Volume 9, Issue 10, October– 2024 International Journal of Innovative Science and Research Technology
ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24OCT456

Current Developmentsand Prospects for Nanotechnology-Based Ocular Drug Delivery System

Snehal Rathod[1]; Prachee Kawade[2]; Laxmi Korde[3]; Mohammed Sufiyan[4] (Guide); Zahid Anwer[5]; Shaikh Faizan[6]
Valmik Naik College of Pharmacy Telwadi Tal., Kannad. Dist., Aurangabad
431103. State. Maharashtra, (India)

Abstract:- Ophthalmologists and drug delivery experts have faced numerous anatomical and physiological obstacles when it comes to ocular drug delivery. Ocular barriers, both static and dynamic, block the entrance of foreign substances and obstruct the active absorption of therapeutic medications. This overview provides more details on the eye's anatomy and related limitations. An example of a few prevalent visual disorders, such as glaucoma, and the current clinical treatments for it are shown below, highlighting the importance of medication therapy in the treatment of ocular diseases. Then, some common research is presented along with recommendations for improvements in ocular medication delivery methods, particularly those based on nanotechnology

Keywords:- *Ocular Drug Delivery Systems, Nanotechnology, Ocular Barriers: Features and Clinical History.*

I. INTRODUCTION

Approximately 80% of all sensory input is obtained through the eye, making it the most significant, solitary, and specialized sense organ in the human body [1]. Both Barriers that are both static and dynamic shield the anatomical ocular tissues [2].The removal of foreign objects from the eye's surface is accomplished by nasolacrimal drainage, reflex blinking, and tear turnover [3]. The outside of the eye is covered and shielded by the eyelid, conjunctiva, and corneal epithelium [4]. Furthermore, substances from the circulatory system are restricted from entering the body by the blood-retina barriers (BRB) and blood-aqueous barriers (BAB)[5].Enzymes and other barriers (such as the retina and sclera) support this defense system even more[6].The eyeball has several defense mechanisms, but because of its correspondence with the outside world, it is nevertheless susceptible to infection, trauma, and other injuries[7].For most eye conditions, medication therapy is the main course of treatment[8].One of the main areas of current study is how to deliver medications to target the tissues of the eyes at the desired therapeutic dose without endangering healthy tissues[9].The The objectives of ocular drug delivery systems (ODDS) are: (1) get past ocular obstacles in order to administermedications to target eye conditions; (2) enhance medication stability and treatment efficacy; (3) extend drug retention period and lower dosage frequency; (4) allow for the use of multiple drug combinations; and (5) enhance patient adherence and lower adverse event rates associated with medication[10].Conventional delivery techniques, which are still in widespread use in clinical settings and have had some therapeutic effects, include intravitreal injection, retrobulbar injection, topical eye drops, conjunctival and scleral administration, and systemic administration[11].As was previously indicated, though, the existence of ocular barriers presents a substantial barrier to therapies in terms of getting to the intended spot and remaining there long enough. Because of this, these treatments' bioavailability is frequently restricted and usually less than 5% [12]. The area of eye medication delivery has advanced significantly with the advent of nanotechnology, offering new therapeutic approaches for ocular illnesses [13].

- *The Anatomy and Barriers of the Eye*

The sections in front and back of the eyeball's anatomical structure can be distinguished by the lens. The human eye's anatomy is shown in Figure 1. The sclera, choroid, retina, and vitreous body are included in the posterior segment, whereas the cornea, conjunctiva, iris, ciliary body, aqueous humor, and lens are included in the anterior section [14]. They are briefly separated into barriers, both dynamic and static, to stop foreign objects—including medicinal agents—from going aftervarious sections of the eye [15]. The ocular static barriers comprise the cornea, sclera, conjunctiva, and vitreal barrier, BAB, and BRB, whereas the tear film and tear the ocular bioavailability of many drugs is decreased as a result of these obstacles, which restrict thepassive absorption of various medicinal compounds. To learn more about the absorption barriers, see the details that are provided below.

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24OCT456

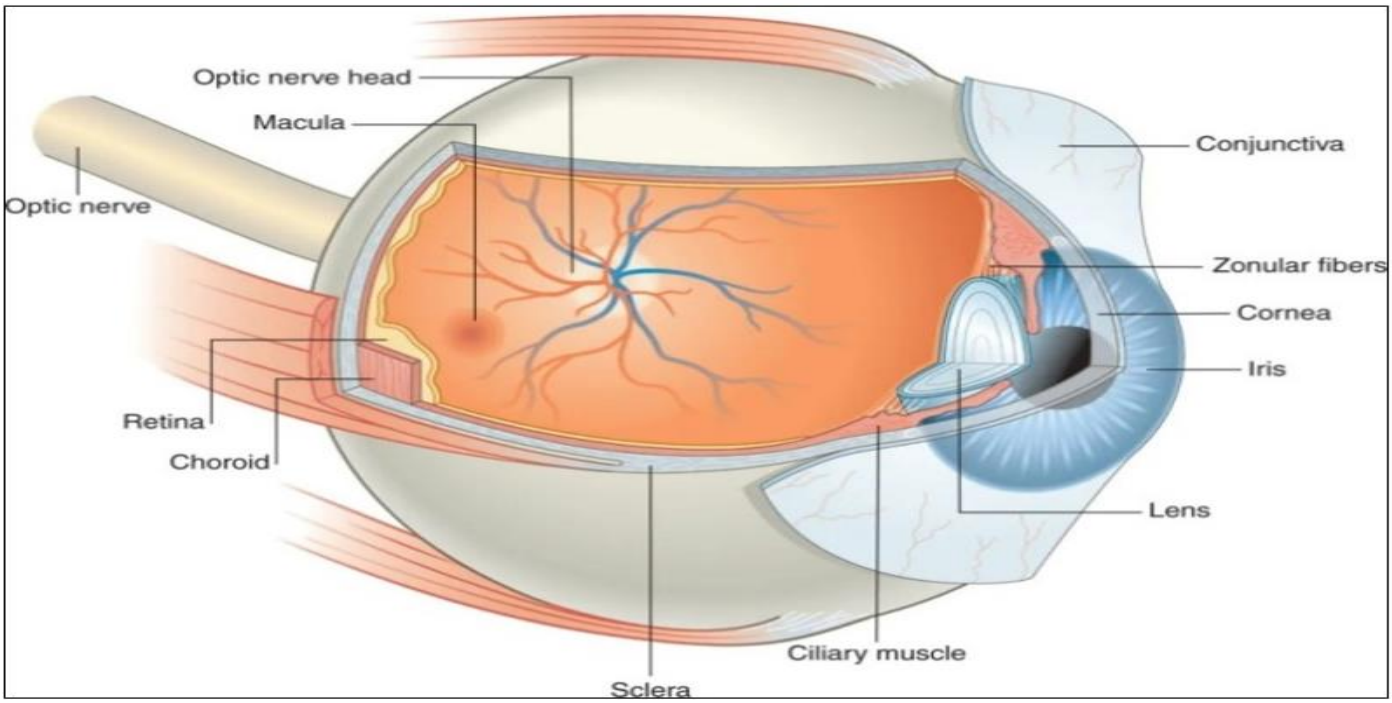

Fig 1 The Anatomy of Eye

- *Tear Film, Discharge of the Nasolacrimal Duct, Tear Turnover*

In addition, non-specific medication binding to tear proteins, mucin layers, and enzymes (like lysozyme) Drugs cannot enter the cornea or anterior chamber due to albumin [16]. Furthermore, topical insolation of pharmaceuticals enhances tear turnover, which leads to fast drug molecule elimination by nasolacrimal drainage (in one to two minutes) [17].

- *Cornea*

The primary barrier preventing foreign objects from entering the anterior chamber is the healthy cornea, which is a transparent, avascular tissue [18]. The primary barriers that hinder the introduction of medications into parenchyma are the endothelial, stromal, and epithelial layers[19].Another factor contributing to limited medication bioavailability is the presence of drug efflux pumps and cytochrome P450, which are enzymes that break down drugs, in epithelial cells[20]. The highly hydrated matrix structure, however, in contrast, is a layered configuration of collagen fibers submerged in the extracellular matrix that prevents lipophilic medications from diffusing [21].

- *Conjunctival and Scleral Barriers*

The conjunctiva and sclera make up the non-corneal route, which is an alternate pathway for medication entrance into the eye following topical instillation [22]. The mucous conjunctiva membrane which forms on the outer region of the cornea and on the posterior aspect of the eyelid. It consists of an inner stromal layer and a vascularized epithelial group [23]. In addition, The portion of the conjunctiva's surface that is roughly 17 times more than the cornea's, which makes it more porous and provides a better channel for the absorption of hydrophilic chemicals and macromolecules [24]. The conjunctiva is nevertheless very vascularized. Medication that penetrates one can methodically absorb the conjunctiva from the nasal cavity or conjunctival sac and dispersed throughout the body, instead of remaining confined in the intraocular segment [25].

- *The Blood Aqueous Barrier*

The primary barrier in the anterior region of the eye that blocks the random entry of different solutes into the intraocular environment is the blood-aqueous barrier, which consists of the endothelial cells' epithelial tissue and the non-pigmented ciliary body of the iris vasculature [26]. The osmotic pressure and the physicochemical characteristics of drug molecules control the permeability of pharmaceuticals across the BAB [27]. Compared to hydrophilic and large-molecule medicines, lipophilic and small-molecule medications can pass through the BAB and escape the anterior compartment more quickly. Pilocarpine, for example, was found to have a quicker clearance rate than inulin [28]. Ocular medication distribution is nevertheless hampered by its unique tissue barriers, which can reduce therapeutic efficacy.

- *The Blood Retinal Barrier*

The most significant barrier in the posterior region of the eye is the blood-retinal barrier, which consists of both internal and exterior components [29]. Tight connections among the endothelial cells of the retina form the inner border of the blood vessel, whilst close connections between retinal pigment epithelium cells form the outer border [30]. Water, plasma constituents, and hazardous materials are kept out of the retina by Te BRB [31].

- *Ocular Diseases*

Currently, about 500 various kinds of eyes illnesses are recognized, including diabetic retinopathy, glaucoma, macular degeneration, and dry eye disease (DED). Ocular disorders are becoming more common as a result of aging populations and

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24OCT456

shifting eye usage habits. The severe effects of these illnesses on people's health and quality of life highlight the pressing need for effective therapies. Without a doubt, drug therapy is essential to the treatment of many eye illnesses.

- *Glaucoma*

Glaucoma is a disease. of the eyes that causes gradual loss of vision and is the second biggest cause of blindness globally, after cataracts [32]. By 2040, there will likely be 111.8 million glaucoma patients worldwide, according to estimates [33]. High intraocular pressure can also cause the retinal blood vessels to constrict, which can harm the retinal ganglion cells and the optic nerve [34]. Despite the fact that glaucoma is a complex illness, the primary goal of current treatment for the condition is to lower intraocular pressure in order to delay orlessen potential vision loss [35]. Topical anti-glaucoma drugs are typically used as the first line of treatment. However, because to the substantial precorneal loss and minimal corneal penetration, topical treatment has a lower bioavailability than 5% [36]. Therefore, to effectively transport medications, increase bioavailability, and preserve the effectiveness of antiglaucoma medications, nanotechnology is required.

- *Age Related Macular Degeneration*

Globally, the third is AMD. Most common cause of severe permanent vision loss, and by 2040, there will likely be close to 300 million AMD sufferers [37]. Clinically speaking, it is separated into early and late AMD. The clinical manifestations of early AMD comprise of changes in retinal pigmentation and medium-sized stone fruit. Neovascular (also known as wet or exudative) or non-neovascular (also known as atrophic, dry, or non-exudative) late AMD is characterized by the possibility of central vision loss and legal blindness [38]. High dosages of antioxidant vitamin supplements and zinc can stop the development of disease from its early stages to its advanced stages [39]. Growth factors that oppose vascular endothelial cells (VEGF) can be injected intravitreal (IVT) to treat neovascular AMD, although this procedure is still invasive and uses drugs like bevacizumab (Bev), afibercept, etc [40]. Therefore, it is especially crucial to take advantage of novel drug delivery technologies for customized drug delivery.

- *Diabetic Retinopathy*

Diabetes's chronic consequence that is the primary cause of blindness and vision loss worldwide is diabetic retinopathy [41]. Retinal detachment can cause progressive symptoms such as ocular foaters, distorted vision, impaired vision, and even partial or whole vision loss in extreme situations [42]. Clinically, Retinal circulation is able to increased retinal neovascularization and vitreous hemorrhage can be prevented should laser therapy be administered on time. However, in order to alleviate macular oedema and enhance vision in patients with the condition, anti-VEGF injections are typically required [43]. Regretfully, frequent intravitreal injections may harm the ocular tissue, and not every patient will react as well as they should [44]. When proliferative vitreoretinopathy or fundus bleeding occur, a vitrectomy is required [45]. Considering the poor bioavailability of medications, possible side effects, and unavoidable dangers associated with major surgery, innovative drug delivery techniques are needed to generate fresh concepts for DR therapy.

- *Dry Eye Disease*

Dry keratoconjunctivitis, also referred to as dry eye disease, is a multifactorial ocular surface condition [46]. Tear film instability, hypertonicity, inflammation, injury to the ocular surface, and nerve paresthesia are its defining characteristics [47]. Five to fifty percent of people worldwide have dry eye [48]. Ocular irritation, inflammation, soreness, a feeling of a foreign body in the eye, and impaired vision are among the symptoms of DED. DED has a major negative influence on the standard of care received by patientslife, contributes to psychological worry, and places a significant financial strain on society [49]. Although the pathophysiology of DED has not yet occurred completely understood, the majority of researchers believe that inflammation is the primary cause of the disease [50]. There aretwo primary types for the diagnosis of DED and treatment: evaporation type and dehydration type [51].Localsecretagogues, corticosteroids, immunosuppressants, and artificial tears are common medication therapies. However, there are adverse effects that can include glaucoma, high intraocular pressure, limited patient compliance, and eye pain [52]. It Is very important to take use of novel drug delivery techniques in order to enhance medication bioavailability and get beyond ocular obstacles.

- *Conventional Methods of Administering Medications*

The most common customary administrative pathways are systemic routes, intracameral routes, intrabulbar and intravitreal injections, topical routes, conjunctival and scleral routes, et cetera [53]. Fig. 2 illustrates the conventional methods of administering medications to the eyes. One or more ocular obstacles may need to be overcome, depending on the delivery route, in order for the medication to reach the intended location.

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24OCT456

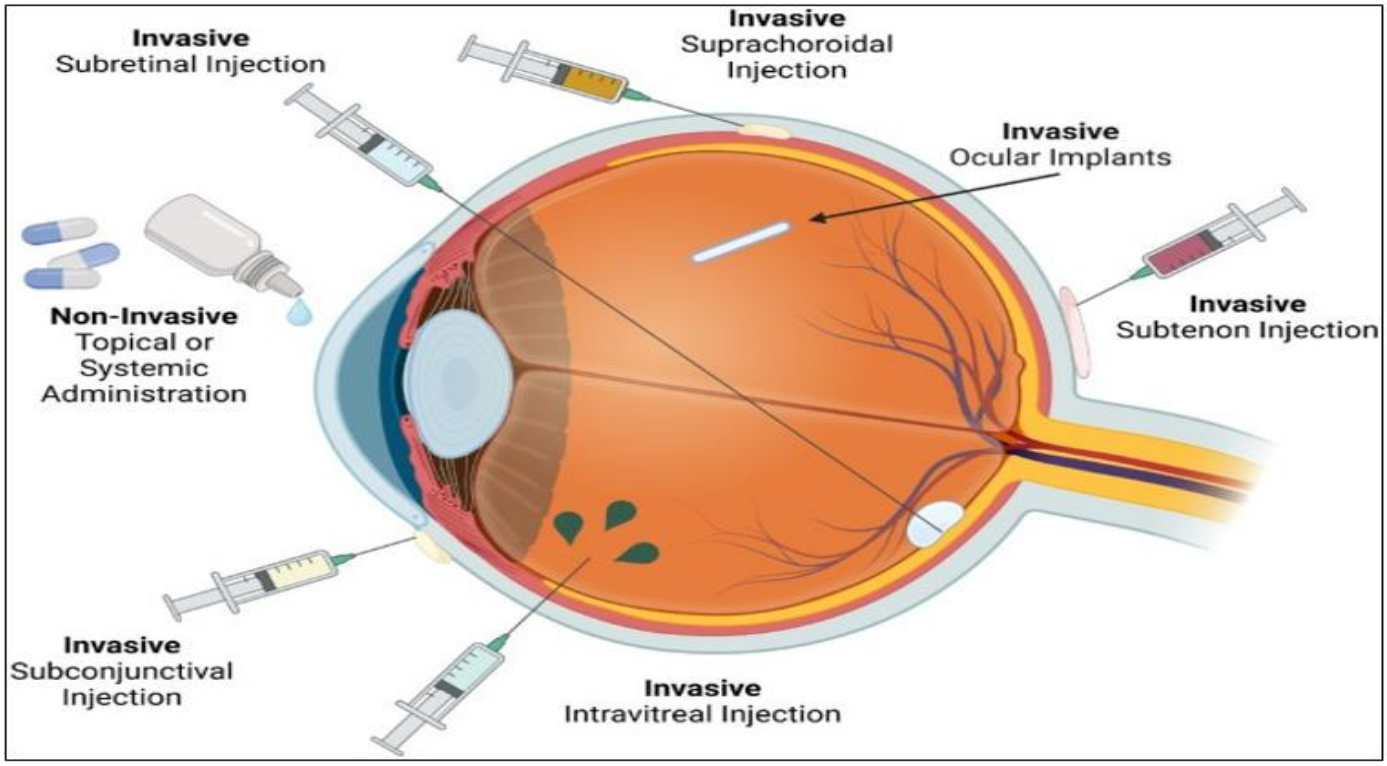

Fig 2 Routes of Drug Administration for Ocular Delivery

- *Topical Administration*

The most popular and simple method of ocular medication administration is topical application [54]. It has the advantages over systemic administration in that it is : (1) comparatively on-invasive;(2)minimizes the drug's systemic side effects; and (3) is comparably easier for patients to administer [55]. Since many eye conditions, including infection, glaucoma, inflammation, DED, and allergies, can only be treated with ophthalmic solutions, they are the primary option [56]. In the international market for eye drugs, topical solutions are thought to make up 95% of the currently available products [57]. Drug transport in the eye is restricted, and bioavailability is often less than 5%, owing to the distinct the physiological makeup and anatomic composition of the eye [58].

- *Subconjunctival and Transscleral*

Drugs can be delivered either the posterior or anterior chamber of the eye usingsubconjunctival injection, which is a less intrusive and effective method that avoidsthe barriers between blood and the cornea, possible sideeffects, as well as some systemic first-pass metabolism medications [59]. Due the conjunctiva's blood and lymphatic outflow, the subconjunctival route, however, may cause medication loss[60]. Converselytransscleral administration is a more straightforward, patient-friendly, and minimally invasive technique. The barriers in the front portion of the eye can be avoided using this path [61]. Antioxidants, neuroprotective drugs, or anti-angiogenic agents may be delivered to specific locations in the retina thanks to the sclera's vast surface area, which makes up over 95% of the the portion of the surface that eye [62]. It is known that molecules as small as 70 kDacan easily traverse the sclera, whereas molecules smaller than 1 kDa can pass through the cornea [63].

- *Intracameral Administration*

Drugs are injected immediately into the eye's anterior chamber during intracameral administration [64]. Some systemic medicines have first-pass metabolism, which can be avoided with this local delivery method. Additionally, it avoids the BAB, conjunctiva, and cornea at the same time [65]. Intracameral injections, therefore, enable reasonably simple and effective medication administration to the anterior portion of the eye[66]. Nowadays, preventive antibiotics or anaesthetics related to eye procedures are administered by intracameral injections [67]. The posterior internal eye chamber cannot receive medication administered in the anterior chamber. Also, medications in the anterior chamber typically need to be rearranged, diluted, sterile, prepared specifically without preservatives, and administered at the right concentrations and dosages [68]. If the wrong dosages and preparations are employed, corneal endothelial cell toxicity and harmful anterior segment syndrome could happen [69].

- *Intravitreal Injection*

The recommended way of administering medication to treat ocular illnesses in the eyeball is intravitreal injection, which takes place in the posterior region of the eye [70]. After IVT injections, free medications can be swiftly eliminated due to vitreous fluid turnover [71].Obtaining good treatment results requires frequent IVTs, which can have adverse effects such high intraocular pressure, eye infection and retinal detachment, and endophthalmitis [72].Hence, the best course of action for IVT is to inject the medication once without retracting the needle and to keep the ocular system closed. Recent research has concentrated on preserving therapeutic effects, extending treatment durations, and safeguarding healthy ocular tissues. Preclinical and clinical studies are being

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24OCT456

conducted on NPs, hydrogels, combinatorial systems, intravitreal implants, and minimally invasive procedures as safer and more effective ways to treat ocular illnesses [73].

- *Retrobulbar Injection*

Putting needles through the orbital fascia and eyelid to deliver medication to the ret-robulbar region is known as the retrobulbarroute[74]. Treatment for macular oedema brought on by retinal vein occlusion involves retrobulbarinjection of triamcinolone acetonide [75]. Amphotericin B injection via retrobulbar route had a greater antifungal impact than injection via intravenous route [76]. Painful blind eyes are treated with a retrobulbar injection of chlorpromazine [77].

- *Systemic Administration*

An alternate technique for delivering medication is systemic administration, which includes parenteral and oral dosage. Antibodies, antibiotics, and carbonic anhydrase inhibitors are being used systemically to treat conditions like uveitis, endophthalmitis, and increased intraocular pressure [78]. However, frequent administrations are essential for obtaining the intended treatment result because of the ocular barriers and the retinal pigment epithelium's tight junctions, which only allow one to two percent of the medication to the vitreous and retinal regions. This could lead to systemic side effects and poor patient compliance [79]. It is not the best method of administration as a result.

- *Pharmacokinetics*

Penetration and elimination in ocular pharmacokinetics are key aspects of covered in detail, with a focus on thedrug administration and ocular obstacles previously mentioned. As seen in Figure3 [80]. It mostly consists of the following pathways: (1) medication from the bloodstream crosses BAB and enters the anterior chamber via the tears and cornea; (2) non-corneal penetration to the front uvea via the conjunctiva and sclera; and (3) drug distribution from the circulation through BRB to the posterior segment of the eye, (4) medication from the aqueous humor crosses BAB to enter the systemic circulation; (5) medication removal from the aqueous humor enters Schlemm's canal and the trabecular meshwork; and (6) medication distribution enters the systemic circulation via BRB. (7) intravitreal administration; (8) removal of the vitreous body by an anterior route into the posterior compartment; and (9) removal of the vitreous body through a posterior route via BRB.

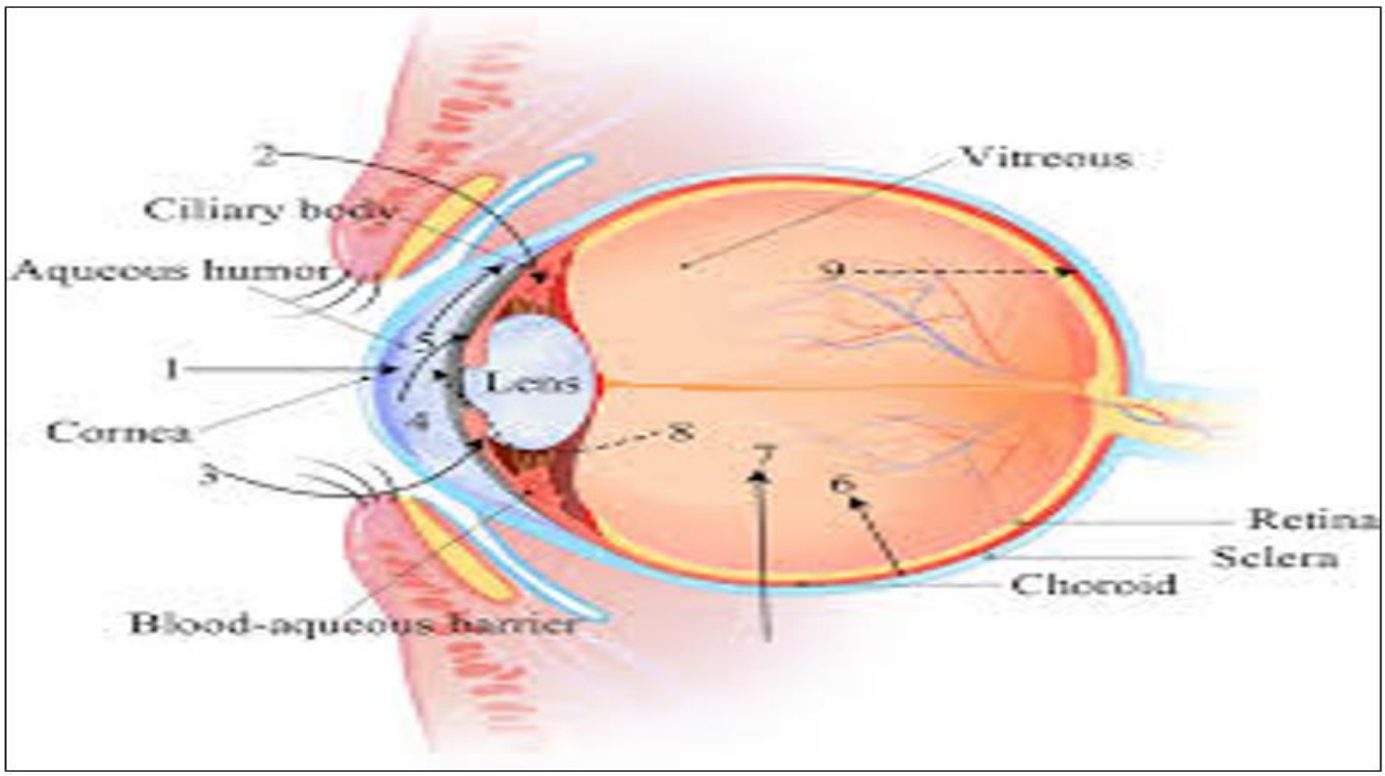

Fig 3 The Pathways of Drug Metabolism

- *Nanotechnology-Based Ocular Drug Delivery System*

Novel drug delivery technologies have been created to enhance medication bioavailability and get past obstacles to ocular drug delivery. The development of nanocarriers has numerous benefits, such as the ability to target and deliver genes, overcome ocular barriers, increase transcorneal permeability, extend the duration of drug residence, decrease dosage frequency, enhance patient compliance, and reduce drugdegradation[81].

- *Nanomicelles*

Core-shell nanocarriers known as nanomicelles are created when amphiphilic copolymers spontaneouslyassemble into an exterior shell of hydrophilic groups and a core of hydrophobic groups[82].They fall into three categories: polymers, surfactants, and multi-ion composite nanomicelles, and their typical particle size varies from 10 to 100 nm[83].In addition, the forces that propel the production of polymer micelles include hydrophobic interactions, hydrogen bonds, electrostatic interactions, etc[84].When the hydrophilic

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24OCT456

moiety is oriented outward to maximize interaction with water and the hydrophobic moiety forms clusters within the core, positive micelles are typically generated.Likewise, the aggregates are known as reverse micelles when the opposite arrangement takes place[85].Hydrophobic medications are delivered, dissolved, and encapsulated by positive micelles, while hydrophilic pharmaceuticals are encapsulated and delivered by reverse nanomicelles[86].

- *Nanoparticles*

The optimal sizes of NPs, colloidal drug carriers, are between 10 and 100 nm[87].They fall mostly into two categories: lipid NPs and polymers[88].Polymers such as albumin, sodium alginate, chitosan, polylactide-coglycolide (PLGA), polylactic acid (PLA), and PCL are examples of natural or synthetic polymers that are employed as NPs in ocular treatments[89].Additionally, the effective ocular absorption of NPs is greatly influenced by their surface charge. Catalytic nanoparticles (NPs) have a longer retention period on the ocular surface than anionic NPs because the surfaces of corneal and conjunctival tissues are negatively charged[90]. To date, NPs have been used widely to deliver drugs to the targeted tissue in the eye, with the advantages of: (1) smaller and less irritating; (2) providing sustained drug release to avoid repeated dosing; (3) preventing non-specifc uptake or premature degradation; (4) providing better absorption and improving intracellular penetration; and (5) targeted delivery to desired tissues[91].PLGA is a synthetic polymer that has been extensively utilized in the preparation of NPs for ocular drug release because of its high biocompatibility, biodegradability, and ability to modify the release of drugs by changing the lactide-to-glycoside ratio, molecular weight, and terminal groups[92].

- *Nanosuspensions*

Submicron colloidal dispersions of drug nanocrystals are the only constituents of the nanosuspension. Steadying the delivery of poorly soluble active substances is one of the most promising methods when stabilizers are used[93].A carrier material is not necessary for nanosuspension, in contrast to traditional matrix-framed nanosystems. It is often stabilized with surfactants or polymers and includes only 100% pure medication NPs in the nanometerrange[94].Their benefits include longer residence times, longer medication release, and better drug solubility[95].Additionally, immunosuppressive drugs have been delivered to the eyes using nanosuspensions as a platform[96].

- *Nanoemulsions*

Nanoemulsions, which range in size from 20 to 500 nm, are transparent or translucent, thermodynamically unstable but kinetically stable systems[97].The categorization of the dispersed phase system divides NEs primarily into three categories: (1) water-in-oil (w/o) NEs, which are continuous phase-containing dispersion of water droplets; (2) oil-in-water (o/w) NEs, which are continuous phase-containing dispersion of oil droplets; and (3) bi-continuous NEs, which are composed of water and oil microdomains mixed together in the system, as well as different NEs modifications[98].Also, it can be used to treat a variety of eye conditions, including glaucoma, herpes simplex keratitis infection, fungal keratitis, DED, etc[99].

- *Microemulsions*

Microemulsions are colloidal dispersions consist of distinct phases, such as an oil phase, cosurfactant, surfactant, and aqueous phase, in particular ratios. The size of their droplets varies from 10 to 100nm[100].The three categories of microemulsions include o/w, w/o, and bi-continuous structures, depending on the kinds and concentration of surfactant in the formulation[101].In general, w/o microemulsion has a higher oil comparison compared to o/w microemulsion, which often has a higher water comparison. In order to overcome several challenges and decrease the frequency of daily eye drops, microemulsions have been thoroughly investigated as a drug delivery mechanism for ocular preparations[102].If the medicine is poorly soluble in water, microemulsions are the most promisingsubmicron drug carriers. Microemulsions can be made cheaply, easily, and with thermodynamic stability all at the same time[103].

- *Nanofibers*

The diameter of nanofibers ranges from 1 to 100 nm[104].Nanofibers can be produced using the electrospinning method using a variety of natural polymers (such chitosan, fibronectin, gelatin, collagen, silk, and ethyl cellulose) or synthetic polymers (like PLA, PLGA, and PCL) or combinations of both[105].The benefits of nanofibers include strong drug loading capacity, high porosity, high encapsulation efficiency, high surface-to-volume ratio, and simultaneous delivery of numerous therapeutic agents[106].Additionally, medications can be delivered via nanofibers to specific tissues and overcome physiological barriers, resulting in regulated release of the drug over an extended period of time with minimal dissemination to other parts of the body[107].A number of chronic and degenerative eye illnesses, including AMD, DR, and glaucoma, are linked to retinal degeneration and neuronal loss. MEL has neuroprotective benefits on these conditions [108].

- *Characterization of Nanotechnology-Based Drug Delivery Systems*

Treatment of structures at the nanoscale level, which varies in size from 1 to 100 nm and is roughly equivalent to peptide medications, is referred to as nanotechnology.[109]Their therapeutic effectiveness in the ocular pathological environment is closely correlated with their basic physicochemical properties, which include size, visual appearance, zeta potential, refractive index, pH, retention, viscosity, osmolality, biodegradability, surface charge, hydrophobicity, and biodegradability.[110]

- *Visual Appearance*

Depending on the size of the particle, the kind of oil, the concentration, and the surfactant or cosurfactant, most NPs have a transparent, translucent, or translucent to milky look. Using a UV spectrophotometer, one can determine the transmittance (%T) at 520 nm to determine whether nanocarriers are transparent.[111]

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24OCT456

- *Particle Size (PS) and Polydispersity Index (PDI)*

Physical stability is primarily determined by PS and PDI, which are fundamental properties of nanocarriers. Dynamic light scattering or photon correlation spectroscopy are the primary methods used to evaluate these values.[112] Smaller particles have a higher absorption of aqueous humor and enter the tear film's inner mucin layer more quickly than larger particles.[113]A homogeneous system in PDI is represented by 0 and a heterogeneous system by 1.[114]The colloidal system is considered to be of good quality if the PDI value is less than 0.1, and bad quality.[115]Small PS and PDI are typically chosen for the administration of drugs to the eyes due to their superior stability, high patient compliance, and biodistribution qualities.[116]

- *Morphology*

The morphology of nanocarriers was examined using microscopic methods. When analyzing liquid samples, electron microscopy techniques such as transmission electron microscopy (TEM), freeze-fracture transmission electron microscopy (FFTEM), and negative staining transmission electron microscopy (NS-TEM) are recommended; for solid samples, scanning electron microscopy is needed.[117]Additionally, data from dynamic light scattering measurements or photon correlation spectroscopy can be confirmed using atomic force microscopy (AFM) and TEM techniques.[118]

- *Zeta Potential (Zp)*

A nano system's physical stability can be determined using its zeta potential. One of the factors that has been examined the most is the electrophoretic mobility of particles in an electric field.[119] Positively charged particles enhance electrostatic interactions with negatively charged ocular surfaces, resulting in improved bioavailability and activity.[120]

- *Stability*

The centrifugation test, freeze-thaw cycle, heating-cooling cycle, and high-temperature storage can all be used to gauge the stability of various nano systems. Short-term stability (3 months).[121]Pegylated is a potentially effective method for enhancing biological stability. By limiting contact with the surrounding environment (oxidants, enzymes, and other degraders), PEG, a hydrophilic non-ionic polymer with high chain flexibility, when linked or coated on the surface of nanocarriers, can impede macrophage clearance.[122]Additionally, as demonstrated by in vivo drug flow experiments, at two hours after delivery, pegylated nanostructured lipid carriers had approximately twice as much ciprofloxacin in all ocular tissues as non-pegylated nanostructured lipid carriers.[123]

- *Refractive Index (RI)*

The water content, salinity, and sugar concentration of soft contact lenses are tested using Abbe's refractometer to calculate their refractive index.[124] The tear RI ranged from 1.340 to 1.360. The RI value for ocular preparations should be less than 1.476.[125]

- *Challenges and Future Perspectives*

First, we reviewed the architecture and barriers of the eye in this review. Because of the variety of diseases and the presence of ocular barriers, particularly in the posterior portion of the eye, finding effective treatments and delivering drugs to patients are major obstacles.Some disadvantages, such as inadequate permeability, ineffective distribution, and insufficient bioavailability, persist even if traditional medication administration has shown some efficacy in treating ocular disorders.The efficacy of existing treatments can be greatly increased by using innovative drug delivery techniques such liposomes, contact lenses, aqueous gels, nanomicelles, NPs, nanosuspensions, microemulsions, dendrimers, liposomes, and MNs.Simultaneously, ongoing advancements in exosomes and gene delivery appear to hold great promise for drug delivery.There are still a number of obstacles to overcome in the development of innovative ocular medication delivery methods, even with significant advances. The clinical translation of nanotechnology-based ocular medication delivery systems is restricted by various factors, such as the intricacy of production technology and processes.To reduce potential issues, nanocarrier stability and safety must also be improved.Many novel drug delivery methods lack thorough in vivo assessments in human eyes and are instead mostly investigated in vitro or on animals.It is unclear what happens to nanocarriers during their metabolism in the eye, and their targeting skills need to be improved.These technologies' high manufacturing costs and technical requirements have also prevented them from being widely used in clinical settings and from being produced commercially.To progress ocular medication delivery and encourage its effective application in clinical practice, it is imperative to address these obstacles.The development of innovative non-invasive ODDS that can penetrate past ocular barriers, extend the duration of drug release, and maintain therapeutic concentration at the lesion targets should receive more attention in the future. Thus, it is necessary to maximize the following characteristics of nanocarriers: size, zeta potential, refractive index, safety, stability, pH, surface tension, and osmotic pressure.In order to more accurately forecast the safety and effectiveness of delivery vectors, more in vitro and in vivo studies should be conducted, animal models of eye illnesses more akin to those in humans should be developed, and therapeutic impact evaluation techniques should be further enhanced.Furthermore, new approaches to ocular drug delivery are offered via tissue engineering, exosomes, and gene therapy.In conclusion, new drug-delivery methods have indisputable benefits for ocular applications, and novel nanocarriers will be utilized in clinical practice more and more in the future.

II. CONCLUSION

Nanotechnology-based ocular drug delivery systems (ODDS) represent a significant advancement in addressing the challenges of conventional ocular treatments. The eye's intricate barriers and anatomical complexity make drug delivery difficult, especially for treating diseases like glaucoma, age-related macular degeneration (AMD), diabetic retinopathy (DR), and dry eye disease (DED). Traditional methods have shown limited bioavailability and therapeutic

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24OCT456

effectiveness, which nanotechnology aims to overcome by improving drug permeability, retention, and targeted delivery.

Nanocarriers such as nanoparticles, nanomicelles, nanosuspensions, and nanoemulsions offer enhanced drug delivery, reduced dosing frequency, and increased patient compliance. However, challenges remain in terms of safety, stability, clinical translation, and large-scale production. Future developments should focus on optimizing the physicochemical properties of nanocarriers, conducting more in vivo studies, and exploring emerging fields like gene therapy and tissue engineering for more effective and non-invasive treatments. With continuous progress, nanotechnology-based ODDS hold the potential to transform ocular drug delivery and improve treatment outcomes for eye diseases.

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