# REVIEW ARTICLE

## DRUG DELIVERY TO RETINA: A REVIEW

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**ABSTRACT**

The drug delivery to posterior segment especially to retina of eye is difficult due to various barriers. The diseases affecting the retina of eye are increasing and hence there is need to develop approaches for drug delivery to retina. This review describes the anatomy of retina, barriers associated with it, and diseases of retina. The drug delivery to retina by systemic, topical, intravitreal injection, intravitreal implant along with advance nanotechnology based and transporter mediated drug delivery is discussed here. The recent technologies in retinal drug delivery are also discussed to give comprehensive recent information about retinal drug delivery.

**Keywords:** Retina, Retinal Drug delivery, Transporter, Nanotechnology, Intravitreal.

### INTRODUCTION

Drug delivery to the posterior segment of eye is challenging. The retina is the primary target for different vascular, degenerative and proliferative disorders. Because of anatomical and physiological barriers associated with the retina, it remains a challenge for drug delivery to achieve continuous therapeutic concentrations of the drug at the retina. In case of chronic therapy, required in conditions like age related macular degeneration and diabetic retinopathy the challenge is reversed. The topical administration of drug in the lower cal-de-sac has been successful for treatment of diseases affecting the anterior segment of the eye. The cornea and conjunctiva are primary barriers after topical administration of ocular drugs. The other barriers like nasolacrimal drainage, protein binding, long diffusional path lengths, drug metabolism and lens barrier hinders the uptake of drug into the retina after topical administration. Systemic administration of drug to retina is the also limited by blood ocular barriers namely blood aqueous and blood retinal barriers[1]. The blood retinal barrier is formed by retinal pigmented epithelium (RPE) and endothelium of retinal vessels. The blood aqueous barrier includes endothelium of the iris vessels and non-pigmented layer of the ciliary epithelium[2]. Due to the presence of these barriers, the achievement of therapeutic effect in the retina requires a higher systemic dose but that can produce harmful side effects. Various local modes of administration like intravitreal, intracameral and periocular routes were also investigated to improve retinal drug delivery. The injection of drug into the anterior chamber is recognized as intracameral injections. By this route only up to 100 µL volume can be administered[3–6]. These injections are used in management of anterior segment diseases and cataract surgery. However was significant concentrations of drug to the posterior segment cannot be delivered by this route.

Intravitreal injection is found to have wide clinical applications in treating vitreoretinal disorders. The first report on administration of this mode was in 1944. This route provides a higher concentration of drug to the neural retina since different barriers are not involved. But higher dose intravitreal injections resulted in higher local concentration of drug, which causes retinal toxicity e.g. gentamicin[7]. The repeated administration of injections through the intravitreal route results in retinal detachment. With increase in molecular weight, in vitreous the elimination half-lifes of drugs also increase where as in plasma, protein and peptide drugs show shorter half-lifes. Due to unique vitreal clearance property, macromolecules like vascular endothelial growth factor (VEGF) antibody and VEGF aptamer are under development for intravitreal administration[8]. Such drugs require repeated intravitreal administration hence they might increase the risk in treating chronic disorders.

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In spite of many advances in the field of formulation of ocular drug delivery, targeting drug to the posterior segment of the eye remained challenging due to different barriers in delivery. The increasing aging population and age-related retinal disease[9], is worrying because it is increasing the burden to the global health care system. There is a clear and urgent requirement to develop smarter formulation strategies to overcome the barriers associated with the posterior eye and cater to this increasing patient need.

The intravitreal injection is currently the most effective and practical route for the treatment of retinal diseases but it has risk because of the poor rate of patient acceptability. There are many formulation strategies aiming to improve intravitreal delivery and efficacy while reducing the frequency of treatment[10]. There is need to gain better understanding of anatomy and physiology of the targets to achieve this goal by researchers. This review gives a comprehensive idea about the anatomy of the eye especially retina of the eye, the diseases associated with retina and drug delivery strategies used in the treatment of retinal disease. This review will explore the advances in drug delivery systems like nanoparticles, transporters and transporter mediated drug delivery approaches for the retina.

## ANATOMY OF EYE AND RETINA

### Structure of eye

Fig. 1 depicts structure of eye in a schematic form. The eye is composed of two major segments as the anterior segment and posterior segment divided by lens. The Posterior segment is of three major layers as outer sclera, middle choroid and inner retina. The vitreous chamber is main body filled with gel like vitreous humor surrounded by three layers. The outer sclera provides structural stability while middle choroid is highly vascular layer which provide nourishment to retina and metabolite clearance from the retina. The retina is the innermost and important layer composed of the complex neurosensory layer of the retina. The vitreous humor is about 4 mL and composed of water (99%), collegens, non-collagenous proteins and glycosaminoglycans. The vitreous humor has two key roles

(i) integrity of structure and (ii) transportation of nutrients to the retina and metabolites from the retina[11].

### Structure of Retina

Fig. 2 represents structure of retina. The retina has two main parts Neural retina and Retinal pigmented epithelium (RPE) and the space separating these two parts known as the subretinal space[12]. The neural retina is also known as neuro sensory retina and is composed of a seven layered structure. The light enters from the Ganglionic cell layer (GCL) and penetrates all layers to reach the Rods and Cones. This signal in the form of a transduced signal is conduced out of the retina via the optic nerve to the brain and an image is formed.

The RPE is a single cell layer separating the outer surface of neural retina from choroid. The RPE has two portions apical portion and basolateral portion. The apical portion faces the neural retina and basolateral portion is next to the choroid. The apical portion is made up of numerous microvilli while the basolateral portion is made us of small convoluted foldings which increases the area of absorption for the choroid side. Together the RPE is the specific nutrient transport system which maintains the environment of retina.

The neural element portion of retina is separated from the blood supply by the endothelial cell of retinal blood vessels. Together the Endothelial cell of the retinal blood vessel and RPE is known as the Blood Retinal Barrier (BRB) because it regulates the diffusion of substances from the blood into the vitreous and retina[8].

The blood vessels in the choroid have large fenestrations and it allows the diffusion of substances into and out of the choroidal stroma. The Bruch's membrane is membrane that separates the choroid from the RPE and it acts as the diffusional barrier and allows only macromolecules like proteins, oligonucleotides and genes. The RPE is the constituted of tight junctions which is the barrier to the entry of small molecules from the choroidal stroma to the retina[13].

The efflux pumps like p-glycoproteins, multidrug resistance proteins (MRP) are observed on the RPE and it limits the permeation of various xenobiotics and endogenous compounds. Thus, both transcellular and paracellular passage of molecules across the RPE is restricted only to selected nutrients[14].

In neural retina, the major blood vessels are in the innermost retinal layer which is the layer next to the inner limiting membrane which is the diffusional barrier between the retina and the vitreous. The innermost retinal layer has the ultra-structure of retinal blood capillaries which is uniform throughout the retina. These capillaries are of the endothelium are surrounded by the thick basement

membrane. Astrocytes are present close to the retinal blood vessels like blood vessels forming the blood brain barrier (BBB) in the brain[15]. The endothelium present is different. It does not show signs of fenestrations and has tight junction in a conserved manner. Thus, RPE and Retinal endothelial blood vessels collectively forms the BRB. It restricts the passage of molecules from the systemic circulation to the retina.

## DISEASES ORIENTED WITH RETINA

The retina portion of the posterior segment of the eye is present at the back of eye and is responsible for providing images to the brain through the optic nerve. The retinal diseases and disorders alter the normal functioning of the eye which may lead to alteration of vision leading to the point of blindness. The common diseases include the floaters, macular degeneration, diabetic eye disease, retinal detachment and retinitis pigmentosa.

### Floaters

Floaters is a condition in which a spot in the vision is observed. It may be age related but it also occurs in case of severe nearsightendness. In this condition, the jelly portion of the eye becomes more liquid and the clumps formed act as a shadow on the retina which is visualized as spots in vision[9,16,17].

Torn retina can result in floaters. In this case if the tear is not repaired the condition can turn into retinal detachment due to fluid accumulation behind the retina which is responsible for the separation from the eye[18–20].

### Age-related Macular Degeneration (AMD)

AMD is the condition of the retina related to age causing central vision loss. In the individuals over the age of 55, this condition is commonly observed. Approximately 10 million individuals from the United States suffer from this condition. The symptoms are blurry central vision, difficulty in focusing fine details or warped straight lines. This condition can lead to blind spots. There are various treatments like antioxidant supplements which slow down the blocking of healthy blood vessel and progression of the condition.

### Diabetic Macular Edema (DME)

For many patients suffering from diabetes, vision is also affected. The symptoms are blurry vision, floaters, double vision or dark spots, pressure or pain in at least one eye, flashing lights, trouble with peripheral vision or rings[10].

DME is a condition where there is accumulation of fluid in the macula from leaking blood vessels. It is a manifestation of diabetic retinopathy, which causes damage to retinal vessels and vision impairment. Considering the rates of diabetes, the number of cases of diabetic retinopathy in the United States is expected to nearly double by 2050, rising from 7.7 million to 14.6 million. Approximately half of all people with diabetic retinopathy will develop DME[21].

The treatment for diabetic eye disease is laser surgery. The patients suffering from diabetic macular edema are also at risk of cataracts and glaucoma.

### Retinal Detachment

The retinal detachment occurs mainly if too much accumulation of fluid occurs behind the retina leading to separation of the retina. There are other factors that cause retinal detachment.

1. Genetic predisposition
2. Eye injury
3. Previous cataract surgery
4. Extreme near-sightedness
5. Previous retinal detachment in the other eye
6. The presence of other eye disorders

Floaters are indicators of the progress of retinal detachment. In some situations, flashes in the eye may occur and if not treated, it can lead to the permanent vision loss[22]. Other symptoms are seeing a gray curtain in the vision field or decrease in vision.

### Retinitis Pigmentosa

It is genetic condition that causes retinal degradation. As the rods and cones die, the vision gradually declines[23,24]. The conditions classified under retinitis pigmentosa are Usher syndrome, Leber's congenital amaurosis, rod-cone disease, refsum disease and Bardet-Biedel syndrome.

In general, the rods are firstly affected then followed by degeneration of the cones. The early symptom is night blindness but in some situations colour blindness or central vision loss occurs. Since it is an inherited condition, young adults and adolescents are especially vulnerable to this condition.

## DRUG DELIVERY TO RETINA

The mode of drug administration affects the drug level attained in the posterior segment of the eye. The commonly employed modes of drug delivery to the retina are systemic

administration, topical administration, intravitreal injection local injections and ocular implants. Fig. 3 shows various routes of drug administration in retinal disorders.

The systemic drug delivery to the posterior segment of eye, mainly to the retina is difficult due to the presence of the BRB. Different strategies have been used for drug delivery to the retina[25–27]. An attempt has been made to increase transient permeability by modification of the barrier properties of RPE and the retinal endothelial cells by intracarotid infusion of hyper osmotic solutions like arabinose or mannitol. The osmotic gradient method is also used for nonspecific BRB opening but it leds to retinal and nervous system toxicity[28,29]. Chemical modification to the drug molecule is also a widely used method to overcome the BRB. In this approach the drug is converted to lipophilic prodrug so that its transcellular diffusion into the neural retina is increased[1,30].

## Systemic administration

The systemic delivery of drug for various ocular conditions has been attempted, but only 1 to 2% of plasma drug concentration has been is achieved in the vitreous humor. Due to very low level of drug there is requirement of frequent administration of higher doses to achieve minimum therapeutic concentration. Treatment of acute human cytomegalovirus (HCMV) retinitis, includes foscarnet sodium or ganciclovir[23]. The advantage of systemic administration is that it controls the spread of infection to other tissues but the disadvantage is nonspecific absorption by the other tissues may lead to serious toxicities. By considering the advantages and disadvantages of systemic administration for the treatment of ocular pathologies, it is not the ideal approach.

## Topical route of administration

Topical applications of ophthalmic solutions and ointments are efficient drug delivery systems for the anterior segment of the eye (aqueous humor, iris ciliary body and lens), Table I lists topical formulation strategies to improve ocular bioavailability. For drug delivery to the posterior segment of the eye after topical administration, the drug has to traverse through the cornea, aqueous humor and lens. The precorneal constraints also affect bioavailability. Elimination of drug from the anterior segment occurs through the ciliary body or canal of Schlemn.

In the anterior chamber, the enzymatic metabolism that takes place that is responsible for loss of drug before reaching the posterior segment. Following topical administration, attaining the therapeutic drug level in the posterior segment is difficult due to the presence of barriers. However according to reports, in the rabbit eyes therapeutic level of brimonidine (adrenergic agent) is achieved in the posterior segment after topical administration. This drug is used in glaucomatous neuropathy for retinal ganglion cell survival and neuroprotective action[56]. According to literature upon topical administration therapeutic levels of brimonidine were achieved in choroid, retina and vitreous. The BRB penetration is confirmed by the vitreal drug level, which is relevant for neuroprotection[56].

The entry of verapamil in the posterior segment tissue after topical administration in rabbits is reported by Siegner *et al* [57]. The drug concentration levels achieved were from lower to higher in serum, vitreous humor and aqueous humor respectively. But in treatment of infectious diseases such as endophthalmitis and CMV retinitis drug level does not reach minimum therapeutic level after topical administration.

Penetration studies of antibiotics from the systemic circulation to ocular fluids have confirmed that penetration to the vitreous is more restricted than penetration into the aqueous humor. Macha and Mitra studied aqueous and vitreous penetration of fluorescein (paracellular marker) in rabbits[2]. They observed as compared to aqueous humor only 1 to 2% of plasma drug level of fluorescein is achieved in the vitreous humor. Attempts have been made to improve plasma drug level by increasing the amount of dose administered and rapid infusion but it resulted in increased ocular levels, however there is concern of long term systemic toxicity.

## Intravitreal injections

Compared to the topical route, intravitreal administration offers certain advantages for drug delivery to the vitreous and retina. Intravitreal injection increases drug level in the posterior segment of the eye without causing systemic side effects. As this mode avoids BRB, therapeutic levels of drugs can be maintained with lower doses. In case of severe CMV retinitis and endophthalmitis intravitreal injection is the main therapy.

Intravitreal injection has become the backbone for treatment of posterior segment diseases over last 20 years. Antiviral drugs like acyclovir (ACV), ganciclovir (GCV) and foscarnet[58] cidofovir[59] and antibiotics like cefazolin, gentamicin[7], cephalexin and ceftazidime[60] have been administered via the intravitreal route because it allows to optimize pharmacokinetic parameters so as to design proper dose and dosing frequency for the effective treatment of endophthalmitis and CMV retinitis[61].

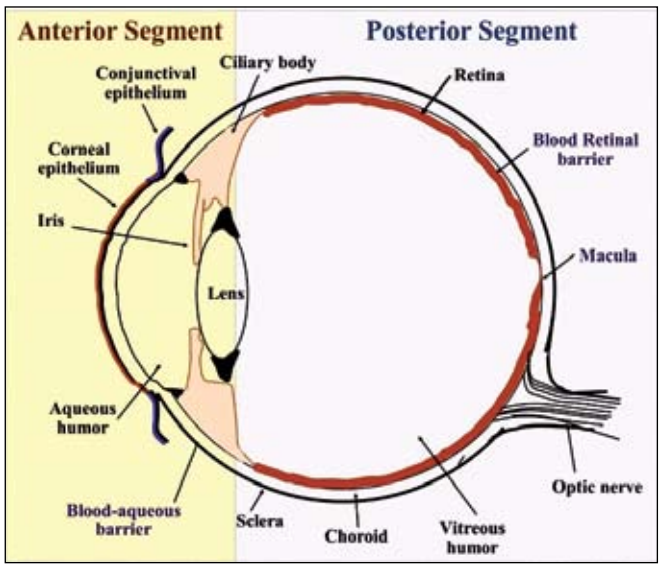


**Fig. 1: Schematic Representation of anatomy of Eye**

Intravitreal injection has major disadvantages like the need for repeated injections, patient noncompliance and infections associated with injections like endothalmitis which can turn to severe conditions like retinal detachment. Researchers have attempted to overcome these shortcomings by increasing the residence time of the drug in vitreous after injection. The liposomes, lipophilic ester prodrugs and microparticles have been used. The particulate substance administration has the risk of blurred vision and risk of infections. The disposition of GCV and its monoester prodrugs have been studied by Macha and Mitra[30]. They noticed that monoester prodrug of GCV generated sustained levels of drug in vitreous for longer periods of time compared to direct parenteral administration.

## Intravitreal implants

Direct intraocular injections overcome the problem of high intravenous dose related toxicity. However, multiple injections are associated with an increased risk of cataract, astigmatism, endophthalmitis, retinal detachment and vitreous haemorrhage[24]. Intravitreal implants have been developed as an alternative to multiple intravitreal injections. Vitrasert (Chiron Vision Corp., CA, USA) is a nonbiodegradable intraocular GCV implant. It is surgically inserted in the posterior segment of the eye, where it delivers GCV locally over a period of 5 – 8 months. Once the device is depleted of drug, it is replaced with a new device. Data from Chiron Vision Phase III trial demonstrated that disease progression was significantly delayed in patients implanted with Vitrasert compared to patients receiving intravenous doses of GCV[62]. However, the risks associated with intravitreal injections are not completely eliminated. Adverse reactions reported for Vitrasert include loss of visual acuity, vitreous haemorrhage, retinal detachment, cataract formation, lens opacities, macular abnormalities, intraocular pressure spikes, optic disk/nerve changes, hyphemas, uveitis and acute or delayed onset endophthalmitis. Also, repeated surgeries are required for implantation and removal of the implant. Like intravitreal injections, intravitreal implants release drug locally into the vitreous humor and may not be able to stem the spread of infections to the contralateral eye. Thus, systemic administration is recommended in conjunction with intravitreal injections and implants.

## Scleral drug delivery

The intravitreal injections and implants are associated with the risk of retinal detachment as result piercing for multiple injections and surgery. To overcome this issue, researchers developed scleral implants. It has been reported that sclera does not present a significant barrier for diffusion of drug into the vitreous. The sclera is found to be five times more permeable than the cornea. The passive diffusion is the primary mechanism of transscleral drug transport via the intracellular aqueous pore pathway. Rather than lipophilicity of the molecule, molecular size is the controlling factor in drug transport[63]. There are two ways of scleral drug delivery to the posterior chamber of eye.

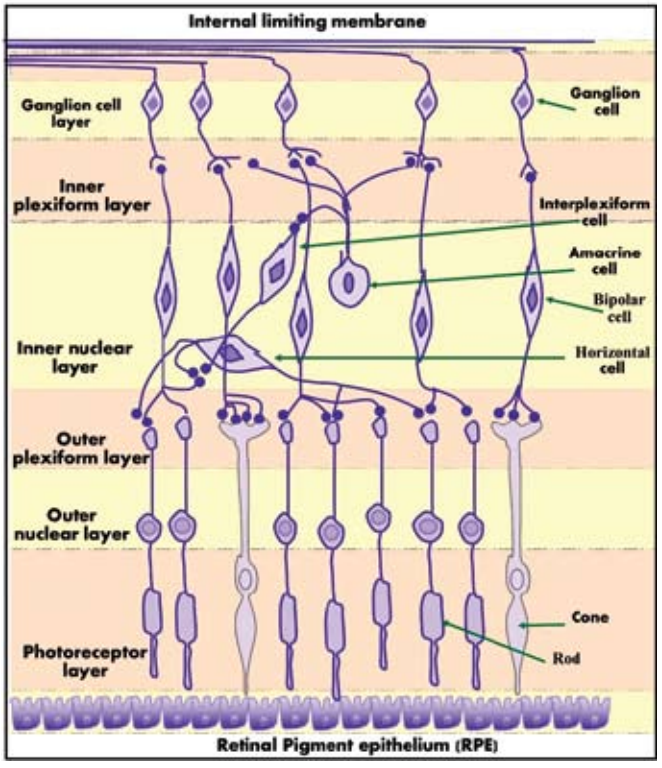


**Fig. 2: Schematic Representation of Anatomy of Retina**

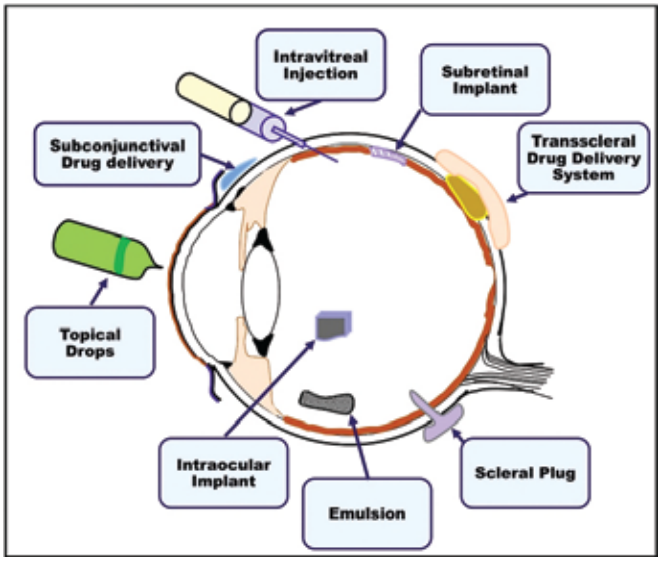


**Fig. 3: Potential current drug delivery for retinal diseases**

### a) Scleral plugs and implants

Sakurai et al. developed biodegradable inserts of poly (DL-lactide) (PLA) and poly (DL-lactidecoglycoide) (PLGA). Inserts were active in the HCMV inoculated eye for a period of 3 weeks. It reduced vitreo-retinal lesions compared to single intravitreal injection of GCV[63]. In other study different blends of PLGA and PLA were examined for suitability in implant[64]. The sustained GCV release over 24 weeks with therapeutic level above the minimum level without burst release effect for the entire period was obtained from PLA-70,000 and 5000 (80/20). The scleral implant can be used to achieve the sustained drug release. The disadvantages of such implants are patient discomfort due to the presence of a foreign body in the eye and the repeated operations involved[64].

### b) Subconjunctival injections

The targeting of drugs to the posterior segment of the eye can be achieved by subconjunctival injections. The sclera and the conjunctiva are the primary surfaces for absorption. The absorption of tilisolol (β-blocker) upon corneal, scleral and conjunctival application into the ocular structure was studied by Sasaki *et. al.*[65]. They observed higher plasma levels after conjunctival application. It can be concluded from the study that conjunctival absorption resulted in drug drainage into the systemic circulation. Scleral application resulted in increased drug level in the intraocular tissues as compared to conjunctival administration. The ocular pharmacokinetics of dacarbazine (anticancer drug) after subconjunctival and systemic administration was studied by Kalsi *et al*[66]. Upon subconjunctival administration elevated dacarbazine levels were observed in the vitreous and aqueous humor compared with intraviral administration.

Polymer based ophthalmic formulations were prepared to achieve sustained drug release of drug after subconjunctival drug injection. The biocompatible and biodegradable polymers are usually used for such purposes because polymers should not cause or induce inflammatory reactions in ocular tissues. The polymer should be degradable or erodible in a controlled manner to achieve zero-order release profile over a prolonged period. The polymers used in ocular drug delivery are pluronics, poloxamers, alginates, poly vinyl alcohol and polyorthoesters. The polymer's efficacy in providing drug release in subconjunctival administration is under investigation[67] biodegradable sustained release system for selected cases of glaucoma filtering surgery.

### Transporters And Transporter-Mediated Drug Delivery

Inspite of recent advances, drug delivery to the retina is still challenging because of several factors as this presence of MDR gene, lipophilicity and drug ionisation. The polar and hydrophobic properties of drugs (GCV, cidofovir, foscarnet) restrict their entry into retinal cell in conditions like CMV retinitis.

The entry into the cell by all active transport can be achieved by targeting the membrane transporters. This approach is successfully being used for improving the permeation of various molecules through biological membranes. In retinal drug delivery, after systemic, transscleral and intravitreal administration the intracellular drug concentration in retina can be increased by using this strategy.

A brief information on transporters and transporter mediated drug delivery and its applications in retinal drug delivery are discussed in following section.

### Transporters

In transporter mediated drug delivery, the drug molecules are targeted to membrane transporters for the effective passage of the drug across the cell membrane. Different nutrient transporters like amino acid, folate, peptide, monocarboxylic acid, organic amino, nucleoside, nucleobase and cationic transporters are usually targeted[68]. For targeting of parent drug to the membrane transporter, it is coupled with a promoiety which is an endogenous substrate for that transporter. The Promoiety

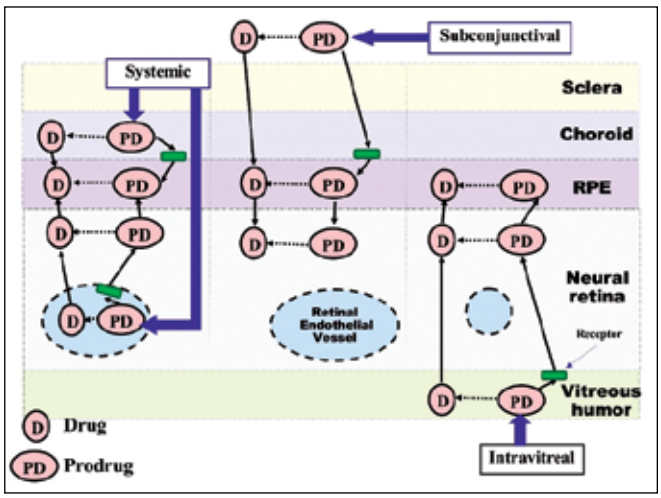


**Fig. 4: Routes of Prodrug administration (Adopted from Duvvuri S et. al.[1])**

is a transporter which translocates the prodrug across the cell membrane. Then, the drug is released from the transporter intracellularly via enzymatic cleavage of the drug ligand bond. There is no toxicity issue from the ligand as it is a nutrient.

By using this approach, the transporters expressed on RPE and neural retina can be targeted with drug after systemic and intravitreal administration respectively (Fig. 4). As compared to conventional lipophilic prodrug design, transport targeted prodrug design has higher solubility and higher dose administration potential.

Different nutrient transporters expressed on the retina include glucose[69,] peptide[70,] GABA, taurine, proline, nucleoside-like adenosine[71], glutamine, arginine, tryptophan and amino acids like glycine[72]. Among these transporters, those enhancing retinal drug delivery are discussed here.

### a) Peptide transporter (PepTs)

These transports have been identified on epithelia. The information about their substrate specificity and mechanism is available[73–75]. For small molecules like di- and tripeptides, PepT1 and PepT2 have broad substrate specificity[76–79]. For easy transport across the lipophilic membrane the drug molecule is converted to a substrate known as prodrug modification[78]. Due to this, the solubility of the substrate may be enhanced depending on type of amino acid selected in the peptide promoiety. After the transport, the enzymes like dipeptidase, aminopeptidases and cholinesterases present in the retinal and vitreal tissue cleave the prodrug and then the a parent drug is regenerated. The molecules like zidovudine, GCV and ACV after converting into peptide prodrugs result in a significant increase in the oral bioavailability of the parent drugs[79,80].

The studies confirm the presence of PepT on the RPE side facing blood and on the retina side facing the vitreous[70]. The intravitreal administration of transporters facing the vitreous could be targeted to increase the intracellular drug concentration and after systemic administration transporters present on the RPE can increase vitreal and retinal drug concentrations.

### b) Amino acid transporters

Amino acid transporters have been extensively studied on the blood brain barrier and the intestinal mucosa. These transporters are highly substrate specific and transport only specific amino acids. Different amino acid transporters such as glycine, tryptophan, glutamine, GABA and proline have been identified on the retina. The prodrugs can be designed for targeting the a carrier protein due to the expression of such a transporter system on the RPE or the retina[72].

### c) Monocarboxylic acid transport systems (MCTs)

The proton coupled MCTs take up and excrete pyruvate, monocarboxylic acids and lactate of mammalian cells[81]. The isoforms of MCT 1 to 9 have been identified. Monocarboxylic drugs transported through MCTs in the small intestine are pravastatin and salicylic acid[82–84]. The MCT transports carboxylate drugs and prodrugs after transscleral or systemic administration into the retina from the choroid or blood, respectively.

### d) Folate transport system

For entry of folate into the mammalian cell, two transport processes have been reported. In one process transporter protein along with multiple membrane spanning domains known as reduced folate transporter is utilized. Instead of folate, protein interacts more effectively with the reduced folate[86]. In the second process folate receptor binds and internalises bound folate through receptor mediated endocytosis. The liposome mediated drug delivery and the entry of anticancer drugs to cancer cells is facilitated by targeting them to folate receptors[87]. The drug level in vitreous can be improved by targeting them to folate receptors. As in most normal tissues, folate receptor is absent except in the placenta and in the choroid plexus or, present at low levels. Drug delivery to the retina can be achieved after systemic administration by using a folate ester prodrug[88].

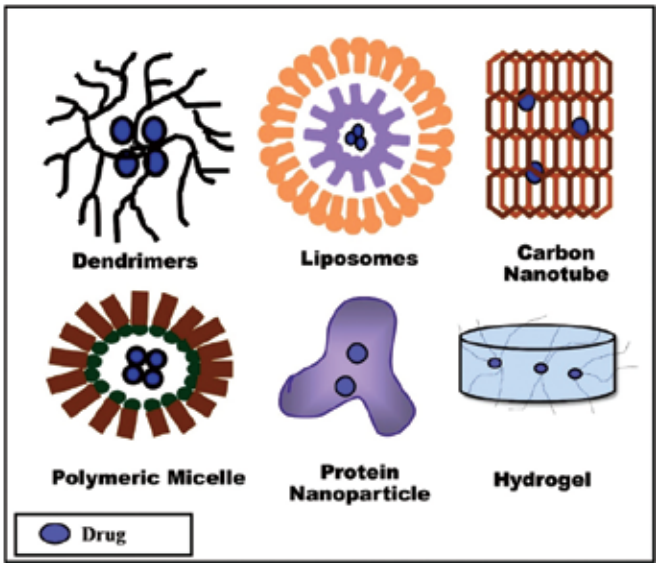


**Fig. 5: Nanotechnological approaches for drug delivery (Adopted from Sibo Jiang *et al.*[93])**

## Strategies to improve ocular bioavailability by transporter-mediated drug delivery

Expression of transporters on the retina, particularly the RPE and endothelial cells of the retinal blood vessels, provides us with an opportunity to increase the retinal and vitreal levels of various drugs, thereby increasing their efficacy and decreasing the required dose. Compounds can be targeted to the transporter by delivery through any of the three main routes as follows[1].

### a) Systemic administration of prodrugs

As discussed earlier, vitreal drug levels achieved upon systemic administration are around 1 – 2% of plasma levels. If a drug is targeted to a transporter expressed on the BRB, it could result in enhanced concentrations in the retina. Prodrug cleavage in the retinal cells may also facilitate greater drug levels in the vitreous humor.

The main disadvantage with this strategy is that drug uptake will be nonspecific, due to the possible distribution of the transporter at multiple tissues.

### b) Intravitreal administration

In order to avoid the nonspecific absorption of drugs into all the tissues and to avoid systemic toxicity, intravitreal administration of prodrugs may be justified. In this strategy the prodrug is injected directly into the vitreous humor, thereby targeting it to the transporter expressed on the retinal cell membranes. Prodrug uptake by the neural retina and RPE cells may be more efficient than the parent drug itself.

### c) Subconjunctival administration

Subconjunctival administration usually results in higher vitreal concentrations than systemic administration. Moreover, subconjunctival injections of particulate dosage forms may result in sustained drug release over a prolonged period of time, thereby decreasing the frequency of administration. This route may be used to deliver prodrugs targeted to specific transporters expressed on the basolateral side of the RPE. Following subconjunctival administration, the prodrug first diffuses into the sclera and then into the choroidal circulation,where it interacts with transporters expressed on the RPE. These transporters will then carry the prodrug into the retinal tissue, where it is cleaved into the parent drug. If the drug is incorporated into a polymeric vehicle, which controls the release of the prodrug, a sustained delivery of the drug to the retina and vitreous humor may be achieved[1].

## Nanotechnology in Retinal Drug Delivery

The Nanomaterials include nanosized particles with a size range of 1 to 100 nm. Different kinds of nanoparticles are used as tools in medicine[89]. The nanoparticles have a higher surface area to volume ratio as compared with other macroscopic materials hence they have greater capability of carrying different drug molecules and facilitate greater attachment to the targeting moiety. Different nanoparticles with different size, shape and chemical characteristics can be engineered for a wide range of applications. The solubility of poorly water-soluble ophthalmic agents can be improved by attaching it to nanoparticles. Targeting the drug to the retina by enhancement of cellular drug uptake is a tool for drug transport through biological barriers. It increases the residence time and protects the drug from degradation. Because of the different advantages of the nanomedicines, it provides on excellent platform for designing the drug delivery system that is non-invasive and can deliver drug to retina in sustained manner[89].

The commonly employed nanoparticles include synthetic polymers (dendrimers, polymeric micelles, hydrogel), proteins (albumin nanoparticles), lipids (liposomes) and inorganic compounds (Cerium oxide nanoparticles)[90]. Dendrimers are highly branched macromolecular structures while polymeric micelles are structures formed by self-assembly of amphiphilic copolymers with a hydrophobic core and a hydrophilic shell. Hydrogels are three-dimensional structures with

**Table II: Nanoparticulate drug delivery to eye**

| Nanoparticle type | Drug | Route | Application | References |
|---|---|---|---|---|
| Pentablock copolymer | IgG-Fab fragment | General retinal disease | Intravitreal | 99 |
| Light responsive | Nintebanib | Neovascularization | Intravitreal | 100 |
| Liposome | Rpe65 DNA | Rpe65 associated blindness | Subretinal | 101 |
| PMMA dendrimer | Carboplatin | Retinoblastoma | Subconjunctival | 43 |
| PLGA | Bevacizumab | Wet AMD | Intravitreal | 102 |
| Naked siRNA | Claudin-5 siRNA | Modulation of BRB | Systemic | 103 |

a high level of water content and having a network of hydrophilic polymers. The protein (like albumin) nanoparticles act by drug attachment to the protein surface. Albumin is a natural protein present abundantly in serum of most animals. Liposomes are the vesicles of lipid made up of lipid bilayer and enclose the aqueous core[47]. Due to presence of a lipid bilayer and hydrophilic core, liposomes have the capability to carry both hydrophilic and lipophilic drugs[91,92].

To use nanotechnology in ocular drug delivery different properties of nanoparticles like size, shape and material surface properties need to be considered. The size of nanoparticles should be large enough so that it should not rapidly leak into the blood vessels and small enough to penetrate through the biological barrier of the retina[94]. The study suggested that after intravitreal administration of 2 µm particles, particles remained in the vitreous fluid whereas for 200 nm sized particles, they uniformly distributed in the vitreous fluid and the inner limiting membrane of the retina. The 50 nm sized smaller nanoparticles were found in retina after two months of administration[95]. The nanoparticles with similar size but different surface properties show different distribution inside the eye. Hence a retinal drug delivery system can be designed by changing the surface properties and optimizing the physicochemical properties of nanoparticles[35]. For the drugs which cannot be delivered by other routes, their nanoparticles can be prepared for efficient delivery of such drugs. With the use of nanoparticles, there is a higher chance of drug reaching the target site at the back of the eye to treat the diseases affecting the retina. The clinical study for the safety and efficacy of nanoparticles are still in progress. Ideally the nanoparticles should be inert and biocompatible[34]. FDA has approved various polymers and excipients for human use like poly (ethylene glycol), poly lactic-co-glycolic acid (PLGA) and poly (hydroxyalkanoates) (PHAs). For ocular drug delivery chitosan, bovine serum albumin (BSA), poly acrylic acid (PAA) and Eudragit RS (ERS) have been used[96].

Despite the advantages of nanoparticles, there is a growing issue regarding potential toxicity of nanoparticles developed from the synthetic materials[97]. Recently published literature on nanoparticles claims minimal or no toxicity of nanoparticles to cell lines and animals but very few literature focus modified of nanoparticles associated with toxicity[98]. However, the toxicity of nanomaterials is to be examined in long term studies in future. Table II enlists various nanoparticulate drug delivery systems for the eye.

## Fundamental Breakthroughs In Development Of Drug Delivery To Posterior Segment:

### VITRASERT® (Ganciclovir insert)

Approval of the first sustained release posterior drug delivery system by FDA was in March 1996, 'Vitrasert®'. Vitrasert is a pellet of 4.5 mg ganciclovir coated with a biocompatible polymer by lamination for delivery of drug over long time for five to eight months[62]. This was for patients with acquired immunodeficiency syndrome (AIDS) for the local treatment of cytomegalovirus retinitis. The Vitrasert® was withdrawn from the European market on 2nd April 2002 voluntarily by the marketing authorisation holder but the generic product may be available in market[104].

### RETISERT® (fluocinolone acetonide intravitreal implant)

This intravitreal implant was approved by the FDA on 8th April 2005, for posterior segment chronic

**Table III: Recent advances in Posterior segment drug delivery systems**

| Sr. No. | Advance Drug Delivery System | Manufacturer | Market Status | Reference |
|---|---|---|---|---|
| 1 | Yutiq™ | Eye Point Pharmaceuticals | FdA Approved On 12th October 2018; Commercially Available On 4th February 2019 | 109 |
| 2 | Xipere™ | Clearside Biomedical | NDA Submitted To FDA On 19th December 2018 Phase 3 Trials Complete | 110 |
| 3 | Port Delivery System | Roche/ Genentech | Sept. 2018 Phase 3 Trial Began | 111 |
| 4 | Gb-102 | Graybug Vision | January 2019 Phase 1/2a Study Initial Data Analysis Reported Phase 2b Study Enrollment Expected In 2019 | 112 |
| 5 | DexAmethasone Intravitreal Implant (Ar 1105) With Print® Technology | Aerie Pharmaceuticals | Ar-1105 Phase 2 Trial Began In Early 2019; Ar-13503 (Rho Kinase/Protein Kinase C Inhibitor) Phase 2 Trial To Be Initiated In June 2019 | 113 |

non-infectious uveitis. It is 0.59 mg sterile implant constructed to release fluocinolone acetonide locally to the posterior segment at an initial rate of 0.6 µg/day and decreasing after the first month to a steady state of 0.3-0.4 µg/day for approximately 30 months[105]. It is a synthetic corticosteroid fluocinolone acetonide drug. This drug delivery system controls inflammation effectively but it requires surgery for its placement. It also has side effects such as increase in intraocular pressure (IOP) and cataract which require additional surgery for control[106].

### Ozurdex® (Allergan)

It is a sustained release biodegradable intravitreal corticosteroid implant of 0.7 mg dexamethasone for six months treatment. On 17th June 2009, FDA approved this for the treatment of macular edema followed by retinal vein occlusion. Afterwords, it was approved for non-infectious uveitis of the posterior segment of the eye in 2010 and for diabetic the macular edema in 2014[107]. Allergan voluntarily recalled 22 lots of this dosage form after noting detachment of approximately 300µm diameter of silicon particle from needle sleeve during administration[106].

### Iluvien® (Alimera)

It is a non-bio erodible, sustained-release intravitreal implant approved by the FDA on 26th September 2014 for diabetic macular edema treatment. It is capable of continuous 36-month treatment of low dose corticosteroid after single injection[108].

## Advances In Posterior Segment Drug Delivery Systems

Table III lists recent advances in posterior segment drug delivery. The table is followed by a detailed discussion.

### YUTIQ™

YUTIQ™ (fluocinolone acetonide intravitreal implant) is indicated for the treatment of chronic non-infectious uveitis affecting the posterior segment of the eye. It is a non-bio erodible intravitreal implant containing 0.18 mg fluocinolone acetonide, designed to release fluocinolone acetonide at an initial rate of 0.25 mcg/day, and lasting 36 months[109].

### XIPERE™

It is a suspension of corticosteroid triamcinolone acetonide for the treatment of macular edema associated with uveitis and administered through the back of the eye through suprachoroidal injection in the space between choroid and sclera. It is a proprietary treatment approach for rapid dispersion of drug at the back of the eye to reach adequate drug concentrations and stay at the a site of disease. It has potential to act for a longer period and minimizes harm to healthy parts. This approach provides the efficacy and requires less treatments[110].

### Port Delivery System (PDS)

Ranibizumab (PDS) is the port delivery system of Genentech. It is a small device which is refillable,

slightly longer than a rice grain. It is uniquely designed for continuous delivery of ranibizumab over time and surgically implanted in the eye.

In the standard treatment patient with Age Related Macular Degeneration (AMD), monthly eye injection PDS was developed to reduce frequent eye injections. It allows the people with wet AMD to refill the implant.

In the patients using PDS, it requires six months or a longer time for the first refill of the implant. In patients with a high dose, PDS has achieved the same vision outcome as ranibizumab eye injection[111].

### GB-102

GB-102 is a depot formulation of sunitinib malate encapsulated in bioabsorbable microparticles intended for treatment of patients with wet AMD (leading cause of vision the loss in adult) via the intravitreal (IVT) route. It is next generation therapy for retinal diseases which has a drug-elution profile supporting twice a year IVT injections, hence, reducing the care associated with frequent injection. The sunitinib is a tyrosine kinase inhibitor (TKI) receptor blocker that potentially blocks the intracellular receptor which is known to be associated with proliferation, angiogenesis, fibrosis and vascular permeability. The sunitinib is also known to demonstrate neuroprotective effect to retinal ganglion cells and photoreceptors during preclinical models of neural injury[26]. In this depot formulation, the microparticles aggregate into a biodegradable depot in the inferior vitreal cavity. The unique surface treatment of formulation minimizes the inflammations observed with traditional PLGA microparticles. Graybug is also planning development of GB-102 in other diseases of the retina including retinal vein occlusion (RVO) and diabetic macular edema (DME)[112].

### Dexamethasone Intravitreal Implant (AR-1105) with PRINT® Technology

AR-1105 is biodegradable intravitreal PRINT® manufactured implant of steroid dexamethasone. The implant is expected to provide a six month duration of action and reduces multiple injections and care associated with other treatments of DME. Aerie filed an Investigational New drug (IND) application for AR-1105 in December 2018. The FDA has reviewed the IND and it is in effect. The Phase 2 Trial was initiated in March 2019 for treatment of macular edema due to retinal vein occlusion (RVO)[113].

## CONCLUSION

Drug delivery to the retina remains a challenge to all professionals treating retina ailments like Age related macular degeneration, Diabetic macular edema, Retinal pigmentosa, Retinal detachment and Floaters. In this review, we have attempted to give a comprehensive overview of treatment approaches developed by researchers to overcome challenges and the barriers associated with posterior segment especially retinal drug delivery with their advantages and disadvantages. This review has attempted to describe the magnitude of the challenges, efforts of researchers to accomplish safe and efficacious drug delivery to the retina.

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