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CARRIER CENTRIC APPROACH OF TARGETING DRUGS TO THE POSTERIOR SEGMENT OF THE EYE

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ABSTRACT

Posterior segment of the human eye remains the focal target of majority of diseases and disorders risking reduced visual activity or blindness. Successful targeting of posterior segment of the eye has been explored using various biodegradable and non-biodegradable implants, and direct intervention using injections, with exemplary effect. But, often these models are affiliated with serious complications, namely vitreous haemorrhage, retinal detachment, cataract, and endophthalmitis. Novel lipid and polymer based carrier loaded drug delivery systems along with the improved drug delivery techniques such as dendrimers, iontophoresis, microneedles etc., more compliant with the frangible structure of human eye, are part of the revolutionised targeting strategies to the posterior eye. These profound, sustained drug delivery strategies can also be successfully modulated to improve the bioavailability of the drug in posterior segment of human eye. As a result, the uncomplicated topical administration using such novel drug delivery systems is currently under vigorous experimental scrutiny.

Keywords: Routes of delivery, Barriers, Posterior eye disorders, Biomaterials, Liposomes, Nanoparticles, Nanomicelles, Implants, Contact Lenses, Iontophoresis, Gene delivery

INTRODUCTION

Ocular drug delivery is an intricate and challenging task. To formulate drugs catering to the ocular system, the atypical structure of the eye is required to be studied closely (Fig. 1).

The various barriers and limitations to drug delivery and the systems which can encompass those limitations to reach the desired site of action, need to be closely studied as well (Table No. 1).

From drug delivery point of view, the eye is majorly segmented into anterior and posterior segments. Anterior segment of the eye is the starting 1/3rd portion consisting of the optical region preceding vitreous humor. It comprises of cornea, pupil, aqueous humor, iris, lens, and ciliary body. Posterior segment is the latter 2/3rd portion of the eye that mainly includes sclera, choroid, retina, vitreous humor, macula, and optical nerve. The majority (about 90%) of the ocular preparations available in the market are for topical administration. The corneal and non-corneal routes following topical drug instillation, offer a number of barriers to drug permeation. These barriers include physical barriers viz., epithelium, stroma and endothelium, and chemical barrier viz., the polarity of the individual layers. Simultaneously, several factors associated with topical instillation (such as precorneal drainage, tear turnover, etc.) contribute to significant drug loss. As a result, at an average about 5% of the drug reaches the target site. This calls for major technological transformation of ocular drug delivery systems to form targeted drug delivery systems, especially in the posterior region of the eye. The posterior region is a secluded area and the major site for most of the current day ocular eye disorders (Table No. 2).

Conventional and carrier focused targeting routes to the posterior segment of the eye have been discussed in the present review to gain a better apprehension of the current day scenario of

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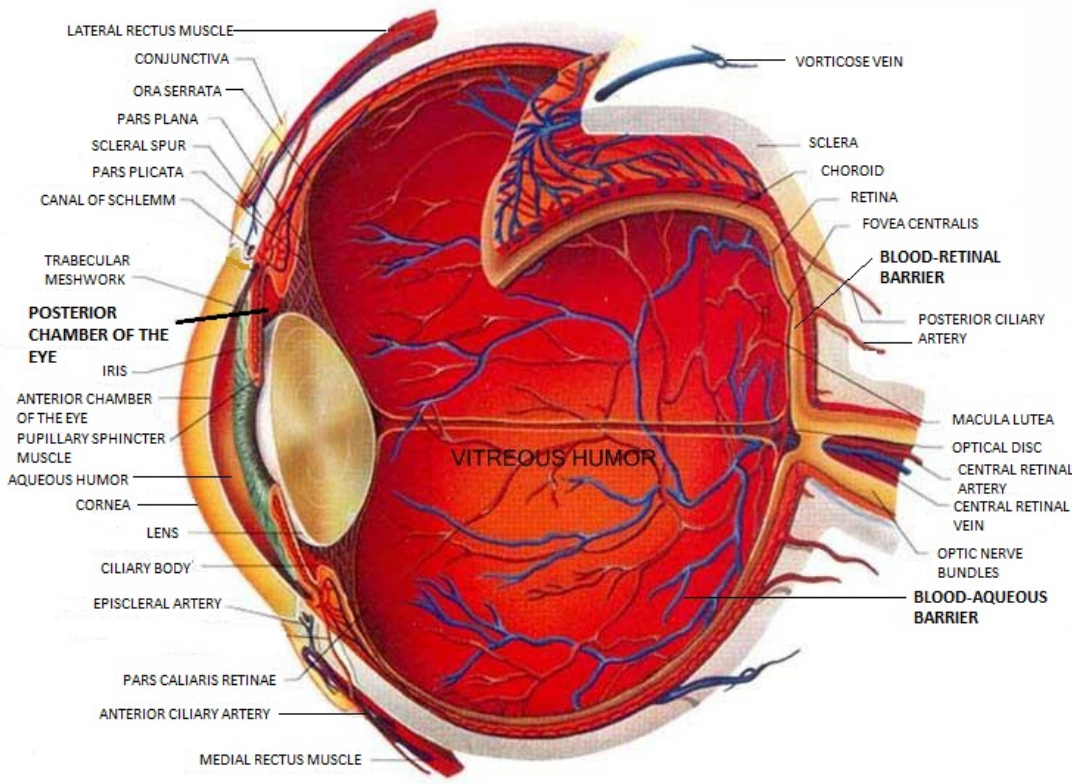

Fig. 1 Detailed structure of the human eye with the barriers limiting specific targeting of therapeutic agents to various regions. (Retrieved from http://www.myeyeworld.com, with modifications)

targeted ocular drug delivery systems.

CONVENTIONAL ROUTES TO TARGET POSTERIOR SECTION OF EYE

Non-invasive routes

Non-invasive routes of drug delivery to the eye include drug administration without destruction to healthy tissue, usually by not involving invasive medical procedures such as injection to the eyes. The restrictions to targeting posterior segment of the eye by conventional routes are summarised in Fig. 2. The routes of drug administration falling under this category are as follows:

Topical delivery: The inaugural invention for treating ocular disorders began with the advent of topical formulations in the form of liquids, solutions, emulsions, suspensions and ointments[1]. This mode of drug delivery required frequent instillation of large doses to attain therapeutic concentrations in the posterior segment of the eye[2]. Albeit this, about 90% of the administered drug drained out as a result of tear turnover, nasolacrimal drainage, and tear dilution, engendering less than 5% ocular bioavailability[3,4]. Drug absorption ensued by two major routes: Corneal route (cornea to intraocular tissues via aqueous humor), and non corneal route (crossing conjunctiva, sclera and retinal pigment epithelium)[5]. Additionally, limited volume of administration (30 µL), metabolism of active pharmaceutical ingredient by tear enzymes, unfruitful uptake into systemic circulation through the profoundly vascularized conjunctiva, uveal tract and inner retina, anterior membrane barriers, aqueous humor outflow, and factional long diffusion path, negatively impacts the pharmacokinetics and distribution of topically applied drugs[6].

Systemic/Oral delivery: It is drug absorption following systemic administration as tablets, capsules or intravenous injections. Drug absorption through this route is limited by the blood retinal barrier (BRB), which is only selectively permeable to highly hydrophobic molecules[7]. Oral delivery alone or in combination with topical delivery has remained an accepted patient compliant route for chronic retinal disorders. However, it is requisite for the molecules to be able to cross the blood aqueous

Table No.1: Anatomical and physical barriers to targeting drugs to posterior segment of eye, and the systems commonly implemented to surpass the barrier selectively

BARRIER	EXPLANATION	SYSTEM THAT SUSRPASSES IT	REF.
Inner Limiting Membrane	Vitreous humour to inner retinal layers composed of matrix proteins. Layers rich in glycosaminoglycans which bind to cationic molecules and limit their transport through the retina.	Intra-vitreal injection	[13]
Blood Retinal Barrier	Composed of retinal capillary cells and retinal pigment epithelium (RPE) cells. RPE restricts entry of cells from choroid to retina.	Selectively permeable to highly hydrophobic drug with frequent dosing	[101, 103]
Blood Aqueous Barrier	Present in the ciliary epithelium. It prevents the passage of plasma proteins to the posterior segment of eye.	Intra-vitreal injection	[77]
Corneal Epithelium	Anterior most layer, blocks exogenous substances, composed of epithelium, stroma, endothelium.	Low permeability, optimum logD value between 2-3	[44]
Conjunctiva	Conjunctival blood capillaries and lymphatics cause loss to systemic circulation.	Suprachoroidal delivery	[29, 102]
Efflux transporters	These are membrane bound proteins that work by effluxing the molecules out of cell membrane and cytoplasm and hence lower the bioavailability. Eg. P-gp, MRP, BCRP (on ocular tissues).	Drug specific	[103]
Protein binding	To melanin, tissue proteins.	Drug specific	[108]
Diffusion through vitreous chamber	Viscoelastic connective tissue composed of glucosaminoglycans and phagocytic cells-hyalocytes. Acts as reservoir or temporary storage depot. Hydrophilic drugs have prolonged half lives.	Injection or iontophoresis	[8, 13, 96]
Sclera	Positively charged molecules exhibit poor permeability presumably due to their binding to the negatively charged proteoglycan matrix. Inversely proportional to the molecular weight as well as lipophilicity of drug molecules.	Trans-scleral delivery	[85, 107]
Choroid	Choroidal cells of choroid plexus.	Intra-vitreal injection	[103, 99, 45]

barrier (BAB) and BRB to reach the targeted site (Table No. 1)[8]. To overcome such barriers large doses of the drug is required, which climactically prompts increased systemic toxicity, and adverse drug reactions. Bioavailability via systemic route varies between 1-5% [9]. Intravenous delivery of drugs also falls under this category.

Invasive routes

Invasive routes of drug delivery to the eye include drug administration involving invasive medical procedures such as injection to the eyes. Such procedures may cause infiltration and destruction to the healthy tissues, which fall in the way of the delivery route. The routes of drug administration under this category are as follows:

Intra-vitreal delivery: It is a direct injection of the drug formulation as solution, suspension, depot or implants, through the pars plana with a 30-G needle into the posterior section of the eye[10]. Such delivery warrants high drug concentrations in the retinal neurons, and attenuates side-effects owing to direct interaction. However, the drug distribution is not uniform. Smaller molecules rapidly diffuse through vitreous fluid, whereas the distribution of macromolecules is restrained.

Table No. 2: List of chronic, acute, degenerative, and fatal posterior eye disorders with selective drugs used for their treatment, and the conventional route for targeting.

DISEASE/ DISORDER		DRUG(S) FOR TREATMENT	TARGET ROUTE	REF.
Degenerative Diseases	Age-related Macular Degeneration (AMD)	Pegaptanib sodium	Intravitreally	[99]
	Retinitis pigmentosa	Diltiazem	Oral	[103]
	Retinoblastoma	Cisplatin	Subconjunctival	[106]
	Glaucoma	Acetazolamide, Pilocarpine, Timolol, Brimonidine	Topical	[61]
Inflammatory diseases	Uveitis	Prednisolone	Topical	[83, 87]
	Diabetic macular oedema	Ranibizumab, Bevacizumab	Intravitreal	[103]
	Optic neuritis	Prednisone, Methylprednisolone	Topical, Injection	[104]
Vascular diseases	Diabetic retinopathy	Ranibizumab, Bevacizumab	Intravitreal	[103]
	Retinal vein or arterial occlusion	Blood pressure medication cholesterol medication improved diabetes control laser surgery for abnormal vessel growth in the eye	Topical, oral, surgical	[103]
	Retinopathy or prematurity	Anti- VEGF, Vitrectomy	Topical	[19]
	Age-related Macular Degeneration (AMD)	Ranibizumab	Intravitreal	[99, 45, 82]
	Choroidal neovascularisation	PKC412, Dendrimerporphyrin micelles, RNA aptamer	Periocular, Intravenous, transcleral	[92]
Proliferative diseases	Proliferative vitreoretinopathy	Repository steroids	Topical, subconjunctival	[103]
Infectious diseases	Endophthalmitis	Vancomycin, Ciprofloxacin	Topical	[103]
	CMV retinitis	Ganciclovir	Intravitreal	[103, 105]
Others	Post glaucoma filtering surgery	Dexamethasone, 5-Fluorouracil,	Subconjunctival	[12, 14, 35]
	Post cataract surgery	Dexamethasone	Intravitreal	[45, 83]

Additionally, drugs with molecular weight less than 500 Da (when administered intravitreally) are drained off from the site of application with a half-life of less than 3 days[11]. This connotes a need for frequent injections. Inevitable complications such as vitreous haemorrhage, retinal detachment (0.05% cases), cataract, and endophthalmitis (0.2% cases) are associated with this route of delivery[12]. Moreover, such regimens are painful, invasive, require hospitalization, and specially trained physician for administration, adding to the cost and discomfort of the patient. To reduce complications, biodegradable and non-biodegradable implants can now be effectively placed intra-vitreous for sustained release therapies[13].

Periocular delivery: Periocular route pertains to the administration of drug to the area circumambient to the eye[14]. It includes:

- Sub-conjunctival delivery- Introduction of an active ingredient beneath the conjunctiva where the conjunctival epithelium is the rate limiting barrier for water soluble compounds.
- Sub-tenon delivery- Injection into the tenon's capsule located under the upper portion of the eye and into the belly of the superior rectus muscle. This technique is chiefly used for anaesthesia during ocular surgery.
- Retro-bulbar delivery- Injection in the conical compartment within the rectus muscles and the intramuscular septa. These injections cater

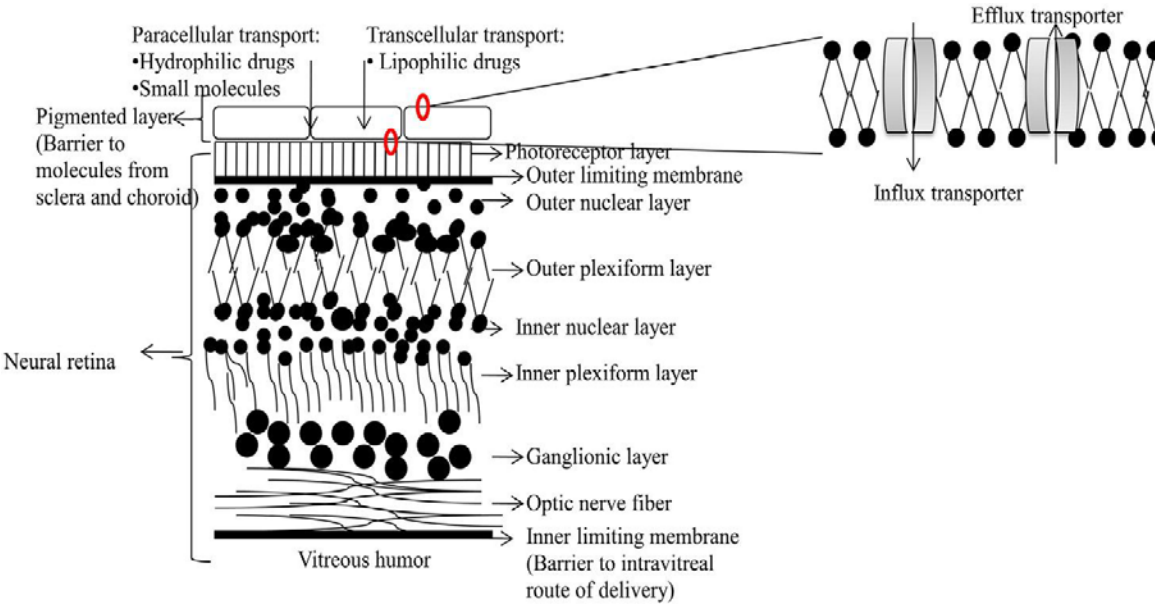

Fig. 2 Layers of the retinal pigment epithelium (RPE) outlining barrier limitations to drug delivery to the posterior region of the eye

high local drug concentration with minimum effect on intra-ocular pressure (IOP).

- Peri-bulbar delivery- Injection in the extracellular spaces of the rectus muscles and their intramuscular septa. Despite being safer, this route is less effective than retro-bulbar route.
- Trans-scleral delivery- This route bypasses cornea-conjunctiva barrier and provides a less invasive route of administration than intra-vitreal delivery. Diffusion through the human sclera is facilitated owing to its hypocellular nature, high permeability for both low and high molecular weight drugs to the retina (depending on their lipophilicity), and large surface area (17.0 ±0.5 cm2) i.e. about 95% of total eye surface[15]. Transscleral route may be convenient for the delivery of biotechnologically prepared drugs to the retina and vitreous, if appropriate delivery systems are developed.

Scope of periocular drug delivery: A better retinal and vitreal drug bioavailability (about 0.01–0.1%) is achieved through periocular route, in comparison to the topical route of application (about 0.001% or less)[16]. Consequent periocular administrations under local anaesthesia are possible without direct interference with the vision. Volumes as high as 500–5000µl of drug solution can be administered in humans as opposed to only 50–100µl being administrable through intra-vitreal route. There is evidence to suggest higher concentrations of drug in the ocular tissue following periocular routes of administration compared to intra-venous, topical and oral administration[17,18]. Sustained release drug delivery systems are feasible employing periocular route, but several anterior segment side-effects like increased IOP, cataract, hyphema, strabismus, and corneal decompensation have been reported[19].

Suprachoroidal delivery: Placement of therapeutic drugs in the suprachoroidal space (SCS), which is the space found between sclera and choroid, with the help of injections is called suprachoroidal delivery. The SCS can be accessed by surgically cutting through the conjunctiva and sclera, and intricately affixing a catheter to the SCS behind the macula[20,21]. Recent studies indicate the use of microneedle to penetrate the sclera, and delivery of drug suspension or solution into the SCS[22, 23]. SCS delivery provides higher bioavailability, higher local concentration of drug in the choroid, lesser side-effects due to focal targeting, and no obstruction of the visual axis. SCS injections are mainly efficient in treating choroidal diseases, compared with intravitreal injections, pertaining to direct delivery to choroid target tissue. However, high blood flow in the chorio-capillaries acts as a sink that washes away active ingredient delivered in the SCS[24, 25]. Thus, SCS injections may prove their significant best when used with sustained-release delivery systems.

Subretinal delivery: Delivery of drugs directly in the extracellular space that exists between the photoreceptors of the retina and the retinal pigment epithelium (RPE) layer is called subretinal

delivery. Subretinal delivery overcomes the barrier properties of the retinal inner limiting membrane (ILM) and also successfully pervades the RPE. Subretinal delivery of macromolecules to the retinal cells is an established targeting technique in gene therapy. Subretinal injections are usually administered through transcorneal (through iris-lens-vitreous), or transscleral (through pars plana-vitreous) routes[26, 27, 28]. Subretinal space injection is in use clinically, but long-term safety of this route of drug delivery is still speculative, as it may result in detachment of the photoreceptors from the RPE, and cause irreversible death of photoreceptors if not reversed quickly[29].

CARRIER FOCUSSED TARGETING TO THE POSTERIOR SEGMENT OF EYE

Drug loaded in a carrier system may be specially designed to serve specific advantages to the delivery system, such as: improved bioavailability, improved effectiveness by reduced drug metabolism, lower toxicity and side-effects, and/or sustained release action. Such carrier systems have been discussed as follows:

Liposomes: Liposomes are vesicular systems which comprises phospholipid bilayers (natural or synthetic) of size in the range 10nm-1µm, or even greater. Liposomes are structurally classified based on the number of phospholipid bilayers, and liposomal size, e.g. small unilamellar vesicles (SUVs, 20nm-200nm), or multilamellar vesicles (MLVs, >0.5µm), large unilamellar vesicles (LUVs, 200nm-1µm), and giant unilamellar vesicles (GUVs, >1µm)[30,31]. Liposomes can encapsulate both lipophilic and hydrophilic molecules. Drug loading capacity of liposomes is decided by a number of aspects such as: size, nature of lipid, physicochemical properties of active pharmaceutical ingredient, and method of preparation.

Liposome encapsulated drug is delivered when phospholipase and high density lipoprotein (HDL) present in blood erodes phospholipid layers of liposome causing vesicle damage, and hence releasing encapsulated drug in the cell. The rate of drug release is dependent on the stretch of liposomal membrane erosion[32]. It has also been studied that liposomes follow the non-corneal route in order to target the inner regions of the posterior eye.

Liposomes are stable, biocompatible, and biodegradable liquid preparations. The colloidal nature is a characteristic feature of these carrier systems enabling a much more effective permeation through ocular epithelium layers. Additionally, the surface properties of lipid emulsion are a deciding element for permeation and drug delivery. Various surfactants and biocompatible lipids play a major role in defining these surface properties. For liposomal drug delivery system, particle size also holds a deciding effect in intraocular delivery to posterior eye. A particle size of 100nm or below in colloidal systems is considered optimum.

Immunoliposomes of antiviral drugs (ganciclovir, iododeoxyuridine) for treatment in herpes simplex viral (HSV) infections showed higher transcorneal permeability than conventional routes. Liposomal solutions also had higher drug concentration in the vitreous humour resulting in much advanced ocular tissue distribution[33]. Encapsulating antisense oligonucleotides in liposomal system to treat cytomegalovirus (CMV) retinitis has been found to be much more effective in targeting human retina. Research has showed that 37% of antiviral oligonucleotides in the form of liposomes were retained in the vitreous humor even fifteen days after administration. In another finding, investigators reported 4 times increased *in vitro* flux from penicillin G-loaded SUVs[34].

Liposomal drug delivery is an effective route to provide sustained release for prolonged effect. Liposomes epitomize the first injectable systems for intravitreal drug delivery. Additionally, liposomal formulations show decreased tissue toxicity, and increase the intravitreal $t_{1/2}$ of drugs by minimising rapid clearing from vitreous cavity. Liposomes administered via subconjunctival injection furnish absorptive effect and constant release at delivery site achieving higher drug concentrations. Subconjunctival delivery has added benefit of less frequent administrations and improved patient compliance[35,36]. Recently explored ways of targeting liposomes to posterior segment of eye are as follows:

- Liposomes topical solution- improved transcorneal permeation
- Liposomal hydrogel- five-fold transcorneal permeation
- Liposomes attached to contact lens- drug release by first order for >6 days
- Liposomes periocular immunization
- Uncharged and surface charged liposomes- positively charged liposomes reduce IOP and show sustained effect compared to negatively charged liposomes
- Rhodamine conjugated liposomes- these get internalized by glial cells in retinal muller and macrophages

- Cationic liposomes- improve transfection effectiveness of pDNA
- Cationic lipoplexes- cationic lipoplexes with PEG of size >500nm show excellent vitreous movability

Furthermore, research can be done using surface-modified liposomes to explore targeting of posterior eye disorders by direct intervention of receptors present on the cornea and retina.

Nanoparticles: Nanomedicine has revolutionised the genre of ocular therapy and treatment. The use of nanoparticulate systems—nanoparticles, nanomicelles, solid-lipid nanoparticles, nanostructured lipid carriers, and nanoemulsions, with size upto 1000nm have been explored as an appropriate, safer, and more effective substitute to conventional options[37,38].

Nano-carriers bypass various ocular barriers owing to their peculiar structure and small size, and help in transport of drugs more efficiently to the posterior segment of the eye[39]. Nano size avoids irritation, which is generally an issue with microsized ocular suspensions[40]. Moreover, significantly improved biopharmaceutical properties such as solubility, stability, permeability, retention at the application site, and sustained release of drug for a prolonged period are few other benefits of incorporating the drug in a nanoparticulate system. Such advantageous features of a nanoparticulate carrier system is complemented with a simple and inexpensive sterile production by using methods like aseptic filtration (particle size usually less than 100nm), and also by the use of an autoclave[41,42]. Both lipophilic and hydrophilic drugs can be embodied in a nanoparticulate system using different methods of preparation.

Nanosized targeted formulations may be of various types, such as:-

Polymeric nanoparticles (PNPs): These are polymer based colloidal particles which adsorb, absorb, attach, or encapsulate (dissolve or disperse) drug molecules[43]. The polymers used can be of synthetic or natural, biocompatible origin. PNPs formulated from natural materials like albumin are biodegradable, nontoxic, and nonimmunogenic. Hence, these materials cause minimal side-effects and complications. Fluorescent-labelled PNPs were studied to be internalized into the retina, which remained in the RPE cells for about four months without any toxic effect following a single intravitreal injection[44]. Zhang *et al.* showed that the dexamethasone-PLGA nanoparticle prolonged the drug release for at least 50 days in the rabbit eyes, with somewhat constant drug concentration for a month in the vitreous humour ($Conc._{mean}$ of 3.85 mg/L)[45]. PNPs can also achieve cellular delivery either through endocytosis or phagocytosis, providing internal capture of entrapped material, which could be proteins, DNA, siRNA, lipids, and organic/inorganic substances. They additionally provide protection to the molecular integrity of the encapsulated therapeutic agent, thereby preventing their rapid *in vivo* degradation[46]. PLGA nanoparticles have been shown to evade the endo-lysosomal formation, hence providing protection to the genetic material.

Mucoadhesive nano-carriers: Mucoadhesive nano-carriers have multiple advantages as methods of targeting posterior segment, pertaining to the increased precorneal adherence of the drug while simultaneously being drug permeability enhancers. For improving the retention of the liposomes on the corneal or conjunctival surface, liposomal dispersion is formulated in mucoadhesive gels or a coating of mucoadhesive polymers[47].

Nanomicelles: Polymeric micelles are nanosized (10 to 100nm) self-assembly of amphiphilic block copolymers above critical micellar concentration (CMC). They contain a hydrophobic core (encapsulates lipophilic drugs), and hydrophilic shell (traps hydrophilic drugs)[48]. The shell is responsible for micelle stabilization, and in particular circumstances interact with biomembranes. Amphiphilic block copolymers can be surface modified to induce bioadhesion, increase stability by protection against ocular enzymes, and to modify or sustain drug release kinetics. The advantages of using nanomicellar system are: enhanced solubility of hydrophobic drugs, nanosize for limited irritation to ocular tissues, scope of formulation as an aqueous dispersion, minimization or prohibition of drug degradation, lower adverse side-effects, and improved drug permeation through ocular epithelia. This beneficially leads to enhanced ocular bioavailability[49]. Polymers such as polyethylene glycol, i.e., PEG derivatives are most commonly used shell-forming agents. These polymeric micelles have been studied to have better stability than surfactant micelles even on intravenous injection due to low CMC (1000 fold) values (10^{-6}–10^{-7} M) as compared to other surfactants[50,51].

Solid lipid nanoparticles (SLNs): These comprise a nanosized solid-lipid core matrix stabilized by a layer of surfactants (emulsifiers). SLNs offer various benefits over other conventional colloidal

carriers, *viz.*: controlled drug release, encapsulation of both hydrophilic or lipophilic drugs, long-term stability, high encapsulation efficiency, prevention or limited degradation of active therapeutic entity, biocompatibility pertaining to the use of physiological lipids, easy sterilization by autoclaving, and easy scale-up for large-scale production. Moreover, due to their nano size (~10-100nm), and lipidic nature, SLNs can effectively diffuse through corneal epithelium barrier, and attain higher ocular drug concentration by enhanced corneal absorption. As a result SLNs provide improved ocular bioavailability, prolonged ocular retention time, and a sustained drug release profile[52]. SLNs consisting of tranfecting non viral genes have been studied on *in vitro* cells with positive results, which include nonviral gene vectors such as protamine, dextran, and plasmid pCEP4-RS1. These transfecting non viral genes were also studied for their ability to transfect *in vitro* ARPE 19 cells with marginally good results in producing retinosquisin (deficiency causes X-linked juvenile retinoschisis). These vectors showed ability to transfect ocular cells following topical application as eyedrops. The productivity to transfect RPE cells along photoreceptors was also compared for subretinal and intravitreal injections of the formulated SLNs with vectors with promising results[53].

Nanostructured lipid carriers (NLCs): These are the enhanced version of solid lipid nanoparticles with controlled nanostructuring of solid lipids with spatially discordant liquids forming the lipid matrix. The result is augmentation of encapsulation efficiency (drug load), and also restriction of its discharge[54]. These nanoparticles stick to the surface of the eyes and show retention intrinsically as well as by interacting with the epithelium due to their physiochemical characteristics, such as size, shape, and surface charge[55].The impressive targeting of the posterior eye disease can be achieved through intrinsic characteristics of surface adhesion, improved surface area, and smooth particle size. A mixture of hydrophilic and lipophilic surfactants is observed to increase stability, and also increases the range for combined hydrophilic and lipophilic loading of the drug.

NLCs have an edge due to their reduced precorneal drug loss pertaining to bioadhesion, and hence sustained drug delivery. They can be dispensed by least invasive route of ocular topical instillation with augmented ocular absorption. This route as a hopeful approach to target retinal and other posterior eye diseases has been investigated by *in vivo* tests on the models of mice[56].

Nanoemulsions: Nanoemulsions are composed of two immiscible liquids out of which one liquid is dispersed as droplets in another liquid, and stabilized by the use of surfactants over a wide range of varied oil to water ratios[57]. This homogeneous system is a low viscosity fluid which can be topically applied to the eye. The surfactant in combination with a suitable co-surfactant reduces the interfacial tension and facilitates dispersion during the formulation process. This results in a nanoemulsion comprised of a flexible film that can readily deform around the droplets[58]. Such a surfactant-co-surfactant system beneficially shows enhanced membrane permeability, increased drug uptake, and hence facilitated corneal permeation[59]. The choice of surfactant, oil, and co-surfactant should be so as to provide a non-irritating, non-toxic, and biocompatible system for the sensitive ocular tissues and corneal surface. Advantages of nanoemulsion system are the same as nanoparticulate system, i.e., steady release of the drug over a long duration, facilitated penetration in the deeper layers of the ocular structure, low viscosity, their capacity to accommodate both hydrophilic and lipophilic drugs, and their ease of sterilization. Thus, these systems can achieve a faster therapeutic action with a smaller dose resulting in fewer systemic (due to localized delivery), and ocular side-effects. Adverse reactions are also reduced due to less frequent need to repeat the applications per day. This factor ultimately helps to attain better patient compliance[60].

Contact lenses: Therapeutic contact lenses are developed as a result of the latest involvement in targeted drug release to posterior eye. These therapeutic lenses focus on prolonging the delivery of medications[61]. Development of a sustained drug delivery device in the eyes may diminish the lack of pliability associated with eye drops in glaucoma therapy, by making a single instillation therapeutically viable for an extended period of time. Augmentation in bioavailability, reduction in side effects, decreased frequency of drug administration, and better clinical results in glaucoma are some of the added advantages of this non invasive source of drug delivery. Howsoever, the major limitation of delivering drug through contact lenses is controlling the drug release. Commercially available contact lenses can absorb and release drugs, but the duration of release tends to be limited to only several hours[62]. Recent research has focused on extending the duration of drug release by modification of the contact lens design. From a

structural point of view, soft contact lenses are made of hydrogel (a three-dimensional polymer network) capable of absorbing requisite volume of aqueous medium[63]. When submerged in a concentrated solution of a drug, the aqueous phase can absorb small amounts of the drug or take it into the polymer mesh by means of non-specific absorption. The improved ocular bioavailability of drugs can be obtained when wearing drug impregnated conventional soft contact lenses. The amount of drug which is diffused toward the corneal surface is five times higher than that released toward the external lachrymal fluid. Accordingly, the cornea remains in contact with high concentrations of the drug for longer periods of time, and drug penetration is more efficient. In controlled drug delivery system for the correction of ocular diseases, soft contact lenses can be used due to cheap manufacturing processes and their uncomplicated administration[64]. This makes them an enticing carrier for controlled drug release. Before these contact lenses can be made available to public, more *in vivo* trials are still needed. The major issue to resolve is to extend the duration of drug delivery beyond a few hours. Various methods are under study to meliorate the same, such as:-

- Incorporation of nano drug delivery systems such as: liposomes, micelles and microemulsions[65].
- Adhering drug loaded liposomes can increase the release duration[66].
- Developing biomimetic contact lenses, and lenses with a polymer layer containing suspended drug particles[67].
- Loading contact lenses with vitamin E[68].

Several of these studies cited above have been explored experimentally for extended delivery of timolol with both success and failures. There are several advantages and disadvantages with each of these delivery systems, which include: restriction on amount of drug loading and release duration, effect on transparency, modulus, ion and oxygen penetration ability, instability during production, storage and administration, and drug release during storage of lens. For prolonged delivery of timolol, many approaches mentioned have been investigated for augmenting its delivery with different levels of achievement[69].

In-situ gelling systems: *In situ*-forming gels involve low-viscosity solutions that encounter phase transition to form gel after a stimulus. The phase transition could be resolved by various stimuli, such as: changes in temperature, pH, and ionic composition. Numerous *in situ* polymeric gelling (or thickening) systems, such as chitosan, poloxamer, hydroxypropylmethylcellulose (HPMC), and polycaprolactone have been developed for use in the eye[70]. *In situ* gelling systems are generally used as a method to increase the precorneal residence time of topically applied drugs with increase in bioavailability of small-molecule drugs, but these may not be applicable to macromolecules pertaining to their extremely poor permeability across the corneal epithelium[71]. This system allows easy administration of sustained release materials to the desired site; however, it is difficult to get long-term release of macromolecules for more than a few weeks or months at a therapeutic level[72]. *In situ* gelling formulations have been studied for delivering macromolecules as injectables, which avoid surgical implantation, and effect prolonged drug release, such as:

- Suprachoroidal delivery of anti-VEGF therapy demonstrated for 60 days *in vivo* using a light-activated *in situ* forming gel[73].
- A thermosensitive *in situ* gelling injectable for ocular delivery of bevacizumab which demonstrated *in vitro* release of bevacizumab for 18 days[74].

Microneedles: Microneedle is a rapidly advancing technique to target posterior ocular diseases such as age related macular degeneration (AMD), diabetic retinopathy, and posterior uveitis, which are mostly serious vision compensating disorders[75,76]. Authors have concluded that microneedle based minor invasive strategies may help to deliver high-level of both drugs and nanocarriers to retinal tissues. This method may also help to reduce the risk and complications experienced with intravitreal injections such as retinal detachment, hemorrhage, cataract, endophthalmitis, and pseudoendophthalmitis. Moreover, it may also be used to deliver therapeutic drug levels to retina or choroid circumventing the BRB[77].

Ocular implants: These are miniscule devices capable of loading drug and providing sustained release of a therapeutically active ingredient when implanted or placed in the ocular cavity. Biodegradable or nonbiodegradable inserts, punctal plugs, contact lenses, intra-ocular lenses (IOLs), and mini-devices affixed to IOL haptics come under this category of targeted drug release[78]. Ocular implants can be classified as follows:-

Biodegradable polymeric implants: Biodegradable polymers can also be formulated as implants that encapsulate drugs for controlled release to treat

ocular disorders. Predominant advantage of using biodegradable implants is the larger drug loading pertaining to the larger dosage form size, along with the smaller surface-to-volume ratio of the biodegradable implants compared to polymeric particles, therefore allowing prolonged drug release (upto months). Several implants are placed directly in the vitreous humor, or on the sclera for effective drug administration into the posterior eye. Currently, ophthalmic biodegradable implants for macromolecular drugs are not available clinically. Challenges faced by this system of drug delivery are much similar to biodegradable polymeric particle system, such as: maintaining stability, control of release rate, duration of release, and safety of biodegradable products. Additionally, the release profile from implants can be affected by different parameters such as drug loading, surface area and volume of implant, polymer composition and molecular weight, and solubility of the drug[79,80]. Biodegradable implants are more likely to show non-linear release kinetics, and burst release compared to nonbiodegradable implants. These implants if made small enough can be inserted into the eye using minimal surgical procedure. A few biodegradable ophthalmic implants for delivering small molecular weight drugs to the eye are:

- Biodegradable intravitreal implant for macromolecule t-PA, a thrombolytic agent has been studied preclinically to release recombinant tissue plasminogen activator at a rate upto 0.5µg/day for 2 weeks[81].
- Ozurdex (Allergan, Irvine, CA): A biodegradable implant consisting of 0.7mg of dexamethasone within a PLGA copolymer matrix, implanted in the vitreal cavity and capable of releasing drug for 6 months. It is approved for the treatment of macular edema, but has been used off-label for uveitis too[82, 83].

Non-biodegradable implants: These are also called reservoir type implants as they typically contain a drug reservoir in centre, ensphered by a semi-permeable membrane, allowing steady release of drug with zero-order kinetics for up to months or years[84]. However, these implants require to be removed or refilled, calling for a second surgical intervention after they are exhausted. Minor surgery is required to place the implant at the pars plana and to typically anchor it to the sclera via a suture. Because of this surgical procedure, non-biodegradable implants are more prone to complications such as retinal detachment. For the extra-ocular non-biodegradable implants, possible chronic irritation, and scar formation are some major drawbacks. Till date, non-biodegradable implants for macromolecular weight drugs have not yet reached the market. Non-biodegradable implant systems for sustained release delivery of macromolecules could be an enticing and efficient dosage form if smaller sized implant design can be implemented with affordable stability, and minimum complications to the patient. There are a few clinically approved non-biodegradable implants that release small-molecule drugs into the vitreous for a long period of time such as:

- An osmotic pump implant which delivers IgG across sclera for 28 days. However, pertaining to the large size of the implant the main compartment was implanted in the subcutaneous space, and connected to the sclera using a brain infusion kit[85].
- The first reservoir-type implant approved was the Vitrasert® (Bausch & Lomb, Rochester, NY), that releases drug ganciclovir in the treatment of cytomegalovirus (CMV) retinitis. It is capable of releasing drug for up to 5 to 8 months[86].
- Retisert® (Bausch & Lomb) is another reservoir-type non-biodegradable implant that releases fluocinolone acetonide for chronic non-infectious uveitis. It has also been used for diabetic macular edema off-label[87,88].

Other implantable devices: For the cure of chronic and refractory ocular diseases, a micro-electrochemical system (MEMS) has also been explored. There are two generation of MEMS in which the first generation is manually controlled, restricted by variations in duration of the drug release and force applied for depressing the reservoir. In the second generation reservoir a refill port for drug reservoir, a battery/cell, and assistive electronic components are present. The prolonged therapy without a surgery is allowed as device can be refilled with the drug. It uses electrolysis to signal required dosage volume.

PDS (Port Delivery System) is another device which can be refilled and is used for long-term delivery. It is placed surgically through sclera incision, and can accommodate small or large molecules. Investigators reported improvement in best corrected visual acuity, reduction in macular thickness, and reduction in CNV leakage area. A longer phase 2 trial is planned for the device, which is being developed by Forsight Vision[89].

Biomaterials: Biomaterials are majorly employed during surgical procedures to treat serious eye diseases. Their use is chiefly to serve two basic purposes, *viz.*, maintaining rigid support at a fixed position, and keeping constant drug release over long periods of time. The support function works

essentially in retinal detachment surgery. Scleral buckles or tamponade agents are envisaged for effective securing of the retina in position, seal retinal breaks, and secure retinal reattachment[90]. Controlled release systems are effective in the treatment of microbial infections of the posterior segment, such as cytomegalovirus (CMV) retinitis[91]. Such systems are also helpful in preventing cell proliferation, usually observed in patients suffering from proliferative vitreoretinopathy (PVR).

Dendrimers: A dendrimer is a structure that is symmetrical around the core and often adopts a spherical 3-D morphology comprising of nanosized, highly branched, and star shaped polymeric system. They occur in several molecular weights. The terminal functional group (amine, hydroxyl or carboxyl) may be used to conjugate targeting moieties. The wide range of drugs (hydrophobic, and hydrophilic) can be integrated with dendrimers due to their vastly branched structure. A handful of promising results have been reported with the dendrimers[92,93]. The administration of these highly branched structures can be an encouraging option for prolonging residence time, increasing ocular bioavailability, and getting preferable results. In ocular drug delivery system, polydendrimers (amidoamines PAMAM) are extensively used[94]. For example:

- In albino rabbits (*Orycolagus cuniculus*), pilocarpine nitrate and tropicamide (which are cholinergic agonist, and antimuscarinic, respectively) when co-administered with PAMAM dendrimers showed higher miotic and mydriatic activity.
- For the prevention of scar tissue formation usually occurring after glaucoma filtration surgery, conjugates of PAMAM dendrimers (with glucosamine and glucosamine-6-sulphate) were employed to impart immunomodulatory, and anti-angiogenic activities.
- The reduction in the emergence of the scar tissue is due to the subconjunctival administration of these improved PAMAM dendrimers in rabbit model of glaucoma filtration surgery[95].

Iontophoresis: In this technique an electric current is applied to move drugs (which itself presents as a conductor) in the form of ions through a tissue or a membrane[96]. It is a noninvasive technique. A feeble direct current helps in the movement of the charged molecules or ions through the sclera, and into the choroid, retina, and vitreous. This technique does not cause any changes in the eye structure or function. The decrease in the frequency of required treatments pertaining to sustained release action, allows ocular iontophoresis technique to be possibly applied to create a drug store in the sclera. The Aciont is working on the iontophoretic ocular drug delivery systems[97].

Gene delivery: On a regular basis the cells of the body are instigated to produce therapeutic proteins which are being focused in gene therapy[98]. It is a potentially exciting area for development of targeted systems to treat posterior eye diseases. A number of companies and centres are exploring these possibilities. One such company, Avalanche, is exploring the use of adeno-associated viral vectors to deliver a gene to express a therapeutic molecule in patients with AMD[99]. A phase 1/2 clinical trial, in which 2 different doses of the biologic called rAAV sFlt-1, is delivered via subretinal injection, will be compared with ranibizumab-only therapy, has begun in Australia. Gene delivery is an area that is rapidly changing and growing, and a comprehensive review of efforts in this space is beyond the scope of this article.

CONCLUSION

Drug targeting to the posterior region of human eye to treat alarmingly prevalent ocular diseases is of paramount importance. Several promising new methods are under study and it can be said that this league is taking a revolutionary turn. The advent of nanoparticulate technology, use of biodegradable polymers, and various drug delivery routes, are under vigorous experimental scrutiny. As a result, extended release effect of drugs with significant targeting action may soon get clinically actualised, which shall help recuperate millions of affected ocular patients.

The U.S. Food and Drug Administration (FDA) has acceded to two drug delivery devices for disorders of retina/vitreous. A biodegradable implant of Ozurdex (Allergan) has been recently granted approval to elongate delivery of steroids for macular edema, succeeding central and branch retinal vein occlusion. It will be administered with the help of 22-gauge applicator, intravitreally. The official trials have shown safety with respect to IOP and cataract. Another implant Retisert (Bausch & Lomb), which is non-biodegradable has been accepted for non-infectious posterior uveitis. It will be implanted into the sclera through surgery. In spite of positive results on visual acuity in diabetic macular edema, secondary glaucoma is caused by Retisert, which is corrected by filtering surgery in approximately 40% patients. Implants which are

biodegradable are now in focus of research and also that do not need to be explanted. Nanoparticle technology may prove to be pivotal in the treatment of potentially blinding diseases in future [100].

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