

# A review on Niosomes: Recently tested drugs and their application in different treatment

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## Abstract

Niosomes are self-assembly vesicular nano-carriers produced by the hydration of surfactants, cholesterol or different amphiphilic moiety. These all components provides flexible delivery of drugs with a range of applications vary from dermal to brain-targeted delivery. Niosomes are the proficient carrier for the water insoluble drugs enhance their solubility and efficacy. In this review we summarise the basic details of niosomes such as their advantages, disadvantages, composition, factor that affect niosomes formulation, method of preparation, evaluation parameters and some recently studied application of niosomes for various treatment.

**Keyword:** Niosome, method of preparation, factor affecting formulation, Evaluation parameter, Recently tested drugs.

## Introduction

Niosomes are a vesicular, novel drug delivery system that helps to release the drugs in a sustained, regulated, and targeted manner [1,2]. Firstly liposomes were prepared to provide the vesicular drug delivery system due to their range of drawbacks including toxicity and problem of stability[1] Scientist focus has moved toward niosomes. Niosomes exist in various forms like Unilamellar, oligolamellar and multilamellar [3]. Niosomes are named after the non-ionic surfactants that are used to prepare them, and they are non-toxic as a result of these surfactants. They can also contain cholesterol or its derivatives, as well as charged molecules, in addition to non-ionic surfactants. Cholesterol gives the structure rigidity, and the charged molecule is responsible to keep the preparation stable. The self-assembly of nonionic surface-active agents results in the production of niosomes. Due to the structure of the niosome it is capable to entrap both hydrophilic and lipophilic drugs[2,4,5,6]. Firstly in 1970s and 1980s, investigator from L'Oréal (Clichy, France) documented applications of niosomes in cosmetic. After that, niosomes have been researched widely in a range of areas, including medicinal, food sciences and cosmetic, resulting in a huge number of publications and patents [7]. By this system drug can be given through the various route such as orally, parenterally or topically and improve the quantity of the drug at the targeted region. It was studied that Antimonials entrapped inside niosomes are adopted by mononuclear cells, leading to localization of medication, enhance the potency, and reduction in systemic toxic effects[8].

## Structure of niosome

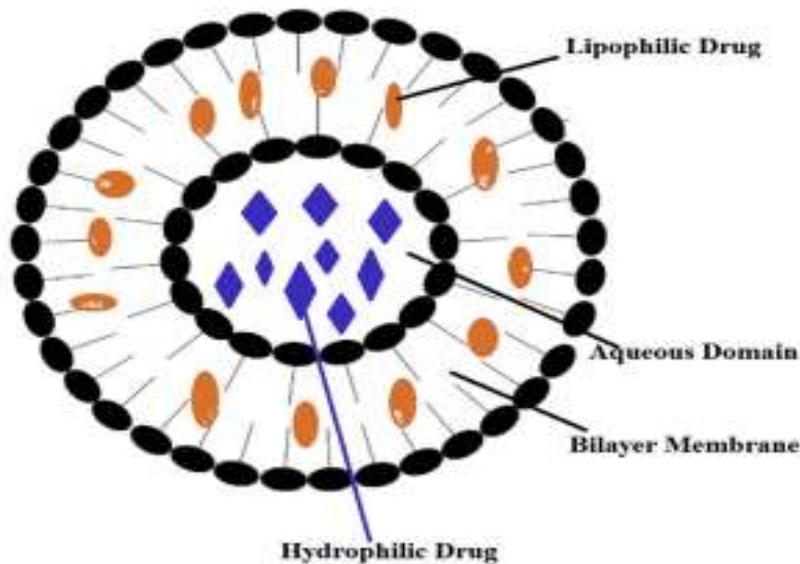


figure 1. Bilayer Structure of niosomes displaying entrapment region of hydrophobic and lipophilic drugs[9]

### Advantages of niosomes

Lipid vesicles and non ionic surfactants vesicles system having the following therapeutic applications

1. Niosomes are osmotically active and consist long storage time.
2. Niosomes are biodegradable, biocompatible, nonimmunogenic, show less toxicity and enhance patient compliance.
3. Niosomes enhance the stability of the entrapped drug.
4. Penetration of the drug is enhanced when given by the transdermal route .
5. By crossing the blood brain barrier they are able to deliver the drug in brain.
6. They enhance the oral bioavailability of water insoluble drug.
7. There is no need of special circumstances for production and storage of the niosomes. .

### Disadvantages

1. Shelf life of the aqueous suspension of the niosome is less because aggregation, hydrolysis and permeability of the encapsulated drug.
2. Formulation process of multilamellar vesicles with the help of thin film hydration method require more time [10].

### Compositions of niosomes

The following are the two main ingredients used to produce niosomes:

1. Cholesterol
2. Nonionic surfactants

1. Cholesterol is a type of fat.

Cholesterol is derivative from steroid that is employed to provide niosome preparations rigidity, shape, and conformation.

2. For the preparation of niosomes, the given non-ionic surfactants are widely employed. As an example,

a) Spans (span 60, 40, 20, 85, 80)

b) Tweens (tween 20, 40, 60, 80)

c) Brij (brij 30, 35, 52, 58, 72, 76)

A hydrophilic head and a hydrophobic tail are found in nonionic surfactants [11].

## Method of preparation

There is various method that are employed to formulate the niosomes some of them are explained below.

### Thin film hydration technique

It is also named as hand shaking technique. Multilamellar vesicles are usually formulate by this technique. In this technique the non-ionic surfactant and organic solvent are dissolved together and added in the round bottom flask. And by applying rotary vacuum pressure the organic solvent is removed followed by evaporation. By evaporation thin dry layer of surfactants are formed inside the flask. This thin layer is hydrated with the aqueous solvents like phosphate buffer and water until layer is completely dissolved. Hydration process is carried out at the higher temperature than the surfactant transition temperature. This method is more favourable for the water insoluble drugs. Vesicles obtained with method ranges from 0.5um to 10um[4,6,12,13,14].

### Bubble method

This technique are used to produce the large unilamellar vesicles. There is no use of organic solvent to produce the niosomes. In this technique a three neck flask is used which is keep on the water bath to maintain the temperature. All the ingredients such as non ionic -surfactants, cholesterol and phosphate buffer are blend at the same time and added into the flask. In one neck of the flask thermometer is placed, nitrogen gas is passed by the second neck and in third neck condenser system is placed to cool the water. At 70 °C all the ingredient are scattered and homogenized for 15 minute and right after nitrogen gas is delivered to the blended ingredient. To obtain small vesicles niosomes are further introduce into the size reduction process[6,15,16].

### Ether injection method

This technique is performed by blending the all the ingredients such as surfactants, cholesterol and organic solvent in a beaker. And this blended mixture is introduced into the syringe and with the help of needle the mixture is gradually introduced into the preheated aqueous solution such as phosphate buffer in which the drug is present. The solution is heated at the 60 °C. When the evaporation of the solvent occur the unilamellar vesicles are prepared in which drug is entrapped [6,16].

### Reverse phase evaporation technique

It is performed by dissolving the components like surfactant and cholesterol in the organic solvent. And apart from this water based solution of drug is generated. After that the aqueous phase where drug is present is mixed with organic phase. On mixing a system containing two phase is generated. This two phase system is homogenized and using negative pressure the organic phase is eliminated. Formation of large unilamellar vesicles occurs through this phase [1,17].

### Micro fluidization

It is a relatively new technique based on the concept of a submerged jet. Two fluidized streams communicate at ultra high velocities inside the interaction chamber and travel forward through clearly identified micro channels. The thin liquid layer impact together with general front is organized in a way that the energy given to the system stays between the niosome generation region, resulting in smaller size, better uniformity of produced niosomes [18].

## Sonication method

To perform this technique a probe sonicator is employed to generate the multilamellar vesicle. For example Bansal et al. Employed this technique to formulate the cefdinir niosomes. Firstly they dissolve the drug in buffer after that he added the blend of cholesterol and surfactant into the prepared drug solution with the help of the probe sonicator this whole mixture is sonicated at around 60 °C to generate the multilamellar vesicle. To obtain the unilamellar vesicle the prepared niosomes were ultrasonicated to generate unilamellar vesicles [19].

## Factors that affects niosomal formulation

### 1. Cholesterol

Cholesterol affects the attribute of the biological membrane as the same way it effects the properties of the niosome. It decreases the elasticity of membrane also decrease the permeation of drug across the membrane. Amount of the cholesterol added in the formulation lies on the surfactant HLB value [9].

### 2. Nature of Surfactant

HLB value of the surfactants play important role in the formulation of niosomes. Surfactants with larger HLB value increases the size of the niosomes it occurs because the increased in hydrophobicity of the surfactants causes decrease in the surface free energy. Surfactants with HLB value in range of 14 to 17 are not appropriate to formulate the niosome. It was studied that the Surfactants with HLB value 8.6 showed the maximum entrapment efficiency. On other hand HLB value 8.6 to 1.7 is responsible for decreasing the entrapment efficiency .

### 3. Nature of Entrapped Drug

Physical and chemical characteristics of the enclosed drug affects the rigidity and charge of the bilayer. During production the drug interact with the head group of the surfactants as a result of this charge increases and causes repulsion of the bilayer and size of the vesicle is increased. HLB value of the drug also affect the degree of the encapsulation of the drug.

### 4. Hydration Temperature

During the formulation of the niosomes hydration temperature could effect the size and shape of the vesicles. Temperature of hydration should higher than the transition phase temperature of the surfactant. If temperature is changes it can effect the shape of vesicles. Drug leakage issues is generated when the inappropriate hydration temperature, volume of hydration medium and time is selected for the production of the niosomes. It also generates fragile niosomes.

### 5. Charge

Occurrence of charge enhances the entrapped volume of the drug because charge expand the inter lamellar distance within the bilayer of multi lamellar vesicles.

### 6. Resistivity to Osmotic Stress

When the hypertonic solution is introduced in the niosomal suspension it reduce diameter of the vesicle. In case of hypotonic solution, supression of eluted fluid from vesicles leads to quick liberation firstly succeeded by slow release[20,8].

## Evaluation parameter of niosome

### Size and Vesicle Charge

The stability and drug entrapment of vesicles is primarily determined by small size and charge. The size of vesicles were determined via repulsion forces within the bilayers as well as the encapsulated drug in a multifunctional zeta potential analysis. Electron microscopy and molecular sieve fluorescence, membrane

filtration, photon correlation, and optical, to freeze motion electron microscopy can be employed to measure the size of vesicles [21].

### Zeta Potential

Physical stability of niosomes is an important factor which depends on the surface charge of the niosomes zeta potential is helpful to determine the charge. Particle image systems and information can be used to determine the surface factor, and the degree of the zeta potential represents the extent of electrostatic aversion among the two neighboring particles. Niosomes having a zeta potential of greater than +30 mV or less than -30 mV are thought to be stable [22,23,24].

### Entrapment efficiency (EE)

When the drug is entrapped inside the niosomes it is unpaired as EE, and it can be expressed using the following equation:

The quantity of the drug entangled / total quantity of drug introduced X 100%

The total amount of drug means the quantity of drug employed during the formulation, while the amount of drug entrapped mention the real quantity of drug that is effectively enclosed in niosomes. Techniques like dialysis, filtration, and centrifugation must be employed to separate the free drug particles from the enclosed drug. Spectrophotometry and gel electrophoresis accompanied by UV densitometry can be employed to determine the EE of genetic materials. This parameter also can be determined by using an ionization product like calcein to determine the number of marker molecules enclosed [25].

### In Vitro Release Study

This analysis often employs the dialysis membrane procedure. In this procedure, a tiny quantity of niosomes is put in a dialysis bag and tied at both sides. The dialysis bag is taken in a beaker with suitable dissolution media, which is kept at 37°C and stirred with the help of magnetic stirrer. A sample solution is collected from the beaker at period of times and substituted with fresh dissolution media. Concentrations of drugs in a sample is checked at specific wavelengths as defined in the respective drug monograph [17].

### Stability of Niosome

During the production of niosome formulations, the stability of the niosomes is considered as a critical parameter. The method of preparation, the loaded medicines, and the types of membrane forming materials has used all have an effect on stability [26]. Changes in particle size, morphology, zeta potential and loaded drug leaky rate can all be evaluated to determine the stability of niosomes during the preservation period. The scale, polydispersity index (PDI), and the encapsulation effectiveness of the samples was used to determine the stability of the niosomal formulation during their preservation period at two temperatures (i.e., room temperature of 25 °C and refrigerator storage temperature of 4 °C). However, storing niosomes at room temperature causes a significant increase in their size and PDI, as well as a reduction in their entrapment effectiveness because of breaking and swelling of the niosomes [27, 28].

### Recently tested drugs for Niosomes and their Applications

S. N.	Drugs / extract	Material used	Method	Treatment	References
1.	Resveratrol	Span 80, Span 60, and cholesterol	Mechanical agitation and sonication	Antioxidant	[29]
2.	Ammonium glycyrrhizinate	Tween 20, Cholesterol, Cholesteryl	Thin-layer evaporation method	Anti-inflammatory activity	[30]

		hemisuccinate			
3.	Moxifloxacin niosomes gel (Topical delivery)	Span 20, Span 60, Tween 20, Tween 40, Tween 60, Tween 80, cholesterol and chitosan	Thin film hydration	Antimicrobial	[31]
4.	Fluconazole-loaded niosomal gels (Ocular route )	Span 60, Tween 80, Cholesterol, poloxamar 407	For noisome Film hydration method and Cold method to produce gel	Antifungal activity	[32]
5.	Tacrolimus (Ocular delivery )	Poloxamer 188, soybean phosphatidylcholine and cholesterol Hyaluronic acid	By reconstituting the proniosomes	Corneal allograft rejection	[33]
6.	Febuxostat Niosomal gel (Transdermal delivery)	Span 60, Tween 20, cholesterol	Thin film hydration	Gout	[34]
7.	Lacidipine (Transdermal delivery )	Cholesterol, Span 60, soya and Carbopol 934 phosphatidylcholine 70	Thin film hydration	Antihypertensive	[35]
8.	Ibuprofen and Lidocaine	Tween-20 or Tween-20 glycine derivative and cholesterol and organic solvent	Thin film hydration	Cytotoxicity; antinociceptive/antoinflammatory	[36]
9.	Rifampicin	Cholesterol, Span 60, Pluronic L121 and dicetyl phosphate	By probe sonication method	Antitubercular/ antimicrobial	[37]
10.	Bromocriptine Mesylate (Intranasal brain targeting delivery )	Span 60 and cholesterol	Ether injection method	Parkinson's Disease	[38]
11.	Pilocarpine hcl loaded noisome (Ocular delivery)	Tweens and Spans (20, 40, 60 & 80) and cholesterol	Thin film hydration	Glaucoma	[39]
12.	N-Acetylcysteine	Span 60, Cholesterol and	Film hydration	Acetaminophen poisoning as a	[40]

	(Oral route)	PEG	method	antidote	
13.	Minocycline (coated implants )	Span 60 and cholesterol	Thin film hydration	Peri-implant diseases	[41]
14.	doxycycline-l	Span 60, Tween 60, and cholesterol	Thin-layer hydration	Prostate cancer infection	[42]
15.	Letrozole (Oral, parenteral )	Cholesterol and Tween 80	Slurry-based proniosome method	Estrogen-positive breast cancer in postmenopausal women	[43]
16.	Pentoxifylline (Topical delivery )	Tween 40, Tween 60, Span 40, Span 60, Span 80, and cholesterol	Dry film hydration	Wound healing	[44]
17.	Curcumin (Dermal delivery)	tween 20 and span 20 Cholesterol	Thin film hydration	Antinociceptive	[45]
18.	Galangin (Oral route)	Span 20, Span 40, and Span 60) and cholesterol, Dicytylphosphate and Stearylamine	By reverse-phase evaporation	liver cancer	[46]
19.	Ciprofloxacin	Tween 60, Span 60, and cholesterol	Thin film hydration	Antibacterial activity, biofilm inhibition	[47]
20.	17-Hydroxyprogesterone caproate ( Oral route)	Span 60 and cholesterol brij 76, brij 78, myrj 52, poloxamer 188 (permeation enhancer )	Thin film hydration technique pursued by sonication	Reduces the side effects caused by the intramuscular injection of 17-Hydroxyprogesterone caproate	[48]
21.	Arbutin (Dermal delivery)	Surfactant and cholesterol	Ultrasonic method	Hyperpigmentation	[49]
22.	Cyclosporine (Topical delivery)	Cholesterol, Span 60 and Carbopol 940	thin film hydration	Psoriasis	[50]

Table 1. Recently studied application of niosomes for various treatment

## Conclusion

Niosomes are the delivery system which gives the many advantages for delivery of drugs over the conventional dosages form. This system is capable to encapsulate the both hydrophilic and lipophilic drug and enhance their oral absorption and provide the sustain and control release of the drug. Production process of the niosomes is easy. This system is alternative of the liposomes but it also contain the various advantages over the liposome such as it having low cost, and provide the better stability of the formulation. Because of all these benefit and their applications in various field interest toward the niosomes is increasing. As a result, it appears that niosome research will continue to develop, potentially leading better market formulations in the pharmaceutical industry.

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