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A Review on Discomes: An Effective Ophthalmic Drug Carrier

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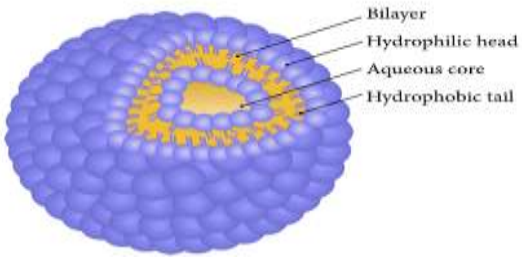
ABSTRACT
Non-ionic surfactant vesicles, commonly called niosomes are the drug carriers used in many formulations for the targeted drug delivery or site-specific drug delivery. These are similar to liposomes but are more stable when compared and are both hydrophilic and lipophilic. This property enables to entrappingof both lipophilic and hydrophilic drug molecules. There are various types of niosomes like polyhedral niosomes, discomes, and many others based on lamellarity. Discomes are mostly used for ophthalmic drug delivery because oftheir large size and higher entrapment efficiency. These niosomes increase the bioavailability of the drugs and lower the side effects caused by them. Potent drugs can be easily delivered to the target site by niosomes as carriers. Preparation methods are simple for the niosomes and further procedures differ based on the type of niosomes to be manufactured. Evaluation of the niosomes includes their size determination, morphology,surface properties, and entrapment efficiency. Applications of niosomes and discomes are briefly discussed.

Keywords
Niosomes, discomes, polyhedral niosomes, lamellarity,solulan C24, entrapment efficiency, franz cell.

I. INTRODUCTION

Discomes are the disc-likeniosomesthat are about a size of 11-65μm. The incorporation of poly-24-oxyethylene cholesteryl ether into niosomes gives the new niosomal structures called polyhedral niosomes and discomes. Niosomes are non-ionic surfactant-based vehicles. They are similar to liposomes but have greater advantages over them. The major difference between them is, that liposomes are made up of charged or uncharged double-chain phospholipids but niosomes are made up of uncharged single-chain non-ionic surfactants.[1]Niosomes can entrap both the hydrophilic drugs and lipophilic drugs into the bilayer domain. The niosome vesicles are formed by a proper mixture of surfactant and the membrane stabilizing agent at a temperature above the liquid transition temperature [2]. The non-ionic surfactants form a bilayer vesicle in such a way that the hydrophobic parts are oriented away from the aqueous solvent and the hydrophilic part in contact with it. The force maintaining the vesicular structure of niosome are van der Waals forces among the surfactant molecules, electrostatic forces between charged groups, repulsive forces of the head groups, etc. [3] The first niosomes were developed by L'Oréal in the year 1975 but not used in drug delivery. They were later used for



Structure of Niosome

the delivery of anticancer drugs. This reduces the side effects caused by the anticancer drugs as they are delivered to the site of the tumor. The niosomes are taken up by the reticuloendothelial system, hence this method of delivery can be used in the treatment of diseases that are affecting the liver and spleen.[4]niosomes can also be used as a carrier for hemoglobin. Based on the vesicle size,niosomes are of three types:

1) UnilamellarNiosomes: These are small when compared to others and vesicle size ranges from 10-100nm.
2) Large unilamellarNiosomes: These are of large size up to0.05μm.
3) Multilamellarniosomes: The size of this type of niosomes is greater than5μm.[5]

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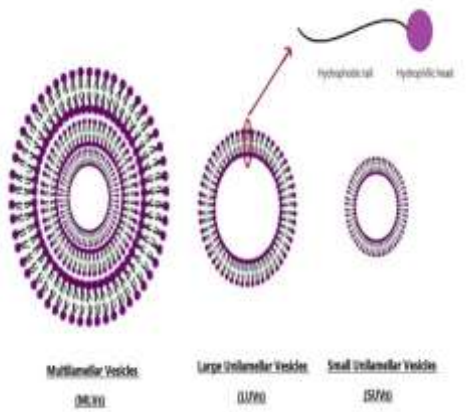

In a few cases, the size of niosomes would be greater in size up to 15μm such as discomes. On addition of Solulan C_{24} to the basic niosomes gives the discomes and polyhedral niosomes.

Polyhedral Niosomes

Polyhedralniosomes are the non-uniform spherical vesicles that are obtained from surfactants. These are typically prepared from hexadecyl diglycerol ether and solulan C24. An alternative method includes the formulation from $C_{16}G_{2,}$ Solulan C24, and cholesterol. They can entrap and slowly release water-soluble drugs or formulations.[6]

Discomes

Theseare formed by incubation of the preformed conventional niosomal dispersion with Solulan C_{24} in a shaking water bath at a temperature of 74^{o}C for 1hr. Gaintdiscomes are prepared by usage of higher Solulan C_{24}. These are thermo-responsive vesicles which means they release the solution entrapped with an increase in temperature. This property of discomesis used for the ophthalmic drug delivery so to prevent drainage due to bigger size and increased bioavailability. Recent preparation is the naltrexone hydrochloride discomes for the treatment of corneal disorder.[7]

Methods of vesicle Preparation

1. Ether Injection Method

Surfactants and other additives are dissolved in ether. This solution is transferred into an injection, and injected into the aqueous solution of drug which is maintained at a constant temperature by using a magnetic stirrer which maintains the temperature. The temperature is set to be above the boiling point of organic solvent used. A rotary evaporator is used to evaporate the organic solvent.[8] Single-layered vesicles emerge during the vaporization process.[9]

2. Thin-Film Hydration Method

The thin-film hydration method is a well-known and straightforward preparation method. Surfactants, cholesterol, and other additives like-charged molecules are dissolved in an organic solvent in a round-bottomed flask in this process.[10]The organic solvent is then evaporated using a rotary vacuum evaporator to leave a thin film on the flasks inside the wall. The aqueous drug solution is added, and the dry film is hydrated for a specific time above the surfactant's transition temperature with continual shaking. This approach produces multilamellar niosomes.[11]

3. Micro-fluidization Method

The submerged jet idea is used in the microfluidization procedure. The drug and surfactant fluidized streams interact in precisely specified micro channels within the interaction chamber at ultrahigh velocities in this procedure.[12]Niosomes are formed as a result of the high-speed impact and the energy involved. In the creation of niosomes, this approach provides improved uniformity, smaller size, unilamellar vesicles, and good reproducibility.[13]

4. Reverse Phase Evaporation Method

Niosomal components are dissolved in a mixture of ether and chloroform and then added to an aqueous phase containing the medication in this procedure. The organic phase is evaporated after the mixture has been sonicated to form an emulsion. During the evaporation of the organic solvent, large unilamellar vesicles form.By this method we get unilamellar and uniform sized niosomes.[14][15]

5. $scCO_2$ Method

Supercritical carbon dioxide has been used to prepare niosomes in a more environmentally responsible manner.Under a temperature of 31.1 C and a pressure of 78.8 bars, carbon dioxide gas can be in a fluid state.The solvating properties of $scCO_2$ are excellent. The $scCO_2$ method was used to successfully create niosomes with varied molar ratios of Tween 61: cholesterol combinations, as well as encapsulated glucose. These niosomes had higher drug entrapment efficiency when compared with the niosomes prepared using the TFH method but lacked stability.[16]

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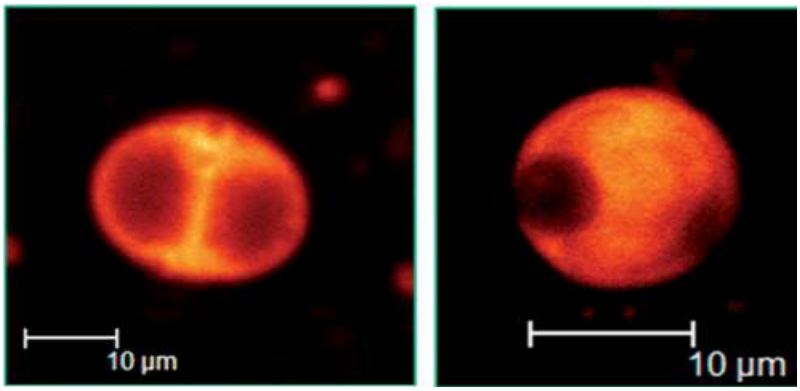
6. The Bubble method

A glass flask with 3 necks is taken and surfactants, additives and buffer are added. At 70^0c niosomes are formd and dispersion id done using a homogenizer. The flask is now placed on a water bath and bubbling of nitrogen gas is done at the same 70^oc, this results in formation of large unilamellar vesicles.[17]

Preparation of Discomes from vesicles

In studies, $C_{16}G_2$ non-ionic surfactant, and alkyl diglycerol ether were used for vesicle formation. Dicetyl phosphate(DCP) which is an ionic surfactant, was incorporated into the bilayer at a level of 5%, to prevent the aggregation of the vesicles. Later solubilization of vesicle bilayer was studied using the Solulan C_{24}, which is a Polyoxyethylene cholesteryl ether. Then they found the large disc-shaped niosomes in the preparation. So, the method of preparation was confined to be as follows. All the lipophilic ingredients with the ratio of$C_{16}G_2$:DCP:Cholesterol, 69:2:29 are dissolved in a 30ml of chloroform in a round-bottomed flask. The organic solvent is evaporated under low pressure and at a temperature of 55^oC. now the lipid film formed is dried under a nitrogen stream for about 20mins and later hydrated with 100ml of water by shaking using a flask shaker, over the water bath at a temperature of 55^oC. The formed vesicles are sonicated using an MSE PG100 150-W probe sonicator. The dispersion is left to cool and thenincubated with various proportions of Solulan C_{24} in a shaking water bath at a temperature of 74^oC for 1hr and discomes are formed.[18]



Discomes under laser scanning micrographs

Drug Loading Methods

There are two types of drug loading methods depending on the time at which the drug solution is loaded. They are:

1) Passive loading method:

In the case of the passive method, the drug is passively encapsulated in the niosomes, during their formation. During the step of hydration, the buffer includes the determined concentration of drug which gets entrapped in the niosomes. Further, sonication is done to reduce the size of the niosomes. But by this method, high entrapment efficiency is not found in the case of discomes or other ophthalmic formulations. Generally, the entrapment efficiency of passive loading techniques is 40.69% ± 3.97% depending on the surfactant used.[19]

2) Active loading method:

Encapsulation is done withthe help of a transmembrane gradient, so the drug passes through the membrane by diffusion and gets entrapped. The gradient can be created in 2 ways

a) Transmembrane pH gradient: In this method, the basic drug is ionized and precipitated in the acidic environment in the niosome. Due to the pH difference the ionized drug cannot escape[20].TFH technique was used to make niosomes and a citric acid buffer at pH 4.0 to hydrate the thin film. Drug-containing aqueous phase was added to the niosomal solution and vortexed after freezing and thawing the vesicles numerous times. Finally, to raise the outside pH to 7.0–7.2, disodium hydrogen phosphate was utilized. They got a greater EE percent using this strategy than with other ways they tried, up to 52.9 percent to 2.35 percent.

b) Transmembrane Ion Gradient: In this method, the precipitation is done by an ion gradient, like sulfate or phosphate. 100% efficacy was seen in his method, in presence of sulfate,

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phosphate, citrate, or acetate ions. [21] Using an ammonium sulfate gradient, drugs could be loaded into niosomes with greater entrapment and stability.

Characterization

I. Size and Morphology

Size is determined by using dynamic light scattering(DLS), electron microscopy like TEM and SEM, and laser diffraction spectroscopy. The size of niosomes generally ranges from 20 to 5000nm. In the case of discomes the size ranges from 10 to 60μm. The parameters that affect the size of a niosome are the type of surfactant used and HLB. Span 20 has the highest HLB followed by span 40 and 60.[22] The size of niosomes increases with an increase in the HLB[23]. Those niosomes prepared from tweens, their size is affected by surfactants used. As the length of the alkyl chain increases in the surfactant, the size of the niosome also increases [24][25]. Atomic force microscopy and electron microscopy techniques are used to study the size distribution and characterization of niosomes.[26][27]

II. Charge of Niosomes

The surface charge of the niosome is one of the parameters that affect the interaction of the niosome with the biological structure and also the drug molecules. Like charges of niosome and drug repel each other and produces a stable structure. Also, positively charged niosomes have better retention than neutral or negatively charged ones.[28]

III. Entrapment Efficiency

This represents the drug entrapment capacity of the niosome. It is found by calculating the amount of initial drug(W_i) in the suspension and the amount of unloaded drug(W_f) remaining in the suspension. This is determined using techniques like spectroscopy, HPLC, and ELISA. [29]

$$EE\% = \frac{W_i - W_f}{W_i} \times 100$$

IV. Stability

Stabilitytests are performed by measuring the size, PDI, and zeta potential of niosomes that have been held at 4 and 25 degrees Celsius for a length of time. Niosomes stored at 4°C kept their size, zeta potential, and stable structure, which is critical for stability. However,Zeta potential values dropped from +40 to 20 mV when stored at 25°C. A drop in zeta results in a decrease in zeta.At 25°C storage, aggregation occurred, and as a result, an increase in size was noted in the situation after 100 days.[30]

V. In Vitro Release

The release kinetics is determined by the dialysis membrane or Franz diffusion cell method. In the case of the dialysis membrane-type experiment, the drug is loaded in it and the membrane is placed in the buffer. The amountof drug released is calculated using spectroscopy techniques for the sample collected at particular time intervals. [31][32][33]

For the Franz cell diffusion method, the cell contains a donor and receptor compartments separated by the membrane. The drug suspension is loaded in the donor compartment and buffer is placed in the receptor unit, drug molecules passively travel into the receptor part. The samples are collected from the receptor compartment at time intervals and drug content is estimated.[34][35] the buffer solution is to be prepared at pH 7.4 to mimic tear fluid and at 35 ± 0.5 ◦C to mimic the ocular surface temperature, whereas to mimic the skin buffer ph would be 7.2 at room temperature.[36]

Niosomesin drug delivery

Niosomes act as the best carriers for the delivery of drugs in the targeted delivery systems. Niosomes being the non-ionic surfactants, they have biocompatibility with the human body and are less toxic compared to others. They can entrap both the hydrophilic and lipophilic drugs in the core and membrane respectively. Poor bioavailability and poorly soluble drugs can be formulated as niosomes as carriers. Due to the encapsulation of drugs, the side effects can be reduced in the case of potent drugs. Also, the improves the stability of the photosensitive drugs due to encapsulation within the aqueous layer.

- Anticancer Drugs Delivery

In the case of chemotherapy, the drug should reach the tumor in the body and perform its action. Penetration into the tumor tissue is poor and also these drugs have several side effects on the healthy tissues. Hence niosomal targeting is done for the cells to reach the target. In research, methotrexate-loaded niosomes were used as alternatives to liposomes[37]. This study found an increase in the therapeutic index of the drug and targeted action. Recent innovations include the magnetic targeting of the niosomes by

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incorporating magnetically responding molecules in the niosomes which help in reaching the target site.[38]

Breast cancer: The film hydration process was used to prepare the tamoxifen citrate niosomes for localized cancer therapy based on in vitro breast cancer cytotoxicity and in vivo solid antitumor effectiveness. On the MCF-7 breast cancer cell line, the improved niosomal formulation of tamoxifen showed dramatically increased cellular absorption (2.8-fold) and significantly better cytotoxic action.[39]

Ovarian cancer: doxorubicin-loaded niosomes were synthesized by Uchegbu et al. A human ovarian cancer cell line and its doxorubicin-resistant subline were tested using doxorubicin in hexadecyl diglycerol ether (C16G2) and Span 60 niosomes. In comparison to the free drug in solution, the IC50 against the resistant cell line was slightly reduced when the medication was encapsulated in Span 60 niosomes, according to the findings.[40]

- Anti-infective drugs delivery

Anti-tuberculosis medicine rifampicin encased in Span 85 niosomes was seen to accumulate in the lungs of mice. [41]As a result, it has the potential to improve anti-tuberculosis treatment. Furthermore, ribavirin was successfully encapsulated by niosomes consisting of Span 60: cholesterol: dicetyl phosphate at a 4:2:1 molar ratio. After an intraperitoneal injection of a single dose of ribavirin, the concentration of the drug in the rat liver obtained from the ribavirin niosomes was 6-fold higher than that obtained from the ribavirin solution. This reveals that niosomes have effective liver targeting characteristics.[42]

- Anti-inflammatory drugs delivery

Marianecci et al. manufactured ammonium glycyrrhizinate (AG) loaded niosomes using multiple surfactants and cholesterol at varied concentrations to examine the possible utility of niosomes for anti-inflammatory drug delivery. For characterization, researchers looked at drug entrapment efficiency, anisotropy, cytotoxicity, and skin tolerability, as well as several other factors. The AG-loaded niosomes had no toxicity and were able to boost anti-inflammatory efficacy in mice with good skin tolerability. Furthermore, on chemically produced cutaneous erythema in humans, the anti-inflammatory effect of the niosome-delivered medication was enhanced.[43]

- Vaccine delivery

The REV approach was used to prepare Span 60 niosomes loaded with tetanus toxoid (TT). To protect the niosomes from an enzymatic breakdown in the gastrointestinal tract and increase their affinity for the antigen-presenting cells of Peyer's patches, they were coated with a modified polysaccharide O-palmitoyl mannan (OPM). Following oral and intramuscular delivery, the results were compared to alum-adsorbed TT, and it was discovered that OPM-coated niosomes produced higher IgG levels than plain uncoated niosomes and alum adsorbed TT.[44]

- Anti-viral drugs delivery

Niosomes have also been shown to be capable of delivering antiviral medicines. Ruckmani and Sankar produced zidovudine, the first anti-HIV drug licenced for clinical use, encased niosomes, and investigated their entrapment efficiency as well as their release sustainability. Tween, Span, and cholesterol proportions were combined to create the niosomes. Tween 80-derived niosomes captured substantial amounts of zidovudine, and the addition of dicetyl phosphate prolonged drug release.[45] In comparison to niosomes maintained at 4°C for 90 days, medication leakage from Tween 80 formulations stored at ambient temperature was substantial. Tween 80 formulations containing dicetyl phosphate were also removed from the circulation after five hours, according to the results of a pharmacokinetic investigation in rabbits.[46]

Type of Drug	Name of the drug	Composition	Year
Anti-inflammatory	Naproxen	Tween 80, tween 20, cholesterol	2016
Antibacterial	cefixime	C-Glycoside derivative surfactant, cholesterol	2016
Anticancer	Doxorubicin	Spam 60, cholesterol, dicetyl phosphate, N-lauryl glucosamine	2016
Antiviral	Nevirapine	Tyloxapol, cholesterol	2015

Recent innovations in niosomal drug delivery[47]

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Discomes Based Treatment Strategies in Ocular Diseases

Niosomes are used for wide range of drugs through ophthalmic delivery, like anticholinergics, anti-glaucoma and antibiotics. Tween 20 based niosomes are generally used for the ophthalmic niosomal formulation and it has shown improvement in the bioavailability of cyclopentolate[48]. Large sized niosomesgenerallydiscomes avoid the pre corneal drainage and increase the bioavailability to a larger extent. Those attributes that niosomes must contain in order to be the potential vehicle for ocular delivery are:

- Size must be large enough to resist the drainage by blinking.MLVs have a larger residence time compared to the ULVs, and also they entrap a larger amount of drugs compared to others. An ideal size would be >10μm. [49]
- Disc or sac shaped are usually preferred for their proper fit into the eyesac. Hence discomes are ideal for ocular drug delivery.[50]
- They should be morethermoresponsive in order to release the drug in a controlled and timely manner.Complete removal of the gel/liquid transition in surfactant-forming niosomes could result in niosomes with a very low release rate for water-soluble medicines, which would be incompatible with the short residence duration of ophthalmic goods.[51]

All the above-mentioned parameters are attributed to discomes and polyhedral niosomes. Discomes have a comparatively lower concentration of cholesterol i.e., ,30%, and have a specific preparation procedure with solulan C_{24} which results in 11-60μm sizediosomes. ‘

➢ **Glaucoma**

Increased intraocular pressure is the most common factor linked to the prognosis of Primary Open Angle Glaucoma (IOP). IOP rises due to an accumulation of aqueous humor in the anterior chamber, which could be caused by excessive fluid production or a blockage of the drainage system.[52] The increased IOP produces an imbalance in retinal blood flow, which leads to optic nerve degeneration.Niosomes are being studied as drug delivery vehicles for the treatment of glaucoma. The use of niosomes for drug delivery as topical eye drops has various advantages, including less frequent administration, longer IOP-lowering efficacy, increased corneal permeability, and reduced ocular toxicity.[53]By using REV procedures, Aggarwal and Kaur created timolol maleate encapsulated chitosan or carbopol-coated niosome formulations. Due to the creation of LUVs that could encapsulate a water-soluble medication in significant numbers, Niosomes created using the Rev. approach demonstrated the highest entrapment efficacy compared to others. In comparison withcarbopol-coated niosomal formulations, chitosan-coated niosomal formulations had a longer control over IOP.[54]

➢ **Conjunctivitis**

The inflammation or infection of the conjunctiva, which is the translucent mucous membrane situated in the sclera, is known as conjunctivitis. Conjunctivitis comes in a variety of forms, including viral, bacterial, and allergic conjunctivitis, which can be acute or chronic [55][56]. Infectious conjunctivitis includes bacterial, viral, fungal, parasitic, and chlamydial conjunctivitis. Allergens, toxicities, and irritants, on the other hand, are the most common causes of non-infectious conjunctivitis. Topical antibiotics, antivirals (acyclovir, trifluridine, and valaciclovir)[57], and antifungals are the most common treatments for conjunctivitis. w. Abdelkader et al. wanted to prepare and test Span 60-based niosomes for naltrexone ocular administration (NTX). Charged lipids such as dicetyl phosphate (DCP) and stearyl amine (STA) were investigated as bilayer membrane additions in combination with the surfactant using four distinct ways. When applied to the surface of a 10-day-old hen's chorioallantoic membrane, the produced niosomal formulations were shown to be non-irritant. The ocular permeability of NTX was improved by its controlled release from a niosomal formulation.[58]

➢ **Retinal Diseases**

Irreversible Retinal Diseases (IRD) are a group of illnesses that cause retinal degeneration.IRD could be caused by mutations in genes related to the inner retinal layer. In most cases, however, altered genes expressed in photoreceptor or retinal pigment epithelium (RPE) cells are to blame. For example, retinitis pigmentosa, the most common form of IRD, has been linked to 30 genes.[59]Mashal et al. wanted to improve retinal gene delivery by incorporating lycopene into cationic niosomes based on DOTMA and a non-ionic surfactant called polysorbate 60. After complexingniosomes with the pCMS-EGFP plasmid, ARPE-19 cells were employed in in vitro investigations. Lycopene improved the efficacy of

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nioplex transfection, although not as much as lipofectamine 2000. Nioplexes were transfected into cells in the retina's inner layers. The potential of nioplexes to transfect the outer segments of the rat retina was demonstrated using subretinal and intravitreal injections.[60]

Toxicity

The is an irritational ability for the span 60 and also the higher concentrations of additives like dicetyl phosphate, solulan C_{24} etc were recently analyzed and studies show they have effect on the corneal opacity and permeability. The studies are done we the invitro conjunctival model by using hen chorioallantoic membrane. Minimal ocular irritations were found in this investigation, demonstrating that niosomes are well tolerated by the eyes.[61]

Limitations

Physical stability issues are seen in niosomes. Niosomes in dispersion are susceptible to aggregation, fusion, drug leakage, and hydrolysis of encapsulated medicines during storage. Furthermore, sterilising niosomes necessitates a significant amount of work. Niosomes are not appropriate for heat sterilisation or membrane filtration. At room temperature, niosomes cannot retain their stability, and the incidence of vesicle aggregation over time shows that proper storage conditions are required.Drug molecules must be transported to a specific portion of the eye, such as the retina in the case of macular degeneration, to treat ophthalmic illnesses so more specific targeting must be done.Niosomes' therapeutic potential and bioavailability should be improved by increasing their capacity to penetrate through ocular barriers and increasing retention time. However, it should be investigated whether the longer retention term has any systemic consequences. Despite the fact that in vivo ocular toxicity tests for niosomal formulations revealed no irritation, inflammation, or redness, more toxicity testing is required for future preclinical or clinical research [62]. As a result, these approaches could constitute the future of niosome research in ophthalmology.As a result, more study is needed in these areas in order to generate economically viable niosomal preparations.[63]

II. CONCLUSION

Niosomes are biocompatible nanocarriers with diameters ranging from tens of nanometers to a few micrometres that are versatile and easy to create. Niosomes are used to transport drugs and genes to both the anterior and posterior parts of the eye, with enhanced corneal permeability, increased ocular bioavailability, and longer drug release. Additionally, approaches such as covering niosomes with a mucoadhesive polymer such as chitosan, carbopol, or HA, or inserting niosomes into in-situ gels augment the advantages of niosomes.The development of new drug delivery methods, such as niosomes, for the treatment of ophthalmologic illnesses, has received a lot of attention in recent years. The considerable effort is still ongoing, particularly in the development of eye drops. We looked at a number of in vitro and in vivo investigations utilizingniosomes for the treatment of a variety of ocular illnesses.

Consent

Consent is not applicable.

Acknowledgments

It is not applicable.

Competing Interests

Authors have declared that no competing interests exist.

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