Niosomes: A Novel Nanocarrier to Advance the Topical Ophthalmic Drug Administration

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Abstract

Niosomes are emerging nanocarriers in the drug delivery industry. They have an amphiphilic structure consisting of non-ionic surfactants to encapsulate various drugs inside. They are often compared to their counterparts, liposomes, which exhibit similar structures. Compared to liposomes, niosomes possess more promising aspects in the drug delivery industry due to their non-toxic and biocompatible nature. The niosomes are also being highlighted as a potential carrier for ocular drug delivery. In the most common ocular drug delivery route, topical administration, 95% of the drug is lost before it reaches the target site. Niosomes' special properties have been found to enhance the permeability and bioavailability of ocular drugs. This paper initially provides general information about niosomes such as components, types, and differences from liposomes. It then moves on to their potential in ocular drug delivery by explaining their unique properties. Finally, it examines the application of niosomes in real disease treatment, recent trends in niosome development, and what can be done to foster the use of niosomes in the ocular industry.

1 Introduction

Niosomes are nanocarriers with amphiphilic structures, both hydrophilic and hydrophobic, which mainly consist of non-ionic surfactants. When the non-ionic surfactants disperse in the water, their self-assembling characteristics make them form microscopic vesicles, which are niosomes. The hydrophilic head of the surfactants surrounds the outmost layer and the innermost layer, while the hydrophobic tail forms a layer in between the hydrophilic ones.

Hence, they are known as versatile nanocarriers as they can carry both hydrophilic and hydrophobic types of substances in them. Niosomes share a similar structure with liposomes, which is why they are often mentioned together. However, liposomes consist of phospholipids, which are the types of surfactants

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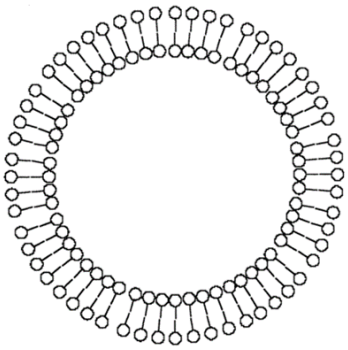


Figure 1: Schematic structure of a typical niosome in which the 'ball and stick' components represent a surfactant bilayer with solvent (usually water) on the inside and outside. [UV98]

that form cell membranes. With similar structures but distinct characteristics, liposomes and niosomes are discussed for different purposes, which will later be elaborated.

In terms of drug delivery, the development of nanotechnology like niosomes has been used to tackle the complicated issues of drug administration. Issues in drug delivery include things like low bioavailability, low concentration rate at the target site, low penetration rate, etc. However, the selection of nanocarriers to assist the drug delivery is painstaking. They should be biocompatible, carry a sufficient amount of drug for higher concentration, and be able to release drugs at a sustained release rate.

In terms of ocular drug delivery, additional challenges are posed as the eyes are one of the most sensitive organs in the human body. The ocular tissues are more easily damaged and are harder to recover, and the eyes possess numerous mechanisms to prevent the entrance of foreign substances which further challenges the drug administration. Niosomes, with their non-toxic, high encapsulation rate, and relatively low cost, demonstrate promising aspects in this field. In this review, the incorporation of niosomes through the topical corneal route is discussed. As the most common method, topical administration benefits from high patient compliance but suffers from poor bioavailability. The review discusses how their structural and functional components can provide assistance to more efficient ocular drug delivery.

2 Basic Components of Niosomes

Niosomes are mainly composed of non-ionic surfactants, but some other complimentary materials are added to amplify several desirable traits such as stability. [KY17]These include cholesterol and charge inducers.

2.1 Non-ionic Surfactants

A surfactant (Surface Active Agent) is an amphiphilic structured molecule that has two opposite sides within it – the hydrophilic and the hydrophobic. Due to its unique characteristic, it is often used in treatments between different surfaces such as oil and water to reduce its surface tensions. the components that create the vesicles. Among those, non-ionic surfactants are surfactants without charges, which makes them less toxic and hemolytic compared to other types of surfactants. Since the type of non-ionic surfactants influences many features of the niosome, they should be selected according to the purpose they are trying to achieve.

Table 1: Commonly used non-ionic surfactants in the composition of niosomes. [Umb21]

Surfactant	Properties
Alkyl Ethers and Alkyl Glyceryl Ethers *Polyoxyethylene 4 Lauryl Ether(brij 30)*	Their HLB value is 9.7 and Phase transition temperature is below 10. Forms LUV when combined with 30 mmol/ L of cholesterol. It causes oxidation when used with benzocaine, tretinoin, and oxidizable medications, leading to discoloration.
Polyoxyethylene Cetyl Ether (Brij 58)	Brij 58 has the capacity of forming inverse vesicles. HLB value 15.7.
Polyoxyethylene Stearyl Ethers (Brij 72 and Brij 76)	HLB value of Brij 72 is 4.9 and Brij 76 is 12.4. The entrapment efficiency of Brij 72 is higher than Brij 76.
Sorbitan Fatty Acid Esters	Usually referred to as Span. Generally used in water-based cosmetic preparations to solubilize oils. With an increase in the carbon chain length transition temperature increases i.e. gel transition temperature of span 60 is higher than span 20 and span 40. Vesicles prepared from a higher span are more stable and less leaky. Niosomes prepared from span 60 give the highest entrapment efficiency. Span 60 is capable of protecting the drug from degradation by proteolytic enzymes.
Polyoxyethylene fatty acid esters	These are derived from fatty acid esterified ethoxylated sorbitans. For niosome preparation usually, Tween 20, 40, 60 and 80 are used.
Pluronic L64 and Pluronic p105	Pluronic L64 and 105 are copolymers made up of polyethylene (EO) oxide and polypropylene oxide (PO). Arranged as EO-PO-EO. Pluronics interact themselves with multidrug-resistant cancer tumors.

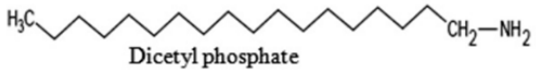
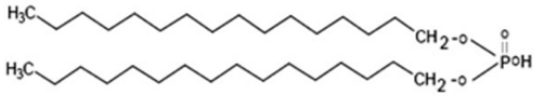
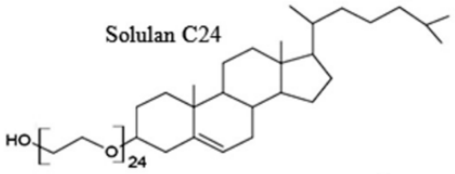
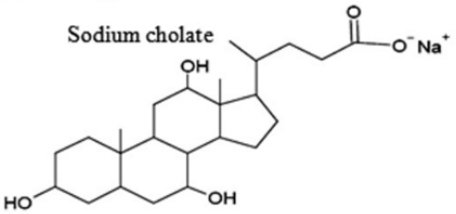
2.2 Cholesterol

Cholesterol is a fatty substance in the human body that assists in the formation of cell membranes. Similarly, cholesterol is added to the niosomes to enhance the rigidity of the vesicles' membrane. [RNSM11] It is also found that it alters the hydrophobic-lipophilic balance (HLB) to influence the size of the vesicle. In the experiment conducted by Fatemeh Nowroozi et al., the increase of cholesterol content from 20 to 40% resulted in a 20-27% decrease in the size of the vesicles composed of Brij 72 and Span 60 niosomes. However, they also noted that this is possibly dependent on the type of surfactants since Tween-based formulations didn't exhibit much difference with the addition of cholesterol. [NAJ+18]

2.3 Charge Inducers

Charge inducers are polymers that induce a charge on the surface of the vesicle to increase the stability of niosomes. They use repulsive forces of the same charges to prevent the surfactants from aggregating. [SBAY15] Commonly used negative charge inducers include dicetyl phosphate (DCP) and stearyl amine (SA).

Table 2: Commonly used negative charge inducers in the composition of niosomes. [AAA14]

Name and structure of the additive	MW	T_m(°C)*	CMC**
Stearyl amine 	269.5	78–79	–
Dicetyl phosphate 	547	50–52	–
Solulan C24 	1443	50–51	0.07mM
Sodium cholate 	430.5	198–200	10mM

3 Types of Niosomes

3.1 Basic Niosomes

Basic niosomes can be divided into three categories: small unilamellar, large unilamellar, and multilamellar vesicles. Small and large unilamellar vesicles have one bilayer structure, and they differ in size. Small unilamellar vesicles typically range from 10-100 nanometers while large unilamellar vesicles range from 100-3000 nanometers. [BTGP20] Multilamellar vesicles are vesicles with more than one bilayer structure.

3.2 Specialized Niosomes

3.2.1 Ethosomes

Ethosomes are niosomes with high concentrations of ethanols. They demonstrate greater elasticity compared to basic niosomes. Ethosomes typically contain higher compositions of ethanol, which gives additional fluidity to the formulation. With their elastic traits, ethosomes can better penetrate through the anatomical barriers.

3.2.2 Proniosomes

Proniosomes are dehydrated versions of niosomes, which pose advantages to preventing fusion, aggregation, or sedimentation compared to normal niosomes. They are hydrated before the drug delivery. They can be classified into two categories: dry granular and liquid crystalline. Dry granular proniosomes are formed by coating a hydrophilic carrier with non-ionic surfactants, while liquid crystalline proniosomes are formed. [KNA+23] It is viewed as a promising drug delivery method as it can easily be formulated into tablets or capsules for convenience. [SRDJ10]

3.2.3 Discomes

Discomes are disc-shaped niosomes that are formed by controlling the ingredient ratio and temperature during niosome formations. In a study conducted by Abdelkader et al. to formulate a system for NTX delivery, discomes were formulated by a single step at 60 degrees Celsius compared to the typical formation which was formed after incubating a preformed niosome at 75. [AIKA11]

4 Difference Compared to Liposomes

Liposomes are nanocarriers that have amphiphilic bilayer structures which are composed of phospholipids. They were discovered before niosomes, in 1965, and are more widely used than niosomes. The below figure demonstrates the similar structure of liposomes and niosomes.

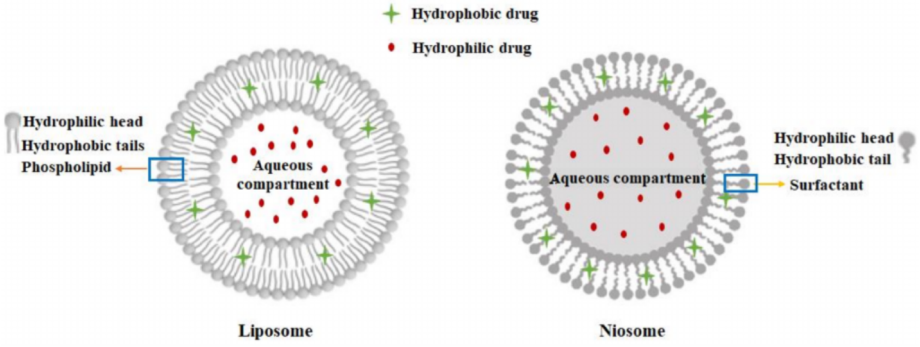


Figure 2: Schematic diagram of liposome and niosome structure which indicates where the drug is encapsulated. [ZECC+23]

Liposomes and niosomes can both encapsulate hydrophilic and lipophilic drugs. Moreover, they can be used for a targeted release of drugs. The key difference between the two vesicles is their composition. Liposomes are composed of phospholipids, which are the type of surfactants that are also used to form cell membranes. Meanwhile, niosomes are made of non-ionic surfactants that

do not have any charge. Niosomes have lower manufacturing costs compared to liposomes, and liposomes are more unstable as they are prone to oxidation and hydrolysis of phospholipids. [RGOW18, BM17]

5 Ocular Barriers

5.1 Challenges in Anatomy

As the most sensitive organ in the human body, there are various barriers to protect the eyes. While the barriers protect the eyes from potential diseases, they also prevent drugs from entering and reaching their target sites. The anatomical barriers in the eyes are mainly divided into two sections: anterior and posterior. Anterior barriers include the cornea, conjunctiva, and blood-aqueous barrier (BAB). The cornea consists of five layers, which are the outer epithelium, Bowman's membrane, intermediate stroma, Descemet's membrane, and endothelial layer. The outer epithelium obtains a lipophilic condition which hinders the permeation of hydrophilic drugs. There are also efflux pumps that pump out the drug molecules, which results in a lower concentration of drugs. In the stroma, there exists an extracellular matrix of the cells which slows the diffusion of lipophilic drugs. The conjunctiva is a mucous membrane covering most of the eye's anterior segment. While it has a big surface area for easier permeation, its highly vascularized nature poses a vulnerability to drug loss and danger to the systemic circulation of the drug. Finally, the blood-aqueous barrier acts as a barrier due to its selective nature in drug permeation. Specific osmotic pressure and physicochemical properties must be achieved in order to cross the barrier. It also highly inhibits the entry of drugs that are hydrophilic and have large-molecule sizes. [LCF23]

The posterior barriers include scleral and blood-retinal barriers (BRB). The sclera is the white part of the eye that is visible from the outside. It is composed of collagen and other proteins, which limits the permeation of drug molecules. Moreover, since its thickness varies on different parts, a consistent and effective distribution of drugs may appear as an issue. The blood-retinal barrier is formed by tight junctions of cells that limit the entry of various molecules. It regulates the substances that are reaching the retina; thus, different strategies should be applied to circumvent or permeate this barrier to reach the retina. [DMM03]

5.2 Dynamic Barriers

In addition to the anatomical barriers, the dynamic barriers are different ocular activities that prevent the drugs from permeating through and reaching their target sites. For instance, tear films are thin, transparent layers formed by lipid, aqueous, and mucin layers. Due to these different types of layers, tear films restrain both hydrophilic and lipophilic drugs from entering the eye.

Tear turnover rate is one of the major factors that hinder the drug absorption. Immediately after the drug has been applied, increased tear secretion

occurs and rapid clearance of the exotic substance occurs. As a result, almost 60% of the drug gets removed after 2 minutes and only about 0.1% remains after 8 minutes of the drug appliance. [BCAS+18]

Along with the tear turnover, nasolacrimal drainage plays a huge part in drug elimination. Approximately 95% of the administered drug gets removed through the conjunctiva and nasolacrimal duct. Ultimately, the drug ends up in the nasal cavity instead of reaching its target site in the eye. Since the lacrimal sac and the nasolacrimal duct are vascularized, a danger for systemic circulation, the circulation of drugs around the whole body, occurs when the drug drains into this route. [LCF23]

Finally, reflex blinking clears out high proportions of the drug after it has been topically administrated. While an average eye drop inputs about 39 µL of solution, the eye can only hold up to approximately 30 µL which removes plenty of solutions prior to the corneal absorption.

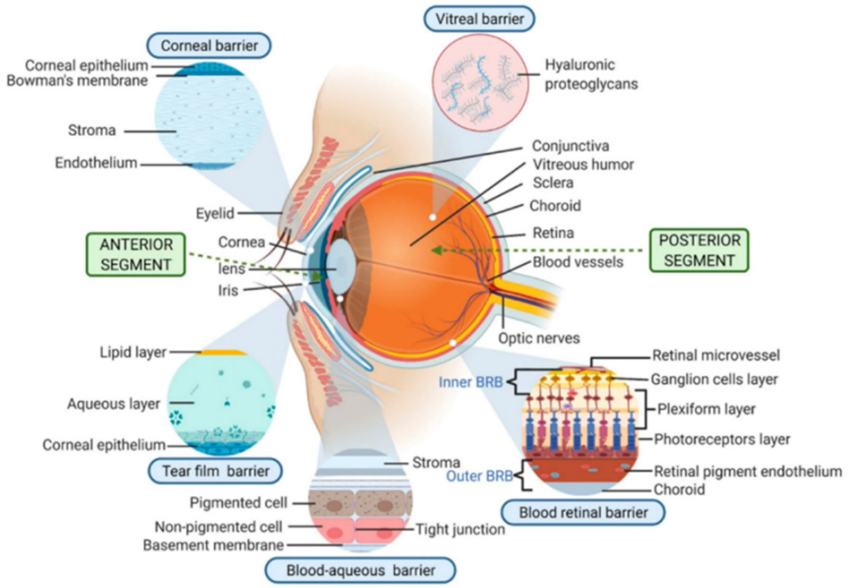


Figure 3: Illustration of various anterior and posterior barriers to ocular drug delivery. [LCF23]

6 Surface Modification of Niosomes

Surface modification is a technology of adding different substances to the vesicles' surface to further achieve the objective of the drug administration. These objectives can be better bioavailability, enhanced penetration, more accurate

targeting, etc.. [PDS22] Various substances are utilized for unique purposes. The following paragraphs address examples of surface modification of niosomes.

6.1 Ligands

Ligands allow an accurate targeting of the vesicles as they can act as a signal to detect other cells. By adding ligands on the surface, the vesicle can be targeted to specific receptors which can take a specific route to minimize the side effects and reach its target site with a higher concentration of the drug to enhance the therapeutic effect.

6.2 Polymers

The addition of polymers can serve numerous purposes based on what molecules the polymers are made of. Eid et al. conducted a study using chitosan-coated niosomes for azithromycin delivery. In the study, they tried to formulate the optimal niosome delivery system by changing the cholesterol: surfactant ratio, chitosan concentration, and surfactant type (Span 60 or Tween 60). The study revealed that zeta potential and mucoadhesive force were heavily dependent on the chitosan concentration. "CTS coating of NSM increased mucoadhesion by 3-fold". [ENA$^+$21]

7 How Niosomes Can Enhance Ocular Drug Delivery

7.1 Mucoadhesive Properties

Conventional eye drops have a significantly low permeation rate due to both anatomic and dynamic barriers. Tight junctions in the cornea restrain drugs from being absorbed, and the reflex blinking quickly removes drugs from the eye. As a result, only 2-3% of the drug succeeds to permeate and reach its target site. Niosomes can enhance drug delivery by having increased permeation compared to these eye drops. With their mucoadhesive properties, niosomes have a better ability to adhere to the corneal surfaces and resist dynamic barriers. Subsequently, they demonstrate higher absorption rates into the cornea. [VTS$^+$21]

7.2 Small Droplet Sizes

In addition, niosomes' small droplet sizes make them advantageous to maneuver through the corneal epithelial cells. Compared to conventional eye drops which have droplet sizes ranging from 20 to 50 nanometers, niosomes' droplets range from 10 nanometer to 5 micrometers. Small droplet sizes allow the niosomes to pass through via the paracellular route through the tight junctions formed by the corneal epithelial cells. This trait also helps with resisting dynamic barriers such as reflex blinking since the droplet is too small to be removed from

blinking (Sepideh Khoee). The small sizes also proved to avoid the "lacrimal flushing effect" from the eye which further prolongs the retention time of the drug. [VTS+21]

7.3 Protection of the Drugs

Simply enough, niosomes act as a carrier for the encapsulated drug which helps it to retain its drug concentration until it reaches the target site. As the ultimate goal is to deliver sufficient concentration of drugs to the target site for therapeutic effects, niosomes also pose an advantage from this perspective.

7.4 Sustained Drug Release

Niosomes are often highlighted for their sustained drug release. For instance, in the study conducted by Hasan et al., niosomes were able to release the drug in a significantly sustained manner compared to the free molecules. [HMW13]

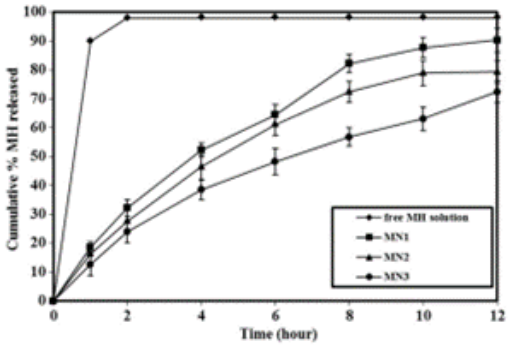


Figure 4: Comparison of drug release rate of free metformin hydrochloride (MH) solutions and metformin hydrochloride encapsulated niosomes. [HMW13]

The researchers analyzed the biphasic release pattern, which is a pattern of faster release of molecules over the first 1-3 hours, then exhibiting a slower release pattern. The above figure depicts the sustained release of metformin hydrochloride (MH) loaded in niosomes (MN1, MN2, MN3).

7.5 Lower Toxicity

Due to its non-ionic nature, niosomes exhibit lower toxicity compared to other nanocarriers. They are more biocompatible and biodegradable which poses great potential for their therapeutic applications.

7.6 Bilayer Structure

With its unique bilayer structure, niosome can incorporate both hydrophilic and lipophilic drugs. This allows a wider range of applications of nanocarriers.

8 Real Life Therapeutic Applications for Ocular Diseases

8.1 Glaucoma

Glaucoma is a disease that impairs the patient's vision by damaging their eyes' optic nerves. The primary factor of this vision loss is an excess accumulation of the aqueous humor, which increases intraocular pressure. Eye drops are frequently prescribed to promote the chemicals that release the aqueous humor. Allam et al. [AEEBE21] formulated a betaxolol-loaded niosomes prepared with in-situ gel as a treatment for glaucoma. Betaxolol is a common medication that is used to control the high blood pressure. The results indicated that betaxolol niosomal in situ gel had a higher maximum decrease of IOP (intraocular pressure) around 10.8 compared to the value of 6.6 for betaxolol eye drops in glaucomatous rabbits. Moreover, these formulated niosomal systems proved to be non-irritating to the rabbits' cornea, conjunctiva, and iris which makes it a promising glaucoma treatment system.

8.2 Conjunctivitis (Pink Eye)

Conjunctivitis, also called pink eye, is an inflammation of the conjunctiva. It can have two different causes: infectious and noninfectious. Infectious conjunctivitis includes bacterial, viral, and fungal conjunctivitis, while noninfectious conjunctivitis is caused by allergies, toxicities, or irritants. The most common treatment for conjunctivitis is the topical administration of antibiotics to fight against the bacteria. Niosomes were also explored as the potential drug delivery system for a more effective conjunctivitis treatment. [DERAY$^+$20] For example, Abdelkader et al. [AIKA11] explored the ocular delivery of naltrexone (NTX) by utilizing the Span-60-based niosomes. The result showed that the constant release from the niosomes increased the corneal permeability of the drug. After experimenting with surfactants Span-60, Solulan C24, sodium cholate, and the additives cholesterol and dicetyl phosphate, it was shown that the niosomes were nonirritant and were biocompatible with the cornea.

8.3 Keratitis

Keratitis is an inflammation of the cornea that can lead to corneal blindness. It is divided into infectious and non-infectious keratitis based on the causes; infectious keratitis is caused by viruses or bacteria, while noninfectious keratitis is caused by injury or allergy. Niosomes can be a helpful carrier in treating infectious keratitis by encapsulating virus-treating drugs inside. Akhter et al.

conducted a study in which they compared the ganciclovir (GCV) encapsulated niosomes and GCV solution in the rabbits' eyes. The results indicated that the ocular retention time for chitosan-coated niosomal nanoparticles (GCV-NDs) was about 4-fold higher than the basic solution. Moreover, the humoral drug availability of niosomal nanoparticles was approximately 7 to 8-fold higher than the GCV solutions. [ARA$^+$13] These results indicate that niosomes have a high potential to be utilized as a delivery system for infectious keratitis treatments.

8.4 Pediatric Eye Examinations

Cyclopentolate is a drug administered in young patients to dilate their pupils for better pediatric eye examinations. Dilated pupil allows ophthalmologists to have a better view of the optic nervous system within the eye, which leads to a better diagnosis. Cyclopentolate-encapsulated niosomes can be administered to dilate the pupil within a shorter amount of time. Saettone et al. formulated niosome vesicles of each pH 5.5 and 7.4. In the in vivo study, both vesicles demonstrated improved bioavailability compared to the reference buffer solution. It can be inferred that by utilizing niosomes as the nanocarrier, the enhanced permeability led to a higher bioavailability. [KGSA04]

9 Prosepcts of Niosomes

9.1 Promising Aspects

Niosomes demonstrate several promising aspects as a nanocarrier. They have cheaper production costs, are easier to formulate, and demonstrate higher stability than liposomes. During the ocular irritation and toxicity tests, lots of the studies showed that niosome vesicles have minimal irritations on the surface, which proves their biocompatible and nontoxic nature. By possessing the aforementioned qualities, niosomes can add much more to the ocular drug industry. Compared to current conventional drugs, niosome formulations exhibit significantly higher bioavailability and retention time. Along with other nanocarriers such as liposomes, niosomes seem to be carrying a high potential in ocular drug delivery.

9.2 Limitations and Challenges

However, several challenges still remain. Primarily, their physical stability is a major concern. Niosomes exhibit vesicle aggregations or leakage of drugs at certain temperatures depending on the gel-liquid phase transition temperature (Tc). Change in the temperature can lead to a change in the nature of their bilayer structure, which causes physical instability. Moreover, there aren't enough toxicological tests yet to utilize niosomes in a clinical context. Although numerous researches state that niosomes exhibited minimal irritation, specific research should be conducted based on the niosome compositions and the application conditions. Finally, sterilization remains a challenge for niosomes. Since

niosomes are temperature sensitive, sterilization methods incorporating heat cannot be applied. [WBD+22] Other methods should be studied for niosomes to be utilized in therapeutic instances.

9.3 Future Research Directions

Additional research can be done to overcome these barriers to utilize niosomes in clinical contexts. Various toxicology tests should be conducted based on the specific conditions the niosomes are being applied. [VTS+21] Moreover, further research should be done to increase the stability of niosomes. Current feasible methods are the dispersion of niosomes in viscous gel and conversion of niosomes into the form of powder; however, the challenge in drug release and production cost remains as the barrier, respectively. [AAA14] Further studies on sterilization methods can also be conducted. Despite having a potentially viable method, gamma irradiation, the method still lacks research on its impact on the niosome vesicles, which can be conducted.

10 Conclusion

With their unique structure and properties, niosomes possess a high potential as ocular drug carriers. Their bilayer structure can encapsulate numerous types of drugs, and properties such as mucoadhesiveness enable better permeation and bioavailability by circumventing the ocular barriers. Niosome surface modification enhances these properties to further achieve the targeted therapeutic effect. They are already being explored as a potential carrier for various ocular diseases like glaucoma. Niosomes are viewed as promising nanocarriers that could provide novel directions to ocular drug administration. The application of niosomes in specific environments such as conditions that require enhanced permeation could facilitate the achievement of drug delivery. By working towards overcoming the limitations of niosome usage, niosomes will be able to secure their place in ocular drug delivery in the near future.

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