesterol. The temperature is reduced and surfactants and other additives are then added to the buffer in which cholesterol is dissolved while stirring continues. Niosomes form at this stage, are left at room temperature, and then are kept at 4-5°C under nitrogen atmosphere until use[8].

3.7. Transmembrane pH Gradient

In this method, surfactant and cholesterol are dissolved in chloroform and evaporated to form a thin lipid film on the wall of a round bottomed flask. The film is hydrated with a solution of citric acid by vortex mixing and the resulting product is freeze-thawed for niosome formation. The aqueous solution of drug is added to this niosomal suspension, after that phosphate buffer is added to maintain pH between 7.0 and 7.2 [70]. According to this method, the interior of niosome has a more acidic pH value than the outer medium. The added unionized drug passes through the niosome membrane and enters into the niosome. The drug ionizes in an acidic medium and cant escape from the niosomal bilayer[23].

3.8. The “Bubble” Method

In this method, surfactants, additives, and the buffer are added into a glass flask with three necks. Niosome components are dispersed at 70°C and the dispersion is mixed with homogenizer. After that, immediately the flask is placed in a

water bath followed by the bubbling of nitrogen gas at 70°C. Nitrogen gas is passed through a sample of homogenized surfactants resulting in formation of large unilamellar vesicles[11].

4. Characterization of Niosomes

4.1. Bilayer Rigidity and Homogeneity

The rigidity of Niosomes bilayer can influence biodistributionandhomogeneityNiosomes which can be characterized by Differential scanning calorimetry (DSC) and Fourier transform-infra red spectroscopy (FT-IR) and pNMR techniques[18].

4.2. Size and Shape

The shape and size of Niosomes can be determined by molecular sieve chromatography, electron microscopy, optical microscopy, photoncorrelation microscopy techniques[5].

4.3. Stability Study

The stability of Niosomes can be determined by storing niosomes formulation at different temperature conditions for a specific time span. The formulations can be checked for stability profile by keeping it at 4°C, 25°C, and 37°C for 3 months[19].

4.4. *In-vitro* Release rate studies for isome can be carriedout using the following methods

4.4.1. Dialysis Tubing

In this method, a dialysis sac is used to check the release profile from Niosomes. Suspension of Niosomes vesicles is kept into a dialysis beg and beg is sealed. After that bag is placed into a 200ml buffer solution in a 250 ml beaker at 25°C with continuous shaking. At different time intervals, samples are withdrawn and analyzed for drug release with suitable methods

4.4.2. Franz Diffusion Cell

Franz diffusion cell can be used to perform in-vitro diffusion studies. Proniosomesare kept in a dor chamber in the Franz diffusion cell attached to a cellophane membrane. Proniosomesare dialyzed with anappropriatedissolution medium at room temperature. Samples can be withdrawn at different time intervals and analyzed with UV spectroscopy for drug content.

4.5. Vesicle Charge

Vesicles charges are a vital characteristic in the behavior of niosomes. Niosomes with charges are the stable form during storage and fusion in comparison to uncharged niosomes.TheZeta potential of Niosomes can be determined using microelectrophoresis.

4.6. Niosomal Drug Loading and EncapsulationEfficiency

For determining drug loading and encapsulation efficacy aqueous suspension of niosomes is taken and centrifuged. Sediment was washed to remove the absorbed drug.

- The niosomal recovery can be calculated as:

% Recovery= Amount of niosomes recovered /Amount of polymer+drug+excipients*100

- The entrapment efficiency (EE) was then calculatedusing the formula:

Entrapment efficiency (EE) = Amount of drug in niosomes/ Amount of drug*100

- The drug loading was calculated as:

Drug loading (%) = 1+Amount of drug in niosomes/Amount of niosomes*100

5. Applications of Niosomes

Niosomal drug delivery has the following applications in the pharmaceutical industry.

5.1. In the delivery of anticancer drugs

Doxorubicin shows anti-tumor activity but causes cardiotoxicity. Niosomal drug delivery of doxorubicindecreases the proliferation of sarcoma. In niosomal drug delivery half-life of the drug increases, drug's time span in blood circulation increases resulting in altered metabolism[11].

5.2. Delivery of peptide drugs

IT has established that lots of peptide drugs have been delivered using niosomes a nacarrier. Studies have shown that the stability of niosomes has enhanced using niosomal drug delivery[7].

5.3. Useful in studying the immune response

Niosomes are used for testing the immune response produced by antigens. Stable and immulogical selectivity with very low toxic effects makes niosomes a good candidate for studying immune response[21].

5.4. Hemoglobin Carrier

Niosomes can act as hemoglobin carriers.

5.5. Transdermal delivery of drugs by niosomes

In transdermal drug delivery, the drug penetrates into the skin at a slow rate which is a major limitation of the transdermal route. Penetration can be enhanced through the skin using niosomes as drug carriers in transdermal drug delivery[22].

5.6. Sustained Release

Drugs having low solubility and a short therapeutic index can be used in sustained release drug delivery using niosomes as a drug carrier8.

5.7. Ophthalmic drug delivery

Achieving the required bioavailabilityof the drug in ophthalmic preparation is t an easy task. Niosomes can act by lowering the intraocular pressure resulting in enhanced drug bioavailability[15].

6. Marketed Formulations of Niosomes

Table 2 Marketed cosmetic preparation of niosomes

S.	Brand
1.	Lancome- Foundation and complexation
2	Orlane – Lipcolor and Lipstick
3.	Loris Azzaro – Chrome
4.	Britney Spears – Curious

7. Future Prospects

Niosomes have already been established as a budding drug delivery system. Niosomes provide a wide range for incorporating a number of drugslike anti-inflammatory, anti-bacterial drugs, anti-viral drugs, etc. Niosomes are the promising drug carriers that target drugs at the specific site of action with enhanced bioavailability. Niosomes can be also used as a nacarrier having special characteristics of reducing the toxic effect of drugs. It has been kwn that ionic carriers are toxic in nature so niosomes are the best alternative with safe results. Niosomes offer an opportunityto researchers to explore the field of advanced drug delivery and nacarriers systems and targeted drug delivery with safe and better outcomes.

8. Conclusion

As discussed in the review article, n-ionic surfactants are the key element in niosomes formation, which are safe with better stability. It has been established that niosomes are one of the best nacarrier systems for delivering drugs with the least side effects.

Some benefits of niosomesthat make niosomes the first choice for selection are low cost of manufacturing, purity, chemical stability, and least toxicity. Niosomes can be used as nacarriers to the delivery drug in different areas such as local delivery of drugs, in eyes, in cosmetics, in parenteral preparations etc.

At last, it can be concluded that niosomes are the ideal nacarriers that can deliver both hydrophobic and hydrophilic drugs effectively with the least side effects and better targeting with enhanced bioavailability, of the drug at the site of action.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict is associated this work.

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