

Ocular Disorders and Associated Drug Development Challenges: The Current Scenario

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Abstract

Vision is one of the most important human sense and hence eye diseases leading to impairment of vision have been the hot topic for drug delivery research lately. Diseases like glaucoma, cataract, age-related macular degeneration, diabetic retinopathy and trachomatous trichiasis have been known for their potential of visual impairment as well as blindness. A vast amount of research has been done in understanding the pathophysiology, risk factors and drug development and drug delivery challenges associated with these diseases, but the clinical success achieved so far is very sparse. This leading to the requirements for the better understanding of the ocular diseases which can be translated to better drug delivery systems. The current review is formulated with the aims to provide a concise summary of these ocular disorders and to address the challenges in their drug development research.

Keywords: Ocular Drug Delivery Systems; Age-Related Macular Degeneration; Glaucoma; Cataract; Diabetic Retinopathy; Trachoma

Abbreviations

AMD: Age Related Macular Degeneration; DR: Diabetic Retinopathy; DME: Diabetic Macular Edema; OcDD: Ocular Drug Delivery Systems; WHO: World Health Organization

Introduction

Vision is one the most coveted sense and even minor decrease in visual efficiency is directly related to deterioration of quality of life [1]. The sense of vision is often indicated by the visual acuity which could be defined as the ability to discriminate two high contrast points in space. It is usually represented as X/Y, where the X refers to the distance at which the chart is being viewed for reading the last line in chart and the Y is the distance at which a "healthy" eye is able to read that line of the vision chart. The visual acuity of 6/12 to 3/60 represent the mild to severe vision impairment whereas the fraction worse than 3/60 indicates blindness [2].

As per WHO report on vision, approximately 2.2 billion population is suffering visual impairment and over 38.5 million cases of blindness are estimated [3]. Cataract, glaucoma and AMD are reported as the major cause of blindness relating to 39%, 10% and 7% of total blindness cases, respectively [4]. There is a suggestive rise in the cases of glaucoma and AMD up to 95.4 million and 243.3 million in 2020-30 which is majorly related to the ageing population and lifestyle [5].

The major ocular disorders that can affect the vision are unaltered refractive errors including myopia and presbyopia, cataract, glaucoma, AMD, diabetic retinopathy including macular edema, and trachomatous trichiasis [6]. Cataract could be defined as clouding of the crystalline lens in eye leading to loss of vision which is often treated by implantation of intraocular lens [7]. Glaucoma can be characterized by increase in intraocular pressure leading to optic neuropathy [8]. AMD is clinically characterized by deposition of small yellowish-white deposits called drusen and changes in retinal pigment epithelium in early stages, while neovascular AMD is caused by protrusion

of abnormal neovascularization in subretinal space leading to haemorrhages, intraretinal edema and fibrosis [9]. Diabetic retinopathy is often result of vascular damage caused in the microvasculature of retina leading to neuropathy and edema [10]. Trachomatous trichiasis is a result of progressive conjunctival scarring caused by recurrent chlamydia trachomatis infection [11].

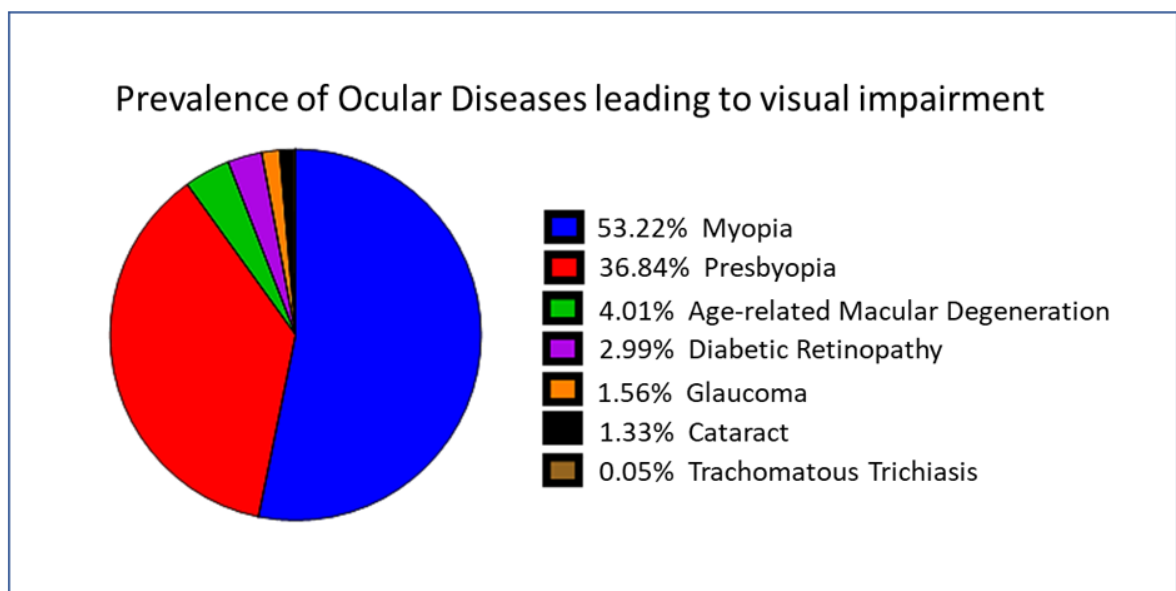


Figure 1: Graph presenting the prevalence of various ocular diseases that can lead to visual impairment. Adapted from WHO report on vision 2020 [3].

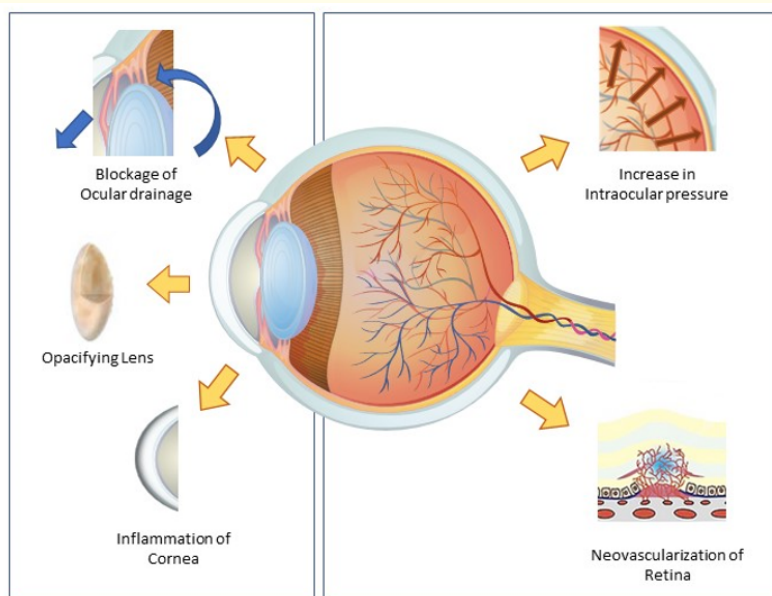


Figure 2: Schematic image suggesting various symptoms of ocular diseases and their site of impact. i.e. lens in cataract, drainage and IOP in glaucoma. Cornea in Trachoma and retinal neovascularization in AMD and DR.

Although several reviews have been reported to explain individual ocular disorders in depth, their management and challenges associated with these ocular disorders, there is a need of publication to discuss all threatening ocular disorders together and discuss the discrete and common challenges associated with them. In this review article, we would be discussing various serious ocular diseases that often lead to visual impairment, their pathophysiology, current treatment and challenges associated with current management of these diseases including discussion on the challenges associated with drug development to treat these disorders.

Diabetic retinopathy

Diabetic retinopathy (DR) is a retinal neovascular disease of the capillaries, arterioles and venules in the retina, and it is characterized by subsequent effects of leakage or occlusion of these abnormal vessels. The insensitivity to the concentration of Insulin is thought to be the major reason towards the projection of DR. The increasing levels of blood glucose leads to rise in retinal glucose levels and subsequent leakage of blood and other fluids in macular region leading to fluid accumulation and impairment of vision. This condition is termed as Diabetic Macular Edema [10].

The pathology of DR was well defined by Claire and Pirie. Essentially, diabetic retinopathy is a disease of the retinal microvasculature. Initially formation of microaneurysm, areas of focal thickening and capillary non-perfusion are observed. The subsequent progression of disease leads to exudates, haemorrhages and the proliferative stages of new vessel formation [12]. The cell signalling dysfunction in DR involves activation of Renin-Angiotensin-Aldosterone System, Alteration of Protein kinase C, Polyol pathway, hexosamine pathway as well as Advanced Glycation End-Products [10].

The treatment of choice for early stages of diabetic retinopathy is photocoagulation techniques but the regressive nature of disease leads to reoccurrence [13]. Panretinal photocoagulation is the most established method for treatment of DR, however, it is particularly effective in optic disc neovascularization [14]. Till date various treatment modalities have been developed which include laser photocoagulation therapy (argon and krypton laser [14], solid state laser [15]), intravitreal corticosteroid injections [16] (triamcinolone acetonide, dexamethasone and fluocinolone acetonide), intravitreal steroidal implants [17], as well as intravitreal anti-vascular endothelial growth factor (anti-VEGF) agents such as ranibizumab (Lucentis®) and aflibercept (Eylea®) and vitreo-retinal surgery which is considered as very costly, highly invasive, and is still unproven for prolonged use and opted in advanced stages of DR [18].

Currently, ILUVIEN® (Fluocinolone acetate implant) is the only injectable implant for the management of diabetic retinopathy that provides a sustained-release drug delivery system for the treatment of diabetic macular oedema for up to 3 years in patients who have been previously treated with corticosteroids and showed insignificant rise in Intraocular pressure in clinical assessments [19].

Age related macular degeneration

AMD is a leading cause of blindness in population over the age of 50 years or older. AMD can be subdivided into two types: dry (non-exudative or non-neovascular) and wet (exudative or neovascular), and nearly around 600,000 people in UK are affected with sight loss due to AMD [9,20]. Worldwide AMD is the third largest cause of preventable blindness nevertheless it is the leading cause in developed nations [3,21]. Although the causes of AMD are not entirely understood clinical studies have suggested that there is an impairment of choroidal blood flow in patients with AMD.

AMD was originally described by Haab in 1885. As per epidemiologic studies soft, large, and diffuse drusen and focal hyperpigmentation are observed during developing the exudative form of AMD commonly termed as basal linear deposit or basal laminar deposit [22-25]. The biomarkers for the progression of AMD have been reported and they include increased levels of C-reactive protein, autoantibodies cholesterol, vascular endothelial growth factor (VEGF), Eotaxin, Soluble FMS-like tyrosine kinase-1 as well as suPAR which represent the chronic as well as subclinical inflammation [21].

High energy laser beam is used for destroying abnormal blood vessels. Photodynamic laser therapy is one of the well accepted treatment methods for AMD in which a light-sensitive drug verteporfin (Visudyne) is injected into patient's bloodstream, after absorption by the abnormal blood vessels, the activation is done by laser to trigger the medication to damage affected blood vessels [26]. Recently, a

combination therapy of photocoagulation and anti-VEGF administration was compared to monotherapy with Lucentis in subjects with wet AMD [27].

The drug delivery system for diabetic retinopathy often coincide with that of AMD as the anti-VEGF therapy is preferred management for both the disorders. Currently Avastin (Bevacizumab), Lucentis (Ranibizumab) and Eylea (Aflibercept) are used for the clinical management of AMD. Brolocizumab is a small antibody fragment of VEGF inhibitor developed by Novartis. It was currently approved by USFDA for the clinical use of in wet-AMD [28].

Glaucoma

Glaucoma is characterized by the emergence of retinal neuropathies due to increased intraocular pressure. There are two major forms of glaucoma first being open angle glaucoma which is described by the resistance of aqueous outflow arising due to trabecular meshwork and the second form of glaucoma is closed angle glaucoma which is caused due to drainage pathway obstruction by the iris [29]. The pathophysiology of glaucoma involves the upregulation of various cellular mediators such as Tumor Necrosis Factor-alpha (TNF-alpha) and glutamate which combined with downregulation of growth factors and mechanical injury due to elevated intraocular pressure leading to cellular apoptosis. The intermediate cellular process such as increased Matrix Metallo Proteinase (MMP) expression and oxidative stress are also known to affect the progression of disease [30].

The clinical management of glaucoma primarily involves the lowering of intraocular pressure which could be achieved by laser treatment (i.e. selective laser trabeculoplasty), surgery (i.e. trabeculectomy and drainage tube implantation) and medication. The medicines used for management of glaucoma are varied and range from cholinergic and adrenoceptor agonist to carbonic anhydrase inhibitors [31].

Various ocular inserts and surgical implants have been developed for the effective management of glaucoma. Ocusert® system was developed for the sustained delivery of pilocarpine and it was able to deliver the pilocarpine for up to 7 days. Ocusert® system consists of poly (ethylene-co-vinyl acetate) membranes attached to each other with the ring of polymer filled with pilocarpine [32,33]. The design of the insert was reimagined to the increase the patient coherence with increased fit. Similar kind of insert has been developed for timolol drug recently [34]. Various other drug delivery systems and devices have also been reported for the management of glaucoma [35].

Cataract

The loss of lens transparency is termed as cataract and it is one of the most common reason for loss of vision. As per the estimates of WHO in 2010 approximately 51% cases of blindness translating to 20 million cases were related to cataract. Cataract can be classified into three forms based upon the clinical appearance, nuclear which is associated with the hardening of lens nucleus and often resulting into lens yellowing. Cortical resulting due to the development of cortical spokes which may or may not involve the visual symptoms and posterior subcapsular cataracts are result of granular opacities occurring in central posterior cortex under the posterior capsule. The etiology of cataract is not fully understood and it is believed to be multifactorial in nature [36]. Oxidative stress is believed to play important role in the pathophysiology of cataract as high concentrations of anti-oxidants such as GSH has shown to prevent the lens transparency [37].

The clinical management of cataract involves the surgical replacement of the opacified lens and it may lead to various postsurgical complications including increased intraocular pressure and uveitis [38]. Drug delivery of various antioxidants have shown to improve the lens transparency but the formulation of ocular inserts for sustained release of drug for management of cataract has been sparse [39].

Trachoma

Trachoma is a mucopurulent inflammation of conjunctiva and cornea, wherein follicular and inflammatory response occurs in upper palpebral conjunctiva. There are basically four types of trachoma reported i.e. allergic conjunctivitis, viral conjunctivitis, bacterial conjunctivitis and inclusion conjunctivitis [40]. The extraocular mucous membranes like nasopharynx can also be infected with *C. tra-*

chomatis. It is one of the most neglected tropical disease and the leading cause of blindness that can be prevented with the help of drug administration [41].

Typical clinical manifestations in an endemic area seems enough for the diagnosis. However, laboratory tests are needed to confirm the diagnosis [42]. Causative agent for trachoma is *Chlamydia trachomatis* serotypes A, B and C intracellular bacteria. Ocular surface infection of chlamydia causes chronic inflammatory reaction leading to infiltration of lymphocytic, monocytic and plasma cells along with macrophages [43].

Eyelid surgery is performed to block the progressive corneal damage preventing chronic pathway to blindness [44]. Although various oral antibiotics were used to prevent *C. trachomatis* such as tetracyclins, erythromycin, macrolides and rifampin, sulphonamides were the first agent to provide specific effective treatment [45]. Nevertheless, patients are required to complete adequate therapeutic period that is 2 - 3 weeks, considering substantial untoward effect of antibiotics more specific and targeted delivery was designed such as oily suspension of 1% tetracyclines. The single dose of antibiotics such as azithromycin was found to be an effective treatment measure for trachoma and it is donated by Pfizer under the International Trachoma Initiative through 2025 Initiative [46,47]. A targeted drug delivery system of Amoxicillin based upon Iron acquisition pathway was developed by Hai., *et al.* The authors reported Human serum transferrin as a trojan horse for the active targeting of the antibiotic. The transferrin-amoxicillin construct was found to be a better treatment strategy than amoxicillin alone [48].

Discussion

The major challenge towards the development of ocular drug delivery systems is imposed by the physiological and anatomical barriers of the eye [49]. Anatomical barriers of eyes could be represented by blood aqueous barriers and blood retinal barriers whereas the physiological barriers such as volume constraints, serious precorneal elimination through nasal cavity, nasolacrimal drainage are the major obstacles in drug delivery to the eye [50].

The involved area for potentially blinding diseases of the eye range from conjunctiva as in case of trachoma to the retina and underlying layers in diabetic retinopathy and AMD. So far various routes of administration, different formulation variables and variety of vesicular drug delivery systems have been developed for the targeted delivery to the affected ocular area [51]. Although topical delivery is widely used due to ease of administration and patient compliance, it is often limited by the inability resulting due to low corneal permeation, less bioavailability to the posterior segment of eye. Hence, various other routes for ocular drug administration have been reported, the benefits and shortcomings of the available routes of administration have been tabulated below.

Route	Benefits	Challenges
Intravitreal	Direct delivery to vitreous and retina, sustained levels of drug, evades blood-retina barrier	Retinal detachment, haemorrhage, cataract, endophthalmitis, patient in compliance
Intracameral	Higher drug levels in anterior chamber, eliminates use of drops, reduces corneal and systemic side effects seen with topical steroid therapy	Toxic anterior segment syndrome, toxic endothelial cell destruction syndrome
Subconjunctival	Anterior and posterior delivery, potential for depot formulations	Conjunctival and corneal circulation
Subtenon	High vitreal drug levels, relatively non-invasive, fewer complications than intravitreal	Retinal pigmented epithelium, chemosis, subconjunctival haemorrhage
Retrobulbar	High local doses of anaesthetics, more effective than peribulbar, minimal effect on intraocular pressure	Retrobulbar haemorrhage, globe perforation, respiratory arrest
Posterior juxtасcleral	Safe for depot delivery, sustained drug levels for up to 6 months to macula, avoids risk of endophthalmitis and intraocular damage	Surgery, retinal pigmented epithelium acts as barrier.
Suprachoroidal [53]	No increase in intraocular pressure, local route for the treatment of noninfectious uveitis	Retinal neovascularization, blurred vision, eye pain, cataract

Table 1: Available route of ocular drug administration, their benefits and challenges adapted and modified from Gaudana., *et al.* 2010 [52].

Worldwide every minute five people are going blind, in developed nations it is macular degeneration, diabetic retinopathy or macular oedema and in rural areas trachoma are the leading causes of blindness. Fifteen years since the market breakthrough, Vascular endothelial growth factor inhibitors (anti-VEGFs) have retained their status in ophthalmology for the promising future. Anti-VEGFs aflibercept and ranibizumab have expanded beyond their original indications for wet AMD, and are now currently approved for macular edema, Retinal vein occlusion, diabetic macular edema and diabetic retinopathy covering a huge spectrum of the blindness causing diseases. With their steady spread to every common condition, anti-VEGFs are driving physicians further away from earlier lasers and steroids treatments. FDA recently approved Lucentis[®] (Ranibizumab) 0.3 mg Prefilled Syringe for diabetic macular edema and diabetic retinopathy which is originally indicated for wet AMD [54]. The recent advances in the drug discovery and development for the management of Wet-AMD has been overwhelming. Currently, Brolucizumab and RGX-314 gene therapy were approved by US FDA for the management of Wet-AMD along with drugs such as Sunitinib, Apl-2 and endoglin, activin and tissue factors are being tested in different level of Clinical trials indicating the high availability of various drugs for combination therapy and better management of Wet-AMD [55,56].

While the extensive research is being carried out in the field of drug molecules and drug delivery, there is a gap in terms of established *in-vitro* or *ex-vivo* models for studying their safety and therapeutic potential. One of the major challenge for the tissue study is degree of variability in the tissues across various species [57]. Martens, *et al.* and Xu, *et al.* have developed *ex-vivo* model using cadaveric cow eye to study large molecules such as viral or non-viral gene carriers. The model is highly relevant allowing us to study static barriers in eye to study intravitreal diffusion of molecules but it is less straightforward in nature [58,59]. The model does not take into account role of dynamic barrier such as motion of vitreous humour during eye movement, aqueous humour convective flow due to temperature gradient between anterior and posterior part [60]. Various co-cultures of blood retinal barrier cell types using astrocytes, pericytes, primary endothelial cells have been developed to study *in-vivo* roles of Blood Retinal Barrier. Retinal explants and diffusion chambers have been used to study rate and extent of penetration of drug molecules into retina [61]. The viability of *ex-vivo* eye is limited to 9 hours limiting the application of *ex-vivo* studies in assessment of long acting implants. This leads to a demand of sustainable and validated *in-vitro*, *in-vivo* and *ex-vivo* techniques for assessment of novel ocular drug delivery systems.

There have been a considerable amount of improvements in ocular treatment from earlier formulations such as laser treatment, topical eye drops, ointments, intravitreal injections to the long-term ocular implants including retinal prosthesis using intelligent medical implants [62]. The Dynamic Phototherapy has also evolved from earlier generalised procedure towards truly personalised procedure for eye treatment with Johnson and Johnson's iDESIGN for the LASIK treatment [63]. Bioengineering and therapeutic sciences are also getting considerable attention to develop a bioengineered polymer-based device for ocular drug delivery. For example, novel photo-crosslinked preformed biodegradable pre-formed implant and in-situ depot forming implants are under development to deliver small molecules and proteins using 27G hypodermic needles for sustained release up to 4 - 6 months [64]. However, the drug delivery systems for ocular delivery are still limited for clinical application as only port delivery systems (PDS) is currently in Phase II clinical trials suggesting requirement for evolution of ocular drug delivery systems [65].

Conclusion

In the past two decades, extensive research has been carried out in the field of new drug development and drug delivery systems but very little is studied about *ex-vivo/in-vivo* models for establishing efficacy and safety of these delivery systems. And, despite technological breakthroughs in molecules and delivery system, patient responsiveness remains major challenge which could be majorly related to the lack of suitable biological techniques that are correlated to real time biological conditions of human. Current biopharmaceuticals are plagued with low bioavailability across ocular tissues, low storage and handling stability, administration challenges, scalability and high manufacturing costs. Therefore, future research should cornerstone on development on non-invasive, highly stable, improve bioavailability of proteins and small molecules including therapeutic peptides as suitable drugs and their delivery systems that could address the need of growing disease statistics.

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Conflict of Interest

Dr Thakur is founder of Re-Vana Therapeutics and Mr Mishra and Miss Gade are PhD students funded by Marie Skłodowska-Curie-H2020-ITN ESR Fellowship.

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