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A Review On Niosomes In Ocular Drug Delivery System (ODDS)

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ABSRACT

Traditional dosage forms limit drug transport to the eye, and therapeutic drug concentrations in target tissues are not maintained for long because the eyes are protected by a unique anatomy and physiology. Various droppable products to prolong the retention time on the ocular surface have been introduced to the market for the treatment of the anterior segment of the eye. Direct intravitreal implants, on the other hand, have been extensively researched for the treatment of chronic vitreoretinal diseases using biodegradable or non-biodegradable polymer technology. There is an urgent need to develop ocular drug delivery systems that provide controlled release for the treatment of chronic diseases while also increasing patient and doctor convenience in order to reduce dosing frequency and invasive treatment. In this review we are focusing on niosomes as nanoparticles and novel drug delivery system in targeting and dealing of ocular diseases and barriers at large.

Key words: novel drug delivery, niosomes, ocular, nanoparticles, nanotechnology

INTRODUCTION

No matter the method of administration such as eve drops, Sub-conjunctiva, sub-tension of intravitreal injection and implant, therapeutic medications must transverse many protective barriers since the eye is an organ that is shielded from foreign substances and external stress. [1]

For many years, ocular scientists have faced a significant barrier in delivering drugs to specific eye tissues, various precorneal, dynamic, and static ocular barriers prevent medication delivery to the targeted ocular tissues. Additionally, target tissues do not retain therapeutic medication levels for an extended period of time. The formulator faces a difficult challenge m getting beyond the eye's protective defenses without enduring long-term tissue damage. [2] For the past two decades, nano vesicular systems have been studied to improve the ocular bioavailability of topically instilled drugs by extending the contact time between the drug and the eye.

the drug and the ocular surface, as well as providing a sustained method of drug delivery, thereby increasing ocular bioavailability[24]. The current review aims to outline the advancements made in existing conventional formulations for ocular distribution, followed by recent developments in formulations based on nanotechnology. Maintaining therapeutic drug concentrations at the target site, lowering dosage frequency, and getting through numerous dynamic and static ocular obstacles are the fundamental goals of any ocular drug delivery system most importantly, the medication delivery mechanism should strive to increase drug bioavailability while causing no negative ocular effects. [3].

Topical ocular eye-drops are typically used to treat conditions of the anterior section of the eye (cornea, conjunctiva, sclera, and anterior uvula) No matter the infused volume, an eye drop frequently leaves the body quickly within five to six minutes of administration, and only a small portion_ actually reaches the intraocular tissue .[4] As a result, it1s challenging to deliver and keep up a sufficient medication concentration in the precorneal area. Ocular drugs are not readily available because more than 75%e of administered ophthalmic solution is lost by nasolachrymal drainage and absorbed systemically through the conjunctiva.

Numerous ophthalmic vehicles, including viscous solutions, suspensions, emulsions, ointments, aqueous gels, and polymeric inserts, have been developed to boost ocular bioavailability and lengthen the retention duration on the ocular surface.Due to underlying factors like the blood-ocular barrier, the cornea, and accelerated removal of eyedrops from the ocular surface caused by rapid nasolacrimal drainage, transferring medication through the ocular route is a difficult task. Additionally, because of the sclera, conjunctiva, cornea, and vitreous barriers, drug penetration to the posterior surface of the eye is insufficient.[5].Recently, ophthalmic formulations

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based on nanotechnology have been investigated, with nanocarriers such as polymeric nanoparticles and nanomicelles being used as DDS for targeted drug delivery.[23] Other promising novel approaches include the use of liposomes, niosomes, nanoemulsions, and nanosuspensions[23]. Nanomedicines make it easier for therapeutic agents to penetrate ocular tissue. The main cause of blindness related to cataract and diabetic retinopathy was addressed by current studies in nanomedicines as a therapeutic approach by reducing intraocular pressure as the nanomedicines enhanced and improved the drug-release profile and therapeutic profile by reducing the side-effects of drugs. Several approaches, such as the use of liposomes, SLN, NLC, hydrogel, nanoemulsion, nanosuspension, noisome, polymeric micelles, and inorganic nanoparticles, have highlighted the need for nanomedicines to target ocular diseases.[6] The numerous traditional and cutting-edge ophthalmic drug delivery methods created to deliver medication to sick ocular tissues for the treatment of ocular disorders and the recent advancement on ocular drug delivery system will be discussed in this review.[7,8].

1.1 Anatomy of the eye

There are three concentric substrates in the eye . The cornea and sclera are located in the outermost section, which is the fibrous tunic. The iris, ciliary body, and choroid make up the mid covering, also known as the uvea or vascular tunic. The retina is the component inside the eye. eye's retina utilizes the blood arteries in the choroid and retina for oxygenation. The cornea is a transparent dome-shaped surface that protects the pupil, the front of the iris, and the front of the eye. The cornea has an average horizontal diameter of 11.5 mm, a vertical diameter of 10.5 mm, and thickness of roughly 0.5 mm. The retina is a light-sensitive nerve lamella located in the back of the eye that is held in a stable and adequate posture by the surrounding cornea and sclera. This area of the eye detects light, converts it into signals, and then sends those signals via the optic nerve to the brain. According to a widely used classification, the human eye is split into two parts: the anterior and posterior segments. The anterior segment, which makes up one-sixth of the eye, contains the iris, cornea, aqueous fluid, and lens. a backward part, which makes up the remaining five-sixths of the eye, is made up of the choroid, back of the sclera, retina, and vitreous body.

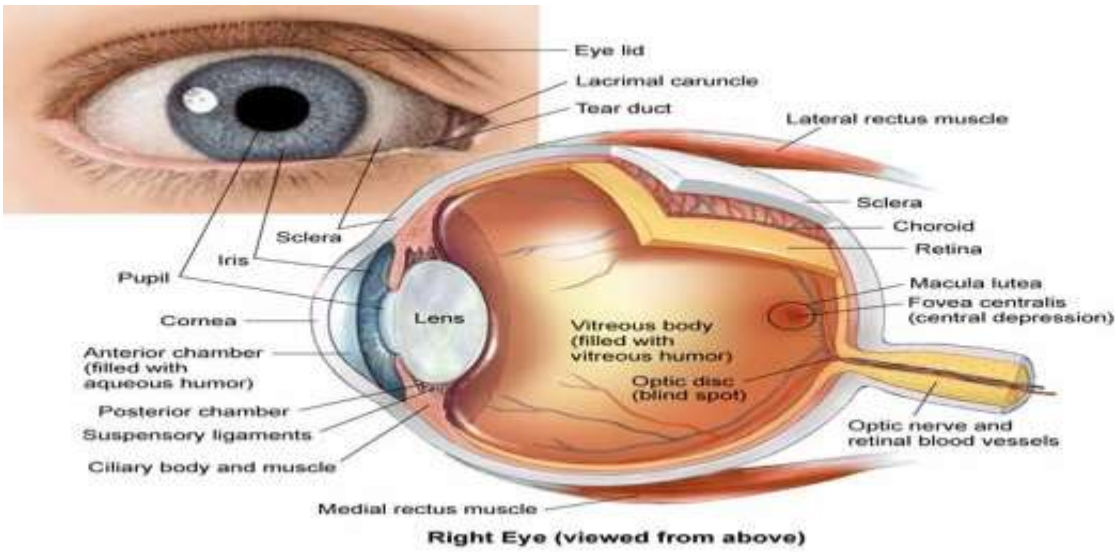

Figure 1: The anatomy of the eye

1.2 Ocular barriers

Tear

Tear film is one of the precorneal barriers that reduces the effective concentration of drugs administered due to dilution by tear turnover (approximately 1 L/min), accelerated clearance, and drug molecule binding to tear proteins. Furthermore, the instillation dosing volume is typically 20-50 L, whereas the size of a cul-de-sac is only 7-10 L. Excess volume may escape through the nasolacrimal duct or spill out on the cheek.[8]

Cornea

The cornea is made up of three layers: epithelium, stroma, and endothelium, as well as a

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mechanical barrier that prevents exogenous substances from entering the eye . (Figure 3). Each layer is polarised differently and has a rate-limiting structure for drug permeation. The corneal epithelium is lipophilic, and tight junctions between cells form to limit paracellular drug permeation from the tear film. The stroma is made up of an extracellular matrix made up of lamellar collagen fibrils. The stroma's highly hydrated structure acts as a barrier to the permeation of lipophilic drug molecules. Corneal endothelium is the innermost monolayer of hexagonal-shaped cells that serves as a barrier between the stroma and the aqueous humour. Endothelial junctions are leaky and allow macromolecules to pass between the aqueous humour and the stroma.[8]

Conjunctiva

The conjunctiva of the eyelids and globe is a thin and transparent membrane that helps to form and maintain the tear film. Furthermore, the conjunctiva or episclera has an abundant supply of capillaries and lymphatics thus, drugs administered in the conjunctival or episcleral space may be cleared via blood and lymph. Because conjunctival blood vessels lack a tight junction barrier , drug molecules can enter the bloodstream via pinocytosis and/or convective transport via paracellular pores in the vascular endothelial layer. Conjunctival lymphatics function as an efflux system, allowing for efficient elimination from the conjunctival space. It was recently reported that at least 10% of a small molecular weight hydrophilic model compound (sodium fluorescein) administered in the subconjunctival space is eliminated via the lymphatics in rat eyes within the first hour . Because interstitial fluid is returned to the systemic circulation after filtration through lymph nodes, drugs transported by lymphatics in conjunction with elimination by blood circulation can contribute to systemic exposure.[8]

Sclera

The sclera is primarily made up of collagen fibres and proteoglycans that are embedded in an extracellular matrix . Scleral permeability has been shown to be strongly dependent on molecular radius, decreasing roughly exponentially with molecular radius . Furthermore, the posterior sclera has a looser weave of collagen fibres than the anterior sclera , and the human sclera is relatively thick near the limbus (0.53 0.14 mm), thin at the equator (0.39 0.17 mm), and significantly thicker near the optic nerve (0.9–1.0 mm). Thus, near the equator, 12-17 mm posterior to the corneoscleral limbus, is the ideal location for transscleral drug delivery. Drug hydrophobicity influences scleral permeability; increasing lipophilicity results in lower permeability; and hydrophilic drugs can diffuse more easily through the aqueous medium of proteoglycans in the fibre matrix pores than lipophilic drugs. Furthermore, the drug molecule's charge influences its permeability across the sclera. Because of their binding to the negatively charged proteoglycan matrix, positively charged compounds may have poor permeability.[8]

Choroid/Bruch's Membrane

The choroid is one of the most vascularized tissues in the body, and it supplies blood to the retina. It has ten times the blood flow per unit tissue weight of the brain. Furthermore, the choroidal capillary endothelial cells are fenestrated and relatively large in diameter (20-40 m) in humans.

The thickness of the retina and choroid can be measured noninvasively using optical coherence tomography (OCT). It has been demonstrated using an OCT that choroidal thickness decreases with age. Previous histological studies have shown that choroidal thickness decreases from 200 m at birth to around 80 m by age 90. Choroidal thickness is also affected by chorioretinal diseases such as AMD with pigment epithelial detachment, central serous chorioretinopathy, age-related choroidal atrophy, and high myopia. Bruch's membrane (BM), on the other hand, thickens with age. These changes result in increased calcification of elastic fibres, increased cross-linking of collagen fibres, and increased glycosaminoglycan turnover. Furthermore, BM accumulates advanced glycation end products and lipofuscin. Drug permeability from the subconjunctiva or episcleral space into the retina and vitreous may be affected by changes in choroid and BM thickness.[8]

Retina

Drugs in the vitreous are eliminated through two main routes: anterior and posterior segments. All drugs can be eliminated through the anterior route. This means that drugs can pass through the vitreous to the posterior chamber and then be eliminated through aqueous turnover and uveal blood flow. Permeation across the retina allows for elimination via the posterior route. The internal limiting membrane (ILM) is one of the barriers to drug penetration from the vitreous to the retina. The ILM connects the retina and the vitreous and is made up of ten different extracellular matrix proteins. Although previous research in primates suggested that molecules larger than 100 kDa could not cross the retinal

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layers into the subretinal space, it has been confirmed by immunohistochemical analysis, a full-length, humanised, anti-vascular endothelial growth factor (VEGF) monoclonal antibody (Bevacizumab, Avastin®, Genentech Inc.), composed of 214 amino acids with a molecular weight of 149 kDa, injected into the vitreous cavity, can penetrate through the sensory retina into retinal pigment epitheliums (RPE), subretinal and choroidal space, in monkey and rabbit . Furthermore, nanometer-sized particles with a mean diameter of less than 200 nm can pass through the sensory retina and into the RPE after intravitreal injection in rabbits. The drugs in the subretinal fluid could theoretically be absorbed by the sensory retinal blood vessels or transported across the RPE, where they could be absorbed into the choroidal vessels or pass through the sclera in an intact retina. Drug transport across the RPE occurs via both transcellular and paracellular pathways. Hydrostatic and osmotic forces drive outward transport of molecules from subretinal spaces, and small molecules may transport via paracellular inter-RPE cellular clefts and active transport via the transcellular route.[8]

Blood-Retinal Barrier

The blood-retinal barrier (BRB) prevents drugs from being transported from the blood into the retina. BRB is made up of tight junctions between retinal capillary endothelial cells and RPE, which are referred to as iBRB for the inner and oBRB for the outer BRB, respectively. Müller cells and astrocytes aid in the function of iBRB. The retinal capillary endothelial cells lack vesicles and are not fenestrated. Endocytosis or transcytosis, which may be receptor-mediated or fluid phase requiring adenosine triphosphate, has been described as the function of these endothelial vesicles. Under normal conditions, Müller cells and retinal capillary vessels have a close spatial relationship that allows the iBRB to uptake nutrients and dispose of metabolites. Under normal conditions, Müller cells are known to support neuronal activity and keep the iBRB functioning properly. They play a role in the regulation and homeostasis of K+ and other ion signalling molecules, as well as the regulation of extracellular pH. Müller cell dysfunction may contribute to iBRB breakdown in a variety of pathological conditions, including diabetes. Under hypoxic and inflammatory conditions, Müller cells increase VEGF secretion. An in vitro study found that VEGF-induced occluding phosphorylation and ubiquitination causes tight junction trafficking and increases retinal vascular permeability. [8]

1.3 Niosomes

As an alternative to liposomes, niosomes are vesicles made of non-ionic surfactants that are biodegradable, comparatively nontoxic, more stable, and less expensive. This article examines the current growth and enlargement of interest in niosomes across a variety of scientific fields, with a focus on their use in medicine [8]

Niosomes are microscopic lamellar structures that are non-toxic surfactant vesicles. They are created by adding cholesterol and a non-toxic surfactant of the alkyl or dialkylpolyglycerol ether class, followed by hydration in water.Niosomes can entrap both hydrophilic and lipophilic drugs, either in an aqueous layer or in a lipid-based vesicular membrane. It is reported to be more stable than liposomes. It has the potential to prolong the circulation of the entrapped drugs. It could be very useful for more effectively targeting the drug for treating ocular disease and other microbial diseases.Niosomes can be SUV (small unilamellar vesicles), MLV(Multi lamellar vesicles) or LUV (large unilamellarvesicles). They can be formulated by thin film hydration,Hand shaking, Ether Injection, Reverse phaseEvaporation, Sonication, microfluidisation and Transmembrane pH gradient.

Niosome properties vary greatly depending on the method of production and the composition of the bilayer. However, the principle remains the same (i.e., formation of lipid phase followed by hydration on aqueous medium leads to the formation of niosomes).[6]

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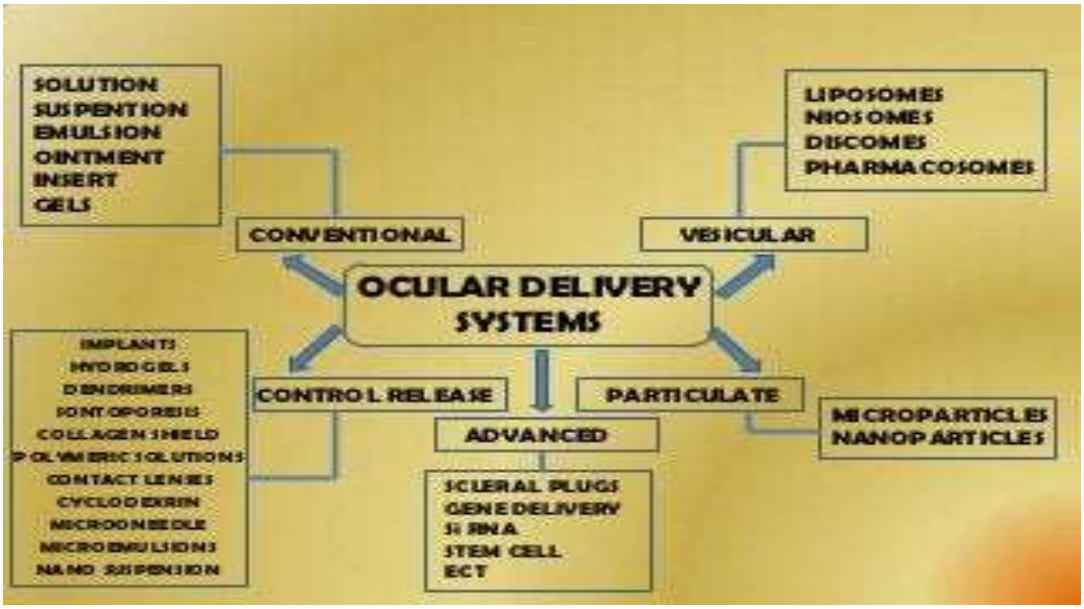

Figure 2: Ocular drug delivery system

1.3 Niosomes in ocular drug delivery system

Because of the significant and pharmacokinetically specific environment that exists in the eye, developing ocular dosage forms is the most appealing and difficult task ever faced by pharmaceutical scientists. The challenge is to get around the eye's shielding barrier without causing permanent tissue damage. The majority of current ocular drug delivery systems are crude and inefficient.[11]. Because of the complex mechanisms that exist in the eye, achieving effective drug concentration in the eye is a very difficult task.Given these considerations, the development of a drug delivery system is crucial in the treatment of various ocular diseases.[13,14] The goals of ocular drug targeting are significant in**:**

1. Improving drug permeation
2. Increasing bioavailability
3. To regulate drug release
4. Drug targeting at the active site

However, using Niosomes to target drugs for ocular therapeutics would be a promising approach.

1.4 Advantage of Niosomes in ocular drug delivery

1. Niosomes can entrap both hydrophilic andlipophilic drug.
2. Enhance skin penetration therapy improvingbioavailability of drug
3. Niosomes are depository for releasing drug insustained or prolonged manner.
4. They have greater bio availability when compared to conventional formulations.
5. Bio degradable, bio compatible and nonimmunogenic to the body.
6. More stable than liposomes.
7. Better patient compatibility better therapeutic effect than conventional.
8. Provide accommodation of drug molecules througha broad range of solubility's.
9. Vesicles may act as a storehouse, releasing the drug in a controlled manner.
10. They are osmotically active and stable as well asthey increase the stability of entrapped drug.
11. Handling and storage of surfactants requires noextraordinary conditions.

1.5 Comparing niosomes to liposome's

Niosomes are now being extensively researched as a potential replacement for liposomes, which have some drawbacks such as – they While costly, their constituents, such as phospholipids, are chemically unstable due to their propensity for oxidative destruction, they need specific handling and storage, and the purity of naturally occurring phospholipids varies.

While liposomes are made from doublechain phospholipids, niosomes are made from uncharged single-chain surfactant and cholesterol (neutral or charged).

Niosomes behave similarly to liposomes in vivo, extending the drug's circulation and changing its organ distribution and metabolic stability. It has

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been demonstrated that encapsulating various anti-neoplastic agents in these carrier vesicles reduces drug-induced toxic side effects, while preserving or, in some cases, improving anti-tumor effectiveness. Such vesicular drug delivery systems affect cellular metabolism, tissue distribution, plasma clearance kinetics, and medication interaction they are anticipated to direct the medication to the intended location of action and/or regulate its release.

STRUCTURE OF NIOSOMES

Niosomes are spherical structures made up of microscopic lamellar structures (unilamellar or multilamellar). Niosomes are composed of a bilayer[21]. Nonionic surfactant-based niosomal bilayer When most surfactants are immersed in water, micellar structures form; however, some surfactants form bilayers that convert to niosomes. Nonionic surfactants with or without cholesterol and a charge inducer form the bilayer. Niosomes are formed by combining various types of surfactants in varying combinations and molar ratios. Alkyl ethers, alkyl glyceryl ethers, sorbitan fatty acid esters, and polyoxyethylene fatty acid esters are examples of surfactants. The addition of cholesterol keeps the double layer rigid and makes niosomes less leaky. Simultaneously, the loading sensor aids in the loading of the vesicles, increasing their size and improving drug absorption efficiency. Negative charge inducers such as dicetyl phosphate, dihexadecyl phosphate, and l

ipoamino acid, as well as positive charge inducers such as stearylamine and cetylpyridinium chloride, aid in vesicle stabilization[21]. Non-ionic surfactants in niosomes tend to orient themselves so that the hydrophilic end points outward (toward the aqueous phase) and the hydrophobic ends point inward to each other, forming a closed two-layer structure that contains dissolved substances in the aqueous solution. As a result, niosomes' closed bilayer structure has hydrophilic inner and outer surfaces, with a sandwiched lipophilic area in between. Energy, such as heat or physical stirring, is required to form a closed two-layer structure. Various forces within the vesicles, such as van der Waals and repulsive forces that exist among surfactant molecules, were discovered to play an important role in preserving the vesicular structure. They are classified as MLVs, LUVs, or SUVs based on their preparation methods. The hydrophobic chains within the niosomal bilayer face each other, and the hydrophobic ends are exposed on the outside and inside of the vesicles. [21]

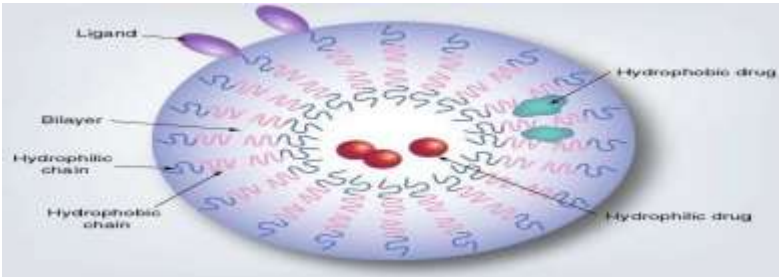

Fig no 3Niosomes structure

A LOOK ON CONVENTIONAL OCULAR DRUG DELIVERY SYSTEM

A patient-friendly and widely recommended route of drug administration is topical drop instillation into the lower precorneal pocket. However, the majority of the topically administered dose is lost due to reflux blinking, with only 20% of the instilled dose remaining in the precorneal pocket. The drug concentration in the precorneal area acts as a driving force for passive diffusion across the cornea. However, high corneal permeation with longer drug cornea contact time is required for efficient ocular drug delivery with eye drops.[16] Several initiatives have been launched to improve precorneal residence time and corneal penetration.Solutions and suspensions are the most common ocular drug delivery systems used in today's ocular disease management. The collyrium, which was attributed to the Romans and Greeks, was the source of solutions and suspensions. The preparation was a cake made of gum that looked like a small bar of soap and contained the drug. To make eye drops, a small piece of cake was dissolved in water, milk, or egg white.[12]

Drugs used in the eye today are classified into several categories, including miotics, mydriatics, cycloplegics, and antibacterial, antiglaucoma drugs, surgical adjuncts, diagnostics, and drugs for other purposes. Aside from the active

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ingredients, therapeutically inactive ingredients are required in ophthalmic solution or suspension to perform one or more of the following functions: Tonicity adjustment, buffering and pH adjustment, stabilization of active ingredients against decomposition, increasing solubility, imparting viscosity, and acting as a solvent. As previously stated, aqueous solutions have the disadvantage of being quietly removed from the front of the eye, resulting in poor ocular bioavailability. Most clinicians agree that a solution or suspension form of a drug delivery system is preferred by the patient if extended duration can be achieved with these forms. [18]. The maximum size limit for micro particles for ophthalmic administrations about 5-10 mm above which a scratchingfeeling in the eye can result upon ocular instillation. That is why microspheres andnanoparticles are promising drug carriers for ophthalmic application.39 Nanoparticles areprepared using bioadhesive polymers to provide sustained effect to the entrapped drugs.[18]

- **Topical eye drops (liquid/solution)**

Topical drops are the most convenient, safe, immediate, patient-compliant, and non-invasive method of ocular treatment. Medication administration following topical drop instillation, an eye drop solution provides a pulse drug permeation, after which its concentration rapidly declines. The kinetics of drug concentration decline may be roughly first order. To improve drug contact time, permeation, and ocular bioavailability, various additives, such as viscosity enhancers, may be added to topical eye drops. [2]

- **Emulsions**

A formulation approach based on emulsions has the advantage of improving both solubility and bioavailability. Of narcotics commercially, two types of emulsions are used as vehicles for active pharmaceuticals: oil in water (o/w) and water in oil (w/o) emulsion systems.The o/w emulsion is commonly used and preferred over the w/o system for ophthalmic drug delivery. The reasons for this include less irritation and improved ocular tolerance of the o/w emulsion. [2]

- **Suspensions**

Another type of non-invasive ocular topical drop drug carrier system is suspensions. Suspension can be specified. as a finely divided insoluble API dispersion in an aqueous solvent containing a suitable suspending and dispersing agent To put it another way, the carrier solvent system is a saturated API solution. Suspension particles retain in the precorneal pocket, increasing drug contact time and duration of action compared to drug solution.[2] Solutions are the most commonly used pharmaceutical forms for administering drugs that must be active on the eye surface or in the eye after passage.via the cornea or the conjunctiva[25] The duration of drug action in suspension is determined by particle size. A smaller particle replenishes the drug that has been absorbed into the ocular tissues via the precorneal pocket. Larger particle size, on the other hand, helps retain particles for a longer period of time and slows drug dissolution. As a result, optimal particle size should result in optimal drug activity. [2]

- **Ointments**

Ophthalmic ointments are another type of carrier system designed for topical use. Ophthalmic ointment consists of a semisolid and solid hydrocarbon (paraffin) mixture with a melting point at physiological ocular temperature (34 °C). The biocompatibility of the hydrocarbon influences its selection. Ointments aid in increasing ocular bioavailability and sustaining drug release. [2]

COMPOSITION OF NIOSOMES

Cholesterol and non-ionic surfactants are two of its key constituents. The right form and stiffness are provided by cholesterol. The surfactants participate in an extremely crucial role in the creation of niosomes. The grades of non-ionic surfactants, such as spans, are span 20, span 40, span 60, span 80, and span 85. Similar to this, there are numerous classes of tweens' surfactant, including tween 20, tween 40, tween 60, and tween 80. Additionally, there are several grades of surfactant brij, including brij 30, brij 35, brij 52, brij 58, brij 72, and brij 76. Usually, these surfactants are employed to prepare niosomes.[7] Other surfactants that are reported to form niosomes are as follows**:**

1. Ether linked surfactant
2. Di-alkyl chain surfactant
3. Ester linked
4. Sorbitan Esters
5. Poly-sorbates

FACTORS GOVERNING NIOSOME FORMATION

Non-ionic surfactant structure: According to theory, the presence of a specific kind of amphiphile and aqueous conditions is necessary for niosome production. solvent. In some circumstances, the formulation must contain cholesterol, and vesicle aggregation, for instance,

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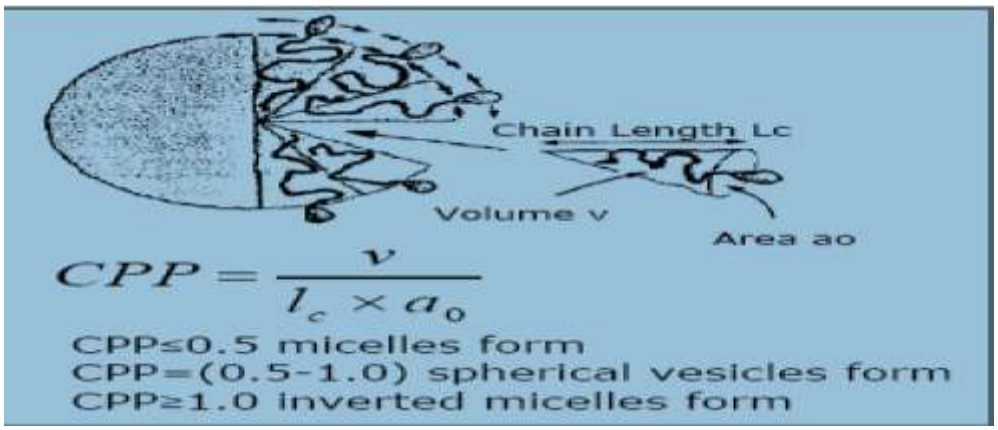
can be avoided by adding molecules that stabilise the system against the growth of aggregates due to repulsive steric or electrostatic effects. The addition of Solulan C24, a cholesteryl poly-24-oxyethylene ether, to doxorubicin (DOX) sorbitan monostearate (Span 60) niosome formulations is an illustration of steric stabilisation. The addition of dicetyl phosphate to 5(6)-carboxyfluorescein (CF) loaded Span 60 based niosomes 26 is an illustration of electrostatic stabilisation.[19]

Surfactant and lipid level: The surfactant/lipid concentration used to make niosomal dispersions is typically 10-30 mM (1- 2.5% w/w). Changing the surfactant:water ratio during the hydration step may affect the microstructure of the system and thus its properties. However, increasing the surfactant/lipid level also increases the total amount of drug encapsulated, though excessive surfactant/lipid levels result in highly viscous systems.[19]

Nature of the encapsulated drug: Another aspect that is frequently disregarded is how an amphiphilic medication affects vesicle formation. The amphipathic medication DOX was attempted to be encapsulated. To ensure a homogeneous formulation free of aggregates, Solulan C24 (poly-24-oxyethylene cholesteryl ether) must be used as a steric stabiliser. A pH-dependent change in the electrophoretic mobility of hexadecyl diglycerol ether (C16G2) niosomes in the presence of DOX suggests that the amphipathic drug has been integrated into the membrane of the vesicle.[19]

Structure of surfactants: The structure of the surfactant-forming vesicle, which is connected to critical packing, has an impact on its geometry. parameters. On the basis of crucial surfactant packing characteristics, one can predict the geometry of the forming vesicle. The following equation can be used to define crucial packing parameters.[19]



CHARACTERISTICS OF NIOSOMES

- **Particle size and zeta potential:** Photon correlation spectroscopy was used to evaluate the niosomal size distribution and zeta potential (Zetasizer Nano ZS, ZEN3600; Malvern Instruments, Malvern, UK). The range of sizes. Analysis was carried out at a temperature of 25 C and a scattering angle of 90. Multimodal analysis was used to determine the mean diameter/zeta potentialSD of six measurements for each sample.[20]
- **Entrapment efficiency:** First, niosomal formulations were dialyzed thoroughly against PBS for 3 hours using dialysis tubing (cellulose membrane 12 000–14 000 molecular weight cutoff). 0.1 millilitres of the dialyzed 1ml of n-propranolol was added to the dispersion and left alone for 5 min to completely break the niosomes. After adding 50% n-propranolol to the resultant solution in PBS, the absorbance was measured at 252.6 nm. The algorithm below was used to compute the percentage of drugs entrapped.[20]

Entrapment efficiency

$$= \frac{\text{Dorzo estimated after breaking of niosomes}}{\text{Dorzo added in hydration fluid}} \times 10$$

0

- **In vitro release profile:** Dorzo was released in vitro from niosomes using a dialysis bag at pH 7.4. A quantity of niosomes equal to 22.2 mg of Dorzo was calculated and placed in a bag that was then placed in a beaker containing 100 ml of PBS.Continuous stirring with a magnetic stirrer aided in vitro release (200 rpm). The temperature was kept at 371 degrees Celsius. Aliquots (4 mL) were removed at regular intervals and replaced with equal volumes of fresh PBS. The test was extended

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for 36 hours. The drug content of the withdrawn samples was then determined spectrophotometrically at 252.6 nm. To test the eventual limiting effects of the dialysis membrane on drug release, a separate experiment was performed with free Dorzo solution in the same PBS.[20].

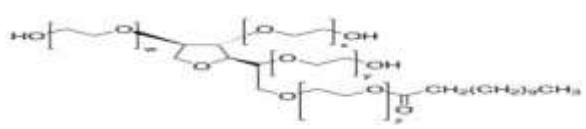
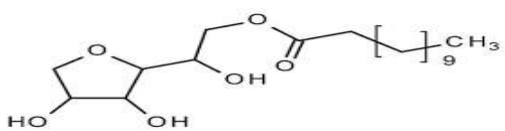
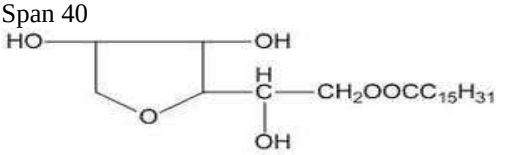
- **Morphology:** By using negative stain electron microscopy, niosomes were examined. On a copper grid that had already been coated, a drop of the vesicle preparation was used, and any extra was wiped away with filter paper. The grid was then given a drop of a 2% uranyl acetate solution, and the extra was taken off after two minutes using filter paper24. With the use of an electron microscope, the stained samples were seen and captured on camera (100 CX, Jeol, Tokyo, Japan). [20]

METHODS OF PREPARATION OF NIOSOMES

Preparation of vesicles: Because the preparation methods should be chosen in accordance with the use of niosomes, influence the number of bilayers, size, size distribution, and entrapment efficiency of the aqueous phase, as well as the vesicle membrane permeability

1. **Ether injection method:** The surfactant/cholesterol mixture is dissolved in diethyl ether and slowly injected via a needle. At 60 degrees Celsius, into the aqueous phase During the evaporation of the ether, large unilamellar vesicles form.[19] The disadvantages of this method include the presence of a small amount of ether in the vesicle suspension, which is frequently difficult to remove.
2. **Method of reverse phase evaporation**: Lipids are dissolved in chloroform and 14 volume of PBS (Phosphate buffer saline). The combination is Sonicated and evaporated at low pressure. The lipids combine to form a gel that is then hydrated. The evaporation process is repeated until the hydration is complete.[19]
3. **Hand shaking (film) method**: In a round bottom flask, dissolve the surfactant/cholesterol mixture in diethyl ether, and add the organic At room temperature and low pressure, the solvent is removed. During gentle agitation, the dried surfactant film is hydrated with an aqueous phase at 50 to 60 degrees Celsius. Preparation of large multilamellar vesicles Aqueous phase is introduced to the surfactant and cholesterol combination in a glass vial before.[19]
4. **sonication**: The combination is then subjected to sonication for a specific time frame. The resulting vesicles are uniformly tiny, unilamellar, and small still. Since niosomes have a maximum diameter of 100 nm, their resultant vesicles are often larger than those of liposomes.[19]
5. **According to handjani- vila's method:** To create a homogenous lamellar phase, equal volumes of lipid (or a mixture of lipids) are mixed and agitated with an aqueous solution of the active ingredient. The resulting mixture is then homogenized using agitation or ultra centrifugation at a regulated temperature. [19]

Table 1: Surfactant commonly used for niosomes preparation

Tween	Span
Tween 20 	Span 20 
Tween 40 	Span 40 
Tween 60	Span 60

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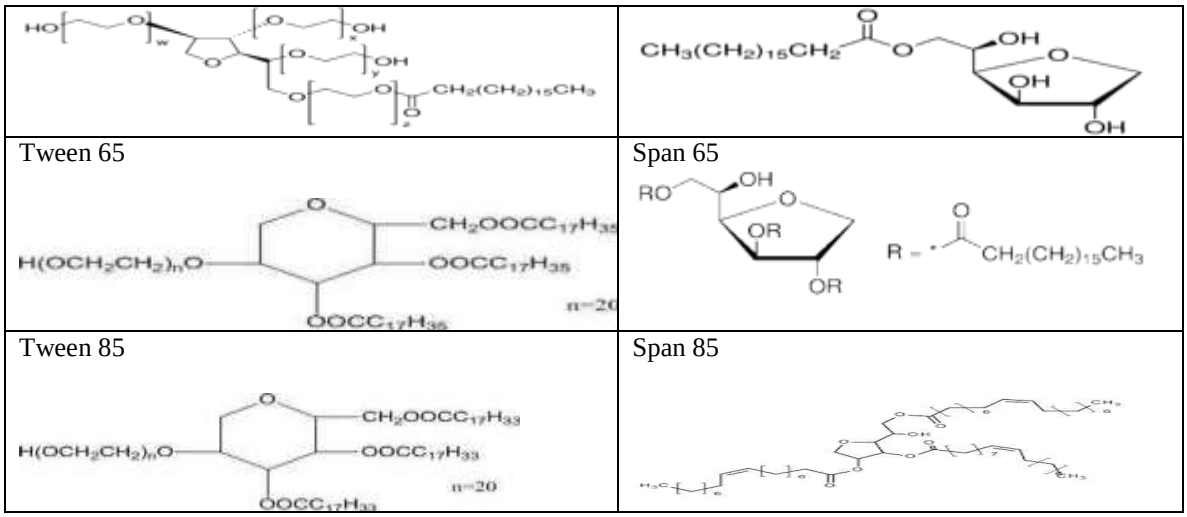

CLASSIFICATION OF NIOSOMES

Niosomes are classified in the following ways.

- Based on number of bilayers
- Based on the size of niosomes

These classifications give the following information about niosomes:

1. Multilamellar vesicles (MLV): MLVs are composed of a number of bilayers surrounded by aqueous lipid bilayers. Multilamellar vesicles (MLVs) typically range in size from 0.5 to 10 m. Multilamellar vesicles (MLVs) are commonly used due to their ease of preparation and long-term stability. Lipophilic compounds are transported by multilamellar vesicles (MLVs).[21]

2. Large unilamellar vesicles (LUV): LUV niosomes range in size from 100 to 300 nm. They have a high compartment ratio of aqueous phase to surfactants.[21]

3. Small unilamellar vesicles (SUV): SUVs range in size from 10-100nm. SUV niosomes are created from MLV using a variety of techniques, including high-pressure homogenization, sonication, and high-pressure extrusion. Small unilamellar vesicles have some drawbacks: they tend to aggregate, the drug loading in these vesicles is comparatively low, and they are thermodynamically unstable. [21]

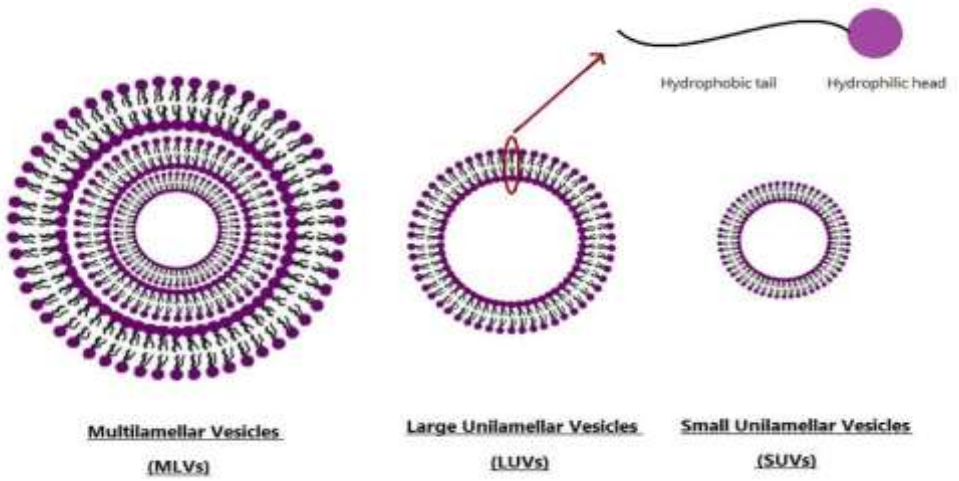

Figure 3: Classification of niosomes

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EVALUATION OF NIOSOMES IN OCULAR DELIVERY

Particle size analysis

Scanning electron microscopy (SEM) is used to examine the surface morphology of niosome particles. Niosome photographs are taken at random. Scan the stub and count it. Each batch's photomicrographs are used to calculate the diameters of about 30 niosomes. Finally, average mean diameters are taken into account.[4]

Stability studies

The stability of the formulated niosomal dispersion is studied by storing it at 4°2°C, 25°2°C, and 40°2°C for three months. The drug content and the invitro After one month, and then every three months, the selected formulations were subjected to release studies.[4]

Rheological properties

Viscosity is the most important parameter in ophthalmic preparations. In general, increased resident time of drug in cul-de-sac improves viscosity. The Ostwald-U-tube method is used to investigate the rheological properties of niosomes by diluting the product with water to the required concentration and allowing it to equilibrate for 1 hour at 25°C. By comparing efflux time to that of water, relative viscosity can be calculated. [4]

Intraocular pressure

Adult male normotensive rabbits weighing 1.5 - 2 kg were used in the study. A tonometer is used to measure changes in intraocular pressure. Prior to drug instillation IOP can be measured in both eyes after a drop of local anaesthetic is injected. The IOP difference (IOP) for each eye is calculated as follows: [4]

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

Aqueous humor analysis

A selection of albino rabbits weighing 2.5 kg will be used in the study.

Throughout the experiment, rabbits are sedated by intramuscular injection of a 50/50 combination of the hydrochlorides of xylazine (10 mg/kg) and ketamine (30 mg/kg). One to two drops of oxybuprocaine are used to anaesthetize the eyes in order to lessen additional discomfort. Just across the cornea, a 25 G needle is placed above the corneoscleral limbus. For analysis, samples are collected and kept at - 20°C. Using HPLC and a UV detector, the amount of drug in the aqueous humour samples could be determined.[4]

Niosomes ocular irritancy

It is possible to assess the formulation's ocular irritancy by checking the eyes for any signs of redness, swelling, or increased tear production. In the study, fit rabbits weighing 2.5 to 3 kilogrammes are chosen. For a total of 40 days, the test and control samples are administered once each to the left and right eyes. Separated eyeballs are fixed and cut vertically. They are then dehydrated, cleared, impregnated in soft and hard paraffin, sectioned at an 8-micron thickness with a microtone, and stained with hemotoxylin and eosin. For corneal histological analyses, stained sections are imaged using optical microscopy.

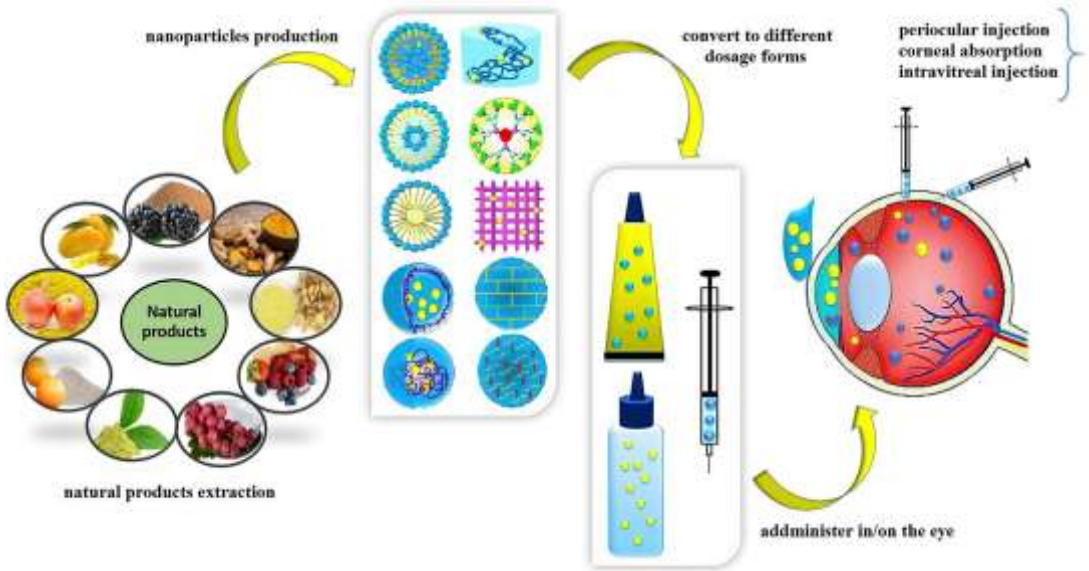

Figure 4 Application of niosomes and other nanostructures in ocular drug delivery.

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