

A Review on Niosomes in Ocular Drug Delivery System

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ABSTRACT

Eye is a complex organ consisting of several protective barriers and defense mechanisms. Most commonly used approach is the topical route of administration and it is inefficient due to low drug bioavailability. Nanotechnology has the ability to overcome these problems. Niosomes are non-ionic surfactant vesicles and emerging nanocarriers in drug delivery applications due to their storage stability and cost-effectiveness. This review describes about the niosome, preparation methods, evaluation and the niosome based treatment strategies in ocular disease.

Keywords: Nanotechnology, Niosomes, Nanocarriers, Vesicular system, Ocular drug delivery.

INTRODUCTION

Eye is the window of our soul. Ocular drug delivery possesses many challenges because of the distinctive anatomy and physiology of the eye. Eye having many barriers such as different layers of cornea, sclera and retina in addition to blood retinal barriers, lachrymal fluid-eye barrier and drug loss from the ocular surface. Major challenge of the formulator is to overcome these barriers.^[1] Topical route of administration is inefficient due to low bioavailability. Most convenient route dosage form is the eye drops. Due to continuous tear flow, it drains away.^[2] Cornea is the anterior layer of eye and consists of epithelium, stroma and

endothelium. Epithelium and endothelium having high lipid content so they obstruct the passage of hydrophilic molecules. Stroma having high water content, so impermeable to lipophilic molecules.^[3] Through conventional dosage forms, only 1-3% drug absorbed through cornea.^[4]

To overcome these problems, nanotechnology can be used. In vesicular systems, drugs encapsulated in the lipid vesicles. Niosomes are non-ionic surfactant vesicles. First niosome formulation was developed and patented by L'Oreal in 1975.^[5] Niosomes are drug carriers and reduce the side effect and improve therapeutic effectiveness in many diseases. As compared to other vesicular systems, niosomes have many advantages such as low toxicity, chemical stability, biocompatible; improve the availability of drug at particular site.^[6] It also provides controlled and sustained action at corneal surface. It prevents the metabolism of the drug from the enzymes present at the surface of cornea/tear epithelium.^[7] Goals of ocular drug delivery are,^[8]

- Improve bioavailability
- Increase drug permeation
- Control release of drug
- Target drug at active site

ANATOMY OF EYE AND ITS BARRIERS

Eye is the most marvellous of the sense organ. It is protected by eyelashes, eyelids, tears and blinking. Tears prevent the bacterial infection and wash away the irritating agents. Eye having three concentric substrates: outermost part (Fibrous tunic), mid covering and internal part (Vascular tunic). Outermost part includes the cornea and sclera. Mid covering called Uvea, which includes the iris, ciliary body and choroid (shown in figure-1).^[9]

i. FIBROUS TUNIC

Cornea is dome-shaped and covers the foreside of the iris, anterior part of eye and the pupil. Cornea consists of five layers from front to back; Epithelium, Bowman's membrane, stroma, Descemet's membrane and endothelium.

Sclera is the "white of the eye". It is a layer of dense connective tissue made up of collagen fibres and fibroblasts.

ii. VASCULAR TUNIC

Iris is the visible colored portion of the eye. Iris epithelium containing pigment granules which absorb light as well as lipophilic drugs.

Ciliary body major function is the production of aqueous humor. It is the major ocular source of drug-metabolizing enzymes which are responsible for drug detoxification and removal from the eye.

Choroid lines the posterior five-sixths of the inner surface of the sclera and it is rich in blood vessels.

iii. RETINA

Retina is the internal part of the eye. For the oxygenation retina uses retinal vessels and choroid blood vessels. Retina senses the light transforms into signals and through optic nerve transfers into brain.

Human eye divided into two segments, anterior and the posterior segments. One-sixth of the eye is anterior portion and includes iris, cornea, aqueous humor and lens. Remaining five-sixth of the eye is posterior portion and includes retina,

vitreous body, back of the sclera, and choroid.^[10]

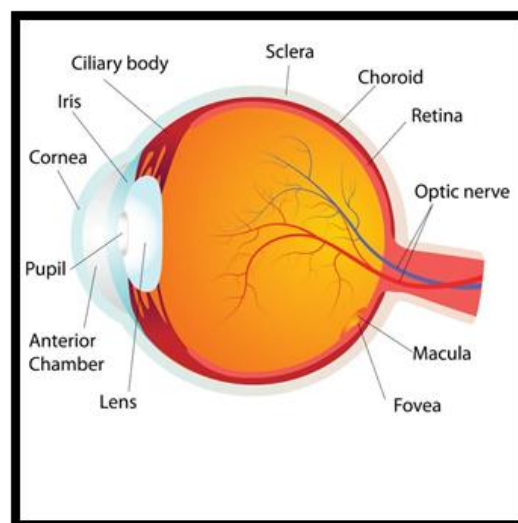


Figure-1: Anatomy of Human eye

There are many barriers present in the ocular compartment. To achieve the efficient ocular drug delivery it must overcome these barriers for protecting the eye from toxicants. From the external environment the eye is protected by corneal epithelium with tight junctions and desmosomes and the mucoaqueous tear layer. There is blood aqueous barrier, formed by the iris blood vessel endothelium, ciliary epithelium and the retinal epithelium. The barrier such as blood-retina barrier, conjunctiva and sclera separate the eye from rest of the body. Due to these barriers prevent the delivery of topically and systemically administered ocular drugs. There are three major groups of barriers in ocular delivery. They are (1) precorneal barrier, (2) static barrier and (3) dynamic barrier. Static barrier mainly includes the various layers of cornea, sclera and the retina, inclusive of the blood-aqueous barrier.^[11]

NIOSOMES

They are vesicles and formed from the hydrated mixtures of cholesterol, charge inducing substance and non-ionic surfactants. In cosmetic industry, the first niosome production began. Their sizes range in nanometric scale. Only by the

proper mixtures of surfactants and charge inducing agents thermodynamically stable vesicles forms. Vesicle formation with the use of non-ionic surfactant mechanism is not clear. Most common theory is that due to the amphiphilic nature of non-ionic surfactants forms a closed bilayer structure. Formation of this structure requires some input of energy by means of physical agitation or heat. In this closed bilayer structure, hydrophilic heads comes in contact with the water while hydrophobic

parts oriented away from the aqueous solvent (shown in figure-2). Niosomes prepared by using different methods. Niosomes are varying depending on the properties of procedure for manufacturing and their composition of bilayer. But the principle is same, i.e., first formation of lipid phase and followed by subsequent hydration on aqueous medium leads to formation of niosomes. The main ingredient used in the structure of niosome is non-ionic surfactant.^[12]

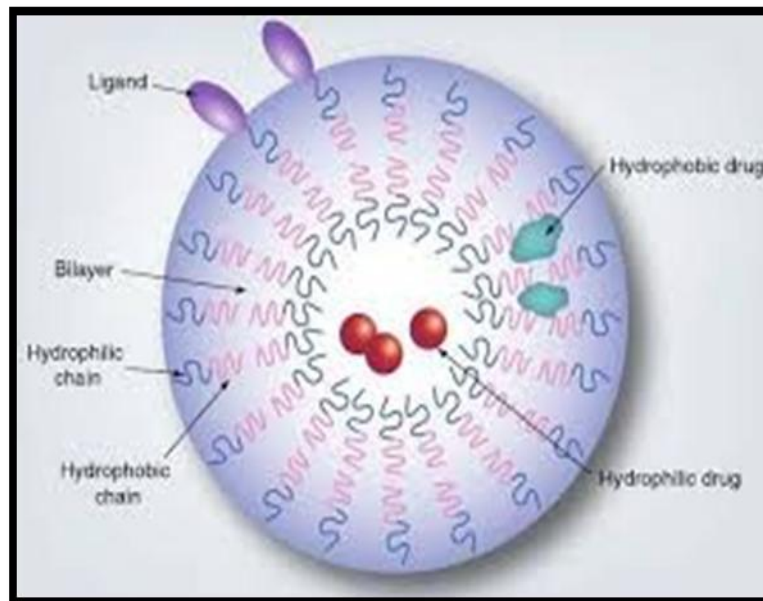


Figure-2: Structure of the Niosome

CLASSIFICATION

Based on their size and number of bilayers niosomes are classified into three (shown in figure-3):^[13]

1. Small Unilamellar Vesicles (SUV)
2. Large Unilamellar Vesicles (LUV)
3. Multi-Lamellar Vesicles (MLV)

1. SMALL UNILAMELLAR VESICLES (SUV)

From Multilamellar vesicles it can be prepared by Sonication method, extrusion method and French press method.

2. LARGE UNILAMELLAR VESICLES (LUV)

It can entrap larger volume of bioactive materials because it having high aqueous/lipid compartment ratio.

3. MULTI-LAMELLAR VESICLES (MLV)

They are most commonly used niosomes. It contains number of bilayers. MLVs are simple to formulate and having size range of 0.5-10 μ m diameter. They are mechanically stable for long period of time on storage.^[14]

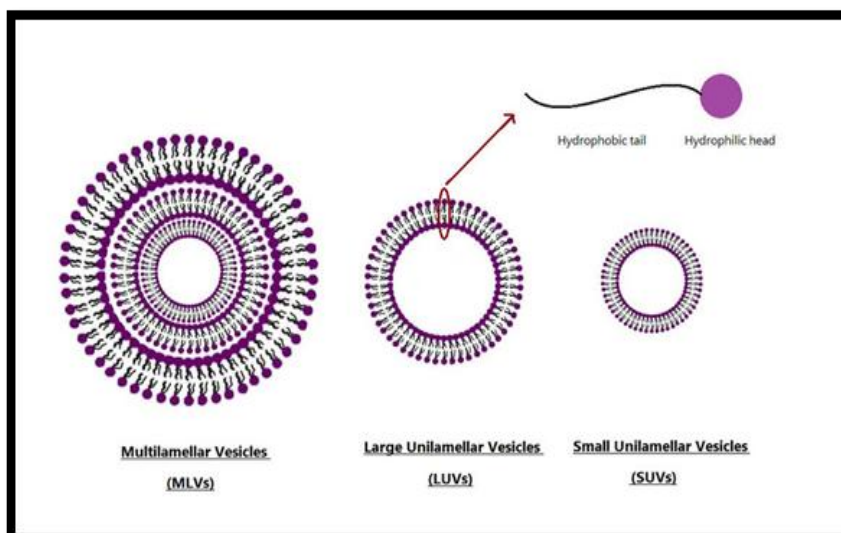


Figure-3: Typical vesicle size of niosomes

The advantages of niosomes compared to other nanoencapsulation technologies are:^[15]

- In niosomes, surfactants used are more stable compared to phospholipids in liposomes.
- Requires only simple method of preparation and large scale production.
- Niosomes production is cost-effective; excipients and equipment's used are not expensive.
- Stable at room temperature compared to liposomes.
- Possess longer shelf-life.

ADVANTAGES OF NIOSOMES^[16]

- Niosomes are economically cheap
- More stable than liposomes, because in liposomes phospholipids are present which easily oxidised.
- They are osmotically active and stable; also increase the stability of entrapped drug.
- They increase the skin penetration of the drugs
- Act as a depot and release the drug in a controllable manner.
- Increase the oral bioavailability of poorly absorbed drugs.
- No special condition requires for the handling of the surfactants in niosomes.
- It can entrap both lipophilic and hydrophilic drugs.

COMPOSITION OF NIOSOMES

The essential components are

1. Cholesterol
2. Non-ionic surfactants
3. Other Additives

1. CHOLESTEROL

In Niosomal systems, cholesterol and its derivatives are the most common additives. It is a waxy steroid metabolite and found in the cell membranes. With non-ionic surfactants it forms the vesicles and provides greater stability and reduces agglomeration. Also, in niosome formation it imparts rigidity and in niosomal bilayer it provides orientational order.^[17]

2. NON-IONIC SURFACTANTS

It possesses hydrophilic head group and a hydrophobic tail. It is the main component in niosome formation. The hydrophobic moiety consists of 1/2/3 alkyl chains or per fluoro group or single stearyl group. Niosomes shows an increased ocular bioavailability when water soluble surfactants such as Tween 20, Tween 80 etc., entrapped because the surfactants act as the penetration enhancer helps to remove the mucus layer and break junctional complexes.^[18]

Commonly used surfactants are span which having many grades such as span 20, span 40, span 60, span 80 and span 85 and also Tweens such as Tween 20, Tween 40, Tween 60 and tween 80. Other surfactants

used are Ether linked surfactant, Di-alkyl chain surfactant, Ester linked, Sorbitan Esters, Poly-sorbates.^[19]

3. OTHER ADDITIVES

Mainly charge inducers play an important role in niosome formulation. It increases the surface charge density and prevents vesicles flocculation, aggregation and fusion. Commonly used charge inducers are Diacetyl phosphate (DCP) – negative charge, Stearyl amine (SA) - positive charge.^[20]

NIOSOMES METHOD OF PREPARATION

General method mainly involves the evaporation of the organic solvents leads to the formation of lipid film and followed by hydration results in the production of niosomes. There are various methods for the preparation:

- Ether injection method
- Ethanol injection method
- Film hydration method
- Sonication
- Reverse phase evaporation
- Micro fluidization
- Multiple membrane extrusion method
- Trans membrane pH gradient process
- Bubble method

FORMULATION OF LARGE UNILAMELLAR VESICLES

• ETHER INJECTION METHOD

Vesicles are prepared by injection or slow introduction of lipids. In this, non-ionic surfactants and cholesterol taken in a beaker and introduce warm water, then maintained the temperature at 60°C (shown in figure-4). Here aqueous solution used is the phosphate buffer. To the aqueous solution ether containing mixture of drug solution is added slowly with the help of 14-gauge needle. Then vaporization of the ether leads to formation of only one layered niosome vesicles.

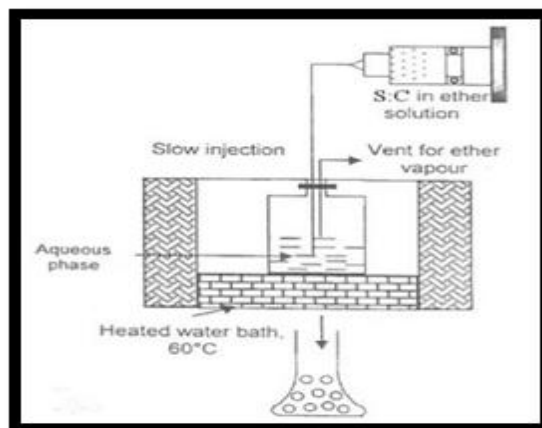


Figure-4: Ether injection method

Niosomes size range varies from 50-1000nm. Existence of small quantity of ether in the vesicle suspension is difficult to remove is the main disadvantage of this method.^[21]

• ETHANOL INJECTION METHOD

In this method, to a preheated aqueous phase slowly injects the surfactant: cholesterol: stearic acid and drug in ethanol through a needle (shown in figure-5). Then slowly evaporate the ethanol solvent and forms an ethanol gradient across the surfactant and cholesterol layer at ethanol-water interface and results the formation of vesicles.^[22]

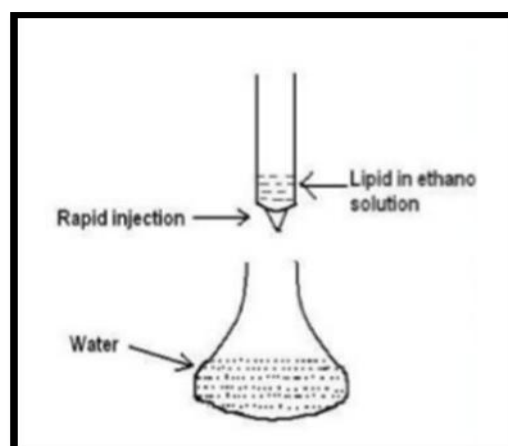


Figure-5: Ethanol injection method

• REVERSE PHASE EVAPORATION

In this method, volatile organic solvent removed by evaporation. Disperse cholesterol and surfactant in equal ratio i.e (1:1) to the mixture of ether and chloroform.

Aqueous phase containing drug added to the above solution and the resulting two phases are sonicated for few minutes. Then add phosphate buffer saline and sonication leads to the formation of clear gel. At low pressure, the organic phase is removed by evaporation. Obtained suspension is further diluted with phosphate buffer saline and heated on water bath at optimum temperature (45°C) for 10min. leads to formation of Niosomes.^[23]

FORMULATION OF MULTI LAMELLAR VESICLES

• FILM HYDRATION METHOD

In a round bottom flask, non-ionic surfactant and membrane stabilizer lipid are mixed in organic solvent like chloroform, methanol and diethyl ether. Then evaporation of volatile solvent leads to the formation of thin film of solid mixture on the wall of round bottom flask. Addition of solvent with gentle agitation leads to the rehydration of film. Through this method multi-lamellar vesicles are formed.^[24]

• TRANS MEMBRANE pH GRADIENT PROCESS

To the organic solvent lipid mixture was dispersed and lipid film was obtained on wall of round bottom flask. To this add acid like citric acid with vigorous agitation leads to the hydration of films and produced multi-lamellar vesicles. These undergo freeze thaw cycle and sonication. Then API aqueous solution was added and agitated. By using disodium phosphate, mixture pH was raised. Then heat the mixture at 65°C to give niosomes.^[24]

FORMULATION OF SMALL UNILAMELLAR VESICLES

• SONICATION

It is a usual technique for the preparation of niosome vesicle. In this method, drug, surfactant and cholesterol taken in 10ml glass vial and mixed with buffer. Mixture was probe sonicated at about 3 minutes with titanium probe produce niosome.^[25]

• MICRO FLUIDIZATION

Jet principle was used for niosome formation. Lipid and aqueous phase interact at high velocity leads to the formation of vesicles.^[25]

MISCELLANEOUS

• MULTIPLE MEMBRANE EXTRUSION METHOD

Non-ionic surfactant, cholesterol and di-acetyl phosphate dissolved in chloroform and evaporated. Results in formation of thin film and followed by hydration of aqueous phase. Through a polycarbonate membrane suspension of niosome is passed.^[26]

• BUBBLE METHOD

In this method, round bottom flask contain three neck areas are used. One for reflux, thermometer and nitrogen supply inlet respectively. The lipid mixture was dispersed in phosphate buffer saline and later undergoes on high pressure homogenizer. Then supply nitrogen gas at 65-70 °C leads to bubble formation and obtained the vesicle.^[26]

CHARACTERIZATION OF NIOSOMES

1. SIZE

Niosome size determined by Laser light scattering method, electron microscopy, molecular sieve chromatography, ultracentrifugation, photon correlation microscopy, optical microscopy and freeze fracture electron microscopy etc. Its shape is sphere.^[27] The release rate and shelf life of preparation depends on the vesicle size so it is an important parameter. Number of lamellae can be determined by NMR spectroscopy, small angle X-ray scattering and Electron microscopy.^[28]

2. SHAPE AND MORPHOLOGY

It is determined by the microscopic technique.^[28]

3. ENTRAPMENT EFFICIENCY

From the niosomal preparation free drug is removed by centrifugation, dialysis etc. methods.

By using the centrifugation method, from the clear supernatants the untrapped drug can be estimated.^[28]

Using this formula the entrapment efficiency was determined:

$$\text{Entrapment Efficiency (\%)} = (A-B/A) \times 100$$

OR

$$\text{Entrapment efficiency (\%)} = (C/A) \times 100$$

Where,

A = Initial concentration drug

B = Drug in supernatant

C = Drug entrapped in niosomes

4. INVITRO RELEASE

Using dialysis method the drug release rate was determined. Dialysis sac is washed and sinks in phosphate buffer or water. Then non-ionic surfactant was filled in the dialysis sac and the sac placed in phosphate buffer solution maintained at 37°C. At specific time intervals the buffer sample was withdrawn and using suitable analytical technique the drug concentration was determined.^[28]

EVALUATION OF NIOSOMES IN OCULAR DRUG DELIVERY^[29,30]

1. PARTICLE SIZE ANALYSIS

The surface morphology was determined by using Scanning Electron Microscopy (SEM). About 30 niosomes diameters are measured from each batch and average mean was considered.

2. STABILITY STUDIES

Mainly three storing conditions are 4°±2°C, 25°±2°C and 40°±2°C for the period of three months. After one month drug content and in-vitro release studies was carried out on the selected formulations and periodically thereafter for three months.

3. RHEOLOGICAL PROPERTIES

Viscosity is the most significant parameter in the ophthalmic preparation. It was determined by using Ostwald- U- tube. Niosome is diluted with water to the required concentration and it is allowed to equilibrate for 1hr at 25°C.

4. OCULAR IRRITANCY OF NIOSOMES

It could be evaluated by observing them for any swelling, redness or increased tear secretions. Rabbits are used for the study. 2.5-3Kg rabbits are selected. The test and

control samples are instilled into the left and right eyes of the rabbits respectively for a period of 40 days by instilling once. Then the eyes are separated, fixed and cut vertically, dehydrate, clear, impregnate in soft and hard paraffin, section at 8µm thickness with the microtone and stain with haemotoxylin and eosin. Using optical microscopy, examine the photographed stained sections for corneal histological examinations.

5. INTRAOCULAR PRESSURE

Adult male normotensive rabbits weight about 1.5 – 2 kg are used. To determine the change in intraocular pressure Tonometer is used. Initially instilling a drop of a local anesthetic after that instillation of drug in both eyes and IOP can be measured.

IOP difference (ΔIOP) for each eye is calculated as follows,

$$\Delta IOP = IOP_{\text{dosed eye}} - IOP_{\text{control eye}}$$

6. AQUEOUS HUMOR ANALYSIS STUDY

Albino rats are used weighing about 2.5Kg. Injecting the 50/50 mixture of ketamine hydrochloride (30 mg/kg) and xylazine hydrochloride (10mg/kg) to the rats for anesthesia. The eyes anaesthetize using one to two drops of oxybuprocaine to diminish further sufferings. Above the coneoscleral limbus just across the cornea needle of 25G is inserted. For analysing the samples, samples are collected and stored at - 20°C. By using HPLC with UV detector amount of drug in the aqueous humor samples could be analysed.

DRUGS USED IN NIOSOMAL DELIVERY^[31]

ROUTES OF DRUG ADMINISTRATION	EXAMPLES OF DRUGS
Intravenous Route	Doxorubicin, methotrexate, tretinoin, Vincristine
Peroral route	DNA vaccines, proteins, peptides, insulin
Ocular route	Timolo maleate, cyclopentolate
Nasal route	Sumatriptan, influenza viral vaccine
Inhalation	All transretinoic acid
Transdermal Route	Fluriprofen, piroxicam, ketorolac
Vaginal	Insulin
Topical	Clobetasol propionate, Rofecoxib, Minoxidil, Propyl thiouracil

NIOSOME BASED TREATMENT STRATEGIES IN OCULAR DISEASES

1. GLAUCOMA

It is a neurodegenerative disease and requires a lifetime treatment. It is an optic neuropathy and characterized with retinal ganglion cell (RGC) death by apoptosis, resulting in degeneration of nerve axons and visual field defects. There are various types of glaucoma. The most important factor associated with Primary Open Angle Glaucoma prognosis is the increased intraocular pressure (IOP) because of the accumulation of aqueous humor in the anterior chamber, due to the overproduction of fluid or the blockage of drainage system. An imbalance occurs in the retinal blood flow due to elevated IOP which leads to the degeneration of the optic nerve. The main aim of the treatment is to reduce the intraocular pressure by various treatment options including drugs, laser treatment and surgery. Niosomes are the drug delivery vehicles for the glaucoma treatment. There are many advantages for the niosomes in drug delivery such as less frequent administration, extended IOP-lowering activity, higher corneal permeation, and low ocular toxicity.^[32]

2. CONJUNCTIVITIS

Conjunctivitis is defined as the inflammation or infection of the conjunctiva, which is the translucent mucous membrane located in the sclera. Different types of conjunctivitis such as viral, bacterial, and allergic conjunctivitis that may occur in acute or chronic forms. Infectious conjunctivitis is bacterial, viral, fungal, parasitic, and chlamydial conjunctivitis. Causes for the noninfectious conjunctivitis are allergens, toxicities, and irritants. Main treatment is the topical administration of antibiotics, antivirals (aciclovir, trifluridine, and valaciclovir and antifungals (polyenes, azoles, imidazoles, triazoles, pyrimidines, and echinocandins). In order to increase the efficacy of these drugs, nanotechnological formulations are being investigated for a while now. Niosomes release the drug in sustained and

determined pattern and found to be they are ultimate ophthalmic drug carriers.^[33]

3. RETINAL DISEASES

The Inherited Retinal Diseases (IRD) is heterogeneous disorders and resulting in retinal degeneration. In the inner retinal layer mutations occurred in genes and result in IRD. In most cases, mutation expressed in the photoreceptor or retinal pigment epithelium (RPE). Retinal gene delivery with niosome carriers for non-viral vectors is investigated and formulated a novel cationic niosome to be used in gene delivery to retina.^[34]

4. KERATITIS

It is the inflammation in the corneal and generated by infections in the presence of pathogens such as bacteria, fungi, and viruses, and constitutes one of the major causes of blindness worldwide. Patients show similar symptoms in the eye such as redness, pain, blurry vision, and tearing. Various niosome formulations was prepared and evaluated and it exhibits extended release of drug.^[35]

CONCLUSION

Niosomes are non-ionic surfactant vesicle system, novel and efficient approach to drug delivery. Niosomes with the ophthalmic drug delivery proved significant advancement in present day. A wide range of drugs can be encapsulated into the niosomes, with the help of non-ionic surfactant and the cholesterol. Niosomes provides sustained release of the encapsulated drug, possess enhanced stability and reduce the toxic effects. Compared to other drug delivery systems such as liposomes, no special condition required for handling and storage of niosomes. In summary, niosome is highly effective tool for drug delivery in therapeutic regime of numerous diseases.^[36]

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