Intravitreal implants for treatment of posterior segment diseases

Essay
Submitted for partial fulfillment of M.Sc. degree in Ophthalmology

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Abstract

In the ongoing armamentarium against sight threatening diseases not only the drug composition is a determining factor but also the way of delivery is a crucial point to consider. Novel methods of ophthalmic drug delivery are being developed to facilitate treatment of a variety of eye diseases.

In order to develop novel methods of ophthalmic drug delivery certain aspects should be considered.

The anatomy and the functional physiology of the eye plays an important role in ocular drug delivery and distribution.

The blood ocular barriers affect the extent of drug absorption and distribution intended to be delivered to the posterior segment of the eye.

Key Words:

Cerium oxide - Cytomegalovirus - Inner oBRB.
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<td>ARPE-19</td>
<td>Activated retinal pigment epithelium</td>
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<tr>
<td>BCVA</td>
<td>Best corrected visual acuity</td>
</tr>
<tr>
<td>BM</td>
<td>Bruch’s membrane</td>
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<tr>
<td>BRB</td>
<td>Blood retinal barrier</td>
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<td>BRVO</td>
<td>Branch retinal vein occlusion</td>
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<tr>
<td>(CeO$_2$)</td>
<td>Cerium oxide</td>
</tr>
<tr>
<td>CME</td>
<td>Cystoid macular edema</td>
</tr>
<tr>
<td>CMT</td>
<td>Central macular thickness</td>
</tr>
<tr>
<td>CMV</td>
<td>Cytomegalo virus</td>
</tr>
<tr>
<td>CNTF</td>
<td>Ciliary neurotrophic factor</td>
</tr>
<tr>
<td>CRVO</td>
<td>Central retinal vein occlusion</td>
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<tr>
<td>3D</td>
<td>3 dimensional</td>
</tr>
<tr>
<td>DDS</td>
<td>Drug delivery system</td>
</tr>
<tr>
<td>DME</td>
<td>Diabetic macular edema</td>
</tr>
<tr>
<td>DMSB</td>
<td>Dexamethasone sodium m-sulfobenzoate</td>
</tr>
<tr>
<td>DNA</td>
<td>Double stranded nucleic acid</td>
</tr>
<tr>
<td>DSMT</td>
<td>Donut-shaped minitablet</td>
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<tr>
<td>EBV</td>
<td>Epstein barr virus</td>
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<td>ECT</td>
<td>Encapsulated cell technology</td>
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<tr>
<td>EVA</td>
<td>Ethylene vinyl acetate</td>
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<tr>
<td>FAME</td>
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<td>FDA</td>
<td>Food and drug administration</td>
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<td>Gd-DTPA</td>
<td>Gadolinium diethylene triamino pentaacetic acid</td>
</tr>
<tr>
<td>kda</td>
<td>atomic mass unit</td>
</tr>
<tr>
<td>iBRB</td>
<td>Inner oBRB</td>
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<tr>
<td>ILM</td>
<td>internal limiting membrane</td>
</tr>
<tr>
<td>IOP</td>
<td>Intraocular pressure</td>
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<td>MEMS</td>
<td>microelectromechanical systems</td>
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<td>MRI</td>
<td>Magnetic resonance imaging</td>
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<td>NY</td>
<td>New York</td>
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<tr>
<td>oBRB</td>
<td>Outer oBRB</td>
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<tr>
<td>PGA</td>
<td>Polyglycolic acid</td>
</tr>
<tr>
<td>PLA</td>
<td>Polylactic acid</td>
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<td>PLGA</td>
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<td>Polymethylidene malonate</td>
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<td>PVA</td>
<td>Polyvinyl alchol</td>
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<td>REETAC</td>
<td>Intravitreal bioerudivel controlled-release triamcinolone microsphere system</td>
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<td>RPE</td>
<td>Retinal pigment epithelium</td>
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<tr>
<td>SVH</td>
<td>simulated vitreous humor</td>
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<tr>
<td>TA</td>
<td>Triamcinolone</td>
</tr>
<tr>
<td>USA</td>
<td>United States of America</td>
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<tr>
<td>VA</td>
<td>Visual acuity</td>
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<tr>
<td>VEGF</td>
<td>Vascular endothelial growth factor</td>
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<td>VZV</td>
<td>Varicella zoster virus</td>
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Introduction

The unique anatomy and physiology of the eye renders it difficult to achieve an effective drug concentration at the target site. Therefore, efficient delivery of a drug past the protective ocular barriers accompanied with minimization of its systemic side effects remains a major challenge (Rupenthal and Alany, 2007).

Diseases affecting the posterior segment of the eye are difficult to treat and take longer to combat by employing conventional topical or systemic drug delivery (Maurice, 2001).

Research has been directed at specialized drug delivery technologies to the tissues of the posterior segment of the eye (Visor, 1994).

Pharmacokinetics describes the quantitative relationship between administered dose and tissue concentration over time, it is an important tool in drug development. To optimize drug concentration at the target sites, pharmacokinetic studies are useful (Kim et al, 2004).

Conventional techniques as fluorescein, MRI and 3D simulation eye models are methods of assessing ocular drug distribution (Li et al, 2008).

A variety of approaches for drug delivery to the posterior segment of the eye have been explored over the last few decades. These approaches include direct intravitreal injections, drug loaded microparticle carriers as microspheres, nanospheres, and liposomes, transscleral drug delivery devices, and intravitreal devices using polymers (Davis et al, 2004).
The pharmaceutical world is becoming more and more aware of intraocular drug delivery challenges, and revolutionary therapeutic advances are being invented and implemented which may have the potential to vastly improve patient care and quality of life. Among these most promising developments are intravitreal drug delivery devices designed to deliver drugs with precision directly to the vitreous, retina, and choroid (Ashton et al, 2000).

An intraocular device can be designed as either bioerodable or non-bioerodable (Choonara et al, 2010).

With the continued development of more potent drugs combined with research into novel delivery methods, there is a realistic hope that optimal therapeutic drug delivery for diseases of the posterior segment will be available in the near future (Shalin et al, 2010).

**Aim of the study:**
To spotlights on the types, indications and complications of the intravitreal implants in the posterior segment of the eye and their future trends.
Anatomical and physiological review

The eye-ball is an organ protected from exogenous substances and external stress by various barriers (Figure 1), therefore, therapeutic drugs must be transported across several protective barriers regardless of which administration route is utilized, such as eye-drops, subconjunctival, sub-tenon’s, intravitreal injection and/or implant. For the treatment of the anterior segment of the eye (cornea, conjunctiva, sclera and anterior uvea), usually topical ocular eye-drops are used. An eye-drop, irrespective of the instilled volume, often eliminates rapidly within five to six minutes after administration, and only a small amount (1–3%) of an eye-drop actually reaches the intraocular tissue (Maurice and Mishima, 1984).

Fig. (1). Schematic of the eye-ball structure. (Kuno and Fuji, 2011).
Thus, it is difficult to provide and maintain an adequate concentration of drug in the precorneal area. More than 75% of applied ophthalmic solution is lost via nasolacrimal drainage and absorbed systemically via conjunctiva, hence ocular drug availability is very low. To increase ocular bioavailability and prolong the retention time on the ocular surface, numerous ophthalmic vehicles such as viscous solutions, suspensions, emulsions, ointments, aqueous gels, and polymeric inserts, have been investigated for topical application to the eye. (Schoenwald, 1997).

In general, topical applied drugs do not reach the posterior segment of the eye (retina, vitreous and choroid), therefore, systemic administration, periocular or intraocular injections of drugs are normally applied in clinical therapeutics, (Lee et al, 2009). However, the unique anatomy and physiology of the eye and its protective barriers prevent the administrated drugs from penetrating into the target tissues. There is also rapidly growing interest in drug delivery systems (DDSs) to the posterior segment of the eye as shown in (Figure 2). This trend is toward a polymeric depot system implanted or injected directly into the vitreous, to obtain long-term, sustained release of drugs (Nordstrom et al, 2005).

Compliance is also problematic, particularly among patients who have chronic diseases such as glaucoma and refractory chorioretinal diseases, including uveitis, macular edema, neovascular (wet) and atrophic (dry) age-related macular degeneration (AMD), and retinitis pigmentosa (RP). It has been reported nearly 50% of glaucoma patients discontinued all topical ocular hypotensive therapy within six months (Nordstrom et al, 2005).
Comparatively, for the treatment of neovascular AMD and macular edema secondary to retinal vein occlusion (RVO), standard therapy is intravitreal injections of ranibizumab, an anti-vascular endothelial growth factor (VEGF) monoclonal antibody fragment (Lucentis®, Genentech, Inc., South SanFrancisco, CA, U.S.) once a month. (Kuno and Fuji, 2011).

The monthly cost of Lucentis® is about $2,000 and that means effective treatment by Lucentis® faces a serious social problem (Patel et al, 2010). In addition, frequent intravitreal injections might cause complications, such as endophthalmitis and retinal detachment (Kuno and Fuji, 2011).

![Diagram of intravitreal drug delivery systems](image)

Fig. (2). Examples of intravitreal drug delivery systems for vitreoretinal diseases. (Satti et al, 2010).
Barriers that Restrict Intraocular Drug Transport

1. Tears

One of the precorneal barriers is tear film which reduces the effective concentration of the administrated drugs due to dilution by the tear turnover (approximately 1 µL/min), accelerated clearance, and binding of the drug molecule to the tear proteins. In addition the dosing volume of instillation is usually 20–50 µL whereas the size of cul-de-sac is only 7–10 µL. The excess volume may spill out on the cheek or exit through the nasolacrimal duct (Schoenwald, 1990).

2. Cornea

The cornea consists of three layers; epithelium, stroma and endothelium, and a mechanical barrier to inhibit transport of exogenous substances into the eye (Pederson, 2006).

Each layer possesses a different polarity and a rate-limiting structure for drug permeation (Figure 3). The corneal epithelium is of a lipophilic nature, and tight junctions among cells are formed to restrict paracellular drug permeation from the tear film. The stroma is composed of an extracellular matrix of a lamellar arrangement of collagen fibrils. The highly hydrated structure of the stroma acts as a barrier to permeation of lipophilic drug molecules. Corneal endothelium is the innermost monolayer of hexagonal-shaped cells, and acts as a separating barrier between the stroma and aqueous humor. The endothelial junctions are leaky and facilitate the
passage of macromolecules between the aqueous humor and stroma (Fischbarg, 2006)

![Diagram of corneal structure and cellular organization](image)

**Fig. (3).** Schematic of corneal structure and its cellular organization of various transport-limiting barriers (Nishida, 2005).

### 3. Conjunctiva

Conjunctiva of the eyelids and globe is a thin and transparent membrane, which is involved in the formation and maintenance of the tear film. In addition, conjunctiva or episclera has a rich supply of capillaries and lymphatics (Singh, 2003).

Therefore, administrated drugs in the conjunctival or episcleral space may be cleared through blood and lymph (*Figure 4*). The conjunctival blood vessels do not form a tight junction barrier, which means drug molecules can enter into the blood circulation by pinocytosis and/or convective transport through paracellular pores in the vascular endothelial layer. The
conjunctival lymphatics act as an efflux system for the efficient elimination from the conjunctival space. It has been reported that at least 10% of a small molecular weight hydrophilic model compound (sodium fluorescein), administered in the subconjunctival space, is eliminated via the lymphatics within the first hour in rat eyes (Lee et al., 2010).

Fig. (4). Shematic representations of subconjunctival or episcleral blood vessels, and lymphatics network (Robinson et al., 2006).

4. Sclera

The sclera mainly consists of collagen fibers and proteoglycans embedded in an extracellular matrix. Scleral permeability has been shown to have a strong dependence on the molecular radius, scleral permeability decreases roughly with molecular radius (Ambati et al., 2000).

Additionally, the posterior sclera is composed of a looser weave of collagen fibers than the anterior sclera and the human sclera is relatively thick near the limbus (0.53 ± 0.14 mm), thin at the equator (0.39 ± 0.17 mm), and much thicker near the optic nerve (0.9–1.0 mm). Thus, the ideal