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AN OVERVIEW ON OCULAR DRUG DELIVERY SYSTEM

Aminu musa Wada*[1], Shehu Yusuf[2]

[1]NIMS Institute of Pharmacy, NIMS University. Jaipur, Rajasthan, India, 303121

ABSTRACT

Ocular medication delivery is the main issue facing pharmacologists and formulation scientists today. The easiest and most widely used kind of treatment is a topical eye drop. Route of drug administration, particularly when treating disorders of the anterior region. 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 ocular preparations consist of sterile, buffered, isotonic solutions. They are employed for quick action. They are unable to hold on for an extended period. The fundamental problem with traditional ocular dose forms is that they cannot keep a therapeutic level. Ophthalmic preparations must be devoid of irritants and their physiological properties must not interfere with the eye's normal functioning or cause blurred vision of any kind. The development of innovative, secure, and patient-compliant medication formulations and drug delivery devices/techniques, which may overcome these obstacles and sustain drug levels in tissues, has increased over the past two decades in the field of ocular drug delivery research. Among the various nanoparticles currently available, lipid-based nanosystems have demonstrated increased efficiency and feasibility in topical formulations, making them an important target for ongoing and thorough research in both preclinical and clinical practice. There are numerous new drug delivery systems available for use in the eye. The current review aims to summarize the existing traditional formulations for ocular distribution and their developments, followed by the most recent innovations in formulations based on nanotechnology. Problems associated with traditional ophthalmic dosage forms may be alleviated by the new drug delivery system. Also highlighted are recent advancements in various ocular drug delivery techniques using in situ gels, implants, contact lenses, and micro needles.

Key words: ocular drug delivery, nanoparticles, nanotechnology, bioavailability

1. INTRODUCTION

The eye is a complicated organ with its own anatomy and physiology. Endophthalmitis, hemorrhage, retinal detachment, and poor patient tolerance are the various eye structures. Trans-sclera drug administration. Ocular drug delivery is extremely difficult; only 1-3% of the instilled drug enters the eyes.[24] The most common ocular dosage form is eye drops. As an alternative mode of drug delivery to the posterior ocular tissues, the periocular administration route has evolved. Although transscleral delivery is less invasive and patient-friendly, drug permeation is hampered by ocular static and dynamic barriers. Static barriers to transscleral drug delivery include sclera, choroid, and retinal pigment epithelium (RPE), as well as dynamic barriers such as lymphatic flow in the conjunctiva and episclera and blood flow in the conjunctiva and choroid.[2] Various conventional and novel drug delivery systems have been developed to overcome ocular drug delivery barriers and improve ocular bioavailability, such as emulsion, ointment, suspension, aqueous gels, nanomicelles, nanoparticles, liposomes, dendrimers, implants, contact lenses, nanosuspensions, microneedles, and thermosensitive gels in situ[2] Choroidal neovascularisation (CNV) secondary to age-related macular degeneration (AMD), diabetic macular oedema (DMO), and retinal vein occlusion (RVO) are examples of retinal diseases.[3] RVOs can cause severe visual complications and even blindness. Treatments for these diseases frequently necessitate repeated intravitreal drug injections, the frequency and duration of which vary depending on the disease. [3] Because of its drug disposition characteristics, the eye is the most interesting organ. In most cases, topical drug application is the preferred method of ophthalmic chemotherapy due to its convenience and safety. The formulator faces a significant challenge in circumventing (bypassing) the protective barriers of the eye without causing permanent tissue damage.[21] The development of newer, more sensitive diagnostic techniques and novel therapeutic agents continues to provide high therapeutic efficacy ocular delivery systems. Traditional ophthalmic formulations such as solution, suspension, and ointment have numerous drawbacks that result in poor drug bioavailability in the ocular cavity. A therapeutic system's specific goal is to achieve an optimal concentration of a drug at the active site for the appropriate duration. [21] Biomaterials and nanotechnology advancements have resulted in significant growth in the research of biodegradable microparticles and nanoparticles, hydrogels, and ocular implants which may contain ocular pharmacologic agents thereby providing improved delivery of a variety of medications.[3] However this review aims to the outline a detail on conventional ocular drug delivery followed by the recent advancement based on nanotechnology.

1.1 Anatomy of the eye

The eye has three concentric substrates. The cornea and sclera are located in the fibrous tunic, which is the outermost section of the eye. The mid covering, also known as the uvea or vascular tunic, is made up of the iris, ciliary body, and choroid. The retina is an internal component of the eye. The retina of the eye gets oxygen from the blood arteries in the choroid and retina. The cornea is a transparent dome-shaped surface that protects the pupil, iris, and front of the eye. The cornea has a horizontal diameter of 11.5 mm, a vertical diameter of 10.5 mm, and a thickness of about 0.5 mm on average. The cornea and sclera around it support the retina, a lamella of light-sensitive nerve tissue, in a sufficient and secure position. This region of the eye captures light, transforms it into signals, and then transmits those

signals to the brain via the optic nerve. The anterior and posterior portions make up the human eye, according to a generally recognised taxonomy. The iris, cornea, aqueous fluid, and lens are all located in the anterior segment, which comprises one-sixth of the eye. The choroid, rear of the sclera, retina, and vitreous body make up the posterior portion of the eye, which comprises the remaining five-sixths of the eye. The human eye is a portal to the phenomenon known as vision because of its exquisite detail and design. The eyeball measures about an inch wide and is spherical in shape. It contains numerous structures that cooperate to improve sight. The layers and internal structures that make up the human eye each serve a specific purpose. The eye's various components include the cornea, sclera, retina, iris, pupil, choroid, acquos humour, conjunctiva, lens, and optic nerve. Below is an explanation of each eye part in further depth.

Sclera

The sclera (white portion of the eye) is a tough white sheath that forms the ball's outer layer. It is a firm fibrous membrane that keeps the eye in an approximately globe shape. It is significantly thicker at the back/posterior of the eye than at the front/anterior of the eye.[21]

Conjunctiva

The conjunctiva is a thin transparent mucous epithelial barrier that lines the inside of the eyelids and covers one-third of the eyeball's anterior surface. The palpebral and bulbar conjunctivae are the two parts of the conjunctiva. The conjunctiva is made up of two layers: the outer epithelium and the stroma beneath it (substantia propria). The tear film covers the exposed surface of the eye, which includes the conjunctiva and cornea. The conjunctiva contributes to tear film formation by secreting significant amounts of electrolytes, fluid, and mucins.[21]

Cornea

The cornea is a prominent clear bulge at the front of the eye. The adult cornea's surface has a radius of about 8mm. It serves an important optical function by refracting light that enters the eye and then passes through the pupil and onto the lens (which then focuses the light onto the retina). The cornea, a non-vascular structure (it lacks blood vessels), obtains nutrients from capillaries that terminate in loops around its circumference. Many nerves derived from the ciliary nerves supply it. These enter the cornea's laminated tissue. As a result, it is extremely sensitive.[21]

Aqueous humor

The aqueous humour is a jelly-like substance found in the eye's outer/front chamber. It is a clear fluid that fills the "anterior chamber of the eye," which is directly behind the cornea and in front of the lens. The aqueous humour is a slightly alkaline salt solution containing trace amounts of sodium and chloride ions. It is continuously produced, primarily by the ciliary processes, flows from the posterior chamber into the anterior chamber via the pupil, and exits via the trabecular and uveoscleral routes.[21]

Pupil

The pupil appears to be the dark "centre" of the eye, but it is actually the circular aperture in the centre of the iris through which light enters the eye. The pupillary reflex controls the size of the pupil (and thus the amount of light admitted into the eye) (also known as the "light reflex").

Iris

The iris is a thin circular contractile curtain located behind the cornea but in front of the lens. The iris is a variable-size diaphragm that regulates the amount of light admitted into the eye by adjusting the size of the pupil. It refers to the coloured part of the eye (shades may vary individually like blue, green, brown, hazel, or grey).

Ciliary Muscle

The ciliary muscle is a ring of striated smooth muscles in the middle layer of the eye that regulates the flow of aqueous humour into Schlemm's canal and controls accommodation for viewing objects at different distances. The muscle is innervated by both parasympathetic and sympathetic nerves. The curvature of the lens is altered by the contraction and relaxation of the ciliary muscle. This process is simply the balance that exists at any given time between two states: Ciliary Muscle relaxed (allowing the eye to focus on distant objects) and Ciliary Muscle contracted (This enables the eye to focus on near objects).[21]

Lens

The lens is a clear structure enclosed in a thin clear capsule. It is situated behind the pupil of the eye and is surrounded by ciliary muscles. It aids in the refraction of light as it passes through the eye (which first refracted by the cornea). The lens focuses light onto the retina, creating an image. It is able to do so because the shape of the lens changes depending on the distance of the object(s) from the person's eye. The ciliary muscles contract and relax to adjust the shape of the lens, which is referred to as accommodation. [21]

Vitreous Humour

The vitreous humour (also known as the vitreous body) is a large area in the human body that occupies approximately 80% of each eye. The vitreous humour is a clear, thin jelly-like substance that fills the chamber behind the eye's lens. It is an albuminous fluid that is surrounded by a delicate transparent membrane known as the hyaloid membrane.[21]

Retina

The human retina is located at the back of the eye. The retina is the "screen" on which an image is formed by light that has passed into the eye via the cornea, aqueous humour, pupil, lens, and finally the vitreous humour. The retina's function is not only to act as a screen onto which an image can be formed, but also to collect the information contained in that image and transmit it to the brain in a form that the body can use. [21]

Macula

The macula is the centre of the retina. The macula is densely packed with photoreceptor cells, which convert light into nerve signals. With the macula, we can see fine details such as newsprint due to the high concentration of photoreceptors. The fovea, or centre of the macula, is the site of our sharpest vision.[21]

Choroid

The choroid layer is located behind the retina and absorbs unused radiation as well as nourishing the retina's outer portions. It is a thin, highly vascular (blood vessel-containing) membrane that is dark brown in colour and contains a pigment that absorbs excess light, preventing blurred vision (due to too much light on the retina). The choroid has the highest blood flow rate in the body. The lamina fusa connects the choroid to the inner surface of the sclera.

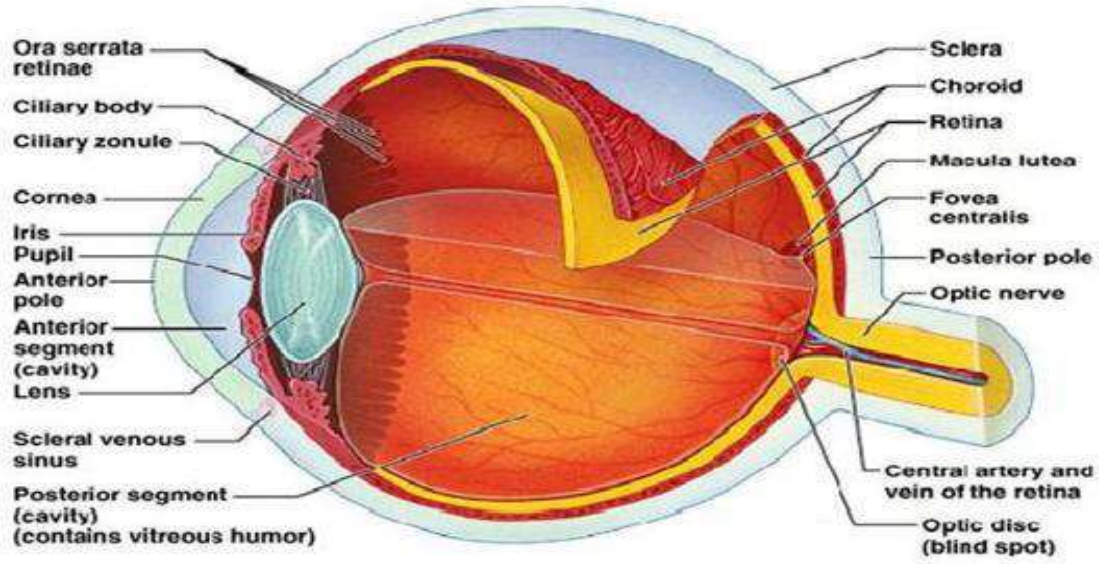

Figure 1: The anatomy of the eye

1.1.1 Ocular barriers

Tear

Tear film is one of the precorneal barriers that reduce 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 mechanical barrier that prevents exogenous substances from entering the eye. 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 humor. 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 sclera 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 of the brain per unit tissue weight. In addition, choroidal capillary endothelial cells in humans are fenestrated and relatively large in diameter (20-40 m). The retina's thickness and Using optical coherence tomography, choroid can be measured noninvasively (OCT). The use of an OCT has shown that choroidal thickness decreases with age. Previous histological research has shown that choroidal thickness decreases from 200 m at birth to around 80 m by the age of 90. Choroidal thickness is also influenced by chorioretinal diseases such as AMD with pigment epithelial detachment, central serous chorioretinopathy, age-related choroidal atrophy, and high choroidal thickness. [8]

Retina

Drugs in the vitreous are eliminated via two routes: the anterior and posterior segments. The anterior route can be used to eliminate all drugs. This means that drugs can enter the posterior chamber via the vitreous and be eliminated via aqueous turnover and uveal blood flow. Permeation across the retina enables elimination through the posterior route. One of the barriers to drug penetration from the vitreous to the retina is the internal limiting membrane (ILM). The ILM is made up of ten different extracellular matrix proteins and connects the retina and the vitreous. Despite previous primal research indicating that molecules larger than 100 kDa could not cross the retinal layers into the sub retinal space.[8]

Blood–aqueous barrier

This barrier is located in the anterior segment of the eye and is made up of uveal endothelial cells. It prevents hydrophilic drugs from entering the aqueous humour from the systemic circulation. This barrier is occasionally disrupted by inflammation, resulting in increased temporary drug permeation. The blood-ocular barrier is formed by the blood-retinal barrier and the blood-retinal barrier. The iris epithelium and cilliary bodies transport anionic drugs from the aqueous humour to the systemic circulation.[26]

The Blood-Retinal Barrier (BRB)

The blood-retinal barrier (BRB) prevents drugs from entering the retina from the blood. Tight junctions between retinal capillary endothelial cells and RPE form the BRB, which is referred to as iBRB for the inner and oBRB for the outer BRB. Müller cells and astrocytes help iBRB function. Endothelial cells in the retinal capillaries lack vesicles and are not fenestrated. The function of these endothelial vesicles has been described as endocytosis or transcytosis, which can be receptor-mediated or fluid phase requiring adenosine triphosphate. Müller cells and retinal capillary vessels have a close spatial relationship under normal conditions, allowing the iBRB to uptake nutrients and dispose of metabolites.[8]

1.1.2 Advantage of ocular deug delivery system

- Increased precision in dosing. To overcome the negative effects of conventional systems' pulsed dosing.
- To provide controlled and sustained drug delivery
- Increase drug ocular bioavailability by increasing corneal contact time. This can be accomplished through effective adherence to the corneal surface.[23]
- To provide targeting within the ocular globe in order to avoid loss of other ocular tissues.
- To get around protective barriers such as drainage, lacrimation, and conjunctival absorption.
- To provide patient comfort, improve patient compliance, and improve drug therapeutic performance.
- to provide better delivery system housing

1.1.3 Route of ocular drug delivery

There are several approaches to drug delivery into the ocular tissues. The route of administration is primarily determined by the target tissue. Traditionally, anterior targets are treated with topical ocular and subconjunctival administrations, while posterior targets are treated with intravitreal administration. The design of the dosage form has a significant impact on the resulting drug concentrations and the duration of drug action.

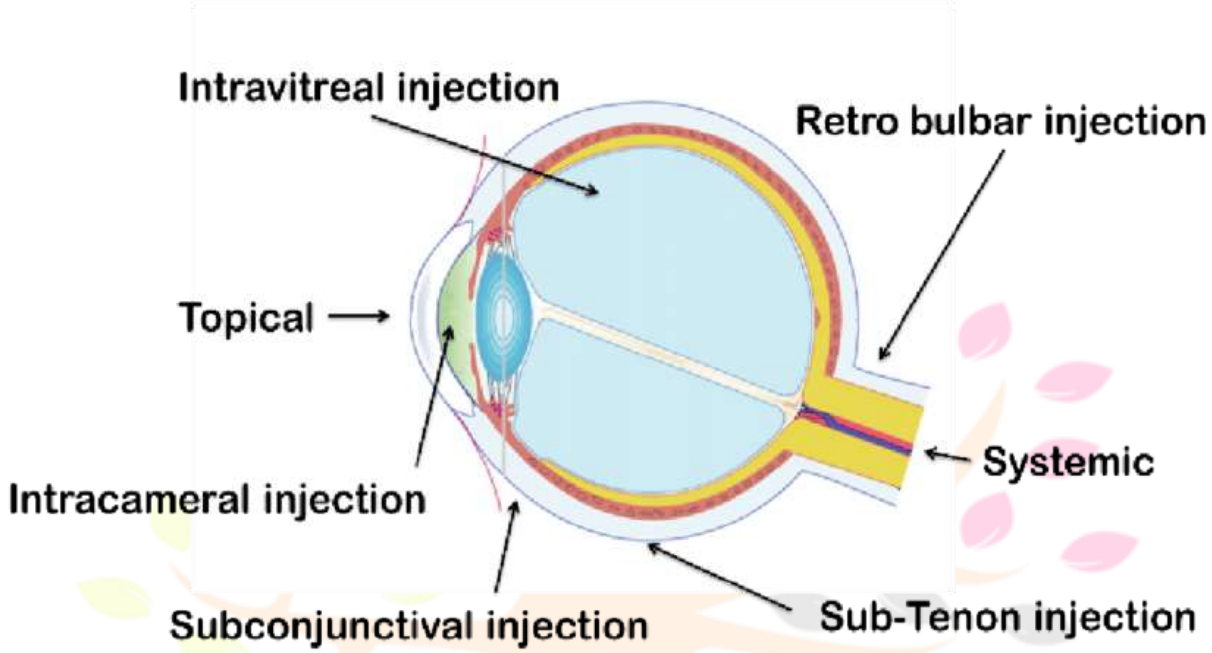

Figure 2: Route of ocular drug delivery

1.2 CONVENTIONAL OCULAR DRUG DELIVERY SYSTEM

Topical drop instillation into the lower precorneal region is a patient-friendly and frequently advised method of medication delivery. But the vast majority of Only 20% of the instilled dose is remained in the precorneal pocket after the topically delivered dose is lost to reflux blinking. Passive diffusion across the cornea is accelerated by the drug concentration in the precorneal region. However, for effective ocular drug delivery with eye drops, high corneal permeation with longer drug cornea contact time is needed. [16] To increase corneal penetration and precorneal residence time, several projects have been started. The most popular ocular medicine delivery methods employed in today's ocular disease therapy are solutions and suspensions. Solutions and suspensions came from the collyrium, which was credited to the Romans and Greeks. The remedy was a gum cake that resembled a tiny bar of soap and contained the drug. A tiny slice of cake was dissolved in water, milk, or egg white to create eye drops. [12] Currently, there are many different types of medications used in the eye, such as miotics, mydriatics, cycloplegics, and antibacterial, antiglaucoma, surgical adjuncts, diagnostics, and medications for other uses. Therapeutically inactive ingredients are necessary in ophthalmic solution or suspension in addition to the active ingredients to carry out one or more of the following tasks: adjusting tonicity, buffering and pH, stabilising the active ingredients against

decomposition, enhancing solubility, introducing viscosity, and acting as a solvent. Aqueous solutions, as was already mentioned, have the drawback of being silently removed from the front of the eye, which leads to poor ocular bioavailability. The majority of practitioners concur that if longer duration can be obtained with these forms, patients will choose a solution or suspension form of a drug delivery system. [18]. The upper size limit for microparticles used in ophthalmic administrations is between 5 and 10 mm, above which ocular instillation might cause an uncomfortable scratching sensation in the eye. [18] The physiologic barriers of the eye are primarily responsible for the poor ocular bioavailability of drugs from conventional eye drops (ie, solution, suspension, and ointments).[27]Eye drops are commonly used to administer topical ocular drugs, but they only have a short contact time on the eye surface. The duration of drug action can be extended by formulation design (e.g., gels, gelifying formulations, ointments, and inserts).[23]

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

It is defined as a liquid preparation in which all of the ingredients are uniformly and completely soluble in solution. The majority of the instilled volume is eliminated from the precorneal area following instillation.[28] The most practical, secure, quick, patient-compliant, non-invasive, noninvasive technique of eye treatment is topical drops. An eye drop solution offers a pulse of drug penetration after topical drop instillation, after which its concentration rapidly decreases. Drug concentration drop kinetics could be roughly first order. Topical eye drops may contain a variety of additives, such as viscosity enhancers, to increase the drug's contact time, penetration, and ocular bioavailability. [2] Topical medications include eye drops, gels, and ointments. These will primarily aid in the treatment of anterior segment ocular conditions like uveitis and conjunctivitis. Topical medications have an effect on the cornea, conjunctiva, sclera, and uvea (i.e. iris and ciliary body).[22] Melanin, which can bind to substances such as drugs, is found in the pigmented epithelium of the iris and ciliary body. As a result of the slow release, the effects of a drug may be prolonged but reduced. Thus, despite being noninvasive, topical administration fails to provide significant therapeutic effects in the posterior segment. [23]

Figure 3: A topical eye drop solution

- **Emulsions**

Emulsion-based formulation strategies have the benefit of enhancing both solubility and bioavailability. Commercially, two different emulsion types—oil in water (o/w) and water in oil (w/o) emulsion systems—are utilized as carriers for active medicinal ingredients in narcotics. For the delivery of ophthalmic drugs, the o/w emulsion is frequently employed and favored over the w/o method. Less irritability and increased ocular tolerance of the o/w emulsion are the causes of this. [2] Following single and multiple topical drop instillations, the results confirmed that emulsion could deliver drug to anterior ocular tissues with only a small amount reaching posterior tissues in the rabbit eye. The cornea had the highest radioactivity in single and multiple topical drop instillation studies, followed by the iris-ciliary body > retina-choroid > conjunctiva > sclera > aqueous humour > lens > and vitreous humour.[2]

- **Suspensions**

Suspensions are formed by dispersing finely divided relatively insoluble drug substances in an aqueous vehicle containing a suitable suspending and dispersing agent. It must contain particles with such chemical properties and small dimensions that they do not irritate the eyes. The particles are better retained in cul-de-sacs, increasing bioavailability and providing a slow release effect.[28] Suspension systems are an additional non-invasive ocular topical drop medication carrier type. You can specify a suspension. As a finely split insoluble API dispersion in an appropriate suspending and dispersing agent-containing aqueous solution In other words, a saturated API solution is the carrier solvent system. Contrary to drug solution, suspension particles remain in the precorneal pocket, lengthening drug contact time and duration of action. [2] the most popular pharmaceutical delivery method for medications that need to remain active on the surface of the eye or in the eye after passage is solutions. Through the conjunctiva or the cornea [25] Particle size determines how long a medicine will function in suspension. 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 yet another type of topical carrier system. Ophthalmic ointment is made up of a semisolid and solid hydrocarbon (paraffin) mixture with a melting point of 34 degrees Celsius. The hydrocarbon's biocompatibility influences its selection. Ointments help to increase ocular bioavailability and maintain drug release. [2] Eye ointments are sterile, semisolid preparations with a homogeneous appearance that are intended to be applied to the conjunctiva or the margin of the eyelids. It has a very low therapeutic effect due to its hydrophobic nature. Because of its greasy nature, it causes vision blur.[28]

Figure 4: A typical representation of administered eye ointment

1.3 NOVEL OCULAR DRUG DELIVERY SYSTEM

In the field of nanotechnology, novel vesicular drug delivery systems have made significant progress. Because these systems have the potential to carry a wide range of drugs, they have been widely used for a variety of purposes, including drug targeting, controlled release, and drug permeation enhancement.[25] These systems are also useful in avoiding the disadvantages of traditional dosage forms, such as low aqueous solubility, poor bioavailability, poor membrane permeability, variable plasma concentration, undesirable effects, poor patient compliance, and finally poor patient efficacy.[25] Various novel drug delivery system approaches, such as solid lipid nanoparticles, dual reverse thermo sensitive systems, complexation, electro spraying, solid dispersions, co-solvency, and nanosizing (nanoemulsion, nanosuspension, nanoparticles, and nanocrystals), have been proposed over the last few decades to address these issues. However, too much emphasis was placed on vesicular drug carriers, such as liposome's or niosomes, for demonstrating effectiveness. [25]

Nanotechnology

Many approaches have been used in the last few decades to treat ocular diseases. One of the approaches currently being pursued for both anterior and posterior segment drug delivery is nanotechnology-based ophthalmic formulations. Nanotechnology-based systems with suitable particle sizes can be designed to ensure low irritation, adequate bioavailability, and ocular tissue compatibility. For ocular drug delivery, several nanocarriers have been developed, including nanoparticles, nanosuspensions, liposomes, nanomicelles, and dendrimers have been created for ocular drug administration. Some have shown promising results in terms of improving ocular bioavailability. [2]

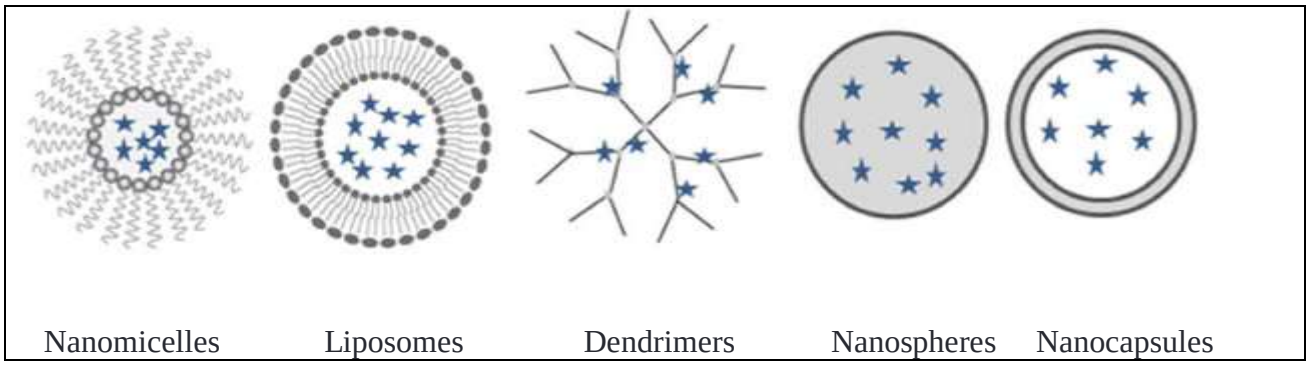

Figure 5: Ocular drug delivery nanocarriers

Nanomecelles

Nanomicelles are the most widely used carrier systems for delivering therapeutic agents into clear aqueous solutions. In general, amphiphilic molecules are used to create these nanomicelles. These molecules could be surfactants or polymers. Currently, there is a lot of interest in developing nanomicellar formulation-based technology for ocular drug delivery. Their high drug encapsulation capability, ease of preparation, small size, and hydrophilic nanomicellar corona generating aqueous solution may be attributed to the reasons. [2]

Niosomes

Niosomes are vesicles made of non-ionic surfactants. They were initially developed as a controlled drug delivery system alternative to liposomes in order to overcome issues with sterilization, large-scale production, and stability.[29] Niosomes are vesicular systems made up of non-ionic surfactants that serve as drug carriers.[22] Niosomes are non-ionic surfactant-containing vesicles that can entrap both hydrophillic and lipophillic drugs in an aqueous layer or a vesicular membrane made of lipid materials21. It aids in the prevention of drug metabolism by enzymes found on the tear/corneal surface.[28] Niosomes have an infrastructure that is mostly hydrophobic and hydrophilic, allowing them to accommodate drug molecules with a wide range of solubility.[30]

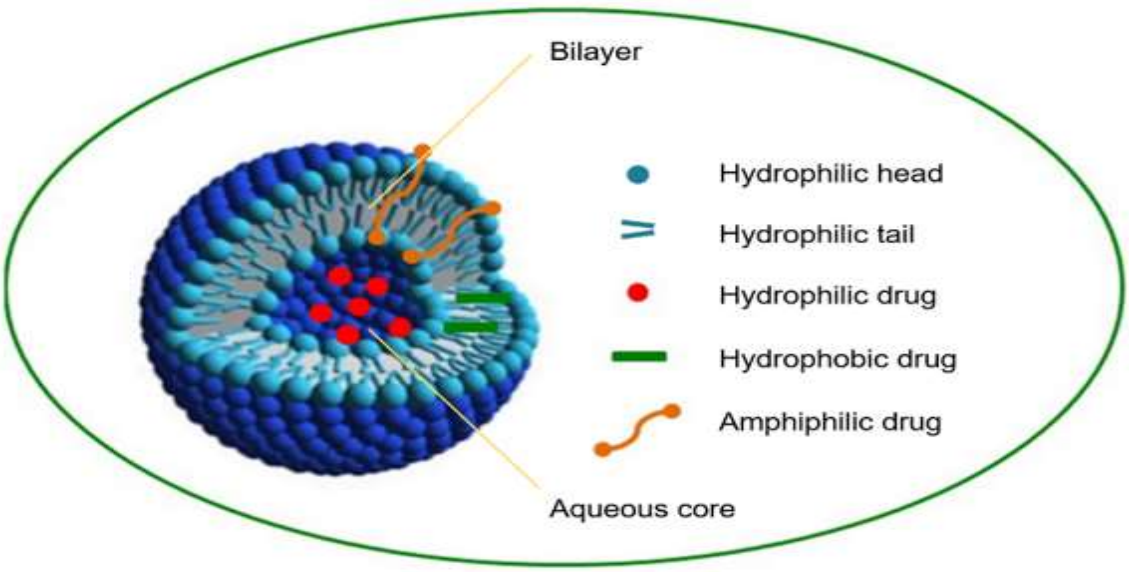

Figure 6: Structure of niosomes

Liposomes

Liposome's are microscopic vesicles made up of membrane-like lipid layers that surround aqueous compartments. The lipid layers are mostly made up of phospholipids. They can trap hydrophilic compounds in the aqueous compartment and incorporate hydrophobic molecules into lipid bilayers.[28] Liposome's were created by combining non-ionic surfactants of the polyoxyethylene cetyl ether class.[29] Because of their unique structure framework, which entraps both lipophilic and hydrophilic drugs and exerts targeted delivery at the site of action, the liposomal formulation helps in minimizing various effects such as endophthalmitis, vitreous hemorrhage, and retinal detachment that are associated with intravitreal instillation of drugs. Low drug bioavailability associated with topical instillation due to deprived precorneal residence time caused by rapid nasolacrimal drainage and tear turnover, resulting in less absorption via the conjunctiva.[6]

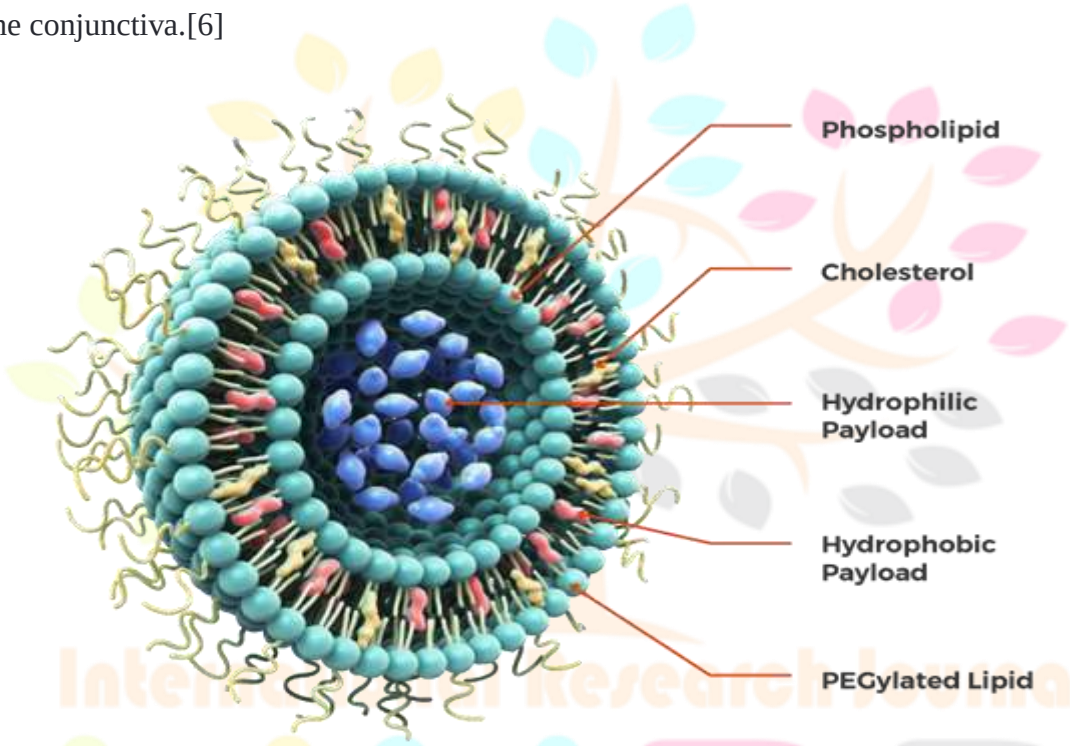

Figure 7: Structure of liposomes

Contact lens

Contact lenses are thin, curved plastic discs that are intended to cover the cornea. Because of surface tension, contact lenses adhere to the tear film over the cornea after application. Drug-loaded contact lenses have been developed for the ocular delivery of a variety of drugs, including -blockers, antihistamines, and antibiotics. It is hypothesised that in the presence of contact lenses, drug molecules have a longer residence time in the post-lens tear film, resulting in higher drug flux through the cornea and less drug inflow into the nasolacrimal duct. Typically, drugs are loaded into contact lenses by immersing them in drug solutions. When compared to conventional eye drops, these soaked contact lenses delivered the drug more efficiently. [2]

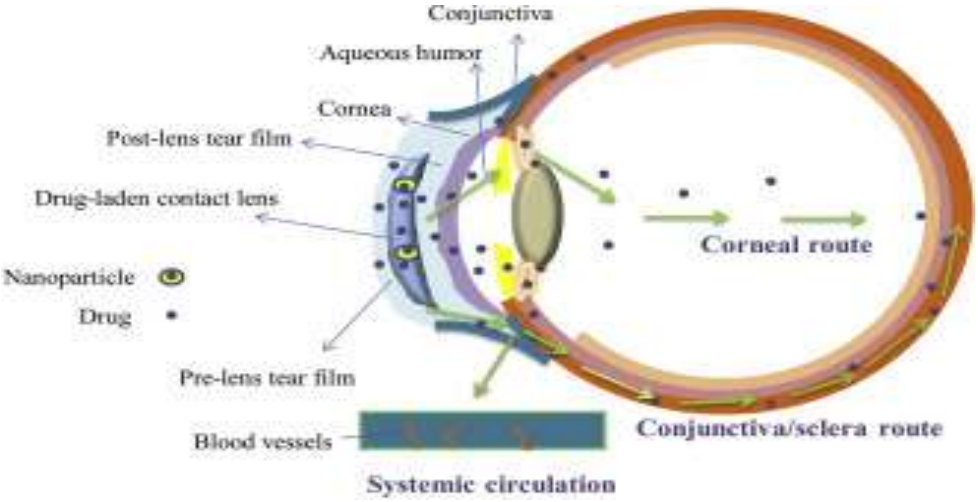

Figure 8: Contact lens for ophthalmic drug delivery

Nanoparticle

Nanoparticles are colloidal carriers that range in size from 10 to 1000 nm. Nanoparticles for ophthalmic delivery are typically made of lipids, proteins, and natural or synthetic polymers such as albumin, sodium alginate, chitosan, poly (lactide-co-glycolide) (PLGA), polylactic acid (PLA), and polycaprolactone. Drug-loaded nanoparticles can take the form of nanocapsules or nanospheres. In nanocapsules, the drug is enclosed within the polymeric shell, whereas in nanospheres, the drug is distributed uniformly throughout the polymeric matrix. [2]

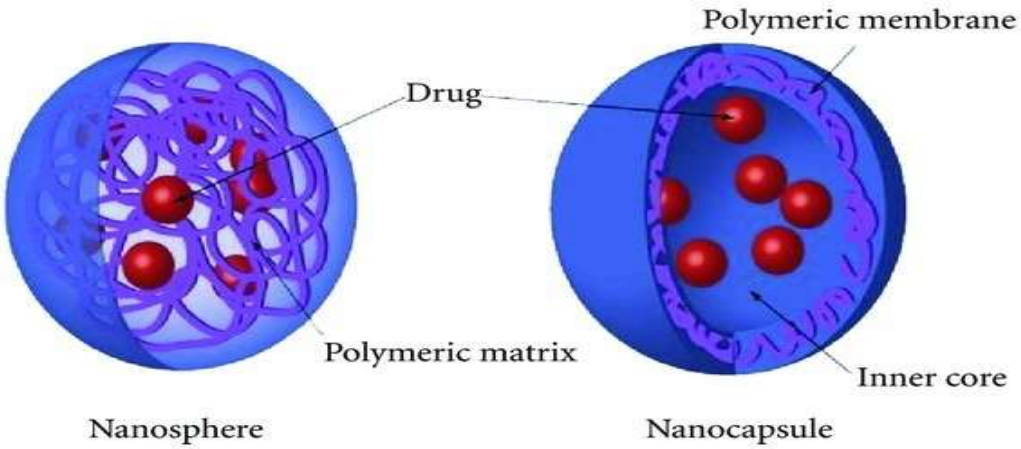

Figure 9: Structure of nanosphere and nanoparticle

Nanosuspension

Colloidal dispersion of submicron drug particles stabilized by polymer(s) or surfactant (s). It has emerged as a promising strategy for the administration of hydrophobic drugs. It has several advantages for ocular delivery, including sterilization, ease of eye drop formulation, less irritation, increased precorneal residence time, and improved ocular bioavailability of drugs that are insoluble in tear fluid. Several research studies have demonstrated the efficacy of nanosuspensions in improving glucocorticoid ocular bioavailability. [2]

Micro needle

Micro needle-based drug delivery to posterior ocular tissues is a new and minimally invasive technique. This method may provide effective treatment. A treatment strategy for vision-threatening posterior ocular diseases such as age-related macular degeneration, diabetic retinopathy, and posterior uveitis. This new microneedle-based administration strategy has the potential to reduce the risk and complications associated with intravitreal injections, such as retinal detachment, haemorrhage, cataract, endophthalmitis, and pseudoendophthalmitis. Furthermore, this strategy may aid in bypassing the blood-retinal barrier and delivering therapeutic drug levels to the retina/choroid. Micro needles are custom designed to penetrate sclera only hundreds of microns deep, avoiding damage to deeper ocular tissues.[2] These needles aid in the delivery of drugs or carrier systems into the sclera or the narrow space between the sclera and the choroid known as the "suprachoroidal space" (SCS).[2]

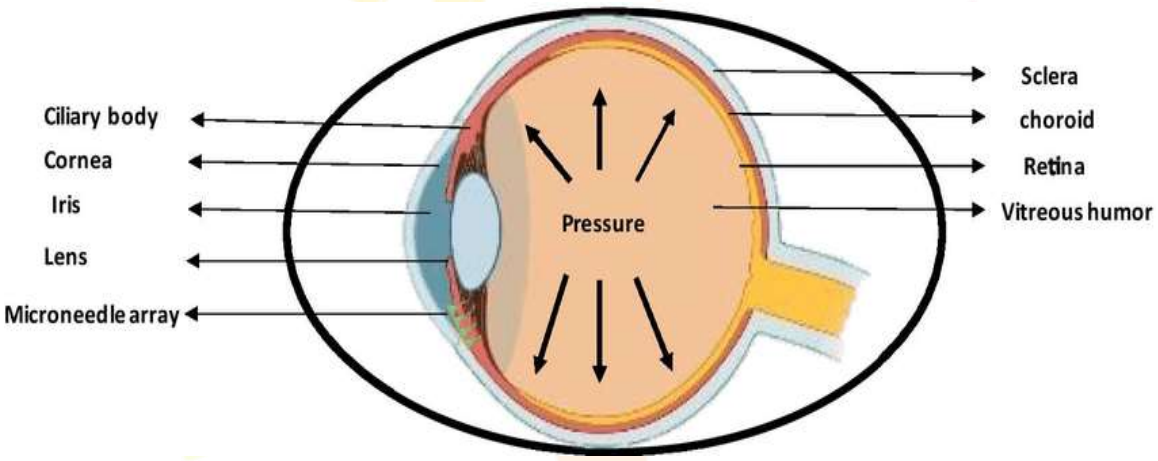

Figure 10: Miconeedle drug delivery to the eye

Dendrimers

Dendrimers are characterized as nanosized, highly branched, star shaped polymeric systems. These branched polymeric\systems are available in different molecular weights\switch terminal end amine, hydroxyl or carboxyl functional \group. Targeting moieties can be conjugated using the terminal functional group. Dendrimers are used in drug delivery as carrier systems. The choice of molecular weight, size, surface charge, molecular geometry, and functional group is critical in drug delivery. Dendrimers' highly branched structure allows for the incorporation of a diverse range of drugs, both hydrophobic and hydrophilic. [2]

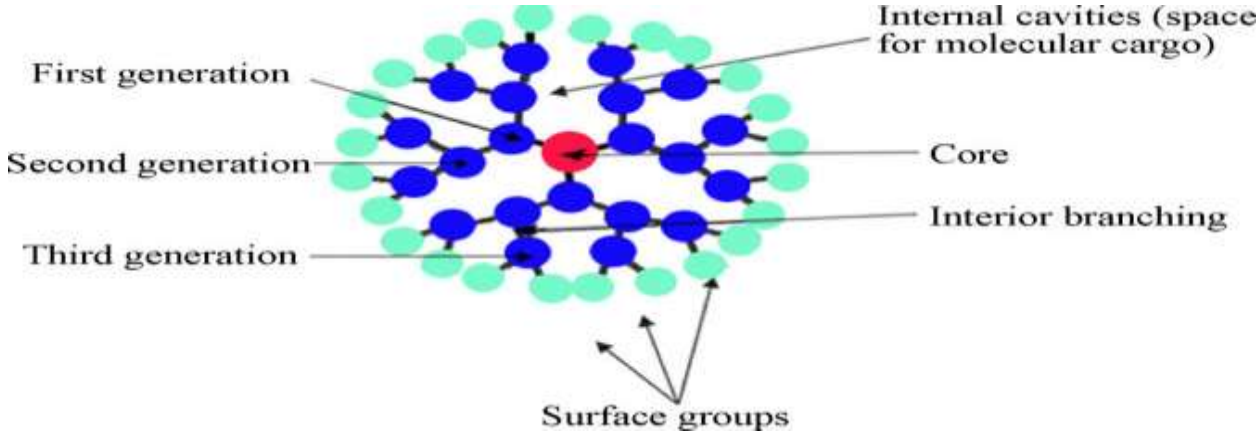

Figure 11: Structure of dendrimers

Implant

Intraocular implants are specifically designed to provide controlled drug release over a long period of time. These devices aid in avoiding multiple intraocular injections and the complications that come with them. Implants are typically placed intravitreally for drug delivery to posterior ocular tissues by making a minor incision at the pars plana, which is located posterior to the lens and anterior to the retina. Despite the fact that implantation is an invasive procedure, these devices are gaining popularity due to their associated benefits such as sustained drug release, local drug release to diseased ocular tissues at therapeutic levels, reduced side effects, and the ability to bypass the blood retina barrier. Several implantable devices for ocular drug delivery, particularly for the treatment of chronic vitreoretinal diseases, have been developed. [2]

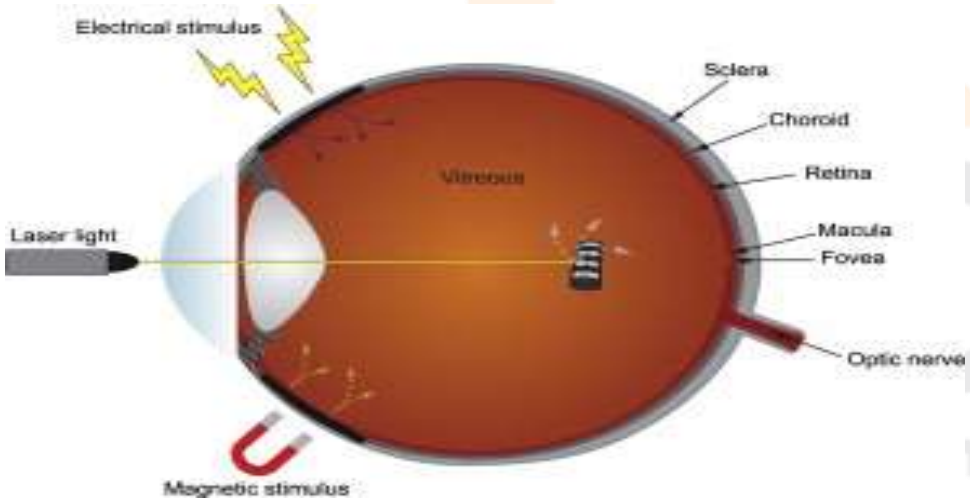

Figure 12: Implants for drug delivery to the posterior segment of the eye

Methodology

Various literature searches have been conducted for ocular drug delivery system by the use of reference books, text books, journals, magazines, and scientific web-based search engines. Google scholar, Research gate, Medley, Pub Med, Science Direct, and Scopus are being utilized as web indexes to gather the articles disseminated. Ocular drug

delivery system has been reviewed and gathered as original research articles, extensive review articles, book chapters, web information, and unpublished proposal works.

Abbreviations

Abbreviations	***Description***
ILM	Internal limiting membrane
API	Active pharmaceutical ingredient
ODDS	Ocular drug delivery system
BRB	Blood retinal barrier
PLA	Polylactic acid
SCS	Suprachoroidal space
OCT	Optical coherence tomography

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