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Review Article

Recent Applications of Niosomes

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ABSTRACT

Niosomes are nonionic surfactant-based vesicles that are biodegradable, relatively nontoxic, more stable, and less expensive than liposomes. The bilayer structure of niosomes makes them one of the greatest transporters. In aqueous media, non-ionic surfactants form a closed bilayer vesicle based on their amphiphilic nature, using energy such as heat or physical agitation to form this structure, with the hydrophobic part remaining away from the aqueous solvent and the hydrophilic part remaining towards the aqueous solvent. The main text of the article provides the overview of the niosomes including the components of the niosomes such as cholesterol and surfactants, their merits and demerits, methods of preparation, and recent advances in application of niosomes with respect to different routes of delivery like including topical, transdermal, oral, and pulmonary, trans mucosal and ocular drug delivery. Niosomes have been intensively explored in recent years for a variety of uses, including topical, transdermal, oral, and pulmonary, trans mucosal and ocular drug delivery. They are simple to prepare and have a lower cost than its analogue system, liposomes, while also having a higher EE. In the disciplines of pharmaceutical and aesthetic sciences, this adaptable drug delivery technology offers a lot of potential.

INTRODUCTION

Non-ionic surfactants of the alkyl or dialkyl polyglycerol ether class, as well as cholesterol, are hydrated in aqueous media to form niosomes. They're biodegradable, nontoxic, more stable, and less expensive. Niosomes are tiny and feature a lamellar structure (Fig. 1). The bilayer structure of niosomes makes them one of the greatest transporters. In aqueous media, non-ionic surfactants form a closed bilayer vesicle based on their amphiphilic nature, using energy such as heat or physical agitation to form this structure, with the hydrophobic part remaining away from the aqueous solvent and the hydrophilic part remaining towards the aqueous solvent. (Fig. 2) Niosomes have been shown to be a viable drug delivery mechanism for a variety of routes, including topical, ocular, and parenteral. They're also a better carrier than liposomes, depending on a variety of parameters like cost and stability.

Niosomes were examined as an alternative to liposomes in 1985 because they had several advantages over liposomes, such as being more stable, nontoxic, and cost-effective due to the low cost of non-ionic surfactant compared to phospholipids, which oxidise [1, 2].

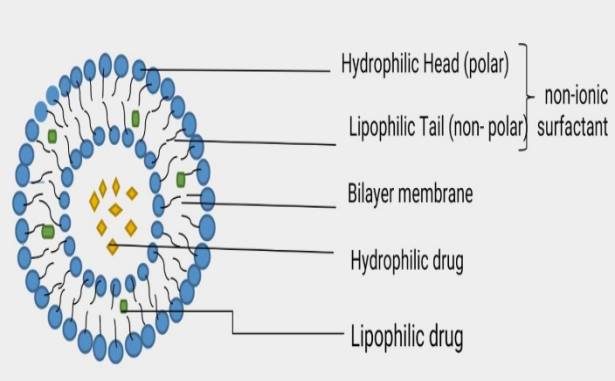

Figure 1: Structure of Niosome

Surfactants included within niosomes may also improve the drug's efficacy, potentially by increasing its uptake by target cells.

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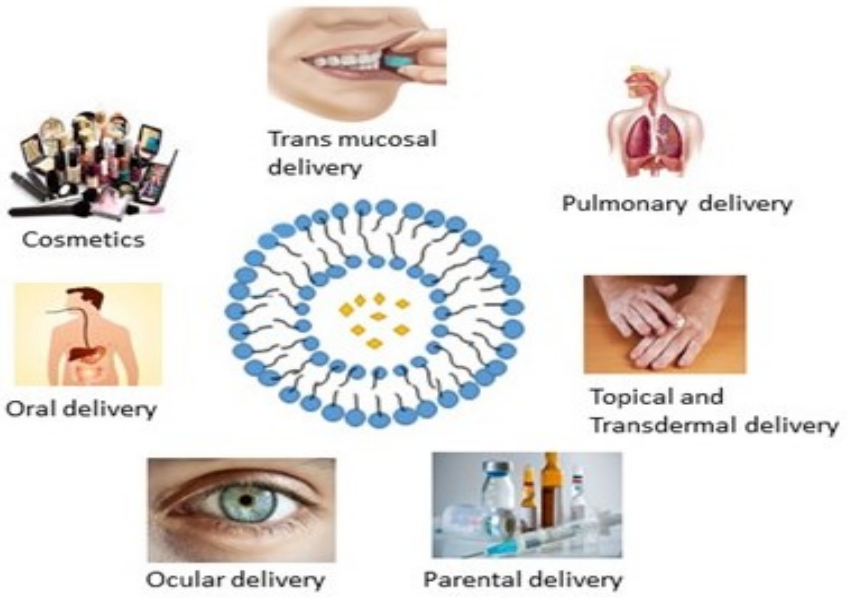

Figure 2: Niosomes as a viable drug delivery mechanism for a variety of routes

The vesicles of niosomes are subjected to a variety of forces, including Vander Waals forces on surfactant molecules, repulsive forces resulting from electrostatic interactions among charged groups of surfactant molecules, entropic repulsive forces of surfactant head groups, short-acting repulsive forces, and so on. The vesicular structure of niosomes is maintained by these pressures. However, the type of surfactant, nature of the encapsulated medication, storage temperature, detergents, use of membrane crossing lipids, and the ion concentration all affect the stability of niosomes The type of surfactant, the nature of the encapsulated drug, storage temperature, detergents, membrane crossing lipids, in situ interfacial polymerisation of surfactant monomers, and the presence of a charged molecule are all factors. By releasing the drug in a regulated manner, these can work as a deport. Biodegradable, biocompatible, and non-immunogenic surfactants should be employed in niosome preparation. Surfactants having alkyl chains ranging from C12 to C18 are best for making niosomes. Spans (60,40,20,85, and 80), tweens (20,40,60, and 80), and Brij (60,40,60, and 80) are the most common non-ionic surfactants utilised for most portions of the niosomes (30,35,52,58,72 and 76). The presence of steroidal compounds, such as cholesterol, improves the stiffness of the bilayer, and cholesterol is a significant component of the cell membrane. It also regulates the cell membrane's fluidity and permeability [2-6].

1. Composition of Niosomes

For the formation of niosome vesicles, there are two components, which are:

a) Lipid Compounds

Cholesterol and L—soya phosphatidylcholine are two examples of lipid molecules. These are utilized to give niosomes a more rigid structure and form.

i) Cholesterol

Cholesterol is an amphiphilic molecule that can work with a surfactant to form hydrogen bonds between the hydroxyl groups of cholesterol and the surfactant's hydrophilic head (Fig. 3). This aids in the enhancement of the membrane's stiffness and leakiness, resulting in increased niosome entrapment.

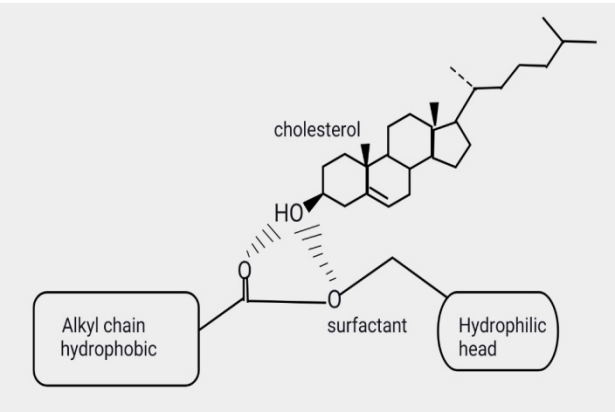

Figure 3: Interaction between cholesterol and surfactants

According to prior research, the amount of cholesterol used in the creation of niosomes must be modified based on the physical and chemical properties of surfactants and the type of medicine utilized. Because of hydrogen bonding, cholesterol interacts with surfactant in the bilayer of niosomes.

b) Non-ionic Surfactants

These are non-immunogenic, biocompatible, and biodegradable. The HLB (hydrophilic-lipophilic balance) is required for the production of niosomes. For the creation of suitable vesicles with high drug compatibility, the HLB range must be between 4 and 8.

The higher the HLB value, the higher they rise in the alkyl chain, and therefore the size of the niosomes grows. Along with these inducers, zeta potential inducers are also utilised because they create repulsion on the surface of the vesicles, inhibiting fusion and improving stability. Table 1 lists some non-ionic surfactant instances [7-10].

Table 1: Examples of non-ionic surfactants

Non-ionic surfactants	Examples
Ethers	Brij, decylglucoside, octyl glucoside, lauryl glucoside
Black copolymers	Poloxamers
Esters	Spans, glyceryl laurate, polysorbates
Fatty alcohols	Cetyl alcohol, cetostearyl alcohol, stearyl alcohol

Aside from these surfactants, a few other surfactants that have been linked to the development of niosomes include:

- Sorbitan Esters, for examples- Sorbitan monostearate, sorbitan monolaurate etc.
- Poly-sorbates, for examples- polysorbates (20,40,60,80)
- Ether linked surfactant, for example- ether-linked fluorocarbon.
- Di-alkyl chain surfactant
- Ester linked surfactant

The following equation uses the Critical Packing Parameter (CPP) to explain the effect of surfactant structure on niosome production:

$$\mathbf{CPP} = \frac{V}{I_c} \times \mathrm{A_o}$$

Where, CPP is the Critical Packing Parameter, V is the hydrophobic group volume, I_c is the critical hydrophobic group length and $\mathrm{A_o}$ is the area of the hydrophilic head group. The type of micellar structure is predicted by CPP value as assumed [11, 12]:

If CPP <1/2 formation of spherical micelles
If 1/2 < CPP <1 formation of bilayer micelles
If CPP >1 formation of inverted micelles

2. Merits of Niosomes

- One of the most important characteristics of nanoparticles is their size, which influences their dispersion, clearance, circulation time, and hence their ability to target a specific organ.
- Niosomes can be utilised for a range of medications because their structure allows them to accommodate hydrophilic, lipophilic, and amphiphilic drug moieties.
- Niosomes can boost the bioavailability of active pharmaceuticals by improving their physical and biological stability. Vesicles have adaptable qualities; by changing vesicle parameters such as composition, size, lamellarity, tapping volume, surface charge, and concentration, appropriate niosomes could be created.
- They are osmotically active, stable, and boost the entrapped drug's stability. Their administration can be done via oral, parenteral, or topical methods.
- The surfactants utilized in the creation of niosomes are biodegradable, biocompatible, and non-immunogenic. Surfactant handling and storage conditions do not require any requirements.
- They can control the drug release rate and administer normal vesicles in an exterior non-aqueous phase by emulsifying aqueous phase niosomal dispersion in a non-aqueous phase.
- Because of their excellent antigen encapsulation efficiency, stability in the gastric environment, and permeability across the intestine, niosomes have been frequently employed for antigen administration.
- When compared to oily dose forms, the aqueous vehicle-based suspension formulation improves patient compliance; additionally, because niosomal dispersion is aqueous, it can be emulsified in a nonaqueous phase to control drug release rate [13-22].

3. Demerits of Niosomes

Niosomes have a number of drawbacks, including reduced shelf life, physical and chemical instability, aggregation, vesicle fusion, and leakage or hydrolysis of the encapsulated medication. Furthermore, methods for creating multilamellar vesicles, such as extrusion or sonication, are time-consuming and may necessitate the use of specialist equipment [23].

4. Types of Niosomes

Niosomes are classified on the basis of size and number of bilayers (Fig. 4):

1. Small Unilamellar Vesicles:

The sonification process is used to prepare small unilamellar vesicles from the multilamellar approach. The size of SUVs has been estimated to be between 10 and 100 nm [24].

2. Large Unilamellar Vesicles:

The LUV has unilamellar vesicles with a large diameter and a single bilayer membrane. The vesicle's aqueous and lipid content is increased to increase its size. LUV vesicles are about 100nm in size. The ether injection method and reverse phase evaporation method are the most common ways for creating these vesicles. LUV has many advantages over MLV, such as high encapsulation of water-soluble drugs, consistent drug release rate, and so on [25-27].

3. Multi lamellar Vesicles:

It is made up of many bilayers that enclose the aqueous lipid compartment individually. The diameter of these vesicles is approximately 0.5-10 m. The most common niosomes are multilamellar vesicles. Lipophilic chemicals are well-suited to these vesicles as medication carriers [28].

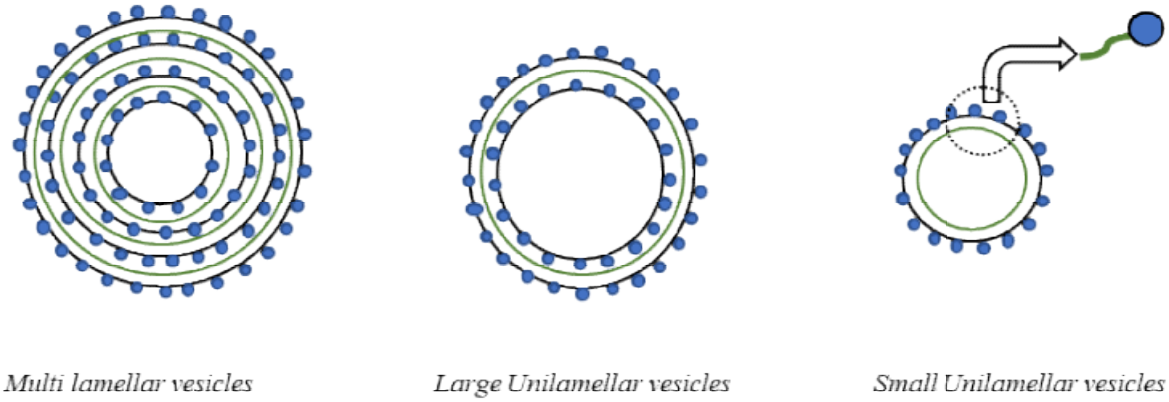

Figure 4: Types of Niosomes

5. Methods of Preparation

There are several methods through which niosomes can be prepared which are as follows-

5.1. Hand Shaking Method

Surfactant and cholesterol combination are dissolved in 10ml diethyl ether in RBF using the hand shaking method. The ether is prepared to be evaporated at room temperature in a rotary evaporator under vacuum. The surfactant swells up and is peeled offed when hydrated. After then, swollen amphiphilic fold to create vesicles. The volume of liquid trapped inside vesicles is only about 5-10% of the total volume [29].

5.2. Ether Injection Method

The surfactant and cholesterol mixture is dissolved in a volatile organic solvent and evaporated in a rotary evaporator, leaving a thin layer of solid mixture on the flask wall. After that, the dried layer is rehydrated with an aqueous solution containing the desired drug. The technique is carried out at room temperature with little agitation [30].

5.3. Micro Fluidization Method

Currently, this approach is being used to make unilamellar vesicles of a specific size. It is based on the submerged jet concept, which involves two fluidized streams spreading at ultra-high velocities in a separate microchannel within the interaction chamber. The intrusion on a full-view thin liquid layer is designed in such a way that the device's energy is provided inside the niosome formulation zone [31].

5.4. The Bubble Method

This method uses an organic solvent to generate liposomes and niosomes in one step. The bubbling machine is made up of an RBF and many collars for measuring the temperature in the water bath. A water-cooled reflux and thermometer are inserted into the first and second necks, as well as the nitrogen supply. Cholesterol and surfactant are mixed with this pH 7.4 buffer at 70°C, homogenized using a higher shear homogenizer for about 15 seconds, and then "bubbled" with nitrogen gas at 70°C [32].

5.5. Sonication Method

Surfactants and cholesterol are mixed together and disseminated in an aqueous solution. The solution is then transferred to a vial and sonicated at 60°C for about 3 minutes. A titanium probe is typically used for sonication. This method is used to make multilamellar vesicles [33].

5.6. Reverse Phase Evaporation Method

The surfactants are distributed in an organic solvent that is volatile in nature, such as chloroform or ether, and the medication is in an aqueous phase in this approach. After the organic solvent evaporates, the niosomes are bathed in water in a two-phase oil emulsion. The emulsion is then dried at 40°C in a Rotovac evaporator to form a semi-solid gel, which is subsequently hydrate to form huge vesicles. A tiny amount of buffer is added to the semisolid gel and sonicated at 4-5°C to create the unilamellar vesicles [34].

5.7. Micro Fluidization

In this technique an interaction chamber is used where two phases interact with each other at an ultra-high speed in microchannel. Due to high speed impingement and energy with the high degree of reproducibility, small and uniform niosomes are formed [35].

Table 2: Methods of preparation with different types of Non-ionic surfactants and stabilizer and its applications.

Methods	Non-ionic Surfactants and Stabilizers	Drugs	Applications	References
Thin film hydration technique	Span 60, Cholesterol	Diltiazem	Calcium channel blocker; hypertension, angina pectoris, and some types of arrhythmia	[36]
Thin film hydration technique	Span 60, Cholesterol	Diacerein	Inhibiting interleukin-1 beta; Osteoarthritis	[37]
Sonication Method	Span 60, Cholesterol, dicetylphosphare (DCP), stearylamine (SA)	Candesartan	Angiotensin II receptor antagonist; Hypertension	[38]
Lipid film hydration method	Span 60, Cholesterol	Loratadine	Antihistamine; Allergies	[39]
Thin film hydration method, and Ether injection method	Tween 40, cholesterol	Ketoprofen	Nonsteroidal anti-inflammatory drugs (NSAID); Inhibiting synthesis of prostaglandin. Analgesic and antipyretic effects.	[40]
Thin film-hydration technique	Span 60, Cholesterol, Solulan C 24	Ketorolac	NSAID	[41]
Thin film-hydration technique	Span 60, Cholesterol, Dicetylphosphate (DCP)	Tenofovi	To treat chronic (long term) HBV	[42]
Lipid layer hydration method	Span 60, Cholesterol	Folic acid	Anaemia	[43]
Thin film-hydration technique	Span 60, Cholesterol, Dicetylphosphate (DCP)	Clarithromycin	To treat Bacterial infections	[44]
Thin film-hydration technique	Tween 80, Cholesterol, Dicetylphosphate (DCP)	Zidovudine	NRTIs; Nucleoside reverse transcriptase inhibitors; to prevent passing the HIV to the unborn baby in pregnant women	[45]
Lipid layer hydration method, Thin film ether injection method	Span 60, Cholesterol, Dicetylphosphate (DCP)	Griseofulvin	To treat skin infections	[46]
Thin film-hydration technique	Span 60, Span 80, Cholesterol	Acyclovir	Anti-viral infections	[47]

8. Applications

8.1 Oral Delivery System

Oral drug delivery is known as the most convenient route of drug administration, but there are still a number of challenges, including formulating oral drugs for the acidic environment of the stomach, enzymatic degradation in the gastrointestinal tract, first pass metabolism, poor absorption, and variable drug bioavailability. Niosomes are designed to decrease or eliminate these issues by increasing the drug's bioavailability and absorption [48-50]. Azmin et al. reported the first use of oral medication delivery in 1985, finding that the niosomal formulation dramatically enhanced methotrexate bioavailability [51]. Oral genetic immunization against hepatitis B has also been examined using niosomes modified with the polysaccharide o-palmitoyl mannan [52]. Niosomes have been studied for the oral delivery of lipophilic pharmaceuticals like diacerein, which has low bioavailability due to its low solubility and is classified as Class II in the Biopharmaceutical Classification System (BCS). Researchers looked at sorbitan monolaurate and Poloxamer 184 based niosomes for diacerein oral delivery and discovered that the niosomal formulations had better *in vitro* dissolving characteristics than the diacerein aqueous suspension [53]. Table 3 lists some of the niosomes that have been produced for oral delivery.

Table 3: Examples of various niosomes of different drugs for oral delivery system.

Drug	Surfactants	Method of preparation	Reference
Celecoxib	Span 60	Proniosome derived niosome method	[54]
Diacerein	Sorbitan monolaurate and poloxamer 184	Thin film hydration	[55]
Ganciclovir	Span 40 and 60	Reverse phase evaporation	[56]
Methotrexate	Tween 80	Thin film hydration	[57]
Paclitaxel	Span 40	Thin film hydration	[58]
Plasmid DNA for Hepatitis B	Span 60	Reverse phase evaporation	[59]
Tetanus toxoid	Span 60 and Tween 20	Reverse phase evaporation	[60]
Tramadol	Tween 80, Tween 40, Span 80 and 40	Proniosome derived niosome method	[61]
Valsartan	Span 60	Proniosome derived niosome method	[62]

8.2 Topical and Transdermal Delivery

Topical drug delivery systems have a number of advantages, including localized drug release and decreased side effects due to reduced systemic absorption [63, 64]. In transdermal drug delivery, the active ingredients are delivered through the skin for systemic circulation, which has several advantages over other routes of administration, including higher bioavailability by avoiding first pass metabolism, no need for a needle and thus better patient compliance, no food drug interactions, and no acidic and enzymatic degradation in the gastrointestinal tract. However, transdermal is limited by the drug molecule's poor penetration rate, with the stratum corenum SC acting as a barrier to drug absorption [65, 66]. Niosome penetration is also influenced by the liquid condition of the niosomes. More aqueous formulations may not stay at the site of application, so niosomes are mixed with some gel to form a niosomal gel, which stays on the skin for longer periods, acting as a reservoir for the drug and also allowing drug absorption through the SC, increasing skin hydration and thus increasing drug penetration through skin. For topical use**, Manosroi and colleagues** produced innovative elastic niosomes entrapped with the non-steroidal anti-inflammatory medication diclofenac diethylammonium. Various formulations containing dipalmitoylphosphatidylcholine, Tween 61, or Span 60 in various molar ratios of cholesterol and ethanol at 0%–25% (v/v) were created. Because of their higher stability, elastic Tween 61 niosomes were used.**Gupta et al.** have looked at employing transfersomes, niosomes, and liposomes to transport tetanus toxoid to the skin for non-invasive immunization. The in vivo study discovered that transfersomes provoked a stronger immunological response than niosomes and liposomes because of their elastic bilayer, which allows transfersomes to bend and pass through the skin's minute pores [67, 68].

Table 4: Examples of niosomes that have been investigated for dermal and transdermal delivery.

Drug	Surfactant	Method of Preparation	Reference
Acetazolamide	Span 60	Thin film hydration	[69]
Antioxidant enzyme catalase	Sugar ester surfactants	Thin film hydration	[70]
Artemisone	Span 60	Thin film hydration	[71]
Capsaicin	Span 60	Thin film hydration	[72]
Diacerein	Span 60	Thin film hydration	[73]
Ellagic acid	Span 60 and Tween 60	Reverse phase evaporation	[74]
Enoxacin	Span 40 and Span 60	A combination of ethanol injection and freeze drying	[75]
Estradiol	Span 40, 60 and 85	Proniosome derived niosome method	[76]
Febuxostat	Tween 20 and Span 60	Thin film hydration	[77]
Finasteride	Brij 52, 72, 97 and Span 40	Thin film hydration	[78]
Gallidermin	Tween 61	Freeze dried	[79]
Hydroxychloroquine	Span 20 and 60, Tween 20, 40, 60 and 80	Thin film hydration	[80]
N-terminal Tat-GFP fusion protein	Tween 61	Freeze dried liposome method	[81]
Papain	Tween 61	Thin film hydration	[82]
Plasmid DNA (Hepatitis B)	Span 85	Reverse phase evaporation	[83]
Propolis	Span 60	Ethanol injection method	[84]
Resveratrol	Span 80, Gelot 64	Thin film hydration and ether injection, Thin film hydration and ethanol injection	[85]
Risperidone	Tween 20, 60 and 80, Span 20, 40, 60, 80	Proniosome derived niosome method	[86]
Roxithromycin	Span 60	Thin film hydration	[87]
Salidroside	Span 40	Thin film hydration	[88]
Sulfadiazine sodium	Pluronic L64 and P105	Modified lipid film method	[89]
Sumatriptan succinate	Brij 72, Eumulgin B2, Span 60 and 80	Thin film hydration	[90]
Tenoxicam	Span 80 and 60, Tween 20 and 60	Proniosome derived niosome method (coacervation phase separation)	[91,92]
Tramadol	Span 20, 40, 60 and 80, Tween 20, 40, 60 and 80	Proniosome derived niosome method (coacervation phase separation)	[93]
Tretinoin	Brij 30, Span 40 and 60	Thin film hydration	[94]
Tretinoin	Pluol Oleique CC	Thin film hydration	[95]
Tretinoin	Alkyl polyglucoside	Thin film hydration	[96]
Ursolic acid	Span 60	Thin film hydration	[97]
Vitamin E	Tween 80 and Span 20	Emulsion evaporation	[98]
8-methoxypsoralen	Span 40 and 60	Thin film hydration	[99]
Sulfasalazine, propranolol, tyrosol	Pluronic L64, sodium bis(2-ethylhexyl) sulfosuccinate)	Thin film hydration	[100]

8.3. Ocular Delivery

Traditional ocular drug delivery preparations such as eye drops, ointments, and suspensions are unable to achieve high bioavailability due to physiological barriers in the eyes, such as the barrier properties of the retinal pigment epithelium and the endothelium lining the inner side of the retinal blood vessels [101]. Previous research has shown that niosomes can overcome these obstacles because, first and foremost, niosomes are better maintained on the ocular surface than other carriers. Second, the nano-sized niosomes may withstand drainage by tearing and blinking reflexively. Hyaluronic acid (HA) coated niosomes were studied by Zeng and colleagues. Because it is a natural component of

the vitreous body and aqueous humour of the eye, HA, a linear polymer comprised of long chains of repeating disaccharide units of N-acetyl glucosamine and glucuronic acid, has gained increased attention in 25 ocular administrations. Because of HA's mucoadhesive properties, the formulation's ocular contact duration is increased, which increases medication absorption and bioavailability. This study found that HA-coated niosomes could prolong pre-corneal retention, improve aqueous humour pharmacokinetics, and boost tacrolimus bioavailability [102]. Proniosome-derived niosomes for topical ocular administration of tacrolimus were recently produced; these niosomes were made with poloxamer 188, lecithin, and cholesterol. Before usage, proniosomes were reconstituted with ethanol and a little amount of water to create niosomes. *In vitro* permeation investigations were conducted on freshly excised rabbit corneas, and it was discovered that the cumulative permeation amount of tacrolimus from niosomes and drug retention in the cornea were much higher than with commercial ointment. Abdelkader and colleagues looked into using niosomes and discomes to deliver naltrexone hydrochloride. They looked at spreading, rheological properties, and their ability to prevent naltrexone hydrochloride from oxidizing in aqueous solutions. The produced niosomes outperformed water medication solutions in terms of wetting and spreading [103].

Table 5: Examples of niosomes investigated for ocular deliver.

Drug	Surfactant	Method of Preparation	Reference
Gatifloxacin	Span 60	Solvent injection method	[104]
Naltrexone	Span 60	Reverse phase evaporation	[105]
Plasmid pCMS-EGFP	Tween 80	Emulsification and thin film hydration	[106]
Plasmid pCMS-EGFP	DOTMA and Tween 60	Reverse phase evaporation	[107]
Plasmid pCMS-EGFP	Tween 80	Solvent emulsification evaporation	[108]
Tacrolimus	Poloxamer 188 and lecithin	Proniosome derived niosome method	[109]

8.4. Pulmonary Delivery

When treating disorders like lung infection, inflammatory diseases of the respiratory tract, or lung cancer, pulmonary medication administration is preferable over oral drug delivery because pharmaceuticals are directly delivered to the site of action for either local or systemic treatment. With an estimated surface size of 50 to 75 square meters, the lung includes the equivalent of around 2400 kilometers of airways and 700 million alveoli. Proniosomes have been studied for the delivery of beclomethasone dipropionate into the lungs. This method allows for the manufacture of drugs in powder form, which are then hydrated to form niosomes before being administered to patients. *In vitro* and in vivo studies using amphotericin B-loaded niosomes for the treatment of leishmaniosis and aspergillosis have been conducted. In a rat model of invasive pulmonary aspergillosis, researchers discovered a considerable reduction in fungal lung burden as well as significant suppression of the Leishmania donovani liver parasite. These findings suggest that amphotericin B-loaded niosomal 27 formulations improved pulmonary delivery while decreasing systemic exposure and toxicity [110, 111].

8.5. Parenteral Delivery

The parenteral route is the most common and efficient method of delivering medicines with low bioavailability and a narrow therapeutic index. Parenteral administration has additional benefits, such as a reduced variation of the steady-state plasma drug level and maximal medication consumption. On the other hand, disadvantages include a restricted ability to alter dosages, difficulty retrieving the medicine in the event of toxicity, and injections might lead to low patient compliance owing to needle phobia [112]. To solve the challenges associated with traditional parenteral administration formulations, some success has been achieved employing Nano carriers, which are capable of enabling targeted medication delivery and sustained release. For acyclovir parenteral administration, Mukherjee and coworkers examined liposomes with niosomes. The goal of this investigation was to see if drug-loaded Nano carriers could achieve prolonged release and hence lessen dose-related systemic toxicity. When compared to liposomes, the results demonstrated that niosomes are better carriers for acyclovir because they displayed better stability and produced sustained release.

Mullaicharam et al. studied the accumulation of rifampicin-loaded niosomes in the lungs of rats after intravenous administration. Thin film hydration was used to make niosomes with Span 20, 40, 60, and 80. In albino rats, the in vivo organ distribution pattern following intravenous injection was investigated to establish the delivery system's potential for site-targeted rifampicin delivery. Between the rifampicin loaded niosomes and the free rifampicin solution, there was a substantial difference in total drug concentration in the lung, liver, 28 kidneys, and blood serum [113].

8.6. Trans Mucosal Drug Delivery

Ocular, nasal, oromucosal (buccal, sublingual, and gingival), pulmonary, gastrointestinal, and vaginal sites are all trans mucosal drug delivery sites. When it comes to the potential for medication administration, each of these locations has its own set of characteristics. These characteristics must be taken into account while constructing a good medication delivery system. Niosomes are versatile drug delivery systems that have been researched for trans mucosal distribution of numerous chemicals through the oral, nasal, and vaginal mucosa due to its benefits**.** El-Alim and colleagues created benzocaine proniosomal gel formulations employing Span 80, Span 85, and combinations of the three to obtain effective buccal delivery of benzocaine for local anesthetic. EE was found to improve if the Span 80 or Span 85 ratio was increased, and *in vitro* drug release experiments revealed a burst release followed by a delayed release. When tested using a chicken pouch as a model mucosal membrane, formulas made with Span 80 and 85 revealed a higher rate and amount of benzocaine permeability. After a month of storage at 4-8C, physical stability testing revealed that more than 90% of the medication was still present. Katare and colleagues created polysaccharide-capped niosomes for tetanus toxoid vaccination of the oral mucosa. Niosomes were made utilizing the reverse phase evaporation process with Span 60, Tween 20, stearylamine, and cholesterol before being coated with a pullulan derivative in this study (O-palmitoyl pullan). The immune boosting impact of the niosomes after oral delivery was assessed by measuring serum immunoglobulin levels. The coated niosomes were able to elicit an immunological response comparable to tetanus toxoid injections [114-116].

8.7. Niosomes in Cosmetics

L'Oréal (Clichy, France) was the first to create and patent niosomes in 1975, and Lancôme (Paris, France) was the first to market products with them in 1987. Since then, a large range of medicinal applications and cosmetic products with varied functions, such as anti-wrinkle, skin whitening, moisturizing, and sunscreen, have been created and commercialized. Because of their benefits such as higher stability of entrapped active components, increased skin penetration, bioavailability, improved surface adherence, and prolonged release qualities, niosomes have been actively researched as a carrier system for cosmetic actives. The usefulness of niosomes in cosmetic formulations has been evaluated with respect to conventional formulations such as emulsions. Niosomes showed lower toxicity, allowing controlled delivery of the loaded active ingredients that exhibit useful properties for skin moisturizing and tanning products. Niosomes have been used to study a variety of plant-based bioactive substances in order to optimize their skin effects. For topical distribution of resveratrol, Pando and colleagues created liposomes and niosomes, with olein serving as a penetration enhancer for both vesicles. We were able to obtain negatively charged vesicles with a mean size of roughly 200 nm. When compared to the control, both vesicles showed substantial resveratrol accumulation and low transdermal delivery; this feature was more pronounced for niosomes, which displayed improved cutaneous resveratrol delivery behavior. Mahmoud and colleagues developed and tested niosomes loaded with caffeine for the treatment of cellulite. When compared to the commercial product Cellu Destock®, histology demonstrated a much larger reduction in the size and thickness of the fatty layer of rat skin for the niosomal gel containing system. Furthermore, the niosomal group had greater caffeine plasma content, implying that incorporating caffeine into a niosomal system increased penetration through the skin and into the underlying fatty layer. This is a promising method for creating a transdermal anti-cellulite caffeine product in a niosomal gel system with increased transdermal bioavailability [117-121].

9. Perspectives and Limitations

Because of various advantages, such as biodegradability, biocompatibility, chemical stability, and the ability to increase the therapeutic effectiveness of drug molecules by adjusting drug release, niosomes have drawn a

lot of interest in controlled drug delivery. Despite countless research and the fact that niosomes have a long way to go before becoming a therapeutic reality, niosomes still face numerous and major hurdles. The main barrier to using niosomes as a potential medication delivery method is sterilizing. Heat sterilization methods such as dry heat and steam sterilization are ineffective and damaging for lipid or surfactant-based formulations with a gel liquid transition temperature lower than the sterilization temperature, as heat can cause extensive drug leakage from the vesicles due to the destruction of the bilayer membranes. Membrane filtration is also ineffective for niosomes that are larger than the membrane filters' pore size (0.22 m). Preparation under aseptic circumstances, as well as procedures that generate less heat, such as gamma irradiation, could be viable options. Niosomes can be manufactured in an aseptic environment by filtering all organic solvents, buffers, surfactant solutions, and drug solutions via anti-bacterial filters, autoclaving glassware, and operating in a laminar fume hood with sterile airflow. The gamma sterilization technique uses Cobalt 60 radiation to destroy bacteria, resulting in a short turnaround time and the ability to quickly permeate packaging and items due to the low heat generated. Many pharmaceutical goods, such as eye ointments, drops, and injectable medicines, are sterilized using gamma radiation. The ocular toxicity of niosomes has recently been explored using hen's egg chorioallantoic membranes and excised bovine corneal opacity and permeability models to assess conjunctival and corneal irritation potential of Span 60 niosomes and surface modified Span 60 niosomes. The study found minor ocular irritations, implying that niosomes are well tolerated by the eyes. There are now four basic techniques to developing and expanding the use of niosomes in pharmaceuticals. The first method involves coating niosomes with ligands to improve the efficiency of targeted medication delivery. Particular targeting is required to increase the specific uptake and permeability of medications across the blood-brain barrier. Encapsulation of drugs in nano-vesicles is not enough for successful drug delivery to locations such as the central nervous system. The second strategy focuses on creating and optimizing novel approaches that improve the quality of niosomes while also allowing for industrial scale-up. Traditional niosome preparation methods include thin film rehydration, reverse phase evaporation, and ether injection. These procedures necessitate the elimination of organic solvents and are both costly and time-consuming.

CONCLUSION

This article provides a quick overview of their structure, composition, benefits, drawbacks, methods of preparations and recent advances in applications. They've devised a promising strategy for delivering the medicine in a regulated and long-term manner. There are no additional handling or storage requirements for them. Niosomes have been intensively explored in recent years for a variety of uses, including topical, transdermal, oral, and pulmonary, trans mucosal and ocular drug delivery. They are simple to prepare and have a lower cost than its analogue system, liposomes, while also having a higher EE. In the disciplines of pharmaceutical and aesthetic sciences, this adaptable drug delivery technology offers a lot of potential. Niosomes are promising delivery systems, and their potential can be further boosted by unique preparation, modification, and formulation components, which allow for targeted distribution, improved drug entrapment efficiency, and the development of vesicles with specific properties.

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