Recent Advances in The Back of The Eye Drug Delivery

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**Introduction**

Once the active treatment agent that is efficacious in the management of posterior segment diseases is determined, the next big obstacle is the back of the eye drug delivery. Topical eye drops are far superior to all other routes of administration with respect to safety, comfort, affordability and ease of use. However topical medications are least effective in delivering therapeutic concentrations of the drug to the retina. Hence the majority of developmental efforts in retina therapeutics is focussed on novel non-topical delivery systems. Intravitreal injections introduced in 1945 provide superior drug bioavailability in the posterior segment compared to topical and systematically delivered agents. However this method of drug administration has several drawbacks which includes frequent (monthly / bimonthly) outpatient visits, and carry the risk of serious complications such as vitreous hemorrhage, retinal detachment and endophthalmitis.

Intraocular implants are designed to provide drug release into the posterior segment for longer periods of time (months or even years) compared to particles or solutions. These implants are usually placed at the level of the parsplana during a surgical procedure. Compared to intravitreal injections, drugs released from implants deliver more consistent levels of the drug, avoids side effects associated with frequent intravitreal injections, minimize peak concentrations and result in smaller quantities of drug being required for treatment. Like solutions and particles implants can also result in unequal drug distribution due to vitreous heterogeneity and placement of implant peripheral to retina to avoid disruption of the visual field. Implants however come close to the zero-order kinetics: ie the level of administered drug remains constant throughout the delivery period.

Implants can be either biodegradable or non biodegradable. Biodegradable implants do not require surgical removal. Their disadvantages are a variability in release kinetics due to differing rates of vitreous turnover and a final burst in drug release profile. Non biodegradable implants provide a more controlled drug delivery but require a second surgical procedure for removal.

Two ocular implants Vitrascert (Ganciclovir 4-5 mg Bausch and Lomb, Rochester, NY) and the recently approved Retisert (flucinolone acetonide 0.59 mg, Bausch and Lomb) are commercially available. Vitrascert releases ganciclovir for approximately 5-8 months while Retisert releases flucinolone for up to 30 months and is currently the only approved treatment for non-infectious uveitis of the posterior segment.

Other implants that have been developed are

1. A novel doughnut shaped biodegradable implant for delivery of ganciclovir and foscarnet. The central hole assures easier suturing and the implant does not need removal.
2. Biodegradable posudrex implant (Allergan, Irvine, CA) for delivery of dexamethasone in treatment...
of macular edema associated with retinal vein occlusions.

3. Iluvien (Alimera, Alpharetta, GA) a non biodegradable implant to deliver flucinolone acetonide in diabetic macular edema and designed to sustain therapy for 24-36 months.

In the past few years researchers have developed intraocular devices with fewer complications, and relatively safe, sustained and effective localized administration. These include

1. Particulate polymeric drug delivery systems (Microparticles / Nanoparticles)
2. Phospholipid bilayer encapsulated drug delivery system (liposomes)
3. Iontophoresis: where an electric current is used to drive ionized drugs into tissues.

**Microparticles, Nanoparticles and Liposomes**

The main problem that limits the effectiveness of intravitreal injections is the lack of homogeneity of the human vitreous caused by gradients. Injected drugs do not therefore spread throughout the vitreous resulting in a significant variability in the drug concentration at the target site. Nano particles or micro particles are new formations which can spread more uniformly throughout the vitreous, increase the duration of action, and decrease the peak concentration.

Injectable nano particles (1nm to 1000 nm in diameter) and microparticles (1 nm to 1000 nm in diameter) made of polymer encapsulated drug are novel drug delivery systems that aim to increase the drug penetration and also increase the duration of action of small molecules.

Particulate system can be in the form of

1. Nanospheres and microspheres: which are uniform polymer drug combinations in which the drug is dispersed homogenously throughout a polymer matrix.
2. Nanocapsules and Microcapsules: where the drug is surrounded by a spherical polymer capsule and released throughout its pores.
3. Polycion complex (PIC) micelles that can be laser activated are in development and have successfully inserted DNA into rat retinas through a process called photochemical internalization in which light induces the transfer of DNA directly into cells.

4. Liposomes: with encapsulated drug can bind to a cell membrane and facilitate drug transfer across the membrane. They are less stable than particles made of polymer. Both hydrophilic and hydrophobic drugs can be encapsulated into liposomes. Research have shown that they can effectively carry genes to the rat retina following injections.

Almost any drug can be encapsulated. This method of drug delivery aids in (1) stabilizing the active form of the drug (2) increases its half life (3) increases drug absorption due to slower elimination rate (4) decreases peak concentrations reducing the risk of toxicity.

One of the major disadvantages of this mode of delivery is that nanoparticles and microparticles are heavier than vitreous. So when they are injected they tend to sink to the bottom of the vitreous cavity. Particles size can also have a profound effect on the drug bioavailability after injection with larger particulate system tending to maintain superior sustained drug release.

Nanotechnology may have an impact on the treatment of retinal diseases through gene delivery, drug delivery, cell delivery, retinal neural prosthetics and nano surgery.

Gene delivery has been attempted with viral vectors but carry the risk of immunogenicity and mutagenesis. Non viral vectors such as polymers and lipids also have the ability to carry genes but with lower risk of immunogenecity, lower cost and greater ease of production than viral vectors. The electrostatic interaction of cationic polymers with RNA or DNA molecules carrying a negative charge results in condensation and formation of the material into particles in the nanoscale range. These polymer nanoparticles can protect genes from enzymes and mediate their entry into cells. Incani and colleagues found that polyplexes complexes of cationic polymer with plasmid DNA can have transfection efficiencies comparable to adenoviral
vectors but with reduced safety risks. Colloidal nano particles carrier systems have been tried for sustained drug delivery for chronic diseases such as glaucoma and macular degeneration. Nano particles are also promising for targeted delivery of drugs to intra ocular tumors. Sustained submacular delivery may be enhanced by the use of biocompatible film that serves as a carrier for drug loaded nanoparticle Fig 1. For an extra ocular approach arrays of hundreds of microneedles that penetrate the sclera to deliver drugs to the posterior segment have been designed using microfabrication technology Fig. 2.

Polymer scaffold engineered on the nanoscale can increase the survival and differentiation of cells for retinal transplantation 13.

Use of nanoparticles in engineering of retinal prosthetics is being investigated with the aim of rejuvenating, by passing, or taking advantage of the residual retinal function in patients with retinitis pigmentosa and other inherited degenerative retinal diseases 14.

**Iontophoresis and Suprachoroidal drug administration**

Iontophoresis is a method of drug delivery in which an electrical current drives charged drug molecule through either the cornea or sclera and into the retina and vitreous. It offers a non invasive alternative to intravitreal injections, particles or implants. The current leader in clinical ocular iontophoresis is Eye Gate pharma (Waltham, MA) which is currently investigating this technology for drug delivery. It uses a reusable battery powered generator and a disposable applicator.

The Eyegate II uses an inert electrode that can accommodate both positive and negatively charged drugs. The mechanism of action of the inert electrode is electrorepulsion of the same charged molecule which creates high velocity to achieve flux to the targeted tissue. Fig. 3

The surface area is important in this technology due to current density. By delivering the current to the sclera, the surface area is maximized and current density is lowered increasing the safety profiled of the device.

The Eyegate II 16,17,18 has shown efficacy in delivering proteins, si RNA, corticosteroids and nanoparticles in rabbit studies. Safety of this device on human sclera 19 was shown using a buffer solution. Phase 2 study of EGP - 437, a corticosteroid delivered using this system for the treatment of dry eye syndrome has been completed. Phase II study in uveitis, glaucoma age related macular degeneration etc is underway.

For patients with retinal tumors, iontophoresis is being researched as a potential alternative to the use of systemic chemotherapy. In a mouse model, investigators found that iontophoresis could successfully transport carboplatin, a cytotoxic compound for the treatment of retinoblastoma.

The suprachoroidal drug delivery using a 300 mm microcatheter 21 (i track -400 , i-science Interventional corporation, Menlo park, CA ), introduced through a small anterior incision at the parsplana has been shown to be able to access the suprachoroidal space. The safety, efficacy and pharmacokinetics with triamcinolone, a combination of triamcinolone A and Avastin is being investigated. (Fig. 5 & 6)

**Transporter Targeted Drug delivery to the retina:**

This method of drug delivery targets nutrient transporters on ocular barriers utilizing a prodrug approach. Nutrient transporters are transmembrane proteins involved in the transportation of essential nutrients and xenobiotics across biological membranes, thereby regulating the supply of essential ingredients into the cell.

Several transporters for nutrients and endogenous compounds are expressed on both the apical and basolateral sides of the epithelial barriers of various tissues such as intestine, kidney, BBB, BRB and placenta.

To take advantage of the nutrient transport system, the parent drug must be covalently conjugated to the nutrient moiety by an enzymatically cleavable bond generating a prodrug. Prodrugs significantly enhance absorption of poorly permeable parent drug. These prodrugs are recognized by the membrane transporters as substrates and are transported across the epithelial or endothelial barriers. Subsequently the prodrugs are enzymatically cleaved to release the parent drug and the ligand which in most cases is a nutrient, non toxic and easily eliminated. (Fig. 7)

**Super selective intra arterial chemotherapy** in retinoblastoma aims to deliver a high concentration of
Fig. 1. Biocompatible film for drug delivery 20 nm thick biocompatible film with multiple drug loaded nanoparticles for sustained drug delivery. [Adapted from Retina Today May/June 2009, Vol.4, No.4]

Fig. 2. Microneedle Array. The size of the experimental microneedle array is shown by its placement on the researcher’s finger. There are 400 needles in the array. [Adapted from Retina Today May June 2009 Vol.4, No.4]

Fig. 3. The Eye Gate II delivery system.

Fig. 4. The EyeGate II applicator is placed directly upon the sclera.

Fig. 5. The Ophthalmic microcathete for suprachoroidal drug delivery.

Fig. 6. (a) & (b) View of the Microtheter beacon tip in suprachoroidal space

The drug to the trauma and achieve less exposure via a low dose systemically to the patient. The goal is to eliminate the need for enucleation and systemic chemotherapy in children with RB. Under general anaesthesia, the femoral artery is catheterized with a microcatheter (450 nm) which is passed up into the abdominal aorta, thoracic aorta, internal carotid arteries and into the ophthalmic artery which measures below 550 nm to 1000 nm in diameter in children.

References


15. EyeGate. Pipeline [Internet]. Waltham, MA, 2009.


