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OCULAR DRUG DELIVERY: AN APPROACH TO CURRENT MEDICATION

Gyan Chand[1]*, Asheesh Kumar Singh[1], Navneet Kumar Verma[2], Vikas Yadav[1], Hariom Srivastava[1]

[1] Students of B. Pharmacy, Buddha Institute of Pharmacy, GIDA, Gorakhpur (U.P.), India-273209
[2] Associate Professor, Buddha Institute of Pharmacy, GIDA, Gorakhpur (U.P.), India-273209

Corresponding Author

Gyan Chand
Students of B. Pharmacy, Buddha Institute of Pharmacy, GIDA, Gorakhpur (U.P.), India-273209

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Abstract

Topical administration is the greatest alternative for ocular medicines since it activates rapidly, doesn't cause systemic toxicity, and requires fewer doses than systemic use. The inner workings of the eye must be reached by drugs applied topically, and trans corneal penetration is assumed to be the primary route for drug absorption. Corneal absorption happens significantly more slowly than elimination. The specific objective of therapeutic system design is to attain the optimal drug concentration at the active site for the appropriate duration of time. The main obstacle to long-term ocular treatment is the capacity to maintain a therapeutic dosage of medication at the site of action. The ocular absorption mode of elimination is significantly slower. For many years, scientists have been interested in the problem of effective topical administration. Their challenging goal is to ensure proper ocular penetration and extend the drug's residence period. Nanotechnology based carriers to ensnare both lipophilic and hydrophilic medicines, improve ocular permeability, prolong residence duration, stabilize pharmaceuticals and in vivo characterization techniques aid in the prediction of the generated nanocarriers' results. Clarifying the architecture of the eye, different ocular disorders, and barriers to ocular delivery are the goals of this review.

Key Words: *Ophthalmic drug delivery, Corneal drug delivery, Controlled and sustained drug delivery.*

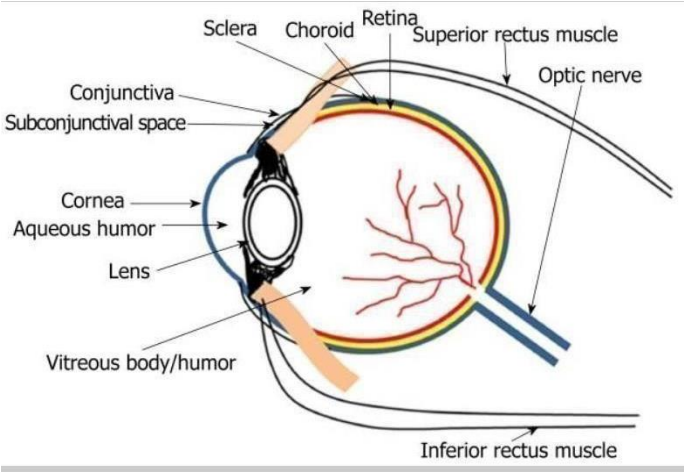
INTRODUCTION

The problems of absorption, distribution, metabolism, and elimination (ADME) must be Considered.[1] taken into account while creating a medication delivery plan. Pharmaceutical distribution poses distinct opportunities and challenges in relation to the eye. Drug delivery for the eyes is one of the most fascinating and difficult projects that pharmaceutical scientists work on.[2] The eye's physiology, anatomy, and biochemistry make it remarkably resistant to outside chemicals. Formulatoris face a problem in getting past the eye's defenses without permanently harming surrounding tissue.[3] The need for the most effective and sophisticated ocular medication delivery systems has increased due to the development of more sophisticated and sensitive diagnostic tools and treatment agents. Finding an effective medication is the aim of pharmacotherapeutics focus for the necessary amount of time at the chosen point of activity. Because the eye is a conduit for medication transport, local therapy is typically employed instead of systemic therapy to reduce the danger of ocular injury from high blood concentrations of drugs not meant for the eye.[4] The structure and physiology of the eye are distinct, making it a complex organ. The anterior segment and posterior segment are the two primary components of the eye's anatomy(Figure1).About one third of the eye is made up of the anterior segment, with the posterior section taking up the remaining space. The anterior section is composed of tissues including the cornea, conjunctiva, aqueous fluid, iris, ciliary body, and lens. The choroid, neural retina, optic nerve, retinal pigment epithelium, sclera, and vitreous humor comprise the posterior portion of the eye. Numerous vision threatening conditions affect the anterior and posterior segments of the eye illnesses. The anterior segment is impacted by a number of diseases, such as cataract, allergic conjunctivitis, anterior uveitis,

and glaucoma. On the other hand, the two most common conditions affecting the posterior portion of the eye are diabetic retinopathy and age-related macular degeneration (AMD). The most popular non-invasive method of administering medication to address conditions affecting the anterior region is topical instillation. Ninety percent of the marketed ophthalmic formulations are in conventional dose forms, like eye drops. Patient compliance and convenience of administration could be the cause. [5,6] However, topical drop delivery results in very limited ocular absorption. Deeper ocular medication absorption is hampered by a number of anatomical and physiological barriers, including nasolachrymal drainage, reflex blinking, tear turnover, and ocular static and dynamic barriers.[7] Because of this, fewerthan5%ofthe dose administered topically reaches the deeper eye structures.[8] The aforementioned obstacles make it challenging to obtain therapeutic medication concentration into posterior segment ocular tissues after topical eye drop instillation. Several delivery methods, including intravitreal injections, periocular injections, and systemic administration, are available for delivering the medication to the posterior segment ocular tissues. However, systemic administration is not a viable technique due to the tiny volume of the eye in comparison to the total body and the presence of blood retinal barriers. The most popular and generally advised method of administering medication to treat illnesses of the posterior eye is intravitreal injection. However, the requirement for repeated intravitreal injections and eye punctures results in a number of adverse consequences, including bleeding, endophthalmitis, retinal detachment, and poor patient outcomes. To attain and maintain an acceptable medication concentration with the least amount of the active therapeutic component, successful ocular absorption requires suitable corneal penetration in addition to an effective precorneal residence duration. Innovative technologies known as nano systems have been developed to overcome ocular obstacles, protect the drug from biological environments, extend the drug's residence time, and enhance the drug's ability to pass past biological barriers and penetrate the cornea [10]. To make sure the built nanosystems cancarryout the necessary task, it is crucial to characterize them. Numerous methods exist for characterizing an object, including but not limited to appearance, stability, size, zeta potential, potential interactions, pH measurement, and other significant ex vivo and in vivo assessments [11]. The shortcomings in other published reviews about ocular medication administration are brought to light by this review. It provided a thorough description of ocular drug delivery from a variety of angles, including the many anatomical characteristics of the eye, various ocular diseases, barriers to ocular delivery, various routes of ocular administration, dosage form classification, various nanostructured platforms, characterization techniques, methods to enhance ocular delivery, and future technologies. These qualities are necessary for this ocular medication delivery method. a strong corneal infiltration. a prolonged period of medication contact with ocular tissue. Installation and removal ease of use a unirritating variation.

Excellent Rheological Qualities

The last 20 years have seen a major focus on the development of the sustained and controlled release medication delivery system. The goal of such a system, which is based on localization at the site of action, is to avoid dose frequency and improve therapeutic impact. Achieving an effective drug concentration during the appropriate duration of the ocular disposition is the primary goal of pharmacotherapeutics at the intended site of action, and its achievement is crucial to the therapeutic agents 'removal. Physicalchemical characteristics in addition to the pertinent anatomy and physiology of the eye. [12] It necessitates a comprehensive understanding of the drug's composition as well as the limitations this ocular route of delivery presents. The numerous strategies aim to lengthen the therapeutic effect of ophthalmic medications and boost their absorption. There are two types of these ocular medication delivery devices. The first is predicated on the application of a sustained drug delivery system, which offers regulated and uninterrupted supply of eye medications. Maximum corneal drug absorption and minimal pre-corneal drug loss comprise the second section. [13] The ideal ophthalmic medication delivery system must be able to maintain drug release and hang about the front of the eye for an extended amount of time. Therefore, one of the most important things to perform is to improve the distribution of ophthalmic drugs. To extend the precorneal medication retention, other polymers can be added, insitu gel or colloidal suspension can be created, or erodible or non-erodible inserts can be used.[14] Intraocular injections and implants can enhance intraocular medicine delivery and the tissue's system, but only when administered by ophthalmologists and trained nurses. The sole therapeutic option for treating posterior segment diseases, such as those affecting the retina and choroid, is intravitreal administration. The cost of injections for patients and the healthcare system is significant. For instance, over 20 million intravitreal injections of antivascular endothelial growth factor (VEFG) are administered annually to treat wet age related muscle degeneration (WAMD). Wearable to create a quantitative sample framework using this multifactorial technique, which will assist in the selection of dosages, their rates of release, and the system without the requirement for pharmacokinetic or pharmacodynamic modeling knowledge.[15] The first one relies on the use of sustained drug delivery systems, which offer the continuous and regulated supply of medications for the eyes. These condentails reducing precorneal drug loss and optimizing corneal drug absorption [16]. A long lasting medication release and the ability to stay in the Neighborhoods of the front of the eye are requirements for the perfect ophthalmic drug delivery system. Therefore, it is essential to optimize the delivery of ocular drugs. Adding polymers of different grades, creating in situ gel or colloidal solution, or utilizing erodible or non erodible inserts to extend the pre-corneal drug retention are some methods to do this [17].



FigureNo.1:Structure of the Eye

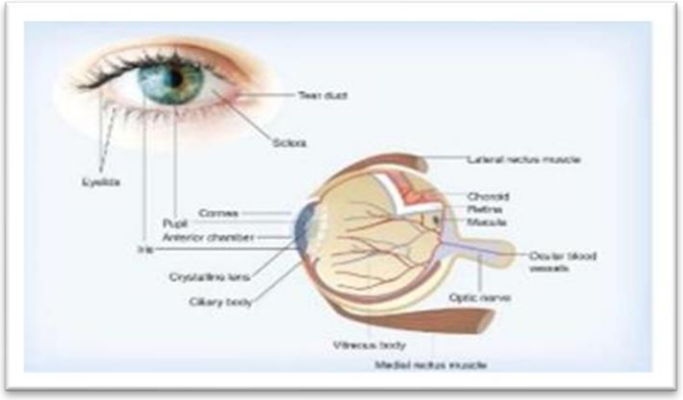


Figure No.2: Ocular drug delivery system

The first one relies on the use of sustained drug delivery systems, which offer the continuous and regulated supply of medications for the eyes. The second entails reducing precorneal drug loss and optimizing corneal drug absorption [16].A long lasting medication release and the ability to stay in the neighborhood of the front of the eye are requirements for the perfect ophthalmic drug delivery system. Therefore, it is essential to optimize the delivery of ocular drugs. Adding polymers of different grades, creating in situ gel or colloidal solution, or utilizing erodible or nonerodible inserts to extend the precorneal drug retention are some methods to do this [17].

IN SITU FORMING GELS FOR OPTHALMIC DRUG DELIVERY

In the realm of modern pharmaceutical design, controlled and sustained drug delivery has emerged as the norm. To this end, a great deal of research has been done to improve drug product effectiveness, reliability, and safety. In this regard, many polymers are very helpful as they undergo a reversible sol to gel phase transition in response to physiological stimuli [18]. Insitu gels are easily dropped as a solution into the conjunctival sac, where they undergo a transition into a gel with its favorable residence time. This occurs as a result of a chemical/physical change induced by the physiological environment. This kind of gel combines the benefit of a solution being patient-friendly with the advantageous residence time of a gel for improving can be brought about by a change in pH, much as cellulose acetate phthalate, a change in temperature, as in the case of Poloxamer 188, thermos gelling, or the presence of cations, as in the case of alginates and deacetylated gellan gum. Thus, pH sensitive, temperature sensitive, and ion activated systems can be used to categorize insitu gelling systems for ophthalmic usage. Since solution or a weak gel is more likely to be eliminated by the fluid dynamics of the eye when dropped in the eye, the rate of gel formation in situ is crucial [8].It is possible to formulate the ion triggered in situ gelling system with sodium alginate,[21].

The Anatomy of the Eye

The human eye serves as a portal to the process known as vision because of its exquisite detail and design. The eyeball is roughly one inch wide and spherical in shape. It is home to numerous buildings that combine to improve vision. The layers and internal structures that make up the human eye each have specific roles to play. Each component of the eye is described in detail below.

A. Sclera

The hard white sheath that makes up the outer layer of the ball is called the sclera, or white component of the eye. The eye's roughly globular form is preserved by its strong fibrous barrier. It is significantly thick erin the posterior (rear) than in the anterior (front) region [22].

B. Conjunctiva

The anterior portion of the eyeball is covered by the conjunctiva, a thin, transparent mucous epithelial barrier that borders the inside of the eyelids. The palpebral and bulbar conjunctiva is the names given to the corresponding portions of the conjunctiva. The stroma (substantia propria), which lies beneath the outer epithelium, makes up the conjunctiva. The tear film covers the conjunctiva and cornea, which are the parts of the eye that are visible. The conjunctiva secretes significant amounts of fluid, mucins, and electrolytes, which aid in the production of the tear film

C. Cornea

The cornea is a prominent, transparent protrusion that sits in front of the eye. The adult cornea's surface has a radius of around 8mm. It refracts light entering the eye, which then travels via the pupil and on to the lens (which focuses the light on to the retina), serving an essential optical function. The capillaries that end in loops at the cornea's periphery provide the required nutrients for the non-vascular tissue, which is devoid of blood vessels. Numerous nerves that are descended from the ciliary nerves supply it. These penetrate the cornea's layered tissue. As a result, it is very sensitive.

D. Aqueous humor

The outer/front chamber of the eye contains a fluid that resembles jelly called aqueous humor. Situated right infront of the lens and behind the cornea, the" anterior chamber of the eye" is filled with this watery fluid. The aqueous humor is a very mildly alkaline salt solution containing minuscule amounts of chloride and sodium ions. It is continuously created, mostly by the ciliary processes, travels through the pupil from the posterior chamber into the anterior chamber, and leaves through the uveoscleral and trabecular routes. Aqueous humour from the anterior chamber is collected by Schlemm's canal, also known as the scleral venous sinus or the canal of Schlemm, and then it is transported into the circulation by the anterior ciliary veins. It situated at the point where the sclera and cornea meet. Aqueous humor turnover in humans occurs at a rate of between 1% and 1.5% of anterior chamber volume each minute. Aqueous formation occurs at a rate of around 2.5 µl/min. There are pressure-dependent and pressure-independent routes in aqueous humor. The trabecular meshwork-schlemm's canal venous system is referred to as the pressure-dependent outflow, whereas any nontrabecular outflow is referred to as the uveoscleral outflow and is pressure independent [23].

E. Pupil Pupil

Though it is actually the circular opening in the center of the iris through which light enters the eye, it generally seems to be the dark "centre" of the eye. The pupillary reflex (sometimes called the "light reflex") controls the size of the pupil and, consequently, the amount of light that enters the eye.

F. Iris

Slender and round, the iris is a contractile curtain situated behind the cornea and in front of the lens. The iris is a diaphragm that may change in size. Its purpose is to control the pupil's size, which in turn controls how much light enters the eye. It's the colored portion of the eye, with different colors that can include blue, green, brown, hazel, or gray.

G. Ciliary Muscle

The ciliary muscle, a ring of striated smooth muscles in the central layer of the eye, controls the flow of aqueous humour into Schlemm's canal and facilitates accommodation for viewing things at different distances. The parasympathetic nervous system and innervation with sympathy. The ciliary muscle's contraction and relaxation changes the lens's curvature. The simplest way to explain this process is as the equilibrium that exists between two states at all times: contracted ciliary muscle, which allows the eye to focus on near things, and relaxed ciliary muscle, which allows the eye to focus on distant objects.

H. Lens

The lens is anarrow, translucen tcapsule that encloses a transparent structure. It is surrounded by the ciliary muscles and situated behind the pupil of the eye. It facilitates the refraction of light entering the eye after it has been initially refracted by the cornea. On the retina, the lens concentrates light to create a picture. This is possible because the lens's shape adjusts to the object(s) a person is looking at and how far away they are from their eyes. Accommodation is the term for this shape adjustment of the lens, which is accomplished by ciliary muscle contraction and relaxation.

I. Vitreous Humour

The huge region that makes up about 80% of each human eye is home to the vitreous humour, sometimes referred to as the vitreous body. The fluid that fills the space behind the lens of the eye is called vitreous humour, and it is completely transparent and thin like jelly. The hyaloids membrane is a thin, translucent membrane that encloses anal buminous fluid.

J. Retina

In the rear of the human eye is where the retina is found. One way to think of the retina is as the" screen "that an image is created on after light enters the eye through the cornea, aqueous humor, pupil, lens, and vitreous humor before arriving at the retina. The retina's role extends beyond serving as a surface for the generation of images; it also gathers information from those images and send it to the brain in a format that the body can use. Thus, the retinal "screen" is a structure that lines the inside of the eye and is sensitive to light. It is made up of rods and cones, which are photosensitive cells, together with the nerve fibers that connect them. These cells translate light into nerve impulses, which are then transmitted by the optic nerve to the brain.

K. Macula

The macula is the name for the retina's central region. A large number of photoreceptor cells, which translate light into nerve signals, are found in the macula. We can perceiveminute details with the macula, such as newspaper, due to the high concentration of photoreceptors. The fovea, where our sharpest eye sight is located, is at the very center of the macula.

L. Choroid

Absorbs unnecessary radiation. It is a thin, dark brown membrane that is extremely vascular, meaning it contains blood vessels. It also has a pigment that absorbs excess light to prevent blurry vision. (because the retina is overexposed to light). The blood flow in the choroid is among the highest in the body. The lamina fusa is responsible for the choroid's slack attachment to the sclera's inner surface.

M. Optic nerve

Nerve impulses are sent from the eye to the brain via the optic nerve, a bundle of more than a million nerve fibers. The brain can process the information on an image included in these nerve signals. The optic disk is the name for the front surface of the optic nerve that is visible on the retina.

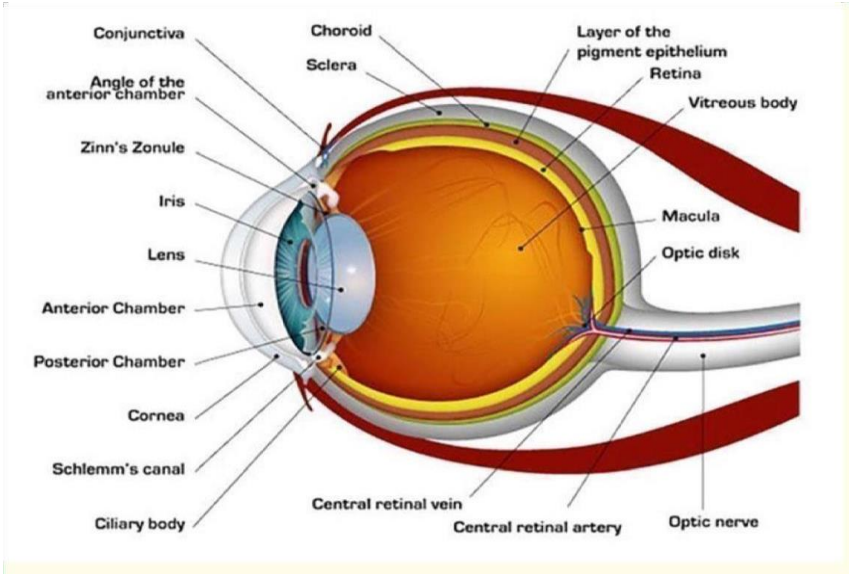


Figure No:3 The Anatomy of the Eye

MECHANISM OF OCULAR DRUG ABSORPTION

Instillation drugs need to enter the eye and enter through the cornea first, then through noncorneal channels. These non-corneal pathways, which entail drug diffusion through the sclera and conjunctiva, seem to be especially crucial for medications that are not well absorbed by the cornea [24].

Various Barriers to drug Absorption:

Directly affect how well a medicine is absorbed into the inner eye through tears. The diffusion mechanism across the corneal membrane is responsible for the majority of ophthalmic medicines' productive absorption. The rate and degree at which the eye's transport mechanisms occur determine the absorption process' efficiency. The physicochemical characteristics of the permeating molecule and its interaction with the membrane determine the flow of any medicinal molecule over the biological membrane. The physiological mechanism of precorneal fluid drainage or turn over contributes to the extent of the transport or absorption process. The cornea can be divided into three main layers for the purpose of transcorneal drug permeation: epithelium, stroma, and endothelium. Between one hundred and the epithelium and endothelium 100 times more lipid substance than the stroma. Consequently, the resistance provided by the different layersvariessignificantlydependingonthephysicochemicalcharacteristicsofadiffusing medication. Due to its lipoidal nature, epithelium serves as a diffusional barrier with strong resistance to ionic or other polar or aqueously soluble substances. On the other hand, in the hydrophilic stroma layer, molecules with comparatively low polarity face a higher diffusional resistance. The" differential solubility concept" is the name given to this much discussed theory of medication penetration

through the corneal membrane.

Various factors responsible for disposition of ocular drugs

The bioavailability of a medicine can be influenced by physiological factors such as drug metabolism, lachrymal drainage, and protein binding. Protein-bound medications' large size prevents them from passing through the corneal epithelium. Because of lachrymal drainage, an ophthalmic solution may only be in the eye for a short while. As a result, if a pharmacological molecule binds to proteins, it may soon lose its therapeutic effect by being inaccessible for absorption. Among the most significant issues with Traditionally, medications are removed from the precorneal lachrymal fluid quickly and thoroughly. It should be mentioned that the eye's propensity to constantly keep its resident volume at 7–10 µL, whereas topically injected quantities range from 20–50 µL, is the cause of this rapid drainage rate. Infact, in vivo studies have shown that 90% of the dose removed in 2 minutes for a 50 µL implanted volume and 4 minutes for a 10 µl instilled volume. As a result, the total absorption of a medicine administered topically is restricted to 1–10%, and the ocular residence duration of typical solutions is limited to a few minutes. Tears contain enzymes, much like other biological fluids do. (like lysozymes) that are able to breakdown the drug's chemical structure metabolically. Other factors, including as the physicochemical qualities of the therapeutic ingredient and the product formulation, are significant in addition to the physiological aspects impacting ocular bioavailability. Drugs with both hydrophilic and lipophilic properties can most easily penetrate the cornea since it is a membrane-barrier with both hydrophilic and lipophilic layers. Increasing the amount of unionized medication in the instilled dose by adjusting the pH of the solution is beneficial for corneal penetration. Due to their high water insoluble content, drugs are not easily absorbed by the cornea [24].

Nasolacrymal drainage system

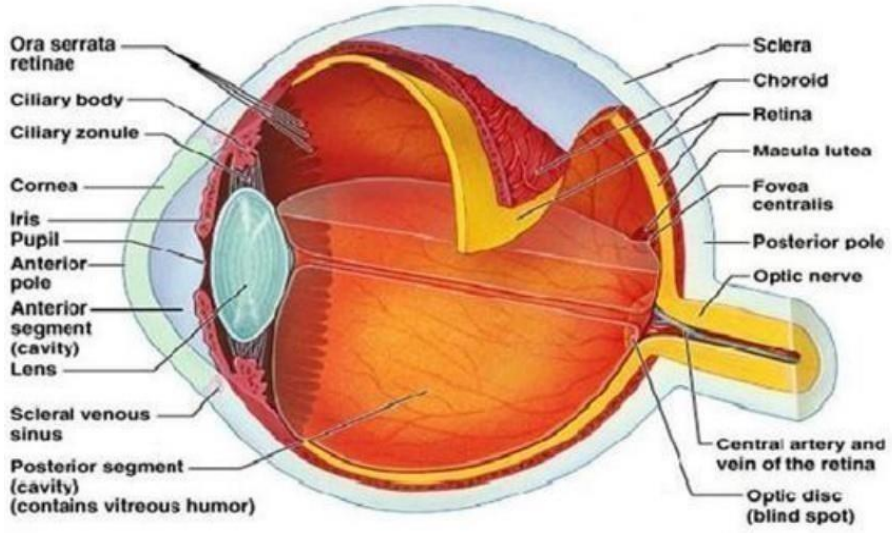
The secretory system, distributive system, and excretory system make up the nasolachrymal drainage system. The secretory system is made up of reflex secretors, which have an efferent para sympathetic nerve supply and secrete in response to physical or emotional stimuli, and fundamental secretors, which are triggered by blinking and temperature changes brought on by evaporating tears. The tear meniscus around the lid edges of an open eye and the eyelids themselves make up the distributive system. When you blink, tears are dispersed over the ocular surface, avoiding the formation of dry patches. The lachrymal puncta, the superior, inferior, and common canaliculi, the lachrymal sac, and the nasolachrymal duct make up the excretory portion of the nasolachrymal drainage system. The two puncta in humans are the apertures of the lachrymal papilla, an elevated region that is home to the lachrymal canaliculi. It is believed that only a tiny portion of tears from the lachrymals a center the nasal route and are mostly absorbed by the mucous membrane lining the ducts [25].

MECHANISMOFACTION

Fluoroquinolones are bactericidal agents because they work by blocking two enzymes that are needed for bacterial DNA replication and are involved in the manufacture of bacterial DNA. These enzymes are called DNA topoisomerase, and they are both absent from human cells. The process of splitting the strands of duplex bacterial DNA, putting a new strand through the break, and then sealing the previously split strands is carried out by DNA topoisomerase. DNA gyrase catalyzes the division of daughter chromosomes by introducing negative super helical twists in the bacterial DNA double helix prior to the replication fork. This process is necessary for the start of DNA replication and permits the binding of starting proteins. At the conclusion of a replication cycle, decatenation the process of eliminating the interlinking between daughter chromosomes—is carried out by topoisomerase IV. Fluoroquinolones cause conformational changes in the enzyme bound DNA complex, such as DNA gyrase with bacterial DNA or topoisomerase IV with bacterial DNA, which inhibits normal enzyme activity. Consequently, the novel medication enzyme DNA combination impedes the replication fork's advancement, impeding regular bacterial DNA synthesis and finally leading to the swift death of bacterial cells. The specificity of enzyme inhibition in various bacterial species is exhibited by older fluoroquinolones in a fairly uniform manner. The dual-binding mechanism of action of the more recent fourth generation fluoroquinolones, such as gatifloxacin and moxifloxacin, inhibits In Grampositive organisms, both DNA gyrase and topoisomerase IV [26, 27].

Table1. Barriers for the Oculardelivery

	Conjunctiva	Cornea	Sclera
Surface area	17.65±2.12cm2	1.04 ± 0.12	16–17
Thickness		0.57 mm	0.4 -0.5mm
Structural composition	Mucusmembrane Epithelium Vasculature	5layers Epithelium Bowman's membrane Stomata Descemet's membrane Endothelium	Collagenfibers Water Proteoglycans Monopolysaccharides Elasticfiber Fibroblast



FigureNo.4Anatomyofeye

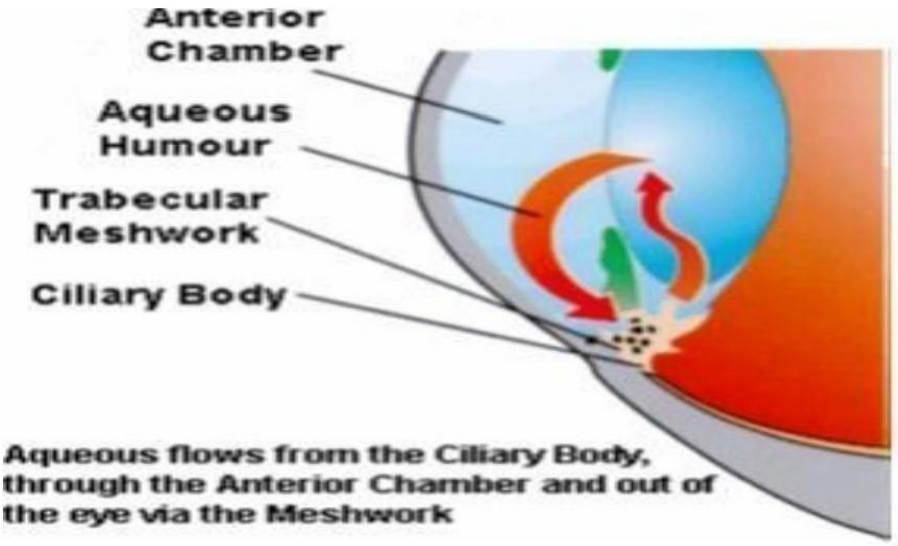


Figure. No5; Pathway of Aqueous Humor

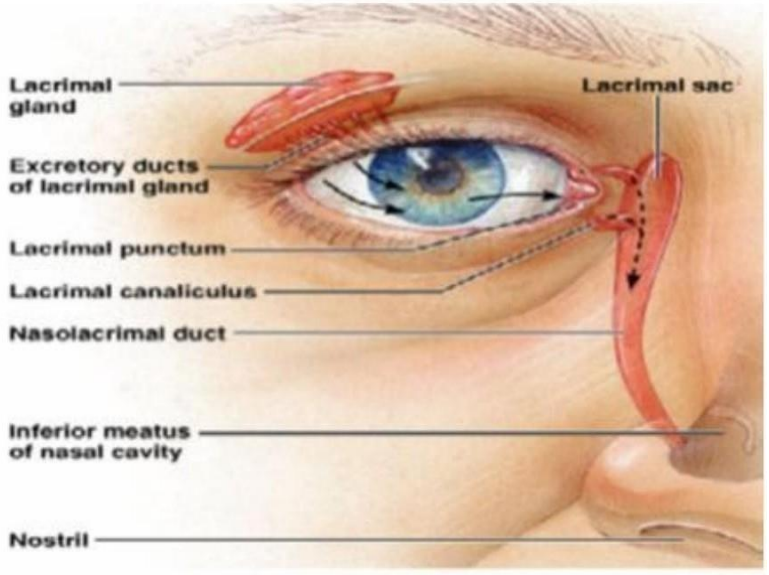


Figure No 6. NasaolachrymalDrainageApparatus

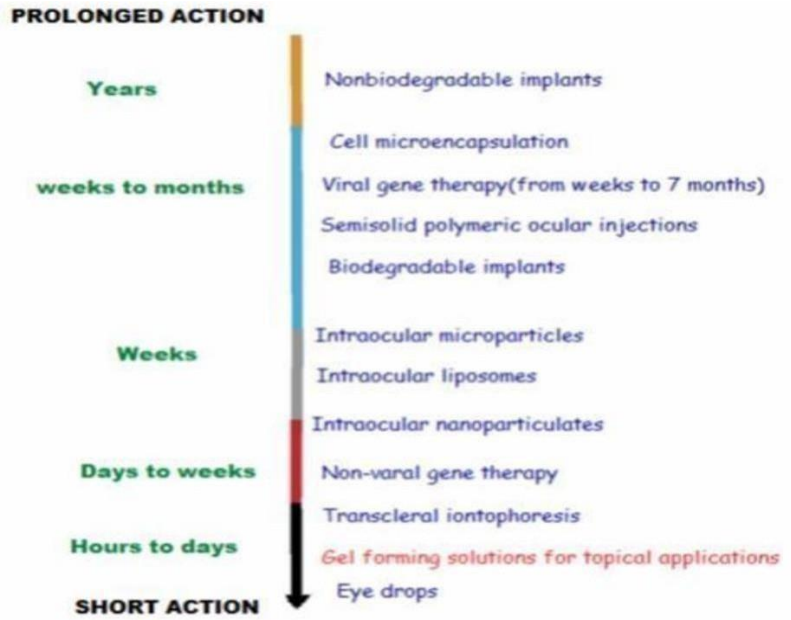


Figure No7. Duration of action of ocular drug delivery systems

Physiological barriers of ODDS

These physiological barriers are generally the diffusion and productive absorption of the topically applied medication. Both the corneal and precorneal areas are home to them. The precorneal constraints that cause the poor ocular bioavailability of typical ophthalmic dose forms include lacrimation, tear turnover, dilution, solution drainage, and conjunctival absorption. The most important component in this drug solution drainage away from the precorneal area has been found to be the one that reduces the drug's contact time with the cornea and, as a result, the dose forms' ocular bioavailability. Within two minutes of the individuals being installed, the precorneal area is in the injected dose of leaves. 50–70µl of the eye drops are delivered by this ophthalmic dropper. If the eyes of these people are not blinking Able to contain approximately 30 µl without overflowing onto the cheek. [28]

Drug loss from the ocular surface

Following the insertion of the lacrimal fluid, the instilled compounds are removed from the surface of the eye, specifically from the corneal and conjunctival superficial layers from the ocular surface that is the contact of the tear film. This ocular surface is typically formed as a defense barrier against the penetration from the undesired molecules. Although the lacrimal turnover rate of the instilled fluid is only approximately 1µl/min, the excess volume is rapidly flown to an aso lacrimal ductin a matter of minutes. Another source of the nonproductive drug is the removal of its systemic adsorption rather than ocular absorption. This systemic absorption rate can occur via the local blood capillaries or after the solution is applied. Flow into the nasal cavity. They are constructing a protective layer on this ocular surface to stop unwanted molecules from penetrating. Just 5% of the entire ocular surface is made up of the cornea; the conjunctiva occupies the remaining 95% of the area. The limited ocular bioavailability—less than 5%— contrasts with this. The concentration of the drug in lacrimal fluid is significantly reduced by drug absorption in the systemic circulation. while a result, the continuous release of medications from the solid delivery system into the tear fluid may only result in an ocular bioavailability of roughly 10%, while the majority of pharmaceuticals are cleared through local systemic absorption.[28]

Lacrimal fluid-eye barriers

The corneal epithelial limits of drug absorption from the lacrimal fluid into the eye have been implicated in these lacrimal fluid-eye barriers. In this case, the drug's corneal epithelial cells usually have a permeability in the cornea that is at least one order of magnitude larger than that of hydrophilic medicines. This corneal barrier develops as the epithelial cells mature. They often move to the apical surface and the cornea's center from the limbal region. Transcorneal permeation is the primary and crucial pathway by which drugs enter the body from the lacrimal fluid. In these, the conjunctiva is often the more permeable epithelium than the cornea, and its surface area is often almost 20 times larger than that of the corneal epithelial layer the humor in water. The absorption of drugs through the bulbar conjunctiva has been receiving more attention lately due to the conjunctiva's fair permeability to hydrophilic compounds. It might also function as the pathway for the absorption of bigger bioorganic substances like peptides and proteins. The majority of these medicinal products are lipophilic.

Blood-ocular barrier

The blood-ocular barriers primarily shield the eye from the xenobiotics in blood steam. This blood-ocular barrier is mostly split into two sections: The blood retina barrier is the posterior blood eye barrier, whereas the blood aqueous barrier

is the anterior blood barrier. The uvea's endothelial cells often make up these anterior blood ocular barriers. These blood ocular barriers inhibit the entry of hydrophilic drugs from the plasma into the aqueous humor as well as preventing the entry of plasma albumin. The posterior barrier, which consists of the retinal pigment epithelium (RPM) and the tight wall of retinal capillaries, separates the bloodstream from the eye. The choroid's vasculature, in contrast to the retinal capillaries, has been the large blood flow and walls that leak. The RPE and retinal endothelial cells restrict the primary medications' ability to enter the choroidal extravascular space and reach their etina. Inflammation can normally compromise the integrity of this barrier in their plasma aqueous humor. As a result, in the absence of specialized targeting, the retina andc horoid get only a small portion of the oral or intravenous medication dose. The blood-ocular barrier has not been able to describe the drug's transporter or the expression of metabolic enzymes. A thorough understanding of the fundamentals of pharmacokinetics is required before delving into the specifics of the blood-ocular barrier.

Ocular wall barriers:

The stiff scleral collagenous shell makes up the skeleton of the eye globe, which in this case represents the ocular wall barriers. The uveal tract typically lines the inside of that. With the exception of the little posterior aperture that houses the optic nerve head, the posterior wall covers 80% of the sclera. The cornea typically covers the anterior portion of the rest of the globe. Collagen bundles, fibroblasts, and a moderate quantity of ground substance makeup this scleralstroma. Usually, this is a seemingly vascular episclera that is essentially a vascular. The sclera allows the arteries and their nerves to flow through to the choroid side through these sizable canals.[29]

Retinal Barriers

Typically, there are ten layers in it.

1.1 The epithelium of retinal pigment.
1.2 External segments of photoreceptors.
1.3 The membrane that limits outside.
1.4 The nuclear outer layer.
1.5 The inner most nuclear layer.
1.6 Inner layer of plexiform
1.7 The layer outside the plexiform structure.
1.8 Layer of Ganglion Cells.
1.9 Layer of nerve fibers.
1.10 The internal membrane of limitation

Mechanism of Drug release of ocular drug delivery system

The following is the mechanism of controlled medication delivery into the eye.

DIFFUSION

Typically, the medicine is delivered into tear fluid across the membrane at a controlled rate and continuously in this diffusion mechanism. The process of diffusing from one area with a greater drug concentration across a concentration grade is how the drug is released. If their inserts are inserted, a solid, non-erodible body with pores and distributed medication is created. Diffusion through the poresis often how the medication is released. The progressive dissolution of the drug that has been spread solidly inside this matrix as a result of the water solution's inward diffusion can further regulate this controlled release. The dissolution process in this soluble device is mostly caused by polymer swelling, as the glassy polymers are not really drug impermeable. There is no diffusion via the arid matrix.

Osmosis

Transverse impermeable elastic membranes are typically used as inserts in this osmosis mechanism, allowing the inserts to pass from the first to the second compartment. The impermeable material and it elastic membrane surround the first compartment, which is surrounded by a semi-permeable membrane leading to an impermeable elastic membrane. This is a drug aperture located in the inserts' impermeable wall. A solute that is impervious to the semipermeable membrane is present in the first compartment. The medication, which is once more in the liquid or gel form, is stored in the second compartment is positioned in the aqueous environment of the eye in these inserts. The elastic membrane extends as the diffuse water enters the first compartment and expands to the in the first compartment and compress into the second, forcing the medication through the drug release hole.

Bio-erosion

In this bio-erosion mechanism, the insert's body is made of a bio-erodible substance, and when the insert comes into contact with tear fluid, the medicine releases over time in a regulated manner through matrix bio-erosion. This medication may be evenly distributed throughout the matrix, but it is generally accepted that when the medication is surface concentrated in the drug matrix, a better regulated release occurs.

Insoluble Ocuserts

This is the only form that is insoluble; it can typically dispense medications using a range of techniques at a regulated, predetermined pace, but it requires removal of the eye when emptied.[30] Inserts that are insoluble are often divided into two groups.

a. Reservoir System: This system releases the medication mostly through osmotic or diffusion processes.

It contains liquids, gels, colloid, semisolids, or carriers that carry medications, that order. I.

Diffusion inserts or ocuserts

The reservoir system's subsystems are these diffusion inserts. This is predicated on the innovative ocular porous membrane occuserts system.

Matrix system

These represent the second class of ocular inserts that are insoluble. They are primarily represented by a specific class of insoluble optical devices and contact lenses. It can produce a three-dimensional network or matrix made of covalently cross-linked hydrophilic or hydrophobic polymers that can hold water, an aqueous drug solution, or a solid compartment.

Contact lenses:

The original purpose of these contact lenses is eyesight correction. The primary benefit of this technology is its ability to concurrently release medications and correct vision. Five components make up this contact lens. Biopolymeric, elastomeric, hydrophilic, semi-rigid, and soft

Soluble concerts

These soluble inserts are typically described as erodible, monolithic polymeric devices that release the medication and do not require removal as they gradually dissolve. True dissolving of these polymers mostly happens during swelling, whereas erosion is related to a chemical or enzymatic hydrolytic process. The glassy polymers used in this swelling controlling device allow the active ingredients to be evenly distributed. When the inserts are inserted into the eye, the water from the tear fluid starts to seep into the matrix, releasing the medication and causing edema and, ultimately, polymer chain relaxation.

The primary benefit of this technique is the drug diffusion, which eliminates the need to remove the application site. Generally speaking, these soluble inserts fall into two groups:

a. Natural polymers
b. Synthetic and semi-synthetic polymers

Natural polymers

Soluble ophthalmic inserts made of these natural polymers can be utilized for preferred collagen. Preferably, the soaking inserts have been absorbed by the therapeutic substances. Before applying this medication-containing solution to the eye, let it dry and then rehydrate. The amount of the drug-loaded well depends on the concentration of the drug solution in which the composite can be soaked, the length of the soaking process, and the quantity of binding agents present. The medication is progressively released from the spaces between the collagen molecules as these natural polymers disintegrate the collagen.[30]

Synthetic and semi-synthetic polymers

The second class of soluble inserts is these synthetic and semi-synthetic polymers. Typically, these rely on the utilization of polymers, namely semi-synthetic polymers (such as derivatives of cellulose). The release rate of the acquired was decreased by the synthetic polymer (example: polyvinyl alcohol) by utilizing eudragit, a polymeric that is often used for the enteric coating or as a coating agent of the insert.

Bio-erodible ocular inserts

These bio-erodible ocular inserts are made of polyester and crosslinked gelatin derivatives, which hydrolyze and dissolve chemical bonds. The main benefit of the bioerodible ocular insert polymer is that it can be modified during synthesis to alter the rate of erosion by adding cationic or anionic surfactant. These are some of the significant ocular inserts that are commercially available for soluble ophthalmic development for collagen shields.[31]

Dosage Forms

Liquid dosage form

Eye Drops

Over 95% of the marketed ocular products are eye drops. They inject the drug into the front portion of the eye. Easy administration and well acknowledged steadiness are two of their benefits. Nevertheless, their drawbacks include a short retention period (less than five minutes), low bioavailability, and severe adverse effects brought on by often administering high concentrations [32]. Numerous nanosystem platforms have been created to address their shortcomings. The

mucoadhesive nanosystem cyclosporine was created using poly (DL-lactide)-b-dextran. The formulation method used was nanoprecipitation. The finished product showed improved permeability, drug retention, and tiny particle size [33]. When hesperetin was formulated as a micellar system, it demonstrated small particle size, high percentage entrapment efficacy, increased penetration, and improved efficacy [34].

Eye Suspensions

Ocular suspensions are aqueous solvent-based dispersions of hydrophobic drugs. Because of the drug's retention in the conjunctival cul-de-sac, their contact time is increased. During the preparation phase, the tear fluid's particle size, solubility, and rate of dissolution are crucial factors [35]. Particles smaller than 10 µm are often more soluble, dissolve more quickly, and have lower surface retention. Particles larger than 10 µm, however, may cause eye discomfort and induce tears [36]. One drawback of ocular suspension is its lack of stability. Because the particles clump together and are difficult to disperse, they cannot be kept in the freezer. Additionally, alterations in crystallinity during medication storage can impact the drug's solubility and bioavailability. Another possible side effect of its administration could be impaired eyesight. enhanced optical Posaconazole administration utilizing a high pressure homogenizing approach in the polymer combination of carbopol 974P and xanthan gum shown improved stability, antifungal activity, and extended retention [37].A high speed liquid-liquids hear technique was used to create anultra-fineocular solution of rebamipide. This mixture demonstrated increased stability, tiny particle size, and transparency [38].

Eye Emulsions

Emulsions are solubilized biphasic systems that have stabilizers or surfactants added to them. The delivery of hydrophobic medications is one benefit of eye emulsions; oil in-water (O/W) emulsions also have improved bioavailability, longer contact times, and reduced ocular irritation [39]. Dexamethasone acetate and polymyxin B sulfate were more effectively delivered to the eyes thanks to the creation of a nanoemulsion using high-pressure homogenization. To improve ocular adherence, a positive charge inducer was used. The final formula had improved retention time, decreased particle size, and increased stability [40]. The triamcinolone acetonide microemulsion was created using the water titration method. [41]

Semisolid Dosage Forms

Eye Gels

Eye gels are a semisolid dose form with a large amount of water. Their viscosity gives them improved absorption and retention time. Even with gels' high water content, visual impairment is still possible. Ocular gels might be made with a variety of polymers, including carboxymethylcellulose, hydroxyl propyl methylcellulose, poly acrylic acid, and acrylic acids [42]. A proniosomal gel containing curcumin was prepared using the coacervation process, which effectively reduced the particle size and improved the anti-inflammatory action [43]. Phytantriol-based lyotropic liquid crystalline gel was formed, demonstrating an increase in pilocarpine's ex vivo permeability and retention time. The vortex approach was used to create that gel [44].

Eye Ointments

Eye ointments are semisolid dose forms that contain mineral oil and white petrolatum. Because they obstruct eyesight, they are exclusively applied to the lower eyelid before sleeping. They are frequently utilized by younger patients. Because of their anhydrous nature, they are an excellent fit for medications that are moisture sensitive and lipophilic. Compared to solutions, they have longer retention times and better bioavailability [45]. 2019 saw the approval of Avaclyr®, an eye ointment containing the antiviral acyclovir for the treatment of herpetic keratitis. Additionally, Lotemax® encloses loteprednol etabonate, an antiinflammatory drug.

They both displayed improved drug release and corneal penetration[46]. Solid Dosage Forms

These are water-sensitive medication dose forms in sterile, solid form. The injectable versions of cefuroxime, moxifoxacin, and voriconazole are administered intracamerally. Voriconazole is reconstituted in water, whereas cefuroxime and moxifoxacin are reconstituted in saline. After reconstitution, cefuroxime and voriconazole solutions remain stable for a period of seven days. Moxifoxacin solution, however, remains steady for a whole month [47, 48].

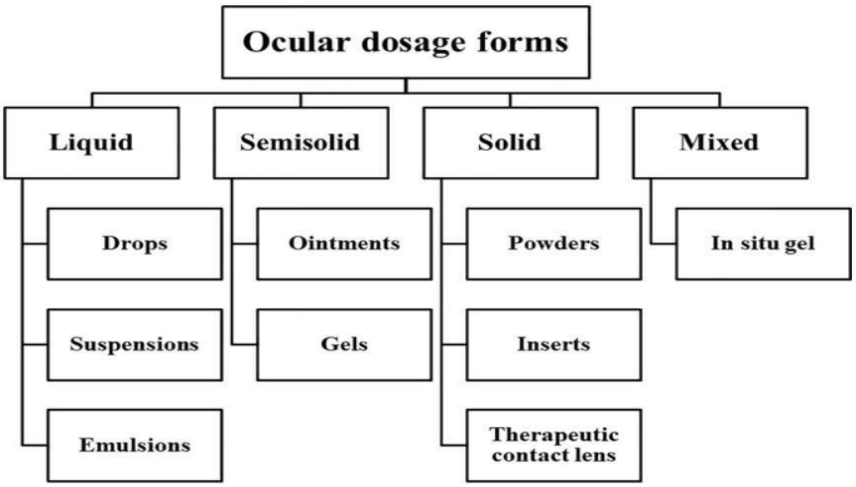
Therapeutic Contact Lens

According to recent research, a therapeutic contact lens's prolonged residence duration and close contact with the cornea can increase bioavailability by more than 50% [49]. They have a residence period ten times longer than traditional eye drops [50].They also shorten the time between doses, the amount needed, and the amount absorbed by the body[51]. Numerous methods, including molecular imprinting, ion ligation, soaking, and the utilization of nanoparticles, can be used to confine the medicine inside a contact lens [52, 53, 54]. Protein attachment, ion and oxygen permeability, medication loss during manufacture or storage, transmission, and lens edema are some of the issues that prevent their clinical usage [55]. The encapsulation process was used to prepare the dexamethasone contact lens. Compared to traditional eye drops, it demonstrated a 200-fold increase in drug retention in the retina [56]. To lessen quick drug release, hyaluronic acid, bimatoprost, or timolol chips have been employed [57].

In Situ Gel

Mixed Dosage Forms

These are low viscosity polymeric solutions. When they came into contact with tear fluid, they changed into pseudo-plastic gels. When compared to simple solutions, they have a prolonged contact time [58]. Based on the transition properties, in situ gel can be classified as temperature, ionic, or pH sensitive [59]. An ion-sensitive sodium alginate and hydroxypropyl methylcellulose in situ gel of ciprofloxacin demonstrated improved residence duration and sustained drug release [60]. Extended drug release and prevented burst release were discovered by thermo sensitive in situ gel of hydrocortisone butyrate [61]. Ketorolac tromethamine thermo sensitive in situ Gel demonstrated enhanced mucoadhesive qualities and a 12-hour drug release [62].



FigureNo.8 Dosage forms

Liposomes

Nanostructured Platforms

Midway through the 1960s, they were found [63]. The safety, biodegradation, ease of manufacturing, and enhanced bioavailability of liposomes are among their benefits [64]. One or more concentric lipid bilayers are used to create these spherical nanocarriers. Hydrophilic medications might be trapped inside, while lipophilic pharmaceuticals could be carried in the lipid region. Their surface charge, susceptibility to ion or Ph changes, temperature variations, and the resulting particle size might all be altered by modifying the production process and composition [63]. Since the corneal epithelium is typically negatively charged, positively charged liposomes would adhere better, retain longer, and absorb more efficiently. These results will increase patient satisfaction and shorten the time between treatments [65]. Zhang and Wang synthesized a liposomal system consisting of chitosan, cholesterol, α tocopherol, and phosphatidyl choline. The High % entrapment, prolonged activity, and improved efficacy were demonstrated by the final formula [66].

Phosphatidylcholine, stearylamine, cholesterol, and hyaluronic acid were employed by Lin et al. Better corneal absorption, increased drug targeting, enhanced % entrapment, and extended penetration were all demonstrated by the finished product [67].

Niosomes

Niosomes are self-aggregating, bilayered nanocarriers made of non-ionic surfactants. They are non-immunogenic, biodegradable, biocompatible, and include both hydrophilic and lipophilic medications. They might increase the drug's effectiveness and permeability while delaying its release [68,69].Niosomes have draw backs such as chemical instability and potential drug hydrolysis, buildup, or loss [70]. To increase the stiffness and stability of niosomes, cholesterol or a derivative of it is added [71]. Awad and Elmotasem created a niosomal system with span 60, cholesterol, cyclodextrin, poloxamer 407, hydroxypropyl methylcellulose, and chitosan. High drug entrapment, improved corneal penetration, and increased activity were demonstrated by the final formula [72].The niosomal system made up of chitosan, cholesterol, and span 60 was investigated by Kaur et al. Higher activity, less adverse effects, and extended release were seen in the finished product [73].

Aggarwal et al. enhanced the the effectiveness and duration of acetazolamide utilizing Carbopol® 934P, cholesterol, and span 60. A niosomal gatifoxacin system consisting of span 60, cholesterol, and chitosan was created by Zubairu et al. Better ocular penetration, notoxicity, and increased antibacterial activity were all displayed by the optimized recipe.

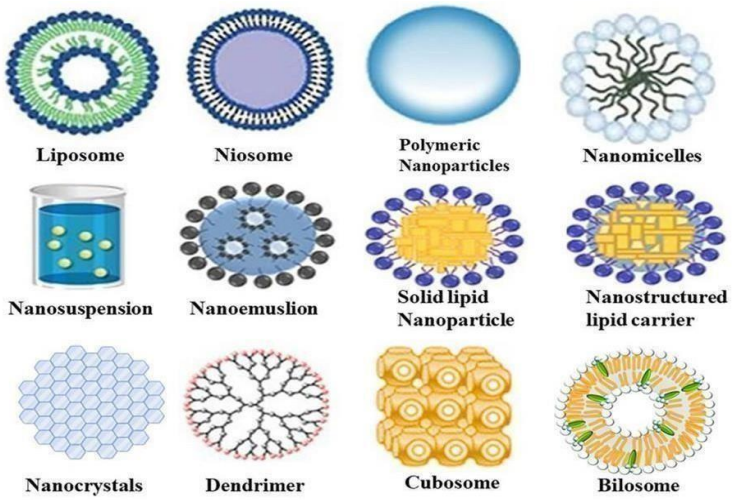


Figure No.9 Nanostructured Platforms

CONCLUSION

For many years, ocular scientists have faced a significant obstacle in the form of drug delivery to specific ocular tissues. Using traditional formulations of medication solutions as topical drops had some disadvantages that led to the development of alternative carrier systems for ocular delivery. A great deal of work is being done in the field of ocular research to create innovative drug delivery systems that are safe and acceptable to patients. Researchers are working very hard right now to enhance traditional formulations 'invivo performance. On the other hand, ocular scientists are becoming increasingly interested in the novel methods, tools, and uses of nanotechnology in medication administration. Drug molecules are administered by invasive, non-invasive, or minimally invasive methods by being encase din nano scale carrier systems or devices. Numerous nanotechnologies based Many carrier systems, including liposomes, nanoparticles, nanomicelles, nanosuspensions, and dendrimers, are being produced and investigated. Only a small number of them are used in clinical settings and are produced on a huge commercial basis. The body of the patient benefits from nanotechnology by experiencing less drug-induced toxicities and visual loss. Additionally, these devices nanocarriers maintain medication release and increase specificity when targeting Employed moieties aid in lowering the frequency of dose. However, after a non-invasive method of medication administration, a carrier system that could reach targeted ocular tissue including the tissues in there is of the eye still has to be developed. A topical drop formulation that maintains a high precorneal residence time, prevents nonspecific drug tissue accumulation, and delivers therapeutic drug levels into targeted ocular tissue (both anterior and posterior) is anticipated as a result of the current pace of ocular research and efforts. In the near future, intravitreal and periocular injections invasive methods of administering drugs to the back of the eye may be replaced by this delivery method.

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