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Vitreoretinal Disease- A Critical Review on Current Technological Perspectives and Innovative Drug Delivery Strategies

Krishnapriya Ma[1], Sharon K Josepha[1], Vishal Kumara[1], Gopal S Pillaib[2] and Sreeja C Naira[1]*

[1]*Amrita School of Pharmacy, Amrita Vishwa Vidyapeetham, India*

[2]*Department of Opthalmology, Amrita Institute of Medical Science, India*

***Corresponding author:** Sreeja C Naira, Amrita School of Pharmacy, Amrita Vishwa Vidyapeetham, Kochi-682041, Kerala, India

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Abbreviations: PSEDs: Posterior Segment Eye Diseases; AMD: Age Related Macular Degeneration; VEGF: Vascular Endothelial Growth Factor Agents

ABSTRACT

Vitreoretinal diseases which are mainly related to posterior segment of the eye are the most catastrophic vision threatening eye diseases that affects a wide range of productive population. The relevance of novel targets are redefined recently. These pathological conditions are in instinct need of multidimensional treatment strategies to traverse the ocular barriers in a patient compliant manner through non invasive routes. The main barriers are biological, physicochemical and metabolic barriers. The potential to accomplish these aforementioned requirements through the current gold standard treatment- intravitreal injections of conventional anti platelet agents and corticosteroids is not satisfactory. More over these are associated with its dose and route related side effects which also bring up the urge of developing new therapeutic molecules and novel route of administration. With the advent of nanotechnology and the polymer science there opens up the new era for painless and targeted therapeutic modalities for effectively combating the posterior eye barriers with minimized side effects. There are certain natural medicaments for not only to delay the progression of vision loss, but also to restore the vision. A holistic approach combining all these pharmaceutical and bio-pharmaceutical principles can be considered as the promising strategy to resolve this global myth.

Keywords: Vitreoretinal Diseases; Ocular Barriers; Intravitreal Injections; Nanotechnology; Bio-Pharmaceutical

Introduction

Eye is the most sensitive and delicate sense organ which opens up the extravaganza of beauty and colour to our life. The ocular route seems to be morphologically simple, but highly unique in terms of its anatomical and physiological aspects which makes it highly protected and isolated organ. Eyeball is broadly divided into two major segments- the anterior segment which consists of the avascular cornea, pupil, iris, ciliary body, conjunctiva, anterior chamber, aqueous humor and lens, occupies one third of the total eye ball and the posterior segment which mainly consists of the sclera, choroid, retina, vitreous humor, and optic nerve, occupies the two third portion of the eye ball. Posterior segment eye diseases [PSEDs] – (mainly vitreoretinal diseases) are the chronic diseases

that affect almost 57% of the total population and if no accurate treatment is given, can lead to permanent loss of vision [1]. Recent statistics shows that about 300 million people are visually impaired and among that 37 million are irreversibly blind which accounts a major group of people in working age [2]. The number of blind individuals increases by approximately 7 million/year [3]. The revenue on PSEDs accounts for almost 43% of the total ocular care cost. The main vitreoretinal diseases include degenerative diseases such as retinitis pigmentosa, age related macular degeneration (AMD), and vascular diseases such as diabetic macular oedema, diabetic retinopathy, proliferative vitreoretinopathy, retinal vein occlusion, posterior uveitis, endophthalmitis etc. The difficulty of reaching the back of the eye tissue is considered to be the most relevant barrier of intraocular drug delivery strategies [4]. A therapeutic moiety has to travel a distance of nearly one inch to reach posterior segment eye tissues and hence shortening of distance between the route of administration and route of action by minimally invasive technique with negligible tissue destruction in a patient compliant manner is the real clinical unmet need. The barriers include the biological barriers or the pathway related barriers, the physicochemical barriers which are related to the strength of the dosage form and the metabolic barriers. Biological barriers include the dynamic (the vasculature of conjunctiva and the choroid, lymphatic elimination, dilution factor due to tear secretion etc.) and static barriers (avascular corneal epithelial layers, blood fluid barrier and blood retinal barrier), all add up on to the complication of the pharmacokinetic processes [5].

The delivery of therapeutic concentration of the active molecule to the of target site in its absolute strength by improving the biopharmaceutical aspects of the drug to reduce the side effects with minimum partitioning to the non specific site is the main challenge for a formulation scientist working on novel ocular drug delivery. The current treatment option for vitreoretinal diseases are direct injections of anti vascular endothelial growth factor agents (Anti VEGF) and corticosteroids to the vitreous humor which is called as intravitreal injections. It posses the advantage of targeted therapy with minimized dose but arrive finally with its inherent dose related adverse effects like endophthalmitis, retinal detachment, glaucoma, invasive nature and high economic burden which emphasises the need for the development of a more patient compliant drug delivery platform technology sidestepping the barriers by launching novel route of administration, reformulation of previously approved molecules, introduction of new therapeutic molecules and by collaborating with nanotechnology approaches [6]. Innovations in biomaterials, polymer science and nanotechnology highlight promising treatment strategies offering the advantage of sustained and predictable therapy by narrowing the one inch distance and hence deceive the limitations by enabling the mass transport, circumnavigating the aforementioned barriers and dose related side effects which will hopefully result in a number of advanced products on the market within the next few years. The system designing factors that need to considered for the development of a novel DDS are mentioned along with its limitations. A special emphasis on in vitro cell culture models and animal models for vitreoretinal diseases are briefly listed. Moreover the natural sources for delaying the progression of the PSEDs are also discussed [7].

Briefing on PSEDs with a Special Focus on its Pathogenesis

Table 1: Classification of PSEDs with their symptoms and treatment.

Disease	Classification	Signs and Symptoms	Treatment
AMD (Age related macular degeneration)	Non-exudative- Dry AMD	Break down of photoreceptors, retinal pigment epithelium (RPE) and chorio-capillaries	Administration of specialized high dose of antioxidants, zinc and vitamin supplements
	Exudative -Wet AMD	Growth of abnormal blood vessels behind the retina, macula, disruption of Bruch's membrane and degeneration of RPE leading to complete loss of vision	Intravitreal injection of anti-VEGF agents like ranibizumab, pegaptanib sodium and bevacizumab
DME (Diabetic macular edema)	Focal or non-cystoid DME	Small aberrations in retinal blood vessels followed by intra-retinal leakage	With the aid of Corticosteroids and Focal or grid laser therapy
	Diffuse or cystoids DME	Formation of microcrysts and dilation of retinal capillaries	

PVR (Proliferative vitreoretinopathy)	Based on the inflammation of retina: focal, diffuse, subretinal, circumferential Based on the location of scar tissue: anterior, posterior	Simple scar formation and proliferation of cells in vitreous and retina	Surgery and adjunctive treatment of 5-fluorouracil and low molecular weight heparin after surgery so as to avoid relapses
Uveitis	Anterior uveitis, intermediate uveitis, posterior uveitis, pan-uveitic uveitis	Inflammation occurs in the middle layer of eye (uvea)	Corticosteroids and immunosuppressive agents
CMV (Cytomegalo virus retinitis)		Inflammation of the retina, retinal detachment and complete blindness	Cidofovir, ganciclovir (GCV) and foscarnet

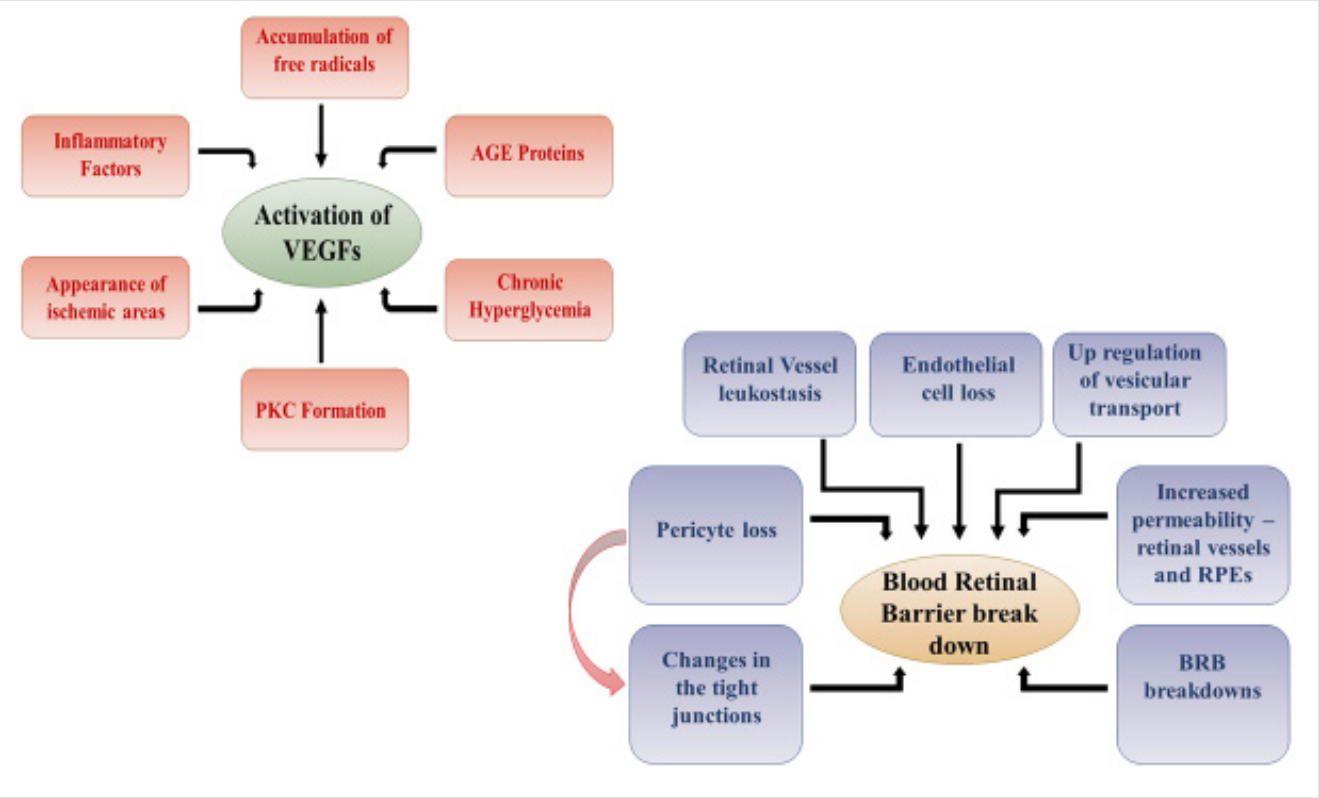

Figure 1: The pathophysiological mechanisms of ocular angiogenesis depicting chemical alterations (yellow) and structural differences (green).

The main vitreoretinal diseases include degenerative diseases such as retinitis pigmentosa, AMD and vascular diseases such as diabetic macular oedema, diabetic retinopathy, proliferative vitreoretinopathy, retinal vein occlusion, posterior uveitis, endophthalmitis, optic neuropathies arising from glaucoma, retinitis vasculitis and polyploidal choroidal vasculopathy [8]. The symptoms and current treatment strategies are as described in (Table 1). The pathogenesis of the PSEDs is multifactorial and is not fully explored. The strong interdependency of these disorders to the age could shed light to their critical impact on affecting the working age population and the expenditure involved. The major anatomical features associated are retinal neurosensory layers, retinal pigment epithelium, blood retinal barrier, chorioretinal capillaries and Bruch's membrane [9]. The triggering factors ranging from metabolic, environmental, and functional to hereditary lineage plays a key role in the ocular neovascular complication following the disruption of blood retinal barrier, which is considered as the main clinical manifestation. The pathophysiological aspects of ocular neovascularisation are described in (Figure 1). The metabolic factors such as persistent hyperglycaemia, chronic hypoxia, accumulation of free radicals, advanced glycation end products (AGE proteins), protein kinase C formation etc. alter the vascular permeability and thereby stimulate the activation vascular endothelial growth factors (VEGF) mainly VEGF A [10]. This attributes various primary changes like endothelial cell lose contributing finally to the emergence of blood retinal barrier (BRB) breakdown. BRB disruption is followed by the fluid accumulation at the interior neuronal layers of the retina and the macula [11].

Analysing the Physiological Barriers and Routes

The backward portion of the eye which is highly protected and shielded by many barriers, mainly consist of sclera, choroid, vitreous humor, retina, macula, and optic nerve. The main component of the back of the eye tissue is the light sensitive retina which is approximately 0.5mm thick, is the visual acuity centre for colour vision and image formation. The role of retina in human eye is similar to that played by a film of a camera and the visual interception of the images is another key role that is accomplished by the optic neuronal fibres of the retina. The central portion of the retina is called as the fovea. The outermost portion of the eye globe is encircled by the sclera which is said to belong to both the anterior and posterior portion of the eye and is more permeable to hydrophilic molecules. Scleral tissues are also intended to provide adequate shape to the eye ball with its extra cellular matrix composed of fibrils of collagen and glycoproteins. Choroid is a pigmented highly vascularised intermediate layer between the retina and the sclera with immense blood circulation, is intended to supply the nutrition and oxygen to photoreceptive retinal tissues as well as the retinal pigmented epithelial RPE. It covers nearly a major portion of the innermost eye tissues and also plays a provident role in maintaining the haemostatic equilibrium and pressure isotherm in ocular cavity. The composition of vitreous body which is nearly 4 mL in volume with its main components is water, proteins such as opticin and fibrillin, collagen, hyaluronic acid (HA) [12]. The main function of hyaluronic acid is to ensure adequate retinal nutrition. The function of viscous gel filled vitreous humor is to hinder the diffusion of big and charged molecules to the layers of retinal tissue. Macromolecules are more likely to undergo precipitation vitreous humor due to their ionic interaction with HA. Both the highly organised anatomical and physiological barriers of the eye make it isolated from the general circulation and immune protected [13]. The main rate limiting ocular barriers include

a. Corneal epithelial barrier

b. Iris blood vessel endothelium

c. Ciliary body epithelium

d. Inner barrier of retina formed by retinal capillary endothelial cells

e. Retinal barrier

Posterior segment is at a distance of one inch from the ocular surface and various barriers need to be traversed to obtain adequate drug delivery to the target site [14]. Scleral, Choroidal and Bruch's membrane barriers perform the role of rate limiting biological barriers for most of the macro molecules. The vitreous humor acts as an effective diffussional barrier for high molecular weight functional moieties. The photo sensitive retina is the main component of the inner eye tissue which covers almost the entire portion of the interior ocular wall. Moving on the detailed biological barrier anatomy, the outer retina is made up of retinal endothelial cells that encompass a significant portion of the Blood retinal barrier (BRB), while the interior retinal tissue is broadly divided into three main regions including the inner, middle and outer segments [15]. The inner segmental cells and tissue consist of neural cells and glial cells which in turn comprises of Muller cells, astrocytes, microglial cells and oligodendroglial cells. However, the photo receptive cells rods and cones and the epithelial cells are located within the middle segment, while exterior portion comprises the main RPE barrier forming specialized cells i.e., the unilayered pigmented cuboidal epithelial cells which contributes to restricted transportation of molecule to the posterior segment of the eye [16]. (Table 2) lists the prevailing drug delivery routes and barriers with its advantages and disadvantages. These biological retinal barriers along with the Blood aqueous barrier make the posterior segment delivery of functional molecules a challenging task [17].

Table 2: Posterior Segment Delivery Routes and Barriers.

ROUTES	BARRIERS	LIMITATIONS	ADVANTAGES
Topical	● Membrane barriers ● Elimination pathways on eye surface ● Cornea structural complexity ● Blood retinal barrier ● Aqueous humor flow gradient ● Tight junctions ● Tear flow (opposite convective flow) ● Dynamic barriers related to tissue vasculature and clearance by lymphatics	● High frequency of instillations ● Nasolacrimal drainage ● Restricted volume of application ● Blurriness of vision ● Pre corneal drug loss ● Blinking reflexes	● Non invasive ● Patient compliant ● Self administrable
Systemic	● Choroidal efflux transporter ● Blood Retinal barrier(more selective to highly lipophillic drug)	● High dose administered to achieve the therapeutic concentration. ● Unintended adverse effects due to undesirable exposure non targeted areas. ● Efflux transporters limit the absorption to the ocular tissues. ● Invasive (sometimes)	● Prevent the damage to ocular tissues due to multiple injections.
Periocular (subconjunctival, subtenon, peribulbar, posterior juxtascleral and retrobulbar injections)	● Scleral width and thickness ● Choroidal vascularisation ● Blood retinal barrier	● Drug loses via the episcleral, conjunctival, lymphatic flow ● Invasive ● Damage to the ocular tissues	● Utilizes the trans-scleral pathway to deliver drugs
Intravitreal	● Blood retinal barrier ● Transient diffusion of large molecules is hindered by the layers of vitreal body which act as a semi permeable membrane. ● The physical membrane barriers of retina such as retinal pigment epithelium (RPE)	● Invasive ● Various side effects such as Glaucoma, cataract, retinal detachment, haemorrhage, degradation of specialised rods and cones and bacterial endophthalmitis	● Highest bioavailability to the vitreo-retinal-choroidal tissue due to the immense potential to circumnavigate back of the ocular tissue barriers.
Suprachoroidal	● Choroidal vascularisation	● Post operative inflammation and choroidal haemorrhage ● Invasive	● Effective therapeutic concentration reaches vitreous humor and choroid. ● An important trans scleral innate route for those bioactives which is administered to the scleral layer.

Corneal and Conjunctival Barriers Via Topical Route

Topical route is the preferred way of ocular delivery of drugs to posterior segment due to its minimally invasive nature which is highly patient compliant. But the targeted delivery to vitreoretinal region could only be accomplished by the circumvention of various barriers as discussed. The primary barriers such as cornea and conjunctiva, made up of non keratinized squamous epithelium are protective in nature against pathogens and drugs as they are equipped with P-glycoprotein (P-gp) which is a major transport efflux pumps on the epithelial tissues of cornea and conjunctiva [18].

Various topical formulations includes the ophthalmic solutions and suspensions like eye drops, ointments, in-situ gels, ocusert, lacrisert, contact lenses etc. The conjunctival route of drug delivery is more preferable for targeting the retinal tissues, as the later route will end up in anterior segment due to high resistance offered by the crystalline lens. The normal tear turnover rate of eye is 0.5–2.2 µL/min with a total tear volume of 7–9 µL, which will get elevated by the topical administration and hence the blinking rate reflex is raised. All this in turn increases the nasolacrimal drainage of excess formulation in case of eye drops. [19]. The systemic drainage of topical formulations happens through the conjunctival and lymphatic circulation thereby enabling the conjunctival absorption to be non productive. Only $1/10000^{th}$ of the topical instilled dose reaches the back of the eye tissues due these physical, chemical and biological barriers, which may cause under dosing. [20]. Apart from these barriers, the contact time with the conjunctival tissues play a pivotal role in attaining the adequate concentration within the target tissues. The main factors affecting the perforation of drugs to the corneal and conjunctival barrier are the biopharmaceutical characteristics of the functional moiety related to the strength of the dosage form including the charge, lipophilicity, molecular weight; concentration gradient; biological and metabolic barrier properties [21]. The lipophilic drugs are more likely to traverse through the epithelial layers via the transcellular pathway, while the hydrophilic drugs traverse via the paracellular pathway. The circumvention of the hydrophilic compounds is considered to be greatly significant as it has to cross over the tight junction of both corneal and the conjunctival epithelium in a size dependent manner. The conjunctival epithelial paracellular pore diameter is about 3 nm which is more than that of the cornea which is about 2 nm and thereby facilitate high permeability of hydrophilic compounds with a size ranging between 5-10kilo Dalton (kDa) through the epithelial tissue, while the compounds with molecular weight of about 500 Dalton (Da) is able to pass through the corneal epithelium. The conjunctival pathway (non corneal pathway) is a relevant route for targeted retinal delivery via topical route, due to its high pore density and significantly bigger net paracellular space [22].

Trans Scleral Route as a Novel Route for Ocular Drug Delivery

Sclera is an opaque outer ocular visco-elastic layer of the eye, whose main component is fibrils of type I collagen immersed in proteoglycans matrix. Additionally, the human sclera consists of collagen Types III, V, VI, VIII and XII. Other structural components are tenon's capsule, spur, episclera, lamina fusca and the stroma. Both the tenon's capsule and the episcleral layers are highly rich in blood supply which covers the posterior portion of the sclera [23]. The external portion of the choroid is fabricated with lamina fusca, and this is also a structural component of uveal tract and sclera. The main composition of stroma includes collagen and elastic fibres. Curtailment of interior fibres of sclera with the limbus fibres lead to the formation of an intransigent ring like structure called the spur. The mean human scleral surface area is 16- 17 cm^2. The thickness offered by the human sclera is varying based on gender difference with male sclera being thicker than that of human female. Studies proved that there is a considerable increase scleral thickness and opacity with age [24]. On the basis of the anatomical and physiological characteristics of scleral tissues it was well understood that the hydrophilic drugs are more adaptable to transscleral diffusion [25]. The factors that must be considered in transscleral delivery include the characteristic pharmacokinetic properties of the drug. The transient diffusion of therapeutic moieties across these barriers is dependent on the molecular dimensions, molecular mass, charge and chemical components of the drug. The permeability of human sclera extends to almost 70 kDa. The most significant predictor of scleral permeability is the radius of the molecule. The hydrophilic lipophilic balance is a characteristic attribute of the determining the solubility of a component and the related interactions [26]. As already mentioned, the permeation of hydrophilic compounds through the sclera is at a faster rate than the lipophilic compounds, due to massive hindrance offered by the transscleral route to these hydrophobic moieties. In another perspective these lipophilic or hydrophobic compounds tend to be more permeable to RPE compared to the hydrophilic molecules. Considering all these, it was well established that the hydrophilic-lipophilic balance (HLB) may be the critical parameter for the effective drug delivery to retina-choroid region via transscleral route. This is proposed to be the safest route for PSEDs than systemic or intravitreal approach, in addition problems such as toxicity may arise due to lack of drug elimination.

More over this route offers a potential and promising route for non-invasive topical applications to the back of the eye tissues [27]. Static barriers are the non moving or restricted movement barriers that represents the various layers of tissues to be penetrated including the sclera, choroid and Bruch's membrane and the retinal pigment epithelium [28]. The scleral drug delivery perspectives are mainly dependent on the molecular radius of the drug as the permeability is inversely proportional to the radius. More over the charge of the therapeutic moiety also plays a significant role in traversing the scleral barrier as the permeability increases with negatively charged solutes. While the permeability via the choroid-Bruch's membrane increases with decreasing lipophilicity and molecular mass of the drug. Anionic molecules are more permeable through this route. Retinal pigment epithelium acts a potential rate limiting barrier to hydrophilic and large radius molecules hindering its transport [29]. Dynamic barriers are circulation dependent barriers including the bulk fluid flow, blood and lymphatic circulation and the channels and the transport proteins. Conjunctival and choroidal tissues are highly vascularised; hence lead to rapid drug elimination with minimal tissue penetration. The convective bulk

flow of fluid also leads to decreased penetration of drugs via transscleral route [30]. The transport proteins, efflux pumps and ion transporters hinder the transient diffusion of drugs. The metabolic barriers act as a relevant barrier for the drug pathway, which iare categorised as Cytochrome P 450 and the lysosomal enzymes [31].

Transscleral Routes

Transscleral routes are otherwise referred as periocular routes figure 2 shows different transscleral routes of administration with their clinical application. These are advantageous in delivering the therapeutic modalities to the deeper eye tissues by passing the firmly organized corneal barrier and the hindrance offered by the crystalline lens [32]. Moreover this route is relatively less enzyme protected. This novel route opens up the new era of relatively less invasive strategies and more over the targeted vitreo-retinal delivery via the topical instillation could be effectively accomplished without compromising the potency and patient compliance [33]. Looking forward from a consistent drug delivery standpoint, the system should not compromise its biopharmaceutical properties in any circumstances [34]. One of the significant factors that affect the pathogenesis and the progression of most of the PSEDs is the age of the patient. The major advantages of the transscleral route are as listed below: [35]

- Enhanced extent and rate of absorption due to improved surface area
- Remarkable diffusion of hydrophilic molecules attributed by the high degree of scleral hydration
- Sclera is metabolically inactive and hence the delivery of metabolic enzyme susceptible agents is facilitated.
- Highly permeable to macromolecules
- Best route for the administration of controlled and sustained release.

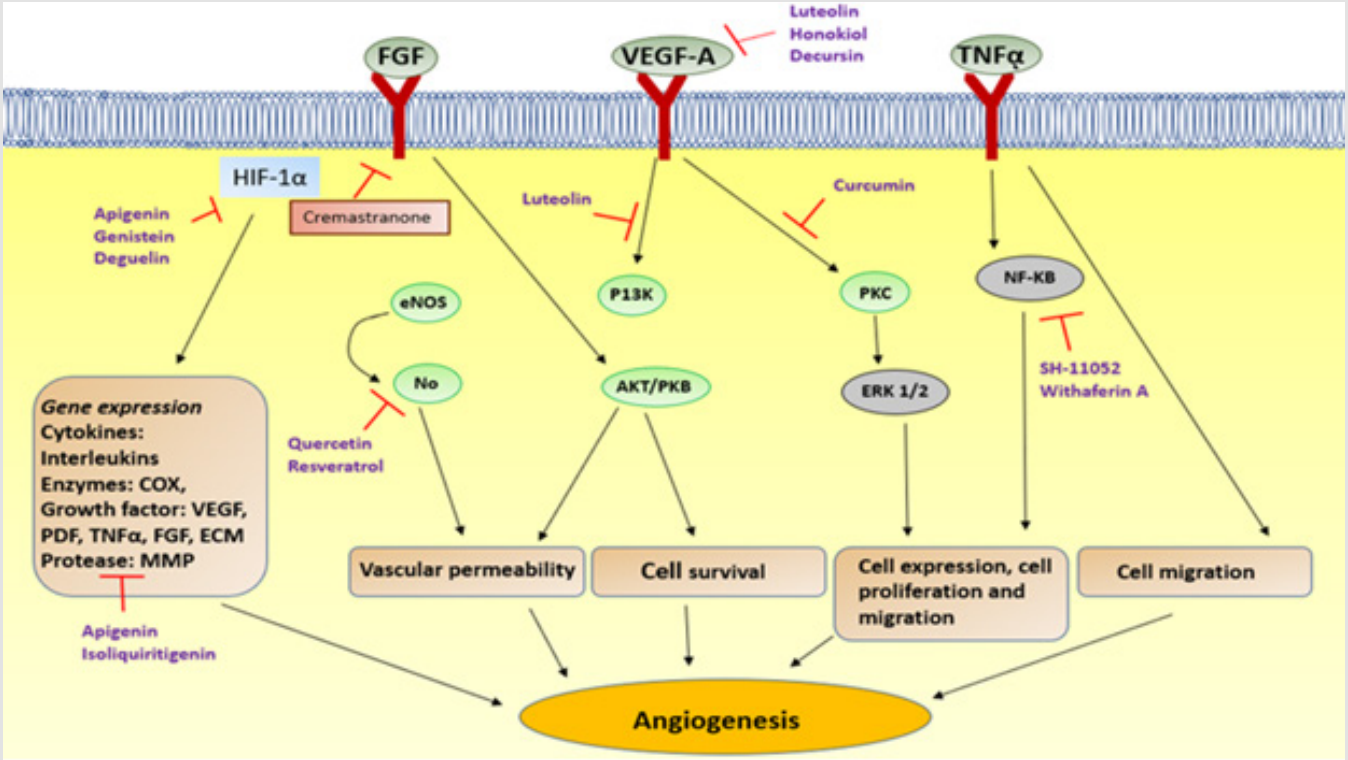

Figure 2: Schematic representation of natural inhibitors for ocular angiogenesis.

Subconjunctival Route (SC): This route is proved to attain sufficient bioavailability to the Vitreal cavity. Here the injection site is just beneath the conjunctival region by passing the conjunctival and the corneal region in a relatively minimal invasive manner compare to the intravitreal route [36]. The maximum dose that could be administered is of 500 µL and is passed through the sclera to the back of the eye tissues to attain a localised effect by appropriate therapeutic quantity to these tissues. The main factors affecting the drug delivery by this route is the pharmacodynamics of drug and diffusion through the scleral- choroidal region. Through this route, there are various predicted pathways to attain vitreal bioavailability. [37]. The direct diffusion to the vitreous humor, circumnavigating the deeper tissues is the first pathway. Another approach could be vitreous diffusion followed by absorption into the aqueous humor. Lastly, the systemic absorption of the drug molecule through the main tissue barriers like sclera, conjunctiva and the circulatory bar-

riers such as the blood flow related and the clearance by lymphatic duct which then get absorbed to the vitreous humor by traversing the BRB [38]. The significant Vitreal bioavailability could only be achieved by the first pathway of direct diffusion to the vitreous humor as evaluated by Lee and Robinson. The productive contribution by the other routes is minimal even though the delivery of therapeutic modalities to the aqueous humor and systemic circulation is achieved. The major therapeutic molecules that could be administered by SC route are bioactive proteins, prostaglandins and Dexamethasone [39].

Retrobulbar Route (RB): This is most accepted route for the administration of large concentration of anaesthetics prior to the cataract surgery or during any eye surgery with minimal elevation in intra ocular pressure (IOP) and here the injection is done to deliver the dosage form into the conical retrobulbar cavity which is equipped with tetra muscles with interstitial muscular septa. A volume of 3 ml can be injected at a time. Retrobulbar hemorrhage, globe perforation, and respiratory arrest can be considered as the main drawbacks associated with this route of administration [40]. One of the major PSED is Cystoid macular edema (CME) where chronic inflammation occurs at the macula adjacent to the fovea. RB route is very advantageous to deliver the adequate therapeutic quantity of the drug to the vicinity of the macula region, which is considered to be the target site of action [41]. The retrobulbar cavity is of larger size and volume, by considering this anatomical characteristic it was demonstrated that this route is more preferable to SC route for delivering the therapeutic molecule from a protein-polymer implant. Studies were conducted with corticosteroid such as Triamcinolone acetonide to study localization effect of corticosteroids [42].

Peribulbar Route (PB): This route is developed as an alternative to retrobulbar route where drug administration is conducted at the up or bottom portion of the globe and thereby considering the safety parameter of injecting the drug molecule to the peripheral region of the tetra rectus muscle and it's inter septal space. Even though this route is less effective than the RB route, it ensures minimal risk to intraorbital structures as the therapeutic accumulation occurs at the outer muscle tone. In case of cataract surgery, this route is suitable for the delivery of anaesthesia. PB route is further categorised as circum-ocular, peri-ocular, peri-conal and apical routes with maximum volume of accommodation to be 8-9 ml [43].

Intra Cameral Route (IC): IC cannot be completely categorised under transscleral route as it is mainly attributed to achieve higher drug concentration in the anterior chamber by injection. This route eliminates the usage of topical eye drops and also prevents adverse effects by topical steroid therapy [44]. IC route is an efficient and cost-effective route for administering antibiotics, anaesthetics, steroids and anti fungal agents and is also suitable to prevent the relapse of endophthalmitis after cataract surgery. This route is a very prominent diagnostic tool for pupil dilation [45].

Sub Tenon's Route (ST): Here injection is preceded towards the tenon's cavity with the upper limit of volume to be accommodated can be nearly 5 ml and this can be administered towards the sub tenon's space which is located between the episclera and tenon's capsule that in turn helps to attain higher vitreal bioavailability [46]. The possible risk factors associated with this route is sub conjunctival haemorrhage and chemosis. The RPE acts as a major physical barrier to this route. Mainly used for the administration of anaesthetics [47].

Posterior Juxtascleral: This is a relatively non invasive technique, which is associated with delivering the drug to the near vicinity of sclera, especially to the close proximity to macular region without the usual eye ball perforation. This process is done with the help of a specialized cannula. The location of therapeutic molecule deposition is adjacent to sub tenon's space. Mainly used for the administration of therapeutic bioactive such as Triamcinolone acetonide [48].

Ocular Pharmacokinetics

The complex anatomy and physiology of the eye makes the biodistribution of the therapeutic molecule within the eye a very cumbersome task. It is highly protected from the external environment and foreign pathogens by its bent architecture, aqueous tear production, selectively permeable membrane barriers, dynamic barriers and naso-lacrimal drainage. The bioavailability depends mainly on various critical constraints such as precorneal drug loss, binding to tear proteins, drug absorption to systemic circulation, factors associated with cornea, binding to melanin pigment and the metabolic factors affecting the drug disposition as described in (Table 3) [49]. Ocular pharmacokinetics is analysed based on the duration of the therapy, dosage form in relation to its cumulative drug absorbed. Ocular areas are primarily divided into various imaginary compartments that help in understanding the intraocular distribution of drugs. Each eye is considered as a separate compartment as there is no common channel for mixing up of the drug administered to the eye either by topical or invasive routes. Moreover as there is more than one compartment, the ocular pharmacokinetics can be better explained by a multi compartment model with uniform drug distribution profile in each intra or extra ocular tissues [50]. The various compartments are

a. Tear film and conjunctival sac

b. Front of the eye tissues (anterior chamber)

c. Vitreous cavity

d. Peri-ocular spaces

The localised bio distribution of the administered / injected formulations is hindered by various barriers and a comprehensive insight to these details are lacking with respect to these ocular pharmacokinetic model. As there is saturation in the preceding compartments the drug gets transported further. The concentration gradient need to be achieved in each of these compartments for reaching the posterior tissues by topical administration which is a very difficult task. Shortening of the distance between the site of administration and the site of action is one of the major challenges faced by any formulation scientist [51].

Table 3: Factors affecting intraocular bioavailability.

Drug binding to tear proteins	• Reduces the ocular bioavailability • Tear protein – 0.7% of total protein • Protein and efflux transporters
Systemic drug absorption	• Nasolacrimal drainage • Non productive
Corneal Factors	Corneal layers- six layered • Lipophilic Dua's layer • Hydrophilic stroma • Endothelium (innermost)- selective permeability, facilitated diffusion, secretary role, maintenance of corneal transparency
Melanin binding	Drugs binding to melanin • Ephedrine • Timolol
Pre corneal drug loss	• Volume of the instillation • pH and partition co efficient • Tonicity • BCS class of drug • Viscosity of the formulation
Metabolic parameters	Enzymes involved • Aldo/ ketone reductase • Cyclooxygenase • Monoamine oxidase • Transferase • Hydrolase • Aldehyde oxidase • Cytochrome P450

Protein Transporters and Efflux Pumps

Various influx and efflux transporters are present on the epithelial membrane. The intake, uptake and secretion of various vitamins and proteins through various paracellular- transcellular movements are mediated by these pumps. Thorough understanding on this ligands and proteins will emphasise its correlation as a detrimental factor in ocular bioavailability [52].

Peptide Transporter: This is a very significant transporter which is mainly present in the retina for the use of peptide and gene pro drug delivery with help of carrier mediated mechanism. From recent literature it shows that it is very prominent and effective in specific drug delivery of various hormone related products and antibiotics. Peptide transporters are proton coupled transporters which aid in the to and fro movement of peptide molecules across the epithelial surface. PepT1, PepT2 and peptide/histidine transporters belong to the sub category of peptide transporters and it also includes (PHT 1 and PHT 2). Various therapeutic moieties including angiotensin converting enzymes (ACE), antibiotics such as β-lactam, renin inhibitors are the main targets for this transporter

[53]. The prodrug strategy is highly relevant to improve the ocular bioavailability of BCS class II and IV drugs so that it can be effectively protected and identified by peptide transporters [54].

Glucose Transporter: The maximum metabolic rate is present in the neural retina and this is satisfied by the metabolism of glucose in the retina. The main speciality of glucose transporter is that they exist in various isoforms and these isoforms possess varying affinity to different substrates such as glucose, fructose and based in these affinity they are categorised as GLUT1 to GLUT7 [55]. In case of any minor change in the metabolic process of these substrates, there will be high consequences in the terms of ocular complications. Glucose is transported across the blood-retinal and blood aqueous barriers by a stereo-specific, saturable process of facilitated diffusion. On a broad comparison among all nutrient transporters, the glucose transporters are of maximum efficiency and immense capacity but it is not widely accepted for the drug delivery perspective due to its improvident substrate specificity renders [56].

Vitamin C Transporter: The main role of vitamin C or ascorbic acid (AA) is the protection of the cornea and other ocular tissues from UV radiations by antioxidant activity. Vitamin C is predominantly found in cornea and lens where aqueous humor is the reservoir of AA and it is partly responsible for preventing cataract. The main two transporter families of vitamin C were identified to have identical sequence homology [57]. One consists of the low affinity and high capacity facilitative hexose transporters and the other consists of high affinity and low capacity sodium dependent vitamin C transporters [58].

Amino Acid Transporter: Maintenance of structural integrity of ocular tissues such as conjunctiva and retinal pigment epithelium is the main role the amino acid transporters. They are also expressed on the corneal epithelial and endothelial surface [59]. Apart from this the transcriptional role of these pumps plays significance in its predominance and they aid in translocation of amino acids such as L-alanine, L arginine and L-phenylalanine with several organs and circulatory blood stream. Translocation of amino acids from circulatory vasculature to different tissues and organs are equipped with the advent of these transporters and are classified based on the substrate specificity and sodium dependency [60]. The chiral centered isoform of amino acids belongs to substrate specific transporter category. The ionic charge such as anionic, cationic and zwitter ionic, amino acid transporters depend on sodium dependency [61].

Efflux Transporters: The main efflux transporters are ABC (ATP-binding cassette). The multidrug resistant efflux pumps are categorised under this cassette of proteins which is the main efflux transporter responsible for chemoresistance [62]. The two main efflux pumps under this category are

a. P-glycoprotein (ABCB1) and

b. Multidrug resistant protein (MRP) (ABCC1)

On another view point the ABC efflux proteins can be broadly classified in to complete transporter and half transporter based on the number of domains and its binding capacity. Detoxification of various lipids, sterols and xenobiotics by regulating their translocation is another prominent role of these cassettes of proteins. P-glycoprotein which is present in the RPE, cornea, iris, conjunctiva, retinal capillary endothelial cells , ciliary non-pigmented epithelium and ciliary muscles, is actively involved reducing drug accumulation inside cells by the efflux of drug molecules thereby [63]. The main locations of expression of MRP are on the basolateral surface of intestine, hepatocytes and kidney cells. Invasion strategy adopted by various permeation enhancers could potentially evade these efflux transporters that could effectively prolong the therapeutic concentration of the drug at the target site [64].

Technology Port Folio Analysis of the Current Treatment Strategies

The vitreoretinal diseases can be inherited related to aging and diabetes. There are various diagnosis strategies for identifying the exact location of abnormality and to understand the stage of disease progression. The current treatment strategies for treating most of the posterior segment eye disorders include intravitreal injection, laser therapy or combination therapy [65]. Pharmacologically active molecules involved in treatment of most of these diseases are Anti vascular endothelial growth factor (Anti- VEGF) as first line agents and corticosteroids as second line agents. The major Anti- VEGF agents are aflibercept, bevacizumab, ranibizumab, pegaptanib and major corticosteroids are triamcinolone acetonide, fluocinolone acetonide and dexamethasone phosphate. Non pharmacologic therapy include use of magnifiers at the time of work and reading; also use brighter lights in the rooms etc have also gained attention during the past years [66]. Recently, there is a shift in paradigm from monotherapy to combination therapy. The next generation Anti- VEGF drugs include brolucizumab, abicipar pegol, conbercept, angiopoietin combination drugs, RG7716 and nesvacumab. The intravitreal therapy of these agents to the retina, choroid and retinal pigment epithelium shortens the pathway related barriers, enabling effective delivery of therapeutic concentration to the targeted site of action [67].

Diagnosis [68,69]

- Amsler Grid Test: This is used to test the central vision clarity. In this test the extent of retinal damage is measured. This is considered to be better predictor of macular degeneration.
- Fluorescein Angiography: The fragile, aberrant blood vessels are considered to be one of the main clinical indications of

most of degenerative and vascular posterior segment disorders. In this test these abnormal vasculature is identified with the help of a special dye. The test dye used can significantly distinguish the retinal neovascular areas with the aid of a particular light source.

- Indocyanine Green Angiography: Deeper aberrant neo vascular areas of the backward portion of the eye specially, the choroid region can be precisely identified using this diagnostic aid equipped with a sensible dye. Here the light source is infrared light.
- Ultrasound: The sound waves used here is of high frequency. This ultrasonography technique helps in the effective identification and treatment of ocular malignancies. The exact location of tumour or any other abnormality can be specified by this technique.
- Computed Tomography and Magnetic Resonance Imaging: Identification of eye injuries and malignancies.

Non Pharmacological Perspectives in PSEDs

Emerging Therapy by Antioxidant Supplementation: Antioxidant supplementation therapy is an innovative semi natural treatment strategy which was found to be very effective for age related ocular clinical manifestations. Prophylactic management of oxidative stress in the macular region is hypothesized to resolve by antioxidant supplementation. Apart from the prophylaxis, this therapy could potentially delay the progression macular degeneration [70]. The most relevant antioxidants which could be used on daily basis are vitamin C (500 mg), vitamin E (400 IU), beta carotene (15 mg), zinc oxide (80 mg), and cupric oxide (2 mg). But on detailed analysis it was found that these compounds were not suitable for all type of patient. These compounds were found to show contradictory effect on certain special type of cardiac and diabetic patients. A more comprehensive study on this subject is required to draw an appropriate conclusion [71].

Life Style and Dietary Modification: The main point to be considered by any individual is to avoid smoking as there exist a direct correlation between smoking and most of vision threatening degenerative diseases. Smokers should attend some smoking cessation programmes to quit smoking and to get rid withdrawal symptoms. Moreover the dietary habits need to be redefined for good ocular health [72]. As already discussed, the diet supplements must include antioxidants. Diet enriched with retinal carotenoids, lutein and zeaxanthin, fish and poly unsaturated fatty acid will help reduce the risk of most of the blinding neovascular diseases. Appropriate control on blood pressure is also recommended. Patients at high risk of vision loss, low-vision devices such as electronic video magnifiers and spectacle-mounted telescopes, as well as low-vision rehabilitation services, may also be of benefit [73].

Ocular Photodynamic and Photocoagulation Therapy: Verteporfin (Visudyne, Novartis) is a photo receptive dye which is administered by intravenous route for the treatment of neovascularisation. It effectively control and prevent the formation of new leaky aberrant blood vessels [74]. This technology does not utilize thermal energy as it requires a powerful laser beam at 689 nm to get activated for chemotoxic reaction. It mainly focuses on the thrombotic neovascularization at the choroidal region to maintain visual acuity and also helps in delaying the progression of vision loss. This cannot be used as a prophylactic measure to prevent the angiogenesis and hence appears to be less prominent than intravitreal anti-VEGF therapy [75]. The persistent use of photodynamic therapy more than six years is not recommended as it may cause serious side effects. The combination therapy with anti-VEGF agents was hypothesized to be more efficacious than monotherapy. Similarly argon-laser photocoagulation therapy is now rarely used to treat choroidal neovascularization that extends by more than 200 μm from the centre of the macula, since this treatment itself can create a large retinal scar associated with permanent visual loss [76].

Vitreoretinal Surgery: This is a least preferred method now. This includes either surgical extraction neovascular areas or translocation of the macular region which is accompanied by utmost risk and this is the reason for its low acceptability. But the combination therapy with any other tissue plasminogen intravitreal injection or anti-VEGF agents is found to be useful to an extent in most of the cases [77].

Radiation Therapy: As in case of cancer chemotherapy, the ionizing radiations can be used for breaking the DNA double strands of leaky fragile neovascular vessels which is the main clinical manifestation of most of the PSEDs [78]. Hence the radiation therapy results in antifibrotic, anti-inflammatory and antineovascular/antiangiogenic activity. Among the vision threatening posterior segment diseases, the age related macular degeneration (AMD) and diabetic macular edema (DME), was found to exhibit clinical relevance by this treatment strategy, but was not widely adopted due to patient non compliance in terms of inconsistent and poor reproducibility of vision acuity improvement [79]. Apart from this, the radiation technology causes destruction to cells at the vicinity and dosage accuracy cannot be guaranteed. Recent advancements in this strategy led to the emergence of more safer, accurate and targeted delivery techniques such as epimacular brachytherapy and robotic stereotactic radiotherapy. The epimacular brachytherapy is applicable to patients after vitreoretinal surgery and the latter is mainly applicable to patients with AMD to manage the choroidal angiogenesis. However the combination therapy with pharmacological molecules was found to show better outcomes than monotherapy [80].

Pharmacological Therapy for Neovascular Ocular Disorders; The State of Art

Intravitreal antiangiogenic therapy is the main treatment strategy adopted. Even though it causes localised action, it is associated with certain unavoidable inherent side effects related to the strength of the dosage form and route of administration [81]. There has been numerous evidential data from clinical trials substantiating the use of these agents for the treatment of various neovascular diseases and it was found to dramatically improve the visual acuity in many cases. Ocular intravitreal implants are effective for long term delivery [82]. Ocular implants are highly customised package proposed to be implanted by non invasive route to a specialized intra ocular tissue. Fabrication of this implant is of great significance in controlled drug delivery perspective to the localised intra ocular tissues [83]. The drug release profile from an implant can be extended up to years based on the type of polymer or the rate controlling membrane used [84].

Targetting VEGF in Ocular Angiogenesis: The VEGF family contain two sub families such as VEGF-A and VEGF-B with differential activity. The VEGF-A is the main target identified which consist of 8 exons and 7 introns and they exist in the form of almost 7 different isoforms, which differ encoding of amino acids [85]. The most prominent member of VEGF family is VEGF A165 followed by VEGF-A121. Most of the isoforms contain varying number amino acids from 121 and 206 amino acids. By the advent of genetic splicing technology the great scientist Bates et al. discovered the VEGF-A165b isoform [86]. The pro-anti conversion is of significant importance which renders suitable for various applications.Alternative splicing technology led to the innovation of pro-angiogenic VEGF-A to anti-angiogenic VEGF B conversion. Evidence based review suggest that under natural conditions the "anti-angiogenic" VEGF-B isoforms is mainly expressed in ocular tissues, compartments and fluids as compared to other VEGF isoforms in particular, VEGF165b is highly expressed in the normal eye (retina, lens, sclera, iris, vitreous) [87]. In patients with diabetic retinopathy and retinal vein occlusion, the vitreous fluid is the main location where this VEGF down regulation occurs to a large extent, where a switch in VEGF splicing from anti- to pro-angiogenic isoforms likely occurs but not with AMD patients. VEGFR-binding site is activated by VEGF-A isoform which mediates VEGF-induced chemo-taxis and inflammation, although with different affinity and potency while most of the serious mitogen triggering, blood vessel generating and penetrability enhancement effects of VEGF are mediated by VEGFR-2 [88]. VEGF-2 is mainly expressed in endothelial cells along with various co-expressers. VEGF-B is weak agonist and hence the VEGF R get poorly activated in comparison to its angiogenic counterpart. Various tissue genotypes are involved in proper maintenance of the normal ocular homeostasis which belong to the tissues of asvascular ECs, pericytes, retina along with neural retina, retinal pigment epithelium (RPE) and star shaped astrocytes and thereby gained high clinical significance due to the secretion of VEGF. In particular, VEGF is a detrimental factor for the homeostasis and plasticity of both blood vessels and neurons. Anti VEGF therapy with ranibizumab and bevacizumab was the frequently used therapy for inhibiting VEGF-A isoforms [89]. The irregular expression of VEGF is found to have a co relatable connection with neurodegenerative disorders which opens up secret of prominent role played by VEGF in neurogenesis and neuroprotection.

Evidence from the cellular studies suggest that, by various cellular mechanisms the VEGF 165 isoform, could help the neuronal survival under stressful conditions [90]. The stress can be multifactorial such as haemorrhage, oxidative stress etc. The survival or protective effects are also mediated through VEGFR-1which is mainly coordinated and expressed on supporting cells, such as microglia cells and star shaped astrocytes [91]. From various studies it was found that severalVEGF165a-induced processes are blocked by VEGF165b such as migration and proliferation of endothelial cell, vasodilatation and malignant neovascularization [92]. The dose dependent anti-angiogenic role played by VEGF165b and VEGF165a was fond to be commentable as it promote the physiological revascularization apart from the normal inhibitory action of chorio-retinal angiogenesis and hence was appreciated as a survival factor for both retinal endothelial and epithelial cells. The VEGF165b which is considered to a weak agonist than its isoform have potential to mediate the inhibitory mechanism of VEGF165a-induced EC migration and proliferation but does not interfere with revascularization process, suggesting that VEGF165b contrasts the invasive phenotype and promotes physiological angiogenesis [93].

The Era of Anti-Vegf Agents: Current marketed therapies high light the relevance and applicability of intravitreal anti-VEGF agents and thereby extend the acceptability across the global market. This treatment strategy could effectively improve the visual acuity of most of the patients by delaying the rate of progression, with rare cases reported with recalcitrant effects, even though it cannot fully eradicate or cure the disease [94]. Corticosteroid therapy and laser treatments have generally become second line therapy. In most of the cases the combination therapy sounds more effective and powerful [95]. Over the past decade, significant progress has been made in the treatment of AMD owing to an increased understanding of the mechanisms of ocular angiogenesis. Recent literature shows the advent on novel compounds like Brolucizumab, Abicipar and Conbercept targeting ocular angiogenesis [96]. Several factors are involved in ocular angiogenesis, with VEGF playing a central role. VEGF-A is a 46 kDa glycoprotein produced by ocular cells in response to oxidative stress. It stimulates endothelial cell growth, promotes vascular permeability and induces dissociation of tight

junction components. Currently, no therapy exists for dry-AMD and only dietary modifications such as increase in intake of antioxidants, cessation of smoking, and control of blood pressure appears to slowdown disease progression. The only approved treatment for dry-AMD is Age- Related Eye Disease Study (AREDS) recommended vitamin supplements that lower the risk of developing advanced stages of AMD [97]. The anti VEGF therapy is not a ultimate therapy as there may be chance of occurrence of resistance during the treatment course of time. The main reasons for the failure of Anti-VEGF treatment may be due to misinterpretation from the clinician and may also be due to certain genetic predisposition and this non compliance may happen at any time course from the beginning or following an initial successful treatment period [98].

Novel Compounds and Combination Therapy: These new anti VEGF agents and novel compounds targeting the least explored but effective mechanisms owing to the induction of neovascularization, has attained a great attention in the recent years. But by taking the difficulty in the availability and the economic factors into consideration, much effort has been taken to combine these different marketed therapies to reduce number of intravitreal injection and hence there cumulative exposure to the adverse drug events associated with these injections could be controlled to an extent without compromising the visual outcomes of the recipients [99]. The potential outcome could be achieved by developing a new dosage regimen by comparing the therapeutic molecule with synergistic effects which is a widely accepted and proven therapeutic strategy as in the case of cancer chemotherapy. The strategy of combining the potential inhibitor, first line anti VEGF with the edema reducing, second line corticosteroids has been an attractive research topic, like combination therapy with ranibizumab and triamcinolone acetonide which could not only reduce the frequency of injections but also able to combat some of the adverse events [99]. The main clinical concern remaining this therapy was the increased vulnerability to glaucoma and endophthalmitis. The other practised combination therapies are synergising antiangiogenic agents with photodynamic therapy (PDT), laser therapy and radiation therapy [100]. Triple therapy with anti VEGF, laser/radiation/PDT and corticosteroids are also effective in reducing the side effects. Combination of the novel therapeutic molecules with various aforementioned therapies was also found to be potential research strategy where all these combination approaches were found to be superior to monotherapy (Table 4) shows some of the novel compounds and combination therapies [101].

Table 4: Some of the novel compounds and combination therapies.

Novel Compound	Mechanism of action	Company	Stage of Development
E10030	PDGF inhibitor	Ophthotech	Phase III
Conbercept	VEGF receptor decoy	Chengdu Kanghong Biotech	Phase III
Sirolimus	mTOR inhibitor	Santen Pharmaceuticals, Inc. and MacuSight, Inc.	Phase III
DARPin/MP0112	VEGF inhibitor	Molecular Partners and Allergan	Phase II
Combretastatin A4 phosphate	Antimitotic agent	OXiGENE	Phase II
ALG-1001	Ophthalmic Integrin receptor blocker	Allegro	Phase II
AAV2-sFlt01	VEGF/PlGF inhibitor	Genzyme	Phase I
adGVPEDF.11D	PEDF gene therapy	GenVec, Inc.	Phase I
Sonepcizumab	anti-S1P	Lpath, Inc.	Phase I

Treatment Strategy	Pharmacologic Class	Combination Therapy
Dual therapy	Anti VEGF + PDT	Bevacizumab + Verteporfin PDT
Triple therapy	Anti VEGF + PDT + Steroid	Bevacizumab + Verteporfin PDT + Dexamethasone
Dual therapy	PDGF inhibitor + Anti VEGF	E10030 + Ranibizumab/ Bevacizumab
Dual therapy	Anti VEGF + Radiation therapy	Ranibizumab/ Bevacizumab + Radiation
Dual therapy	Anti VEGF + CABERNET	Bevacizumab+ Epiretinal brachytherapy
Dual therapy	Antiangiogenic siRNA based drug + Antiangiogenic small molecule	Bevasiranib + Squalamine

Potential Issues and the Need for Strategic Development in Patient Compliance Perspective: It is very often for a retinal specialist to perform approximately 60 intravitreal injections per week and also to come across patients who have done more than 70 injections in the eye without significant improvement in the visual acuity. Economic burden on the healthcare system is very large due to the high cost of these medications, the imaging studies required for the proper identification of the stage of disease along with the lacunae and due to large number of patients requiring multiple injections frequently. With more medications being approved and in the pipeline, the burden of costs will increasingly enter the debate of which medications to use in the treatment of this disease [102]. The potential developmental issues also extends to many systemic and intraocular side effects apart from the invasive nature of the therapy, the requisite of a medical practitioner for performing and the essentiality of preanaesthetics and other supporting medication after the intravitreal injection [103]. Given these many weaknesses involved in the treatment of PSEDs, future therapies are being developed to address this burden. Before the discovery of anti VEGF medication, the mechanism of pathogenesis of these vision threatening diseases were hypothesized to be highly complex, which slightly changed afterwards but the complete cure of blindness were not satisfactorily achieved in spite of all these sufferings, which thus now created a shift in paradigm in a more patient compliant perspective for fighting these blinding eye diseases in a more innovative less-invasive (topical dosage form) and long term drug delivery perspective [104]. The transscleral route need to be further explored for the development of a topical patient compliant self administrable dosage form side stepping all the barriers targeting the posterior segment of the eye [105]. Thus the current research goals are effective restoration of vision in a less invasive manner without significant economic burden, reducing the frequent clinical visits with the aid of novel drug delivery systems which can deliver the therapeutic concentration of the drug to the target at pre-determined intervals on a long term basis [106]. In addition, the combination therapy as already discussed may provide improved results as well as less frequent need for treatment [107].

Natural Product Inhibitors of Ocular Neovascularization

Nature is blessed by its unique diversity and biological specificity. Natural compounds are the valuable gifts of the nature which has the inherent capability to cure many anomalies. Ocular angiogenesis or neovascularisation is the main clinical manifestation of the PSEDs as already discussed (Figure 2) shows various natural products have the immense potential to prevent or treat these pathological angiogenesis conditions affecting the ocular posterior segment. Oxidative stress to the eye tissues is one of the major underlying principles for the exacerbation of the neo-vascular diseases that can be effectively managed by these promising natural therapies [108]. They are useful analogues for the effectual and economic treatment with minimal side effect without compromising the safety profile. These multifunctional natural compounds can be also be used in combination with certain synthetics or biologics and furthermore with the existing gold standard treatments, of non cancerous blinding eye diseases as they are powerful enough to circumvent the resistance offered by various drugs, by smart absorption, distribution, metabolism, excretion, and toxicity (ADMET) characteristics [109]. These natural compounds are of immense potential even to resist the hypoxia induced changes that could be the potential benefit offered by this nature's gift and also they can effectively target the neovascularisation site. In spite of all these, they are in stringent requirement of adequate quality control measures and safety guidelines to ensure the appropriate dosage specifications and route of administration parameters [110]. The

toxicity profile also needs to be thoroughly explored for the development of a fixed dose combination. There are various novel ocular neovascularisation inhibitors such as prolactin- an important endocrine secretion of human that is often involved in the milk production. Prolactin has the significant potential to target the retinal angiogenesis and will effectively inhibit the formation of new leaky vasculature formation [111].

Formulation Design Parameters for Controlled Drug Delivery System (CDDS)

The controlled release (CR) of drug can help in modifying the pharmacokinetic and pharmacodynamic properties of the body thus improving efficacy while reduced toxicity for the clinical advancement. At therapeutic level a control release unit dosage form provides ideal plasma profile that improves the therapy. Thus it is considered as a new therapeutic agent from regulatory perspective that improves the patient care [112]. They have the potential to be substituted for conventional therapy under certain circumstances. For example CR can substitute multiple administration of pilocarpine in the eye in glaucoma treatment. Ocusert is the system that works for CDDS for this purpose.The main parameters to be considered on the development of a formulation is the active pharmaceutical ingredient, type release profile required, duration of release and the route of administration and based on that the polymers, methodology and other constraints were put in to the main scene [113]. CDDS is also known as rate controlled DDS (RCDDS). RCDDS are the systems that release the loaded drug molecule from the DDS at a controlled rate that results in predictable drug profile in the respective compartments in the biological system and that are reproducible. This is accomplished by system designing applying engineering principle that control the molecular diffusion of drug molecules from the delivery system to the surroundings by controlling the diffusion , activation, feedback and site targeting. The classification of RCDDS includes [114].

- Rate pre-programmed drug delivery system- First generation
- Activation modulated drug delivery system- Second generation
- Feedback regulated drug delivery system- Third generation
- Site targeting drug delivery system- Fourth generation

The generations are classified on the basis of physical, chemical, physicochemical, biological phenomena respectively. Considering the CCDS for ocular drug delivery systems the first generation is of prime importance [115].

Rate Pre-Programmed Drug Delivery System

The release of drug molecules from the delivery system has been programmed at specific rate profile. It control the molecular diffusion of drug molecules in or across barrier medium with in surrounding the delivery system. The sub classification of this system includes [116].

- Polymer membrane permeation CDDS
- Polymer matrix diffusion CDDS
- Micro reservoir partition CDDS

Polymer membrane permeation CDDS: The drug formulation is totally or partially encapsulated within the drug reservoir compartment and its drug release surface is covered by a rate controlling polymeric membrane having specific permeability. The encapsulation of drug is carried out by spray coating, microencapsulation or other technique. These are the systems that control the molecular diffusion of the loaded drug by the mechanism of membrane permeation. The drug reservoir exist in solid, suspension or solution form which is a main parameter determining the release profile [117].

- Polymer Matrix Diffusion Cdds: The system that controls the molecular diffusion of the loaded drug by the mechanism of matrix diffusion. The system can be either heterolithic and monolithic which determines the duration of delivery [118]. In heterolithic system the drug reservoir is prepared by homogenously dispersing the drug particle in rate controlling polymer matrix fabricated from a lipophillic or hydrophilic polymer, where in the drug is dispersed in the polymer either by blending a therapeutic dose of freshly ground drug particles with the polymer or a liquid or highly viscous base polymer is mixed with the drug particles [119]. This is then followed by cross linking the polymeric chains. In another approach the drug solids are mixed with a molten polymer which is then casted coated or spray dried or compressed to prepare the drug delivery matrix. It can be casted as a thin sheet, coated over a nuclei or spray dried to prepare the particles [120]. The other approach is fabrication of the polymer matrix by dissolving the drug and polymer in a common solvent followed by solvent evaporation at an elevated temperature under vaccum to form a monolithic system. For short term delivery, monolithic systems that are easily retrievable are more appropriate while for long term delivery, heterolithic system is more preferred [121]. Two kinds of systems can be developed from matrix diffusion system – one using lipophillic membrane that produces a non swellable coating around the drug reservoir swellable polymer and the other using hydrophilic membrane that are less stable. Matrix diffusion based system offers a more long term delivery than polymer membrane permeation DDS [122].
- Micro Reservoir Partition Cdds: They are the system with micron size of drug suspensions that is dispersed in a polymeric matrix. In such systems, the drug reservoir is prepared by

pre-fabricating the microspheres or by emulsifying the drug dispersion followed by moulding or extrusion after dispersing in a polymeric matrix. The matrix can be any material such as polymer or ceramic which can be further coated to prolong the release. This system provides the longest duration of drug delivery among the three systems discussed [123].

Implications of Ocular Nanotherapeutics on Vitreoretinal Delivery

Gene Therapy

The gene therapy for treating the ocular angiogenesis occurs by altering the transcription process of the cell by infecting with a viral vector. For example the phase I trial product Retinostat is designed to deliver ocular neovascularization blockers such as endostatin and angiostatin by lentivirus vector infection and was found to exhibit a consistent expression after sub retinal delivery. Even though it was could showcase appreciable tolerability and localized effect without any systemic intervention, its usage in human body remains certain ambiguities [124]. Other viral vectors and pathways have also been studied. The nanoparticulate has gained attention in the recent years by its unique properties of endocytosis and hence the safe viral gene delivery could be effectively achieved at therapeutic concentration [125].

Introduction to Ocular Nanotherapeutics

The nanotechnology plays a tremendous role in improving the ocular therapy by exhibiting quantum size effect that is otherwise called as dimension dependent effect. Nanomedicines, products of nanotechnology, are fabricated to improve the penetrability to the static and dynamic barriers with improved stealth effect. Typical size range required for novel depot ocular application is below 200nm with almost 20-50 nm for topical ocular application for targeted posterior segment delivery, having at least one dimension in the nanoscale include colloidal system such as nanowafers, nanoparticles, liposomes, micelles, nanocrystals, nanotubes, composite nanosystems and dendrimers, with and without targeting ligands, are making a remarkable hike in the field of ocular drug delivery, gene delivery, and imaging [126]. Additionally, nanofabricated delivery systems including implants, films, ocusert, hydrogels, microparticles, and nanoparticles are described. Although the above nanomedicines may be administered by various routes including topical, intravitreal, intravenous, transscleral, suprachoroidal, and subretinal routes, each nanomedicine should be tailored for the disease, drug, and site of administration. In addition to the nature of materials used in nanomedicine design, depending on the site of nanomedicine administration, clearance and toxicity are expected to differ [127].

The Fundamental Principles of Nanosystems:

- Enhanced Cell Uptake and Gene Delivery: Due its small dimension which is relative to cells and organelles it could be easily up taken by the cells as in case of gene delivery compared to larger particles. Moreover the nano sized formulations have a greater ability to transfect the retinal tissues even by intra vitreal route [128].
- Reduced Settling Velocity: Since it is of small size, the uniform distribution of the suspended particles is promoted before adhering to the cells at the vicinity. So that they have minimized contact with efflux transporters favouring stealth effect and prolonged duration of action which is otherwise called as improved vitreal half life [129].
- Interactions with Large Surface Area of Cell Surface: Brownian movement is inversely proportional to the size of the particles. As the size decreases, the collisions with the large surface area of the cell increases and as the number of collisions increases the more the receptors get activated and hence more pronounced effect [130].
- Sustained Delivery: Due to the fabrication of the nanoparticle, as the drug particle in the reservoir is surrounded by a rate controlling membrane as described in formulation design part, which sustain the release profile. In a closer view, the reason for sustained delivery is, presence of less particles at the surface available for dissolution [131].
- Increased Tissue Accumulation Due to Enhanced Permeation and Retention Effect (Epr): Similar to the tumour vasculature, the ocular neovascular areas highly rich in leaky fragile new vessels which promote the accumulation of macromolecules by reduced lymphatic clearance [132].
- Multifunctional Nanomaterials: Microbubble technology for theragnostics, nanoparticles for imaging studies, magnetic nanoparticles and multi functional dendrimers with sustained release profile, improved cell uptake and improved solubility [133].
- Dose dependent Toxicities: The formulation aspect should concentrate on the selection of ingredients which are biocompatible and generally regarded as safe (GRAS) category. The nanosystem must be easily cleared from the body without causing any interference to the normal clearance mechanisms. The dose dependent toxicities and route related toxicities must be very low for an ideal nanosystem [134].

Application of Nanotherapy for Posterior Eye Delivery [135,136]:

- Bioadhesive nanoparticles with effective internalization
- Surface modified nanoparticles with more ligands

- Controlled delivery of drugs at pre determined interval
- Nanoparticles with enhanced and highly durable transfection
- Stimuli responsive nanoparticles- Light-activated systems, Thermo-responsive systems, In situ gelling systems, Ultrasound-responsive systems ,Conducting polymer based systems, Micro electro mechanical (MEM) systems and Oxidative stress responsive systems
- Diagnostics and imaging study
- Retinal prosthesis – a visual improvement strategy.

Polymeric Colloidal Nanotechnology Approaches – A Schematic Way of Understanding

The schematic way of understanding the colloidal nanoformulations for ocular therapy is discussed in (Figure 3) [137]. The structure, the therapeutic molecule to be encapsulated, the polymers used for formulation, the route of administration, the mechanism of activation and the clinical applications of all these nanoformulations are discussed [138].

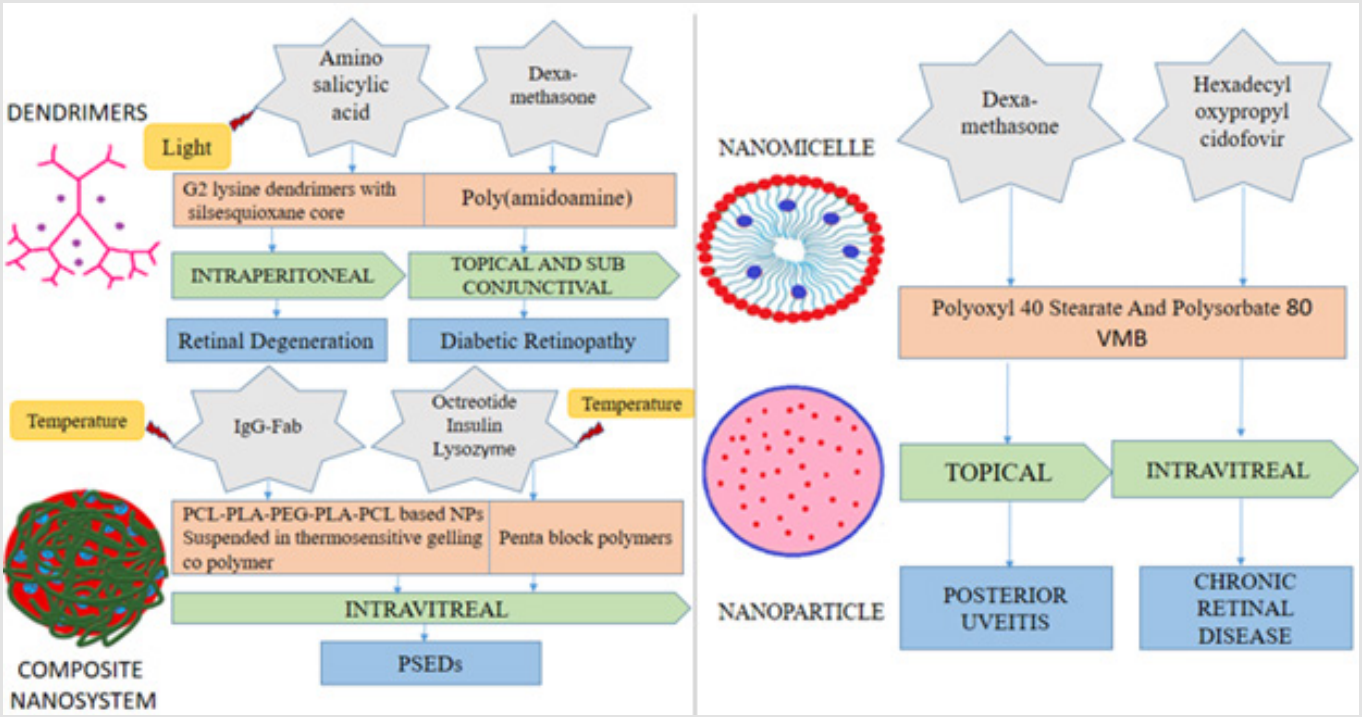

Figure 3: Novel nanoformulations for the treatment of PSEDs.

Non Invasive Strategies for Vitreoretinal Delivery [139]

- Macroesis/Iontophoresis
- Punctal Plugs
- Ocusert
- In situ gelling system
- Specialised nanoparticulate systems by topical route*

Some examples of non invasive strategies are described in Table 5.

Table 5: Investigational non invasive strategies in Posterior segment drug delivery.

Active Drug	Formulation/Approach	Clinical Condition	Site of Action
Bevacizumab	Liposomes	AMD	Cornea and retina
Dexamethasone	Micelles	Glaucoma	Cornea and retina
Amikacin	Iontophoresis	Scleral infections	Sclera

Cell Encapsulation Technology

Retinal cells are encapsulated into a semi-permeable scaffold made of biomaterials that facilitate the influx of nutrients and oxygen to provide the diffusion of therapeutic proteins directly to retina (vitreous humor) thus, bypassing the blood–retinal barrier (BRB) [140].

Future Perspectives and Conclusion

Most of the sight threatening diseases are associated with the vitreoretinal region of the eye which is highly protected by its unique static and dynamic barriers [141]. Technology portfolio analysis unwinds the fact that the current treatment strategies were not fully satisfactory in patient compliance perspective, due to high economic burden, invasive nature, inherent side effects related to the route and the dosage form strength [142]. It is high time to create a shift in paradigm to novel nanoparticulate drug delivery strategies for ocular therapeutics as this could be a promising strategy to develop an effective, long acting safe product that provide an optimal therapeutic effect with a minimum dose, reduced injection frequency, and use of appropriate route of administration with minimal side effects [143]. A more comprehensive understanding on the detrimental factors, rate limiting barriers, metabolic pathways of the drugs used, novel targets, clearance mechanism, significance of natural molecules along with formulation design concepts are required to develop and commercialize a technology in a translational point of view for effective restoration of vision [144,145].

Highlights

- Vitreoretinal diseases, related to posterior segment of the eye are the most catastrophic vision threatening eye diseases.
- Critically evaluated the technology portfolio analysis of current treatment strategies related to vitreoretinal diseases
- Suggested high requirement of novel routes and implications of ocular nanotherapeutics in a patient compliant perspective.
- Current research goals and relevant works are also discussed.

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