Advanced drug delivery and targeting technologies for the ocular diseases

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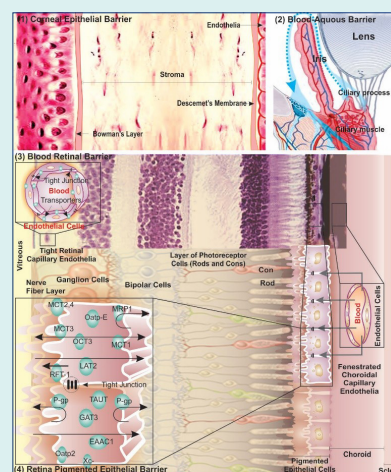
Abstract

Introduction: Ocular targeted therapy has enormously been advanced by implementation of new methods of drug delivery and targeting using implantable drug delivery systems (DDSs) or devices (DDDs), stimuli-responsive advanced biomaterials, multimodal nanomedicines, cell therapy modalities and medical bioMEMs. These technologies tackle several ocular diseases such as inflammation-based diseases (e.g., scleritis, keratitis, uveitis, iritis, conjunctivitis, chorioretinitis, choroiditis, retinitis, retinochoroiditis), ocular hypertension and neuropathy, age-related macular degeneration and mucopolysaccharidosis (MPS) due to accumulation of glycosaminoglycans (GAGs). Such therapies appear to provide ultimate treatments, even though much more effective, yet biocompatible, noninvasive therapies are needed to control some disabling ocular diseases/disorders.

Methods: In the current study, we have reviewed and discussed recent advancements on ocular targeted therapies.

Results: On the ground that the pharmacokinetic and pharmacodynamic analyses of ophthalmic drugs need special techniques, most of ocular DDSs/devices developments have been designed to localized therapy within the eye. Application of advanced DDSs such as Subconjunctival insert/implants (e.g., latanoprost implant, Gamunex-C), episcleral implant (e.g., LX201), cationic emulsions (e.g., Cationorm™, Vekacia™, Cyclokat™), intac/punctal plug DDSs (latanoprost punctal plug delivery system, L-PPDS), and intravitreal implants (I-vitaion™, NT-501, NT-503, MicroPump, Thethadur, IB-20089 Verisome™, Cortiject, DE-102, Retisert™, Iluvein™ and Ozurdex™) have significantly improved the treatment of ocular diseases. However, most of these DDSs/devices are applied invasively and even need surgical procedures. Of these, use of de novo technologies such as advanced stimuli-responsive nanomaterials, multimodal nanosystems (NSs)/nanoconjugates (NCs), biomacromolecualr scaffolds, and bioengineered cell therapies need to be further advanced to get better compliance and higher clinical impacts.

Conclusion: Despite mankind successful battle on ocular diseases, our challenge will continue to battle the ocular disease that happen with aging. Yet, we need to understand the molecular aspects of eye diseases in a holistic way and develop ultimate treatment protocols preferably as non-invasive systems.

Introduction

In the human eye, like all other mammals, non-image-forming photosensitive ganglion cells within the retina function to receive the light signals and react accordingly towards translation of the signals and visualization. The human eye functions perfectly by harmonized co-operation of the related bio-micro-machineries of the eye (e.g., reflection of the pupil, function of eye muscles and lacrimal gland secretory processes), with responsiveness of the related neural centers of the brain (i.e., cortical and subcortical brain regions), functions of the hormonal system (e.g., regulation and suppression of melatonin) and even the regulation of body clock.

Anatomically, the eye globe is divided into anterior and posterior segments, respectively occupying one-third and two-third of ocular tissues. The anterior segment contains

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the cornea, conjunctiva, iris, ciliary body, tear film, and aqueous humor, and the posterior segment encompasses the sclera, choroid, Bruch's membrane, retina and vitreous humor.[1]

Impeccable functionality of the visual cells is largely dependent upon integrity of the cells/tissues in posterior and anterior segments of the eye, where selective restrictiveness of the ocular tissues membranes and barriers control the shuttling of solutes to maintain the ocular homeostasis through perfect functions of ocular biological barriers. These impediments include (a) corneal epithelial barrier, (b) iris blood vessel endothelium, (c) ciliary body epithelium (CEB), (d) inner barrier of retina formed by retinal capillary endothelial cells, and (e) retinal barrier formed by retinal-pigmented epithelial cells. Up until now, different cell models have been used to examine the functions of various barriers of the eye and to address their impacts on topical and/or intraocular delivery of ophthalmic drugs.[2]

As a general principle in the ocular pharmacotherapy, treatment of the ophthalmic diseases often necessitate advanced drug delivery systems (DDSs) and devices (DDDs) ideally for programmed/long-term liberation of drug into the anterior or posterior segments of the eye to enhance the patient adherence to the treatment regimen and hence success of the therapy. However, the currently used conventional therapies often associate with low bioavailability because of physiobiologic barriers of the eye while the systemic DDSs must cross the retinal barriers.

The dry eye syndrome (DES), inflammation, allergies and infections of the eye, macular degeneration, cataracts, diabetic retinopathy and glaucoma are primarily largely age- and/or lifestyle-related diseases.[3]

To address the clinical relevance of ocular barriers in targeted therapy of the ophthalmic diseases, in the current article, we will discuss the recent advancements in crossing and/or circumventing ocular barriers through implementing noninvasive sustained-/controlled release injectable or implantable DDSs.

Ocular pharmacokinetics

Drug pharmacokinetic (PK) analyses in human subjects are prerequisite for any new pharmaceutical. For the ocular drug products, however, the PK studies in human subjects are waved because the serial sampling from the aqueous humor or the vitreous humor is not applicable for PK assessments. As a substitute, animal models (e.g., rabbit, dog, monkey and pig) whose eye sizes are similar to the human eye are used to conduct ophthalmic experiments, even though there exist some differences between human and these models. Despite all these shortcomings, still the rabbits are most commonly used for PK studies.[4] It should be stated that the serial sampling of target tissues of the eye is extremely challenging in terms of sampling procedure and volume, as a result the ocular PK experiments demand a large number of animals to attain reliable PK data such as area under the curve (AUC), time to maximum tissue concentration (T_{max}) and peak tissue concentration (C_{max}) – necessary for the approval of any new drug

application. Taken all, ocular PK studies are very laborious, time consuming and expensive, which require implementation of different techniques such as microdialysis assessment that is based on a capillary dialysis probe for continuous sampling of aqueous and/or vitreous humors from the same eye.[5] In the case of sustained-release DDSs when drug liberation needs to be assessed for a long-period of time, the microdialysis technique cannot be applied and periodic sampling with a designated number of animals can provide adequate data. Further, this approach is not suitable for the continuous drug level assessment in tissues such as the iris-ciliary body and the retina.

Using suitable animal models and drug analyses techniques, drug liberation and distribution can be assessed. PK parameters such as AUC, T_{max} and C_{max} are normally the ones that are used for the relative bioavailability (the so-called "relative amount of absorption") comparison among formulations, while the absolute bioavailability (the so-called "actual fraction of the dose absorbed") can only be calculated upon direct drug dosing in the target tissue.

In 2004, Tojo developed a PK model for the ocular drug delivery based on Fick's second law of diffusion, assuming a modified cylindrical eye with three routes of drug transportation including the anterior aqueous chamber, the posterior aqueous chamber and the retina/choroids/scleral membrane. In this model, parameters such as the diffusion coefficient (DC) and the partition coefficient (PC) were assessed from the in vitro membrane penetration experiments by means of a side-by-side diffusion cell system for various eye tissues, and the DC for a drug can be estimated through the effect of the molecular weight of the model compound. This PK model was proposed to predict the biodistribution in the various fluids or tissues of the eye. The model was claimed to be able to simulate the effects of binding and metabolism in the eye.[6]

Based on a homogeneous biodistribution of drugs within the ocular tissue, as one of the best experiments, Jones and Maurice proposed a method for determining the rate of loss of fluorescein from the aqueous humor in human eye by introducing dye into the cornea using iontophoresis and following the distribution of the dye in the eye.[7] This model was further developed by Maurice and Mishima who capitalized on an assumption that the PK of ophthalmic drugs can be assessed by compartmental models,[8] even though the compartmental analyses may associate with some limitations such as weakness in providing accurate PK data because of lack of detailed information upon the local drug distribution in the eye. Further, drug elimination via various routes of the eye as discussed previously may affect the local tissue concentration, hence the concentration of administered drugs in the aqueous chamber and in the vitreous body will explicitly be inhomogeneous showing a complex distribution pattern. As a result, in vivo data obtained by means of simple compartmental analysis may fail to fully correlate the pharmacological response that might directly be related with the local target concentration and distribution of drug. Taken all, as shown in

Fig. 1, two-compartment model can be used to analyze the drug exchanges that can occur in the eye after the topical administration. In this model, the primary assumptions are (i) negligible loss of drug via tears, (ii) insignificant entry into the aqueous humor from the tears other than the cornea, (iii) trivial exchanges between the cornea and blood at the limbus, and (iv) negligible exchanges of the aqueous humor with the posterior reservoir.[8]

Based on a two-compartment open system of conventional pharmacokinetics,[7,8] one may consider following kinetic equation (Eq.) 1 for the mass transfer aqueous humor to the blood after topical application:

$$\frac{dC_a}{dt} = k_0(C_p r_{ap} - C_a) \qquad \text{Eq. 1}$$

Where, k_0 is the transfer coefficient from the aqueous humor to the blood; C_a and C_p are the concentrations in the aqueous humor and blood plasma, respectively; and r_{ap} is the value of the ratio C_a/C_p at steady state.

The administered drug to the cornea can penetrate to the anterior segment, hence the transfer coefficient k_c may define the exchange of the used drug between the cornea and the aqueous humor and is referred to the volume of the cornea, which can be defined by Eq. 2.

$$\frac{dC_c}{dt} = k_c(C_a r_{ca} - C_c) \qquad \text{Eq. 2}$$

Where, C_c is the corneal concentration defined as the mass of drug in the entire cornea divided by the total volume of the tissue, V_c.

It should be noted that the transfer coefficient k_{ca} shows the drug exchange between the cornea and aqueous humor and is referred to the volume of the aqueous humor, which can be defined by Eq. 3:

$$\frac{k_{ca}}{k_c} = \frac{V_c}{V_a} r_{ca} \qquad \text{Eq. 3}$$

Where, V_a represents the volume of the anterior chamber. The equilibrium ratio r_{ca} is the value of the ratio C_c/C_a when dC_c/dt is zero. The expression $V_c r_{ca}$ can be termed the apparent volume of the cornea. It should be highlighted that since V_c and V_a are determined, only two of the parameters k_{ca}, k_c, and r_{ca} are independent.

Based on Fick's second law, Tojo hypothesized that the concentration of a designated drug in the eye can be given by the following pharmacokinetic model shown as Eq. 4:

$$\{1 + B(x,y,t)\}\frac{\partial C}{\partial t} = \frac{1}{x}\frac{\partial}{\partial}(xD\frac{\partial C}{\partial x}) + \frac{\partial}{\partial y}(D\frac{\partial C}{\partial y}) - R(x,y,t) + S(x,y,t) \quad \text{Eq. 4}$$

Where, D is the diffusion coefficient in the eye, $B(x, y, t)$ is the binding term, $R(x, y, t)$ is the metabolism and degradation rate and $S(x, y, t)$ is the release rate of drug from the DDS implanted or injected into the target site. It should be noted that in this equation D is not considered as constant and varies in the ocular tissues.[6]

All together, the simple compartmental analyses seem to provide satisfactory data for the kinetics of hydrophilic substances. However, such models may not provide accu-
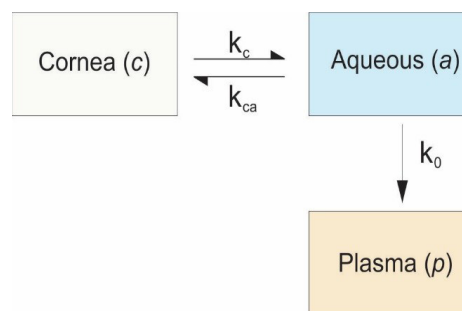

Fig. 1. Schematic representation of two-compartment model for topical use of ocular drugs. The k_c and k_{ca} represents transfer coefficients between the cornea (c) and aqueous humor (a), and k_0 is the loss coefficient from the aqueous to the plasma (p). The model was adapted from previously published works.[8]

rate outcome because drugs can penetrate into different tissues rather than the assumed compartments and show complex distribution patterns in large part due to solubility tendency of drugs in aqueous humor and lipid membranes of different segments of the eye such as the corneal epithelium, the lens, and the uveal tissue that are neglected. Besides, there may be nonlinear relationships between the magnitude of the reservoirs and barriers formed by these tissues and the concentration of the drug.[8] It seems that, in addition to fluorescein used for elucidating the kinetics of hydrophilic drugs, we need to capitalize on some other lipid-soluble fluorescent tracers to be able to interpret the complex pattern of drug distribution in the eye. The PK studies in the eye need further advancements using not only the experimental models but also computer-based simulation and modeling.

Ocular barriers

All the biological membranes and barriers selectively regulate traverse of locally and/or systemically administered drugs and blood-borne molecules to the anterior and posterior compartments of the eye.[9] Fig. 2 schematically represents the perfect function of the ocular biological membranes and barriers. The cornea as an avascular transparent multilayered epithelial cells represent a primary sensitive tissue that can block the translocation of topically administered pharmaceuticals (e.g., eye drops, ointments, gels, or emulsions) into the cul-de-sac. The ocular biological membranes and barriers are considered as the most robust controlling machineries of harmonized group of cells and tissue in an organ.[10] In fact, the consistency of such harmonized functions of the eye is utterly dependent upon the (a) static barriers (e.g., different layers of cornea, sclera, iris/ciliary body through blood-aqueous barrier and retina through blood-retinal barriers), (b) dynamic barriers (e.g., tear dilution, choroidal and conjunctival blood flow, lymphatic clearance), and (c) efflux pumps such as multidrug resistance (MDR) known as P-glycoprotein (P-gp) and multidrug resistance proteins (MRPs). Most of these functions within the ocular capillary are similar to the blood-brain barrier (BBB) functions that controls the inward and/or outward traverse of molecules
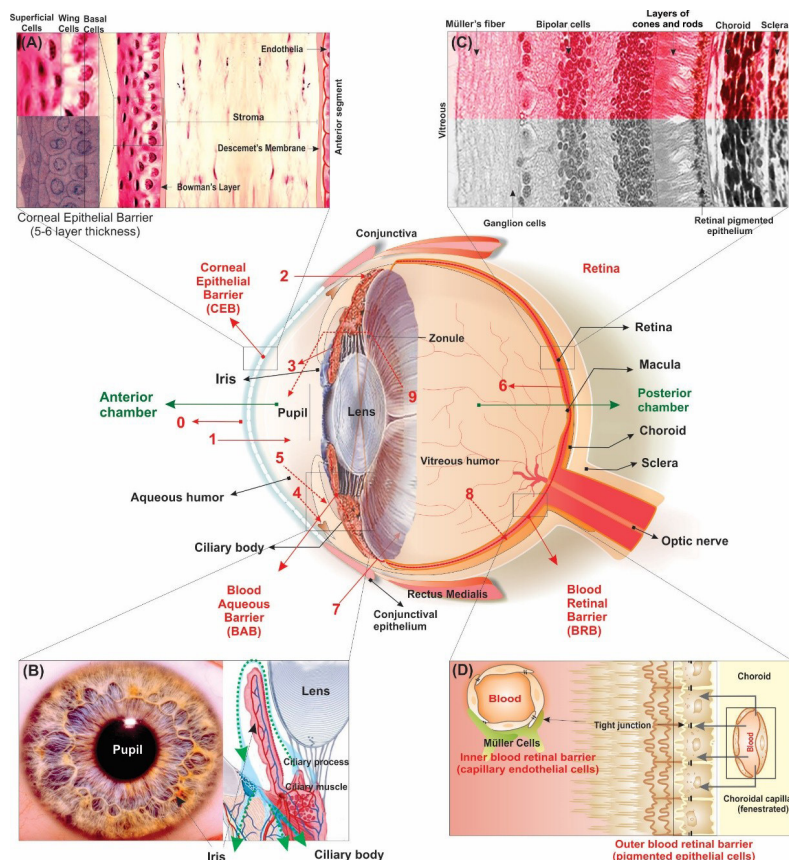
Fig. 2. Schematic demonstration of the anatomy and the biological membranes and barriers of the eye. Panels A, B, C and D represent the corneal epithelial barrier (CEB), the blood aqueous barrier (BAB), the biostructures of retina, and the blood-retinal barriers (BRB) both inner endothelial and outer pigmented epithelial barriers. The hemostasis of eye is performed by several static and dynamic barriers. Tear film is the first physiologic impediment against installed topical pharmaceuticals (0). The cornea forms an excellent obstacle preventing topical drugs to reach the anterior chamber of the eye (1). The conjunctival/scleral route is the most permeable path to the hydrophilic drugs and macromolecules (2). The systemically administered small compounds are able to penetrate from the iris blood vessels into the anterior chamber (3). The administered drugs reached to anterior chamber are subjected to aqueous humor outflow (4). These drugs can be carried away from anterior chamber by venous blood flow (BAB function) after diffusing across the iris surface (5). The systemically administered drugs must cross the BRBs. These drugs must cross the outer retinal barrier, "retinal pigment epithelia (RPE)" and the inner retinal barrier, "retinal capillary endothelia (RCE)" (6). For intravitreal delivery, drugs can directly be injected into the vitreous (7). Drugs can be removed from the vitreous away by the retinal blood vessels (8). Drugs within the vitreous can be diffused into the anterior chamber (9).

into brain.[10-13] It should be noted that, similar to any other biological barriers,[10] the blockade function of the ocular barriers vary significantly. The bio-physiologic nature and barrier functions of the ocular barriers such as blood aqueous barrier (BAB) formed by the endothelial cells in the iris and the blood-retinal barrier (BRB) formed by the retinal inner capillary endothelial cells show different pattern and degree of impediments. This assumption can be proven by the systemic administration of ocular drugs, after which the concentration of drug in the aqueous humor is significantly higher than the vitreous humor. This clearly indicates that the BRB represents much more restrictive barrier functions to drug penetration in comparison with the BAB. While the endothelia of choroid is largely fenestrated, the retinal capillary endothelia (RCE) represent an inner tight barrier which together with the outer barrier formed by the retinal pigmented epithelia (RPE) control the traverse of blood-borne molecules into the posterior segment of the eye.

Similar to the BBB that represents a tight barrier as coop

with pericytes and astrocytes,[14,15] in the retina pericytes and Müller cells interact with the RCE and also contribute to the establishment of the BRB through production of biofactors such as angiopoietin-1 that promote a well-developed junctional complex and endothelial barrier formation. These endothelial cells secrete platelet-derived growth factor beta (PDGF-B) to harness and maintain pericytes by activating Akt, whose activity is the basis of the cell survival.[16] Perhaps, the perfect barrier functions of BRB is based on dual functions of both inner and outer barriers of retina. All these complex biological systems create the anatomical architectural hallmarks of the eye. Technically, as the mostly used ocular pharmaceuticals, the topical dosage forms usually in the forms of solutions and semisolids are routinely locally administered. However, given that most of these medications can be easily washed away from the ocular surface, their administrations result in markedly low bioavailability failing to reach the posterior segments and hence the intended pharmacological effects do not occur. Further, the sys-

temic delivery of ocular drugs into posterior segment of the eye often fails because of the excellent barrier function of BRB. Since the current strategies upon efficiently delivery of the ocular drugs to the site of action within the eye and treat the ocular diseases provide limited successes, intraocular drug delivery and targeted therapy of the ophthalmic diseases appear to be very challenging. At the moment, the intravitreal injection is the main treatment modality of the disabling ocular diseases such as the age-related macular degeneration (AMD) that is basically treated by anti-vascular endothelial growth factor (VEGF) therapies including pegaptanib (Macugen), ranibizumab (Lucentis) and bevacizumab (Avastin).[17-20] Nevertheless, such strategy is an invasive treatment modality that may be inevitably associated with some serious adverse consequences. Systemic administrations are also considered as suitable methods for a number of pharmaceuticals that possess deisred physicochemical and biopharmaceutical characteristics. The ocular diseases pharmacotherapy via subconjunctival and periocular (sub-Tenon's and peribulbar) routes are deemed to provide prolonged pharmacologic impacts with low toxicity. The uses of conventional dosage forms in the ocular diseases, despite showing some benefits, have some pitfalls including (a) necessity for the repetitive use of medicament that results in a poor patient compliance, (b) difficulty of insertion in the case of ocular inserts, and (c) being considered as an invasive approach when injected/implanted that is also associated with some tissue damages too. Fig. 3 represents the currently codified routes of drug administration for the ophthalmic diseases.

Challenges to reach the anterior segment of the eye

To reach the desired target sites of the eye either locally or systemically, the ocular drugs must cross the ocular static, dynamic and metabolic functions. For instance, DuraSite
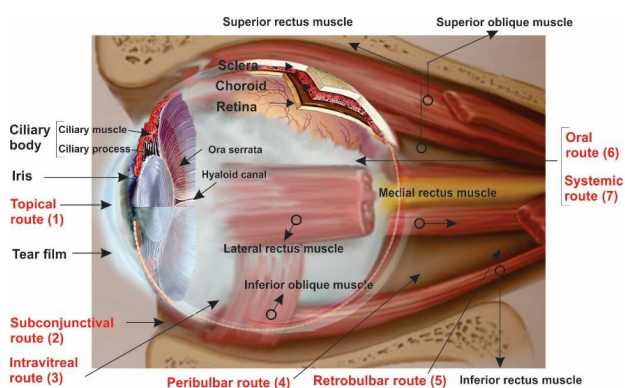
system can be customized to deliver a wide variety of potential drug agents, which has been developed by InSitVision Inc. DuraSite™ is a drug delivery vehicle that enables stabilization of small molecules in a polymeric mucoadhesive matrix that has been used as a carrier for several ophthalmic drugs including azithromycin (AzaSite Plus™; ISV-502), dexamethasone (DexaSite™; ISV-305), bromfenac (BromSite™; ISV-303), tetracycline (ISV-102) and prostaglandin (ISV-620; ISV-215). Likewise, Table 1 represents some of the recently developed ophthalmic medicines used for treatment of ocular diseases in the anterior segment of the eye.

Impacts of corneal barrier

Topically applied drugs face various static (corneal epithelium, corneal stroma, and blood–aqueous barrier) and dynamic (conjunctival blood flow, lymph flow, and tear drainage) barrier functions of the anterior segment while the involved cells are able to control trafficking of the penetrated drugs through regulating the expression of inward and outward transport machineries and even pose metabolic functions on them.[1] Such biological structures can selectively control the transportation of substances within the eye, in which the epithelial and/or endothelial cells are sealed by the tight junctional complexes. Fig. 4 schematically illustrates the corneal barrier.

The layers of corneal epithelial cells (i.e., superficial, wing and basal cells) forms an excellent tight barrier restrictiveness, in which functional expression of tight junctions prevent paracellular trafficking of topical drugs into the anterior segment while the transcellular trafficking of lipophilic drugs may face with selective modulations of carrier-mediated transporters such as P-gp.

Tear film and lacrimation

It should be noted that the amount and composition of the tear film (the so-called tearing or lacrimation) have

Fig. 3. Main routes for the administration of ophthalmologic medicaments. Administered ophthalmologic drugs face with several important physiologic and anatomic modulation and hindrance that make the eye exceedingly impermeable to exogenous substances, including the corneal epithelial barrier against topical dosage forms, non-corneal structures inability in absorption of foreign compounds, lacrimation, effective drainage through the nasolacrimal system and the excellent function of inner endothelial and outer epithelial barriers of retina. Drug administration to the eye is accomplished through non-invasive or invasive methods codified by the US FDA.

Fig. 4. Schematic illustration of the corneal structure. The corneal epithelial cells form 5-6 layers of cells composed of superficial, wing and basal cells creating the static barrier of the cornea. Corneal epithelial barrier (CEB) house some important transport machineries that function in favor of mechanism of CEB through selective regulation of inward and outward traverse of exogenous substances. The passive diffusion of lipophilic compounds as transcellular passage is the main drug penetration path into the anterior segment.

Table 1. The recently developed ophthalmic medicines for the anterior segment of the eye

Drug, dosage form	Brand, manufacturer or stage of development	Clinical indication	Main excipient(s)	Ref
Azithromycin Topical ophthalmic solution	AzaSite™, Inspire Pharmaceuticals Inc.	Bacterial conjunctivitis	DuraSite® drug delivery technology, Polycarbophil	[21, 22]
Azithromycin/Dexamethasone, Topical ophthalmic solution	AzaSite Plus™ (ISV-502), InSite Vision Inc.	Blepharoconjunctivitis	DuraSite® drug delivery technology, Polycarbophil	[23]
Bromfenac Topical ophthalmic solution	BromSite™ (ISV-303); InSite Vision Inc.	Ocular inflammation; Pain; Cataract	DuraSite® drug delivery technology, Polycarbophil	[24, 25]
Dexamethasone, Topical ophthalmic solution	DexaSite™(ISV-305); InSite Vision Inc.	Ocular inflammation such as blepharitis	DuraSite® drug delivery technology, Polycarbophil	[24]
Timolol maleate Topical ophthalmic gelling vehicle	Rysmon™ TG; Wakamoto Pharmaceutical Co.	Glaucoma; ocular hypertension	Thermoresponsive gel	[26, 27]
Timolol maleate Topical ophthalmic solution	Various brands and pharmaceutical companies (Glunil, Lotim Plus, Xalacom, Misopt, Latocom)	Glaucoma	Hydroxpropyl methylcellulose	-
Betaxolol Topical ophthalmic solution	Betoptic S™; Alcon	Glaucoma	Amberlite® IRP-69	[28-30]
Tafluprost Ophthalmic solution	DE-085; Santen Pharmaceutical Co. Ltd.	Glaucoma, ocular hypertension	Solution	[31]
Lomerizine HCl Ophthalmic solution	DE-090; Santen Pharmaceutical Co. Ltd.	Glaucoma, ocular hypertension	Solution	-
Tafluprost/timolol maleate Ophthalmic solution	DE-111; Santen Pharmaceutical Co. Ltd.	Glaucoma, ocular hypertension	Solution	-
Adenosine A$_{2A}$ Ophthalmic solution	DE-112; Santen Pharmaceutical Co. Ltd.	Open-angle glaucoma, ocular hypertension	Solution	-
Latanoprost topical ophthalmic emulsion	Catioprost™; Santen Pharmaceutical Co. Ltd.	Glaucoma and ocular hypertension	Cationic emulsion	[32]
Tobramycin/Dexamethasone Topical ophthalmic solution	TobraDex™ ST	Blepharitis	Xanthan gum	[33, 34]
Cationic ophthalmic emulsion	Cationorm™, Santen Pharmaceutical Co. Ltd.	Dry eye symptoms	Cationic emulsion	[35, 36]
Cyclosporine Cationic ophthalmic emulsion	Vekacia™; Santen Pharmaceutical Co. Ltd.	Vernal keratoconjunctivitis	Cationic emulsion	[37]
Cyclosporine Cationic ophthalmic emulsion	Cyclokat™; Santen Pharmaceutical Co. Ltd.	Dry eye Vernal keratoconjunctivitis	Cationic emulsion	[38]
Epinastine HCl Ophthalmic solution	DE-114; Nippon Boehringer Ingelheim Co., Ltd	Allergic conjunctivitis	Solution	-
Peptide combination Ophthalmic solution	DE-105; Santen Pharmaceutical Co. Ltd.	Persistent corneal epithelial defect	Solution	-
Diquafosol sodium Ophthalmic solution	DE-089; Santen Pharmaceutical Co. Ltd.	Corneal/Conjunctival disease (Dry eye)	Solution	[39]
Rivoglitazone Ophthalmic suspension	DE-101; Santen Pharmaceutical Co. Ltd.	Corneal/Conjunctival disease (Dry eye)	Suspension	
Ketotifen Soft contact lens		Allergic conjunctivitis	Poly(HEMA-co-AA-co-AM-co-NVP-co-PEG200DMA) soft contact lenses	[40]
Latanoprost Subconjunctival insert		Glaucoma, ocular hypertension	Various polymers	[41]
Cyclosporine Episcleral implant	Lucida (LX201), Lux Biosciences, Inc.	Aeratoconjunctivitis	Biosilicone	[42]

profound impact on the healthiness of the ocular surface including the cornea and the conjunctiva, and is largely tightly controlled by the regulation of the orbital glands and also the secretion capacity of the ocular surface epithelia.[43] Anatomically, the organelles involved in tearing include lacrimal gland, superior and inferior lacrimal puncta, lacrimal sac, superior and inferior lacrimal canals and nasolacrimal canal.

The lightly buffered aqueous fluid forms the tear film (pH ~7.2–7.5) on the surface of the cornea. Under normal condition, when the ophthalmic medicine is used it can be washed away by the normal physiologic function of tear film that has a turnover rate of 15%-30% per min with the tear volume restoration of 2-3 min, resulting in loss of the applied medicine within the first 15–30 seconds. As a result, the bioavailability of localized therapy in ocular diseases is very low (less than 5%), in large part because of lacrimation and poor drug penetration. In addition, the penetrated drug molecules are also subjected to the absorption by the conjunctival sac and drainage through the nasal cavity and adsorption by the capillaries of the iris.[44-46] To overcome such physiologic impediments, nanoscaled

medications such as nanosuspension, nanoemulsions and nanoparticles which are able to remain within the local target tissues for a longer period of time or to control the release of encapsulated/incorporated drugs are imperative.[47-53] Further, it should be noted that the drug release pattern from nanoscaled formulations is largely dependent upon the physicochemical properties of carriers and drugs. The tear film (with a pH range of 7.3–7.7) is composed of nutrients, electrolytes, proteins, lipids and mucin. It maintains the health of the cornea and conjunctiva, in which the tear proteins (e.g., lysozyme, secretory immunoglobulin IgA, lactoferrin, lipocalin, and peroxidase) provide anti-bacterial/viral potential.[54] So far, various formulations have been devised to circumvent these physiologic impediments such as gel-forming systems (e.g., Timoptol-LA and Timoptol-XE, used to treat glaucoma) and mucoadhesives polymers/liposomes and microdiscs, which are also able to prolong the desired pharmacologic activities of the incorporated drug molecules within ocular tissue.[55-64] For example, to improve the ocular bioavailability of ciprofloxacin hydrochloride (CPX), mucoadhesive chitosan (CS)-coated liposomes were formulated by means of the thin film hydration technique using L-alpha-phosphatidylcholine (PC), cholesterol (CH), stearylamine (SA) and dicetyl phosphate (DP), for which CS was used to coat the liposomes.[61] This study revealed a prolonged in vitro release of CPX from the CS-coated liposomes and a high bioavailability of ciprofloxacin. In another study, CS or Carbopol (CP) coated niosomal timolol maleate formulations as mucoadhesive opthalmic drug delivery systems were developed and pharmacodynamically evaluated in albino rabbits through assessing the intraocular pressure (IOP) by a non-contact pneumatonometer.[65] As compared to a commercially available in situ gel-forming solution of timolol (Timolet GFS, 0.5%; Sun Pharma), it was found that CS and CP coated niosomes carrying timolol maleate can extend the drug release for up to 8 h and 6 h respectively, and decreasing the cardiovascular adverse reaction of drug. All these highlight that mucoadhesive ophthalmic formulations, in particular as nanosystems (NSs), can provide a better treatment modality for controlled and prolonged delivery of drugs into the anterior segment of the eye.

Corneal and/or noncorneal routes

The corneal and/or noncorneal are the main routes for the local drug delivery to the eye,[56,66-69] hence advanced biocompatible stimuli-responsive formulations as well as biodegradable implants[70,71] may provide much safer methods. However, it should be noted that drug delivery across the conjunctiva and sclera into the intraocular tissues is low in large part because of the functional presence of the local capillary beds that removes the drug from target sites to the general circulation. Despite such pitfall, many drugs (e.g., timolol maleate, gentamicin, and prostaglandin PG-F$_2\alpha$) have poor corneal permeability, and hence intraocular delivery via the conjunctiva and sclera may be the best choice in particular when the subconjunctival implants

are used as the drug depot.[70,72] Peng et al engineered two microfilms using poly [d,l-lactide-co-glycolide] (PLGA) and poly[d,l-lactide-co-caprolactone] (PLC) and evaluated their biocompatibility in rabits upon subconjunctival implantation. They reported that both microfilms showed degradation and surface erosion kinetics with no significant inflammation or vascularization as tested by serial slit-lamp microscopy.

Blood-aqueous barrier

In anterior segment of the eye, the endothelium of the iris/ciliary blood vessels and the non-pigmented epithelium of the ciliary body cell layers form the BAB that displays tight junctional complexes (Fig. 2). The main function of this regulating barrier is to selectively control of the traverse of solutes between the posterior and anterior segments, maintaining the transparency of the eye and the chemical composition of the ocular fluids.[73] It should be pointed out that the capillaries of the ciliary are fenestrated and leaky to macromolecules such as horse radish peroxidase (HRP) with molecular weight of 40 kDa. The microvasculature barrier of iris that controls the travers of the plasma proteins into the aqueous humor is tight,[74] while the traverse of substances from the aqueous humor into the systemic circulation through the capillary endothelia of iris is less restricted and permeated drugs into the aqueous humor can be washed away from the anterior segment by the iris blood vessels.[75] In the anterior segment, small lipophilic drugs are prone to entering into the uveal blood circulation via BAB and subsequent elimination much more rapidly than hydrophilic drugs and macromolecules whose elimination occur solely by aqueous humor turnover. In fact, because of the continuous drainage of the aqueous humor with turnover rate of 2.0–3.0 mL/min, drugs within the anterior segment are not able to enter the posterior segment. Taken all, the locally administered drugs are not able to reach beyond the anterior segment, failing to provide required pharmacological concentration in the posterior segment components such as vitreous, retina and choroid.[76] The repeated systemic and intravitreal injections appear to be the remaining options in the clinic that are also associated with some inevitable consequences.

Controlled drug delivery to anterior segment of the eye

Table 2 represents the FDA approved ophthalmologic drugs from 2000 to 2016. Several advanced medical devices and implants have been clinically examined for their clinical potentials. For example, Lacrisert, a sterile hydroxypropyl cellulose insert, has wiedly been used in the inferior cul-de-sac of the eye for lubricating, stabilizing and thickening the precorneal tear film and prolonging the tear film breakup in patients with dry eye states and keratoconjunctivitis sicca.[77-79] Accordingly, a study upon the efficacy of lacrisert in subsets of patients (418 patients including 86 contact lens wearers, 79 with cataract diagnosis, 52 with prior cataract surgery, 22 with prior laser-assisted in situ keratomileusis, and 15 with glaucoma) with dry eye syndrome has resulted in significant improvement

Table 2. FDA approved drugs for ophthalmologic applications (from 2000 to 2016)

Drug	Clinical indication	Brand, manufacturer	Approved year
Tasimelteon	Treatment of non-24-hour sleep-wake disorder in the totally blind	Hetlioz ™,Vanda Pharmaceuticals	January 2014
Phenylephrine and ketorolac injection	For use during eye surgery to prevent intraoperative miosis and reduce post-operative pain	Omidria™,Omeros	June 2014
Sweet Vernal, Orchard, Perennial Rye, Timothy and Kentucky Blue Grass Mixed Pollens Allergen Extract	Treatment of grass pollen-induced allergic rhinitis with or without conjunctivitis	Oralair™,Greer Labs	April 2014
Cysteamine hydrochloride	Treatment of corneal cystine crystal accumulation due to cystinosis	Cystaran™,Sigma Tau Pharmaceuticals	October 2012
Ocriplasmin	Treatment of symptomatic vitreomacular adhesion	Jetrea™,Thrombogenics	October 2012
Ranibizumab injection	Treatment of diabetic macular edema	Lucentis™, Genentech	August 2012
Tafluprost ophthalmic solution	Treatment of elevated intraocular pressure	Zioptan ™, Merck	February 2012
Aflibercept	Treatment of neovascular (wet) age-related macular degeneration	Eylea™, Regeneron Pharmaceuticals	November 2011
Gatifloxacin ophthalmic solution	Treatment of bacterial conjunctivitis	Zymaxid™,Allergan	May 2010
Ketorolac tromethamine	Treatment of pain and inflammation following cataract surgery	Acuvail ™,Allergan	July 2009
Bepotastine besilate ophthalmic solution	Treatment of itching associated with allergic conjunctivitis	Bepreve™,Ista Pharmaceuticals	September 2009
Besifloxacin ophthalmic suspension	Treatment of bacterial conjunctivitis	Besivance ™, Bausch & Lomb	June 2009
Dexamethasone	Treatment of macular edema following branch retinal vein occlusion or central retinal vein occlusion	Ozurdex ™, Allergan	June 2009
Ganciclovir ophthalmic gel	Treatment of acute herpetic keratitis	Zirgan ™, Sirion Therapeutics	September 2009
Lidocaine hydrochloride	For anesthesia during ophthalmologic procedures	Akten™,Akorn	October 2008
Azelastine hydrochloride nasal spray	Treatment of seasonal and perennial allergic rhinitis	Astepro™,Meda Pharmaceuticals Inc	October 2008
Difluprednate	Treatment of inflammation and pain associated with ocular surgery	Durezol™,Sirion Therapeutics	June 2008
Azithromycin	Treatment of bacterial conjunctivitis	AzaSite™,InSite Vision	April 2007
Ranibizumab	Treatment of neovascular (wet) age related macular degeneration	Lucentis™,Genentech	June 2006
Pegaptanib	Treatment of wet age-related macular degeneration	Macugen™,Pfizer / Eyetech Pharmaceuticals	December 2004
Cyclosporine ophthalmic emulsion	Treatment of low tear production	Restasis™,Allergan	December 2002
Bimatoprost ophthalmic solution	For the reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension	Lumigan™, Allergan	March 2001
Travoprost ophthalmic solution	For the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension	Travatan™, Alcon	March 2001
Valganciclovir HCl	For the treatment of cytomegalovirus retinitis in patients with AIDS	Valcyte™, Roche	March 2001
Levobetaxolol hydrochloride suspension	For lowering IOP in patients with chronic open-angle glaucoma or ocular hypertension	Betaxon™, Alcon	February 2000
Levofloxacin	For treatment of bacterial conjunctivitis	Quixin™, Santen	August 2000
Unoprostone isopropyl ophthalmic solution) 0.15%;	For the treatment of open-angle glaucoma or ocular hypertension	Rescula™, Ciba Vision	August 2000
Verteporfin for injection	For the treatment of wet age-related macular degeneration (wet AMD)	Visudyne™, QLT	April 2000

in the quality of life.[79]

The glaucoma is considered as the second leading cause of blindness, several treatment modalities have been devised to control the glaucoma. Of the anti-glaucoma agents, brimonidine tartrate (BT) is currently widely used, while patient's compliance to BT therapy is low. To tackle this issue, a BT-liberating ocular insert has been engineered using poly(lactic co-glycolic) acid (PLGA) or polyethylene glycol (PEG) with a linear BT-release profile and smooth surfaces.[80] In fact, the ocular insert has significantly advanced the treatment of various eye disease. These DDSs are sterile, thin, multilayered, drug-incorporated solid/semisolid systems that are placed into the cul-de-sac or conjuctival sac. Being composed of a polymeric scaffold,

they provide increased ocular residence and sustained-release of ophthalmic drugs. The liberation of drugs from these DDSs, depending on the physicochemical properties of vehicle and drug, may occur by simple diffusion, osmosis, and bioerosion or even stimuli responsive.[81] Emergence of the bacterial infection after implanting an artificial corneal scaffold is a well-known issue that brings about serious complication, while the anti-bacterial impacts of conventional antibiotic therapy such as topical vancomycin is limited, in large part because of low bioavailability and high dosing requirement. To prevail such issues, a number of researchers have focused on development of the antibiotic-eluting corneal prosthesis with prolonged liberation of scaffold-impregnated drug molecules. In one study, an artificial corneal scaffold was produced by the incorporation of vancomycin in thick collagen hydrogel, which resulted in a sustained drug elution for up to 7 days. Once implanted intrastromally in rabbit corneas replacing the stromal tissue, the vancomcyin was detectable in the aqueous humor for up to 10 days. Upon intrastromal injection of *Staphylococcus aureus* inoculate on day 2 postimplantation, the implanted corneas remained clear and nonedematous on day 3 postinfection, showing a marked reduction in S. aureus in comparison with the blank hydrogel-implanted corneas that developed excessive inflammation and edematous. Such drug-eluting corneal implants appear to provide an excellent preventive scaffold on the cornea inhibiting development of bacterial infections.[82] As shown in Fig. 5A, the ocular punctal plugs (OPPs, the so-called tear duct plugs) with/without active agents are small medical device inserted into the tear duct to block the duct and possibly release desired drugs.[83] The OPPs are usually made from collagen and hence are dissolvable, which can further be advanced to become thermosensitive systems usable for the long-term treatment of the dry eye,[84] even though some side effects such as conjunctivitis may limit their applications.[85,86] Of the ocular devices, the intacs corneal inserts or implants (Fig. 5B), are considered as a minimally invasive surgical option that are primarily used for the treatment of keratoconus. They have originally been approved by the US FDA for the surgical treatment of mild myopia in 1999, and then in 2006 FDA announced it as a therapeutic device, which have been tested worldwide for the safety and efficacy.[87-89] These devices have good potential to become drug-impregnated system to ensure upon the prevention of consequences such as infection.

Further, flexible silicon hydrogels have been devised as flexible contact lens for continuous daily uses including narafilcon A (Acuvue TruEye), lotrafilcon B (Air Optix) and balafilcon A (BAUSCH & LOMB PureVision™). These silicon based systems can be used to depot necessary ophthalmic drugs.[90-94] Table 3 represents some selected ophthalmic drug delivery systems or devices for controlled delivery of medicines to the anterior segment of the eye. Therefore, de novo treatment modalities such as subconjunctival implants and polymeric depot systems and medical devices that can be injected/implanted directly into the vitreous may provide a long-term sustained-release treatment modalities that are yet to be fully examined for
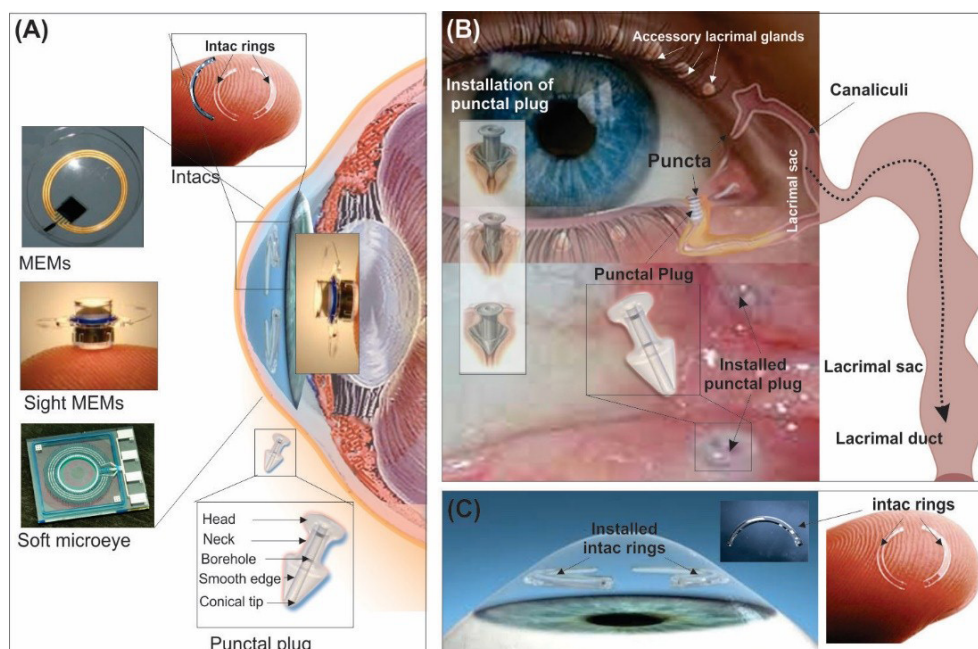

Fig. 5. Selected ocular medical devices. A) Different medical devices used in the anterior segment of the eye, including sight MEMs, soft microeye, intac and punctal plug. The ocular punctal plugs (panel A) and intacs (panel B) used for controlling the dry eye symptoms and Keratoconus, respectively. Punctal plug alone or as impregnated with drug molecules is installed into the punctum. Drug-impregnated punctal plugs can be devised as stimuli sensitive system. Intracorneal rings, intacs, are surgically installed between the layers of the corneal stroma – one crescent ring on each side of the pupil. Readers are directed to see excellent electronic sources in the following URLs from where images were adapted: http://www.allaboutvision.com; http://www.eyedocs.co.uk ; http://www.bouldereyesurgeons.com and http://www.iqlaservision.com as well as MEMS Journal.

Table 3. Selected ophthalmic devices/systems for controlled delivery of medicines to the anterior segment of the eye

Drug delivery system	Clinical trial description	Clinical indication	Sponsor/ Collaborator
Latanoprost punctal plug delivery system (L-PPDS)	A Study of the L-PPDS With Adjunctive Xalatan® Eye Drops in Subjects With OH or OAG (ID: NCT01037036; Phase 2)	Ocular hypertension (OH); open-angle glaucoma (OAG)	Mati Therapeutics Inc.; QLT Inc.
Punctal plug	Safety and Efficacy of Punctal Plug Insertion in Patients With Dry Eye (ID: NCT01684436; Phase 4)	Dry Eye	Allergan
Perforated Punctal Plugs	Perforated Punctal Plugs for Treatment of Papillary Conjunctivitis in Otherwise Healthy Patients (ID: NCT02503956;)	Epiphora; Conjunctivitis	Rabin Medical Center; Alpha Net Co. Ltd.
L-PPDS	Comparison of Latanoprost PPDS With Timolol Maleate GFS in Subjects With Ocular Hypertension or Open-Angle Glaucoma (ID: NCT02014142; Phase 2)	OH; OAG	Mati Therapeutics Inc.
L-PPDS	A Safety Study of the Latanoprost Punctal Plug Delivery System (L-PPDS) in Subjects With Ocular Hypertension or Open Angle Glaucoma (ID: NCT00820300; Phase 2)	Glaucoma; OH; OAG	Mati Therapeutics Inc.
Sirolimus	Subconjunctival Sirolimus for the Treatment of Autoimmune Active Anterior Uveiti (ID: NCT00876434)	Anterior Uveitis	National Eye Institute (NEI)
Gamunex-C	Subconjunctival IVIg (Gamunex-C) Injection for Corneal Neovascularization and Inflammatory Conditions (ID: NCT02042027; Phase 1)	Corneal Neovascularization Corneal Graft Failure Anterior Segment Inflammation	University of Utah
Timolol; Bimatoprost Ocular Insert	Dose-Ranging Study of the Bimatoprost Ocular Insert (ID: NCT02358369; Phase 2)	Glaucoma; OH; OAG	ForSight Vision5, Inc.
DiscoVisc®; Healon®; Amvisc® Plus	To Compare the Ability of DiscoVisc® OVD to Protect the Corneal Endothelium and Maintain Anterior Chamber Space With Healon® and Amvisc® PLUS During Cataract Surgery (ID: NCT00763360; Phase 4)	Cataract	Alcon Research

their impacts in a long period use.

Novel intraocular drug delivery technologies

As an axiom, any ophthalmic dosage form must provide suitable biopharmaceutical characteristics as well as an appropriate ocular tolerability in particular when used for treatment of intraocular diseases. However, the topical administration of ophthalmic solutions (nearly 90% as eye drops) fail to meet such criteria. In fact, an excellent restrictiveness of the tight corneal epithelia controls the permeation of drug molecules into the anterior segment of the eye, and the penetrated molecules are significantly washed away by the capillary bed of the iris/ciliary body and/or lacrimation. As a result, very little part of the topically administered drug molecules can reach the posterior segment of the eye. To tackle such shortcomings, we need to use systemic route for the administration of ophthalmic drugs such as anti-glaucoma agents, corticosteroids and certain antibiotics, nevertheless their use through systemic route face with restrictive barrier functionality of BRB as well as BAB. Alternatively, we must advance intravitreal DDSs or devices to be able to deliver the acquired doses of the designated drugs into the posterior segment of the eye and maintain the therapeutic concentration for a long period of time.[9]

Drug delivery into the posterior segment of the eye

As a thin film light-sensitive tissue, the retina covers the entire inner wall of the eye. The retina includes two main biological barriers that control the entrance of blood-circulating substances into the posterior segment. Such biological barriers together with the functional presence of BAB make drug delivery into the posterior segment a very challenging issue.

Anatomically, in addition to the retinal endothelial cells that form the BRB, the inner part of retina encompasses several cells and tissue including neural cells and glial cells (i.e., Müller cells, astrocytes, microglial cells and oligodendroglial cells). While within the middle part of the retina the photoreceptor cells (rods and cons) are located over the epithelial cells, the outmost part of the retina includes a single layer of specialized pigmented cuboidal epithelial cells that form the excellent impediment function of RPE barrier. The impediment functions of the RPE and BRB are tightly coupled within retina, hence these two barriers of retina play imperative roles in intravitreal drug delivery and targeting. Fig. 6 shows the cellular organization of the retina.

In early 1990s, to achieve much greater compliance, some important sustained-release ophthalmologic DDSs were developed to control ocular diseases. Since then, few success story encouraged researchers to continue on developing more advanced DDSs for the targeted therapy of ocular ailments. In 1996, Vitrasert™ (ganciclovir-loaded implant) was approved for the treatment of cytomegalovirus retinitis that is associated with late-stage AIDS causing blindness. This DDS liberates the ganciclovir directly to the target site for a long period of time up to 6-8 months,
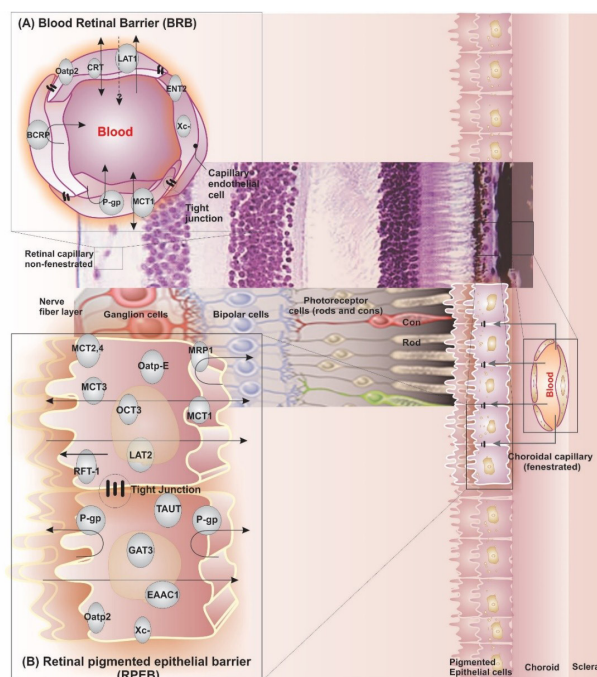
Fig. 6. The retinal cellular structure. A) The inner blood retinal endothelial cells (RECs) form the blood-retinal barrier (BRB). B) The outer pigmented epithelial cells (PECs) form the retinal pigmented epithelial barrier (PREB). As polarized cells, both retinal endothelial and pigmented epithelial cells possess tight junctions and traverse of nutrients are selectively controlled by transport machineries as carrier-mediated transportation and receptor-mediated transportation.

which has successfully been used for the treatment of a large number of patients over the past decades. In addition to Vitrasert™, sustained DDSs can be used as an intravitreal implants including Retisert™ (fluocinolone-loaded implant) and Iluvien™ (fluocinolone-loaded implant) whose drug liberation occurs for up to 3 years, while similar DDSs seem to be necessary for the anterior segment of the eye too.[4] These developments appear as the resurgence of advanced intravitreal DDSs shown schematically in Fig. 7.

Advanced intravitreal drug delivery systems and devices
Ideally, liberation of the ophthalmic drugs from the DDS/delivery device in the posterior segment of the eye should be performed as sustained/controlled-release or even on-demand by an external stimuli. Most of these sustained-release DDSs are injected intravitreally once without any further needs for repeated injections, while some of the intravitreal devices such as micropumps are refillable systems. Of these, the nanoscaled biodegradable DDSs and sol-gel injectable hydrogels are novel effective ophthalmologic formulations that are deemed to provide maximal clinical benefits with minimal side effects. So far a number of advanced DDSs and devices has significantly improved the intravitreal drug delivery and targeting. Among them, smart NSs were shown to be able to efficiently circumvent the related barriers, enter into the posterior segment of the eye and pose minimal adverse

reactions.[95] Selected advanced DDSs and devices used to deliver ocular drugs into the posterior segment of the eye are shown in Fig. 7 and some selected forms are listed in Table 4.

Ocular nanomedicines
Having considered the biological impediments in the posterior segment of the eye imposed mainly by the retinal barriers, the ocular nanomedicines can locally/systemically be administered for the delivery of the drug molecules into the vitreous depending on their size and architecture. These nanoscaled DDSs are deemed to provide sustained/controlled liberation of drugs and prolonged pharmacologic impacts. Such objective can be achieved by localized retention in the cul-de-sac, where the entrapped drug can be liberated based on a simple diffusion mechanism or by the means of an external stimuli such as photodynamic therapies from conveying NS. The nanoscaled ophthalmic formulations can provide longer exposure time at the ocular surface by confronting the clearance mechanisms of the eye providing more drug concentration, reducing the dose and frequency of drug administration,[96] a number of various nanostructured DDSs have also been developed for the intravitreal applications.[97,98] Thus far, different advanced polymer-/lipid-based soft matters have been used for development of a number of nanostructures including nanoparticles (NPs), nanomicelles, nanoemulsions, nanosuspensions, nanocapsules. To attain the best utility of nanomedicines, various parameters should be considered including (a) lipophilic-hydrophilic properties of the advanced materials used, (b) the biocompatibility of the advanced soft materials in association with ocular tissues such as precorneal pocket and subconjunctival tissue, (c) longevity and durability of the NS in biological microenvironment of the eye, (d) drug release profile with or without external stimuli, and (e) the retention efficiency of the NS in the ocular tissues such as precorneal pocket.[9,96,97,99-103] To achieve an optimized effect in the case of topical nanoformulations, it is highly desirable to engineer bioadhesive/mucoadhesive NSs to enhance the reactivity and bioavailability of NSs in the ocular cul-de-sac.[104] Such aims seem to be achievable by using various micellar colloidal NSs, emulsion nanoformulation, biodegradable polymeric NPs, hydrogel based NSs.[105] For instance, amphiphilic molecules with hydrophilic head and hydrophobic tail termed as surfactants can be used for formulation of nanomicelles. These polarized molecules can be found in different status as dipolar/zwitterionic (e.g., dioctanoyl phosphatidyl choline), charged or anionic/cationic (e.g., sodium dodecyl sulfate as an anionic surfactant; dodecyltrimethylammonium bromide as a cationic surfactant), or neutral/non-ionic (e.g., ethylene oxide (N-dodecyl; tetra, C12E4), vitamin E TPGS [d-alpha tocopheryl polyethylene glycol (PEG) 1000 succinate], octoxynol-40). Nanosized micelles are formed when surfactants are dissolved in water at concentration above critical micelle concentration (CMC) under sonication/agitation, showing different architecture (spherical, cylindrical, or planar/discs/bilay-
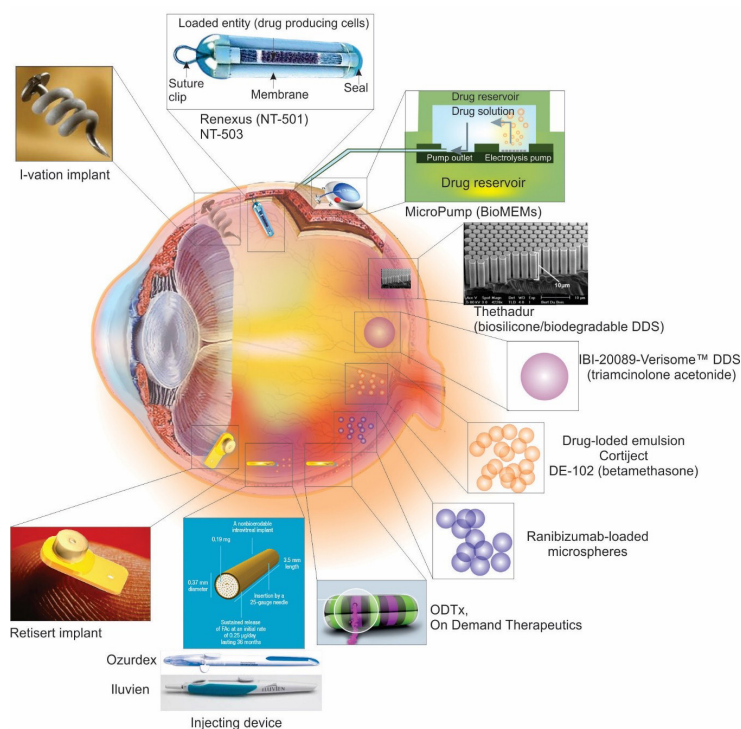
Fig. 7. Advanced intravitreal drug delivery systems and devices.

ers) depending on the aggregation driving force(s). These NSs can be used for controlled topical/intraocular drug delivery.[99]

Zhang et al. formulated dexamethasone (Dex)-loaded PLGA NPs (Dex-NPs) and evaluated their pharmacokinetics and tolerability in rabbits after intravitreal injection.[106] Based on some key ophthalmic examinations (e.g., intraocular pressure measurement, and B-scan ocular ultrasonography), they claimed that the injection of Dex-NPs induce no abnormalities even after 50 days post-injection in rabbits, while the Dex-NPs were able to maintain a sustained liberation of drug for a long period of time (i.e., up to 50 days) in vitreous with a fairly constant level of drug for up to 30 days. The rabbits treated with Dex-NPs showed significantly higher bioavailability of the drug as compared the control group injected with Dex alone.

Jo et al. studied the antiangiogenic impacts of silicate nanoparticles (SiNPs) on the retinal neovascularization, and showed that the SiNPs impose no direct toxicity in the retinal tissues. The intravitreal injection of nanoparticles was able to substantially reduce the anomalous retinal angiogenesis in oxygen-induced retinopathy mice. They claimed that the SiNPs can markedly inhibit the VEGF-elicited angiogenesis through blockage of activation ERK 1/2.[107]

On the basis that the intravitreal injection of DDSs/implants demands relatively large 22 gauge needle, novel dipeptide (phenylalanine-alpha,beta-dehydrophenylalanine; Phe-Phe) based nanotubes (PNTs) were designed by Panda et al.[108] The self-assembled PNTs (with a diameter of ~15-30 nm and a length of ~1500 nm) were designed for the intravitreal delivery of pazopanib with suitable loading efficiency and bioavailability. No cytotoxic impacts were found on the human retinal pigment epithelial (ARPE-19) cells by the PNTs. Once injected, after a period of 15 days in vivo, the PNTs were found to retain the drug levels in the vitreous humor, retina, and choroid-RPE respectively 4.5, 5, and 2.5-folds higher than that of the plain drug.

To treat the macular degeneration and diabetic retinopathy, intravitreal injections every 4-8 weeks are inevitable – a treatment modality that is undoubtedly considers as an invasive uncomfortable retinal damaging intervention. Hence, Huu et al developed a novel stimuli-responsive NP-based reservoir platform for the delivery of nintedanib (BIBF 1120) which is a small molecule angiogenesis inhibitor.[109] To this end, the researchers capitalized on a far ultraviolet (UV) light-degradable polymer to be able to trigger the liberation of the drug molecules on-demand. Once injected, the NSs were found to be able to keep the encapsulated drug molecules in the vitreous for up to 30 weeks without inducing significant inadvertent side effects, while the liberation of cargo drug molecules was plausible through emission of far UV. They showed that the choroidal neovascularization (CNV) in rats can be suppressed 10 weeks after injection of nintedanib carrying NPs.

Hydrogels as novel intravitreal DDSs

Hydrogels are defined as crosslinked polymeric networks capable of holding large quantities of water or other biological fluids due to the presence of hydrophilic groups or domains within their porous polymeric structure. They

Table 4. Selected ophthalmic devices/systems for controlled delivery of medicines to the posterior segment of the eye

Drug, dosage form	Brand, manufacturer or stage of development	Clinical indication	Main excipient/device
Betamethasone Sub-Tenon injection of sustained-release microsphere	DE-102; Santen Pharmaceutical Co. Ltd. and Oakwood Laboratories	Macular edema associated with diabetes and branch retinal vein occlusion	Biodegradable microspheres
Sirolimus Intravitreal injections	DE-109; Santen Pharmaceutical Co. Ltd. and Oakwood Laboratories	Non-infectious uveitis of the posterior eye	A slowly dissolving depot
Biosilicon DDS for small molecules and macromolecules	Thethadur; pSivida Corp.	Intraocular diseases	Honeycomblike nanostructured bioerodible/non-erodible porous silicon
Ganciclovir ophthalmic implant	Vitrasert™, Zirgan™; pSivida Corp.	Cytomegalovirus (CMV) ocular infection	Sustained-release silicon implant
Fuocinolone-loaded ophthalmic implant	Retisert™; pSivida Corp.	Chronic non-infectious posterior uveitis	Sustained-release silicon implant
Fuocinolone-loaded ophthalmic implant	Iluvien™; pSivida Corp.	Chronic non-infectious posterior uveitis	Sustained-release silicon implant
Lntanoprost ophthalmic implant	Durasert™; pSivida Corp.	Ocular hypertension and glaucoma	Sustained-release biodegradable implant
dexamethasone Intravitreal implant	Ozurdex™; Allergan, Inc.	Diabetic macular edema (DME)	Sustained-release silicon implant
Dexamethasone Injectable ophthalmic emulsion	Cortiject™; Santen Pharmaceutical Co. Ltd.	DME; noninfectious inflammation of the uvea; central retinal vein occlusion (CRVO)	Injectable ophthalmic emulsion containing a corticosteroid prodrug
Triamcinolone ophthalmic injection	IBI-20089 Verisome™; Icon Bioscience	Cystoid macular edema (CME)	Sustained-release intravitreal lipid-based DDS as verisome (translucent liquid to form gel in the eye)
BioSilicon-based protein delivery system	Tethadur; pSivida Corp.	Neuroprotective agents	Sustained-release biodegradable (PLGA)/biosilicon implant
Brimonidine Intravitreal implant	NCT02087085; Allergan Inc.	Geographic atrophy, Macular degeneration	Intravitreal Implant
Bimatoprost Sustained-release DDS	NCT02250651; Allergan Inc.	Glaucoma, Open-Angle Ocular Hypertension	Sustained-release DDS
triamcinolone acetonide Sustained-release implant	I-vation™; Surmodics Inc.	DME	Sustained-release DDS poly(methyl methacrylate), ethylene-vinyl acetate copolymer
Laser activated injectable DDS	ODTx	Different diseases in posterior segment of the eye	Controled drug delivery by activating specific reservoirs
Ciliary neurotrophic factor (CNTF) producing cells Semipermeable hollow fiber membrane	Renexus (NT-501); Renexus Group & Noah Group	Atrophic age-relate macular degeneration (AMD)	Semipermeable hollow fiber membrane with ciliary neurotrophic factor (CNTF) producing cells [retinal pigment epithelium (RPE)]
VEGF receptor Fc-fusion protein (VEGFR-Fc)-releasing cells	NT-503; Neurotech	AMD	Semipermeable hollow fiber membrane with ciliary neurotrophic factor (CNTF) producing cells [retinal pigment epithelium (RPE)]
Triamcinolone acetonide (TA) Injection device for DDS	iTrack microcatheter; iScience Interventional	neovascular AMD	Injection device for suprachoroidal delivery of TA
Refilled with drug solution to provide long-term pharmacotherapy		Different diseases in posterior segment of the eye	Microelectromechanical systems (MEMS) as refillable DDD
Ranibizumab Refillable port drug delivery system (PDS)	Genentech, ForSight Vision 4 Inc.	ADM	Ranibizumab controlled-release PDS

are synthesized from both naturally and synthetic polymers by chemical or physical crosslinking methods.[110-112] The key properties associated with hydrogels are their remarkable characteristics such as hydrophilicity, flexibility, elasticity and high water content. All these features make them suitable entities with broad application spectra in different biomedical fields such as tissue engineering, regenerative medicine, protein separation, matrices for cell encapsulation and devices for the controlled release of drugs and proteins.

In general, hydrogels show great compatibility with biological settings and their hydrophilic surface has a low interfacial free energy in contact with body fluids. Such characteristics make hydrogels to show low tendency of adhering to proteins and cells, and hence less aggregation. Moreover, the soft and rubbery nature of the hydrogels minimizes irritation to surrounding tissue.[112-115] Of the hydrogels, the stimuli-responsive or environmentally-sen-
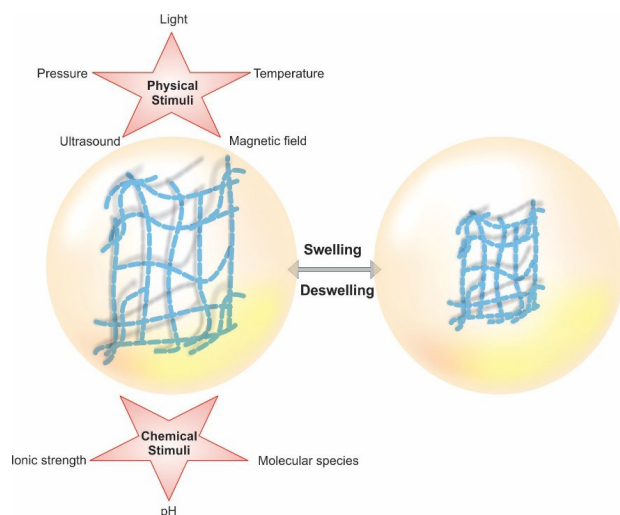
Fig. 8. Schematic representation of stimuli-responsive smart hydrogels.

sitive hydrogels (the so-called smart hydrogels) offer the fantastic swelling – deswelling characteristics (as volume collapse or phase transition) in response to presented physical or chemical stimuli (Fig. 8). They have been used in diverse applications including production of artificial muscles, biomimetic biosensor/bioactuator, immobilization of enzymes and cells, bioseparation and self-regulated DDSs. In situ gel formation makes hydrogels very favorable for the delivery of ophthalmic small and macromolecular drugs as well as tissue engineering. This system provides safe applications in vivo.[116,117] Multiple stimuli-responsive hydrogels have attracted significant research interest because the most pH- and temperature-sensitive dual functional systems have a great importance in biological applications and can mimic the responsive macromolecules founds in nature.[118,119]

As for the ocular applications, it should be noted that the stroma of the cornea is a naturally occurring hydrogel (a water-swollen polymer network), and the basic physicochemical principle of a swelling hydrogel should be applicable to this layer.[120] Further, it should be also pointed out that the vitreous humor as a clear gel fills the posterior segment of the eye. It is composed of 98%-99% water and a type of collagen called vitrosin that forms a network of collagen type II fibrils in association with glycosaminoglycan, hyaluronan, opticin (a protein belonging to a small leucine-rich repeat protein family), and a wide spectra of other soluble proteins, as a result its viscosity is 2-4 folds higher than that of water. The vitreous humor, unlike the continuously replenished aqueous humor, has a gelatinous consistency and is stagnant. Taken all, the intravitreal hydrogels should mimic such characteristics.

Among various types of polymers, for the intraocular drug delivery, the bioadhesive polymers are deemed to provide a better means. Of these, hydroxypropyl cellulose, hydroxypropyl methylcellulose, chitosan, dextran and poly(acrylic acid) derivatives (e.g., carbomer 934 and polycarbophil) have been reported as the most appropriate polymers.

In addition, the high viscosity of the carbomer hydrogels results in the prolonged retention, improving the ocular bioavailability of some drugs. In addition to the effective treatment of edema on the ocular surface[121-123] and applications in soft silicone lenses using polymers like poly (2–hydroxyethyl methacrylate), the hydrogels have been used for the intravitreal delivery of active pharmaceutical agents such as small molecules and macromolecules.[41,124-130]

Intravitreal implants and devices

In an ideal world, the intravitreal DDSs/DDDs should be degraded imposing trivial/no detrimental impacts on the cells/tissue in the posterior segment of the eye. Despite usefulness of the nanoscaled biodegradable NSs in treatment of ocular diseases, some devices used for intravitreal drug delivery are non-biodegradable such as silicone implants/inserts and micro-pumps (Fig. 7). These devices, which contain drug molecules or drug-producing cells, can be either injected or surgically installed in the vitreous to deliver the designated drug. Here, we provide some concise information upon these implants/devices.

Encapsulated cell technology (ECT)

Renexus (NT-501) developed by Neurotech Pharmaceuticals offers an encapsulated cell technology that provides extracellular delivery of ciliary neurotrophic factor (CNTF). The system encompasses the genetically modified human retinal pigment epithelial (RPE) cells (NTC-200 cell line), which can be implanted into the vitreous. As an in-house cellular reactor, the system is able to secrete the recombinant human CNTF and maintain the drug concentration at constant desired doses for a long period of time. RPE cells are mounted on the polyethylene terephthalate yarn scaffold and the produced drug molecules can be released from the device through semipermeable hollow fiber membrane. This ingenious device can protect the mounted exogenous cells from the endogenous immune response of the host while they survive within the vitreous and produce CNTF for inhibition of photoreceptor degradation in patients with retinitis pigmentosa.[131-133] Neurotech Pharmaceuticals has also developed another cell-based DSS named NT-503 ECT that encompasses VEGF receptor Fc-fusion protein (VEGFR-Fc)-releasing cells. Having compared to ranibizumab, this cell-based treatment modality showed significantly higher (20-30 folds higher) VEGF neutralization with a drug liberation longevity for up to 1 year in the rabbit vitreous. Based on a phase I and II trial commenced in 2014, this VEGF neutralizing ECT has been being used for the treatment of recurrent CNV secondary to AMD.[131]

Implants

Here, we provide a concise update on some ocular DDDs that are in clinic or under clinical trial. Of these, I-vation (Surmodics Inc.) is a sustained delivery system that is used as an intravitreal implant to deliver triamcinolone acetonide (TA). It is a titanium helical coil that is coated with

poly(methyl methacrylate) and ethylene-vinyl acetate and the polymer coat has been loaded with TA[131] Further, On Demand Therapeutics has developed intravitreal non-biodegradable implant called ODTx that contains reservoir of drug molecules whose liberation can be triggered by low-energy laser during eye examination.

In addition to few biodegradable intravitreal NSs (see Table 3), pSivida has developed Thethadur which is porous nanoscaled honeycomblike silicon (biosilicon) or biodegradable polymeric device. It can be loaded with the designated drug molecules (e.g., small molecules and biologics such as antibodies) that can be released in a controlled manner once implanted into the vitreous.

Refillable devices

Of the refillable microelectromechanical systems (MEMs), MicroPumps developed by Replenish Inc. is DDD that can be used for the treatment of chronic and refractory ocular diseases such as DME.

In a study, its safety and surgical feasibility has been evaluated as the first-in-man ocular implant of a novel posterior MicroPump DDD in DME patients, proving its safety for a period of 90 days and possibility for its refiling that makes multiple programmable drug delivery feasible.[134] The effectiveness and biocompatibility of the MicroPump DDD has further been followed up in a one-year feasibility study.[135] These systems are deemed to last over a 5-year time course before further need for the replacement.

Final remarks and outlook

The eye possesses bio-micro-machineries (i.e., tear film, corneal epithelia, the ciliary epithelium and capillaries of the iris, retina endothelia and epithelia) that selectively restrictively control the entry of exogenous substances (both topical compounds and blood-borne molecules) into the anterior and posterior segments.

Although the restrictive physiological and biological barriers, functionality of the eye retain the normal function of the eye, it makes ocular drug delivery and targeting very challenging.

The locally administered drugs, mostly as topical ophthalmic solutions, must cross the tear film (with fast turnover) and the corneal epithelial barrier. Once entered into the anterior segment, the drug molecules are often subjected to the absorption by the conjunctival sac and the capillaries of the iris.

While the drug molecules in the anterior segment can scarcely enter the posterior segment of the eye, the systemically delivered drugs face with BRB and cannot reach the desired pharmacologic concentration. As a result, the novel DDSs and DDDs aim to elongate the pharmacologic presence of drug molecules in the ocular segments or tissues to perform maximal therapeutic benefits with minimal undesired side effects.

To date, a number of DDSs/DDDs have been used for increasing the bioavailability of drugs in the ocular segments based on nanoscaled colloidal systems,[136] nanobioadhesives,[137] stimuli-responsive hydrogels,[118,138] subcon-

junctival implants,[70,72] refillable DDDs such as MEMs/NEMs-based micropumps and episcleral exoplants[139-141] as well as encapsulated cell technology.[142] Remarkable characteristics of these systems in extended liberation of drugs in particular for the posterior segment of the eye make some of these advanced systems as the sole treatment modality option for life-devastating diseases such as AMD and DME.

Extra developments are needed to tackle some genetic defects that affect the ocular systems such as mucopolysaccharidoses (MPSs), which are a class of disorders triggered by hereditary genetic defects in lysosomal enzymes resulting in extensive intracellular and extracellular accumulation of glycosaminoglycans (GAGs).[143]

In the eye, MPSs (e.g., MPS I such as IH/S (Hurler/Scheie) and MPS IH (Hurler) because of deficiency in a-L-iduronidase; MPS VI Maroteaux-Lamy due to deficiency in N-acetylgalactosamine-4-sulfatase) manifest as corneal opacification, optic nerve swelling and atrophy, ocular hypertension, and glaucoma.[143] To tackle these ocular malfunctions, one powerful, yet simple, approach seems to be the use of injectable stimuli-responsive and transforming hydrogels that can be used for delivery of gene-based nanomedicines into the eye by a single injection. Once injected into the ocular segment/tissue, it can be triggered to liberate the cargo drug molecules on-demand.[144]

While the advanced treatment modalities for the systemic manifestations of MPSs is bone marrow transplant, the enzyme replacement therapies such as Aldurazyme (laronidase) for MPS I and Naglazyme (galsulfase) for MPS VI appear to be the only treatment modalities for these orphan diseases.

In fact, after proof-of-technologies and several success stories of ocular implants (e.g., Ocusert (1974) for 1 week constant release of pilocarpine from conjunctiva; Vitrasert (1996) for 6 months constant release of ganciclovir from the pars plana area of vitreous; Retisert (2005) for 2.5 years constant release of fluocinolone acetonide; intravitreal injectable biodegradable (Posurdex) and non-biodegradable (Medidur) implants, wouldn't it be fantastic if we implement these technologies or even the encapsulated cell technology or smart hydrogels and multimodal nanomedicines to treat such diseases?

To achieve such goals, we need to empower the translational medicine researches as well as the leading researchers who tackle these issues through capitalizing on new biomimicry technologies in a holistic manner. Such endeavor needs to be advocated by both governmental and private sectors.

Review Highlights

What is current knowledge?

√ Lacrimation, corneal epithelial barrier (CEB) and blood-aqueous barrier (BAB) restrictedly control entrance of topically applied pharmaceuticals into the anterior and posterior segments of the eye.

√ Retinal endothelial and epithelial barriers, together with BAB, can selectively control traverse of blood-borne substances and systemically administered pharmaceuticals into the posterior segment of the eye.

√ Currently used ophthalmic medicines need to be repeatedly administered to maintain the required concentrations of drug.

√ Long-acting ocular drug delivery systems (DDSs) and devices (DDDs) loaded with small molecules or macromolecules can maintain required intravitreal concentration for a long period.

What is new here?

√ Stimuli-responsive DDSs/DDDs with on-demand drug liberation potential can provide maximal impacts with minimal side effects.

√ Nano-scaled targeted DDSs provide much more selective pharmacological effects.

√ Long-term safety of ocular implants needs to be fully addressed.

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