



# Review On Niosome Antifungal Drugs As An Effective Nano carrier System

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## ABSTRSCT

The body's largest organ, the skin, serves as a simple and accessible place for medication delivery. The limited rate of medication penetration through the skin is one of the drawbacks of transdermal drug administration. Nanoparticles have been employed as medication delivery devices to improve therapeutic benefits or lessen toxicity throughout the past few decades. Drug transport into and through the skin is made easier by encapsulating pharmaceuticals in nanoparticulate vesicles.

**KEYWORDS:** Antifungal, Drug Delivery, Liposome, Nanoparticle, Niosome

## INTRODUCTION:

### Niosomes

Among the most promising drug carriers are niosomes, which have a bilayers structure produced by the self association of non-ionic surfactants and cholesterol in an aqueous phase. The tiny lamellar structures known as niosomes or non-ionic surfactant vesicles are created when non-ionic surfactants of the alkyl or dialkyl polyglycerol ether class and cholesterol are combined, followed by hydration in aqueous environments. Since they are non-ionic, niosomes are unilamellar or multilamellar vesicles made from artificial non-ionic surfactants. Niosomes are a potential drug delivery system. They and liposomes are quite similar. In order to fight a variety of illnesses, several pharmacological substances may be able to use niosomal drug delivery. Niosomes are a more effective choice for medication delivery since they have demonstrated promise in release tests. For more effective medication delivery to the right tissue location, the drug is integrated into niosomes.



**Fig. 1: structure of niosome**

Applications of nanotechnology in the medical and health sciences have grown significantly along with the field's progress. Recently, researchers have increasingly used lipid-based nanoformulations, such as nanoemulsions, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and liposomes, as drug carriers. These materials include metallic nanoparticles (particularly gold and silver), polymeric nanoparticles and fibres, and metallic nanoparticles. A carrier is a unique molecule or system that is utilised to carry a loaded medicine efficiently to designated drug delivery sites. Carriers are designed vectors that encapsulate and hold pharmaceuticals on the cell surface or in a subcellular compartment by physical or chemical contact.

Vesicles, particularly lipidic ones, are employed as medication delivery vehicles. Vesicles are extremely helpful in the transport and targeting of active substances via the membranes since they play a significant role in modelling biological membranes. In comparison to other targeted drug delivery methods, the vesicular drug delivery system offers some benefits. The medicine is kept in systemic circulation for a longer period of time thanks to this technology, and because the drug is delivered right to the infection site, it may be less hazardous. Drugs that are both lipophilic and hydrophilic can be incorporated into lipidic vesicles.

Furthermore, lipidic vesicles serve as prolonged release mechanisms for medications that are quickly metabolised by delaying their disposal. Liposomes are straightforward tiny vesicles with lipidic bilayer structures and a central hole completely surrounded by a membrane. Liposomes include a variety of ingredients, including cholesterol and phospholipid. Phosphoglycerides and sphingolipids are two different kinds of phospholipids.

In the realm of topical, transdermal, and targeted drug administration, the utilisation of self-assembled non-ionic surfactant based vesicles or niosomes has recently garnered considerable attention. This is brought on by these vesicles' easy synthesis, affordability, chemical stability, high compatibility, biodegradability, and minimal toxicity (due to their non-ionic nature). The other advantages of niosomes include improved permeability, solubility, and potential for prolonged release as a local reservoir.

L'Oreal created and filed for a patent on the initial niosome compositions in 1975. The earliest application of niosomes was in the delivery of anticancer drugs. Niosomes have the power to change drug metabolism, organ distribution, and pharmacokinetic profiles. Niosomes may transport both hydrophilic and hydrophobic substances and have a core-shell structure. The hydrophilic core serves as a good reservoir for hydrophilic medications, whereas hydrophobic pharmaceuticals are often localised in the outer shell or lipid layer (Figure 1).

The mortality rate linked to invasive mycoses is on the rise. The records show that in 1980, this category of illnesses was the 10th most common cause of deadly infection in the US, causing 828 fatalities. But according to the same dataset, the number of mycosis-related fatalities rose to 2,370 in 1997, making it the seventh-most common lethal infectious illness.

In their lifetimes, the majority of people have superficial fungal infections. These infections can usually be treated easily, but millions of individuals worldwide get invasive, life-threatening infections that are considerably more difficult to identify and treat. A viable strategy for managing fungal illnesses and eliminating resistant fungus is the development of innovative fungicides. As a result, during

the past few decades, work has been done globally to produce fungicides that are incredibly effective. In light of this, the current study was done to examine the data on the usage of niosomes as antifungal drug carriers. The information is organised alphabetically by kind of loaded medicine.

### **SALIENT FEATURES OF NIOSOMES:**

- Niosomes serve as liposomes' substitutes. This prevents problems with the liposomes.
- Stable and osmotically active.
- Niosome makes a medication that is entrapped more stable.
- They can be administered topically, parenterally, or orally to deliver the medication to the site of action.
- Niosome surfactant does not require certain circumstances.
- Niosomes include biodegradable, biocompatible, and nonimmunogenic surfactants.
- By delaying clearance from the blood, they enhance the therapeutic effectiveness of the drug molecules.
- Niosomes may be created to fit any scenario because of their structural flexibility (composition, fluidity, and size).

### **COMPOSITION OF NIOSOMES:**

The two main components of niosomes are cholesterol and nonionic surfactants. Niosomes are given the stiffness and correct form by cholesterol. Surfactants are crucial in the niosome production process. For the manufacture of niosomes, the following non-ionic surfactants are often used: spans (span60,40,20,85,80), tweens (tween 20,40,60,80), and brij (brij 30,35,52,58,72,76). A hydrophilic head and a hydrophobic tail are features of the non-ionic surfactants.

### **TYPES OF NIOSOMES:**

#### **Small Unilamellar Vesicles (SUV)**

Sonication and French press techniques are frequently used to create SUVs. SUVs can be prepared using solvent dilution methods or ultrasonic electro capillary emulsification. (size -0.025-0.05  $\mu\text{m}$ )

#### **Multilamellar Vesicles (MUV)**

Need hand-shaking and show increased-trapped volume and equilibrium solute distribution. They differ in their lipid makeup. (size > 0.05  $\mu\text{m}$ )

#### **Large Unilamellar Vesicles (LUV)**

LUV can spontaneously occur when lipids that have been solubilized in an organic solvent are injected into an aqueous buffer, however reverse phase evaporation or detergent solubilization are superior ways to prepare LUV. (size > 0.10  $\mu\text{m}$ ).

### **ADVANTAGES OF NIOSOMES:**

The suspension of niosomal vesicles is a water-based system. Compared to greasy dose forms, this delivers great patient compliance.

They may accept medicinal molecules with a variety of solubilities because they have an architecture made up of hydrophilic, amphiphilic, and lipophilic moieties.

The vesicle formulation's properties may be altered and controlled. Vesicle features may be changed by adjusting their composition, size, lamellarity, tapping volume, surface charge, and concentration.

The vesicles could serve as a depot, delivering the medication gradually.

They can be made to get to the site of action by oral, parenteral, as well as topical routes.

They improve the oral bioavailability of poorly absorbed medications and promote skin penetration of pharmaceuticals.

By delaying clearance from the circulation, shielding the drug from the biological environment, and limiting effects to target cells, they enhance the therapeutic effectiveness of drug molecules.

To control drug delivery rate and administer normal vesicles in exterior non-aqueous phase, niosomal dispersion in an aqueous phase can be emulsified in a non-aqueous phase.

### THE DATA ARE PRESENTED ALPHABETICALLY ACCORDING TO THE LOADED DRUG:

#### **Ketoconazole**

A synthetic imidazole derivative known as ketoconazole has fungistatic action against yeasts, dermatophytes, and other pathogenic fungi. This antifungal medication is frequently used to address superficial infections as well as significant gastrointestinal and systemic mycoses. It works by preventing the production of ergosterol, which is a crucial part of the surface membrane of fungus cells. There aren't many data on the assessment of the antifungal activity of ketoconazole formulations based on niosomes against *Aspergillus niger*. Niosomes ranged in size from 4860 to 73803.64 nm and exhibited an encapsulation effectiveness of 55.14 to 78.63%, respectively. Niosomal ketoconazole has superior effectiveness over conventional ketoconazole, according to antifungal bioassays.

#### **Clotrimazole**

As an alternative to miconazole, clotrimazole is a synthetic imidazole that is effective against dermatophytes, yeasts, and Gram-positive cocci (species of *Staphylococcus* and *Streptococcus*). Different non-ionic surfactants, including Span 60, Span 40, Brij 72, and Tween 80, are used to create the proniosomal gel of clotrimazole at a given drug dosage (100 mg). The size of the produced formulation is in the micron range, and for Tween 80 and Span 60, respectively, their stated entrapment efficiency rates are 16% and 75%. 60% of the medicine is released in 6 hours using Span 60, which has been demonstrated to produce the optimum release. To assess the effectiveness of this formulation, there is no information on the antifungal test.

#### **Fluconazole**

A triazole derivative having a wide range of antifungal action and quick absorption, fluconazole. The blood-brain barrier is easily crossed by this medication to reach the cerebrospinal fluid. It slowly leaves the body by urination and has a half-life of elimination in plasma of around 30 hours. There aren't many reports about this medication's niosomal version in the literature. In the most recent study, fluconazole's ocular bioavailability in rabbits with fungal keratitis was studied in two formulations: niosomal gel and microemulsion. According to the study's findings, the drug's bioavailability in both forms—namely, niosomes [63.67-117.13 nm] and microemulsions [57.05-59.93 nm]—was much higher than it was in its solution form. Niosomal gels had a greater bioavailability (by two times), an entrapment effectiveness of 56.48-70.67%, and were more long-lasting. In a related investigation, fluconazole-loaded niosomes were used topically to treat eye infections. The formulations' particle sizes ranged from 140 to 280 nm, with entrapment efficiencies between 40 and 84.35%. According to bioassays, fluconazole greatly outperformed the positive standard drug miconazole in terms of antifungal activity. There is proof that the fluconazole formulations liposomal and niosomal with diameters of 348 and 326 nm and encapsulation efficiencies of 32% and 28%, respectively, are effective against cutaneous candidiasis.

#### **Itraconazole**

A triazole derivative with a wide range of antifungal action is itraconazole. This medication is easily absorbed and crosses the blood-brain barrier to reach the cerebrospinal fluid. This medication's plasma half-life is approximately 30 hours. It is processed in the liver before being excreted in the urine. The particle size and encapsulation effectiveness of this formulation were found to be 124 nm and 60- 90%, respectively, in a research investigating itraconazole-loaded niosomes against *C. albicans*. In addition, the zone of inhibition grew from about 10 mm in the commercially available free medication to around 30 in niosomes.

#### **Miconazole**

A synthetic imidazole called miconazole is effective against dermatophytes, yeasts, and Gram-positive bacteria like *Streptococcus* and *Staphylococcus* species. In one investigation, different ratios of cholesterol and surfactant were used to create miconazole niosomes using the thin film hydration technique. The prepared niosomes had an entrapment effectiveness of 80–97% and were in the micron size

range. Although the optimised formulation released 92% of the medicine that was encapsulated in it after 24 hours, there was no mention of an antifungal bioassay in the research in question.

### Amphotericin B

A lipophilic antibiotic called amphotericin B is effective against a variety of filamentous fungus and yeasts. It is assumed that this drug interacts with sterols in the fungal cell wall to change the permeability of the membrane. Due to this medication's limited gastrointestinal absorption, it must be given parenterally or combined with appropriate carriers. The antibacterial, anti-adhesive, and anti-biofilm characteristics of sophorolipids. 63.203.86% entrapment efficiency for amphotericin B with a size of 80 nm was reported for this formulation in a work describing the production and characterisation of niosomes containing sophorolipids. The aforementioned study also included a comparison between the effectiveness of this formulation and that of phosome (liposomal amphotericin B), a commercially available medication. The *Candida albicans* biofilm treated with the generated sophorolipids-based niosomal formulation of amphotericin B had less hyphae, but the biofilm treated with phosomes contained more budding cells. Other benefits of this formulation include the capacity to produce niosome-based formulations at an affordable cost and the applicability of this method for the administration of medications that are poorly soluble, such as amphotericin B, which is used to treat candidiasis.

### Diallyl Disulfide And Diallyl Sulphide

Garlic contains a significant amount of the organosulfur chemical diallyl disulfide (DADS), which has antimutagenic properties against malignant tumours. Epidemiological studies have shown that DADS consumption is related with a decreased incidence of gastrointestinal malignancies. Two reports regarding the creation of niosomes containing DADS and diallyl sulphide (DAS) were found after a review of the literature. In one of these investigations, 14030 nm-sized DADS-loaded niosomes were created. In a model of candidiasis in BALB/c mice, hepatic and renal function tests, as well as histological examinations, revealed that the formulation was safe at the examined dose (12 mg/kg). The size and encapsulation effectiveness of DADS-loaded niosomes were, respectively, 103–110 nm and 54–75% in the other publication. Furthermore, compared to the free form of DAS, niosomal DAS dramatically decreased fungal load and mortality in treated animals and was toxic-free (12 mg/kg body weight of Swiss albino mice).

### Griseofulvin

*Penicillium griseofulvum* is the source of the traditional fungistatic antibiotic griseofulvin. The dermatophytes that cause ringworm (tinea) infections are specifically targeted by this medication's selective fungistatic action; however, it has no effect on *Candida* species or pityriasis (tinea) versicolor. It works by upsetting the fungal cells' mitotic machinery, which prevents the creation of proteins. Tinea infections are a frequent kind of dermatological disorder. Improvement was seen in all three groups when ordinary griseofulvin gel was compared to its niosomal and liposomal gel forms over the course of 3 weeks in a research involving 16 patients. However, the niosomal gel formulation in the aforementioned trial achieved the maximum effectiveness with the fewest negative effects.

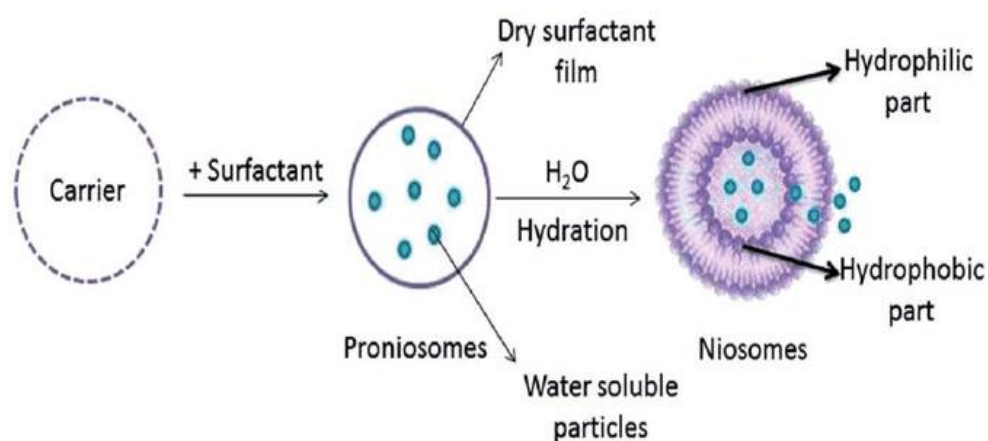


Fig. 2: formation of niosomes by non-ionic surfactant

**METHOD OF PREPARATION:****Method Of Injecting Ether:**

By gradually adding a surfactant solution mixed in diethyl ether (a volatile organic solvent) to warm water kept at 60°C, this technique offers a way to create niosomes. Through a 14-gauge needle, the surfactant combination in ether is injected into the material's aqueous solution. Ether (a volatile organic solvent) vapourization results in the creation of single-layered vesicles. The diameter of the vesicle varies depending on the parameters utilised, from 50 to 1000 nm.

**Sonication Method:**

In this procedure, the surfactant/cholesterol combination in a 10 ml glass vial is mixed with an aliquot of the drug solution in buffer. Using a sonicator with a titanium probe, the mixture is sonicated at 600 C for 3 min to produce noisy

**The “Bubble” Method:**

It is a unique method for making liposomes and niosomes in a single step without the use of organic solvents. The bubbling apparatus consists of a flask with a spherical bottom and three necks that are submerged in water to regulate the temperature. The first and second necks of the reflux are filled with water, while the third neck is used to provide nitrogen. In this buffer (pH 7.4), cholesterol and surfactant are dispersed simultaneously. The dispersion is mixed for 15 seconds with a high shear homogenizer, and is then promptly 'bubbled' at 70°C using nitrogen gas.

**Reverse Phase Evaporation Technique (REV):**

A combination of ether and chloroform is used to dissolve the cholesterol and the surfactant. The resultant two phases are sonicated at 4 to 50 C with the addition of an aqueous phase that contains a medication. After a tiny amount of PBS is added, the transparent gel that has formed is further sonicated. At 40 °C and low pressure, the organic phase is eliminated. In order to produce niosomes, the resultant viscous niosome solution is diluted with PBS and heated on a water bath at 60°C for 10 min.

**Multiple Membrane Extrusion Method**

Evaporation creates a thin layer from a surfactant, cholesterol, and dicetyl phosphate mixture in chloroform. Aqueous drug polycarbonate membranes are used to hydrate the film. The solution is extruded through these membranes in a series of up to 8 passes, followed by the suspension that results. It is an effective way to regulate niosome size.

**Thin Film Hydration Technique:**

In a flask with a flat bottom, the combination of substances that create vesicles, such as surfactant and cholesterol, is dissolved in a volatile organic solvent. Using a rotary evaporator, the organic solvent is evaporated at room temperature (20°C), leaving a thin coating of solid mixture deposited on the flask wall. Rehydrating the dried surfactant film with aqueous phase at 0 to 60 °C while gently stirring is possible. Using this method, conventional multilamellar niosomes are created.

**Micro Fluidization:**

It is a relatively new method for creating unilamellar vesicles with a specific size distribution. This technique is based on the submerged jet concept, in which two fluidized streams contact in precisely planned microchannels inside an interaction chamber at extremely high speeds. The arrangement of the thin liquid sheet impingement along a single front ensures that the energy provided to the system stays in the region where niosomes develop. The generated niosomes are smaller, more consistent, and more repeatable as a consequence.

**Trans Membrane Ph Gradient:**

Remote Loading Process for Drugs In chloroform, surfactant and cholesterol are dissolved. Next, a thin layer is formed on the wall of the flask with a circular bottom as the solvent evaporates under reduced pressure. By vortex mixing, 300 M citric acid (pH 4.0) is hydrated onto the film. Multilamellar vesicles undergo three cycles of freezing and thawing before becoming sonicated. Aqueous solution containing 10 mg/ml of the medication is added and vortexed with this niosomal suspension. The sample's pH is then increased with 1M disodium phosphate to 7.0–7.2. Niosomes are created by heating this mixture for 10 minutes at 60 degrees Celsius.

**Formation Of Niosomes From Proniosomes:**

Coating a water-soluble carrier, such as sorbitol, with surfactant is another way to make niosomes. Dry formulation is the end product of the coating process. wherein a small layer of dry surfactant is applied to each water-soluble particle. Proniosomes are the name given to this preparation. The addition of aqueous phase at  $T > T_m$  and short agitation identify the niosomes.  $T$ =Temperature. The temperature at which phases change,  $T_m$ .

**CHARACTERIZATION OF NIOSOMES**

For the therapeutic uses, niosome characterisation is crucial. Niosome stability and in vivo performance are both significantly influenced by characterization factors. Thus, it is necessary to analyse various factors, including shape, size, polydispersity index, number of lamellae, zeta potential, encapsulation effectiveness, and stability.

**Size And Morphology:**

The most popular techniques for determining niosome sizes and shape are dynamic light scattering, scanning electron microscopy, transmission electron microscopy, freeze fracture replication electron microscopy, and cryotransmission electron microscopy. DLS concurrently gives useful data on the homogeneity of the solution and cumulative information on particle size. A single population of scatterers is implied by a single sharp peak in the DLS profile. In this regard, the PI is beneficial. For colloidal systems, it less than 0.3 equates to a homogeneous population. The morphology of the niosomes is often studied using microscopic methods.

**Zeta Potential:**

Zetasizer and DLS equipment can be used to measure the surface zeta potential of niosomes. Niosome behaviour is significantly influenced by the surface charge of the niosome. Charged niosomes are often more resistant to aggregation than are uncharged vesicles. Niosomes that had been loaded with paclitaxel were made by Bayindir and Yuksel, who also looked at their physicochemical characteristics such zeta potential. They discovered that niosome electrostatic stabilisation requires negative zeta potentials of between 41.7 and 58.4 mV.

**Bilayer Characterization. :**

Niosome bilayer properties are crucial for effective drug entrapment. AFM, NMR, and small angle X-ray scattering for multilamellar vesicles may all be used to determine the number of lamellae. The mobility of a fluorescent probe may be used to determine the membrane stiffness of niosomal formulations as a function of temperature. The most used fluorescent probe is DPH, which is included in niosomal dispersion. DPH often lives in the bilayer membrane's hydrophobic area. Fluorescence polarisation determines how viscous the niosomal membrane is at the microscopic level. strong microviscosity of the membrane is shown by strong fluorescence polarisation. Additionally, the in situ energy-dispersive X-ray diffraction in conjunction with the latter approach may be used to characterise the bilayer thickness.

**Entrapment Efficiency:**

Entrapment efficiency is the percentage of the administered medication that is captured by niosomes. Using centrifugation, dialysis, or gel chromatography, free medication that has not been encapsulated can be eliminated from the niosomal solution. By destroying the vesicles after this phase, the loaded medicine may be released from the niosomes. Niosomal suspension can be made niosome-free by adding 0.1% Triton X-100 or methanol. A high-performance liquid chromatography system or a spectrophotometer can be used to measure the drug concentration in both the loaded and free states.

**Stability.**

By measuring the mean vesicle size, size distribution, and entrapment effectiveness during multiple month storage periods at various temperatures, it is possible to assess the stability of niosomes. Niosomes are collected regularly throughout storage to determine how much of the medicine is maintained in the niosomes, which is then determined using UV spectroscopy or HPLC techniques.

**In Vitro Release:**

An approach that is frequently used to examine in vitro release is one that uses dialysis tubing. A dialysis bag is cleaned and given distilled water to soak in. The drug-loaded niosomal suspension is placed into this bag after 30 minutes. The vesicle-containing bag is continuously shaken in a buffer solution at a temperature of 25°C or 37°C. Samples were taken out of the outer buffer (release medium) at predetermined intervals and replaced with the same amount of brand-new buffer. A suitable assay method is used to determine the drug content of the samples.

**RESULT AND CONCLUSION:**

Nanoparticles have been employed as medication delivery devices to improve therapeutic benefits or lessen toxicity throughout the past few decades. These drug delivery systems, which have several uses in drug delivery and targeting, include niosome nanoparticles. For the parenteral or cutaneous distribution of antifungal medications, the use of niosomes can be particularly advantageous. The low penetration rate of transdermal medication administration is one of its drawbacks.

The stratum corneum, the top layer of skin, is where the majority of medication concentrations are found. Drug delivery into and across the skin is made easier by encapsulating medications in nanocarriers like niosomes. The improvement of medication distribution via the skin is made possible by niosomes. They could serve as organic solvents to help poorly soluble medicines dissolve. Niosomes may also operate as a local repository for the slow release of active substances.

Surfactants may act as penetration enhancers and simplify cutaneous distribution when taking into account their ability to penetrate the stratum corneum [36]. The surfactants are nonimmunogenic, biocompatible, and biodegradable. The potential for drug protection from biological environments, the exertion of restrictive effects on target cells, and their delayed clearance from circulation are the three main justifications for giving niosomes for therapeutic targeting through parenteral route.

According to earlier research, using niosomes as drug carriers, particularly for antifungal drugs, produces greater results than using alternative carriers. The capacity to encapsulate both hydrophilic and hydrophobic medicines, as well as their prolonged stability in circulation, are all major characteristics of niosomes. They also considerably improve drug penetration through the skin. They may make suitable candidates for the treatment of fungi since they are less expensive than liposomes in terms of raw ingredients (mainly surfactants).

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