Novel therapeutic approaches for uveitis and retinitis

M. Thilek Kumar, J.K.Pandit, J.Balasubramaniam
Department of Pharmaceutics, Institute of Technology, Banaras Hindu University, Varanasi, Uttar Pradesh, India

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A virtual increase in the number of patients undergoing immunosuppressant therapy and those suffering from AIDS has created a unique class of population suffering from virulent uveitis and retinopathies. A very common pathogen implicated in retinopathy in such patients is the cytomegalovirus (CMV).

Delivery of antiviral drugs to the vitreous cavity has been attempted by various routes, which suffer from some weakness or the other. Recent developments in this field have been in the form of some novel devices like intravitreal and scleral implants and iontophoretic delivery. In this paper we have described these devices and highlighted on the advantages and disadvantages associated with them.

Most ocular diseases are treated with topical application of solutions administered as eye drops. These conventional dosage forms account for nearly 90% of the currently accessible marketed formulations. Eye drops used for soluble drug require frequent administration of highly concentrated solutions. The practical reasons for selecting solutions are the generally favorable cost advantage, the greater simplicity of formulation development and production and acceptance by patients despite a little blurring.

One of the major problems encountered with the topical delivery of ophthalmic drugs is the rapid pre-corneal loss caused by drainage and tear turn over. After instillation of an eye drop, typically less than 5% of the applied drug penetrates the cornea and reaches intraocular tissues, while a major fraction of the instilled dose is often absorbed systemically via the conjunctiva and naso-lacrimal duct.

Corresponding Author: Jagdish Balasubramaniam, Department of Pharmaceutics, Institute of Technology, Banaras Hindu University, Varanasi, Uttar Pradesh, India. jbsmaniam_2000@rediffmail.com

Physiological considerations

The extent of absorption of an ophthalmic drug is severely limited by physiological constraints. Among the factors that limit ocular absorption is the relatively impermeable corneal barrier. The cornea is a trilaminar tissue, consisting of the epithelium, stroma and the endothelium, that are the main absorptive barriers. The epithelium facing the tears with lipophilic cellular layers acts as a barrier to ion transport. The tight junction of corneal epithelium serves as a selective barrier for small molecules and prevents the diffusion of macromolecules via the para-cellular route. The stroma beneath the epithelium is a highly hydrophilic layer making up 90% of the cornea. The corneal endothelium is responsible for maintaining normal corneal hydration. Obviously then, the more lipophilic the drugs are, the more resistance they will find crossing the stroma. The more hydrophilic a drug, the more resistant the epithelium, whereas the stroma and the endothelium are limited in their resistance.

The conjunctiva is a thin, vascularized mucus membrane that lines the inner surface of the eyelid and covers the anterior part of the sclera up to the cornea. Owing to the relatively high porosity, rich blood flow and large surface area, conjunctival uptake of a topically applied drug from tear fluid is typically an order of magnitude greater than corneal uptake.

Topically applied drugs reach the bloodstream mainly via absorption across the mucosa in the nasal cavity, which is continuous with the conjunctival sac. Consequently, delivery systems that prolong the residence time of the applied dose in the conjunctival sac would be expected to reduce systemic drug absorption.

Physico-chemical drug properties such as lipophilicity, solubility, molecular size and shape, charge and degree of ionization affect the route and rate of permeation in cornea.
TREATMENT APPROACHES IN OPHTHALMOLOGY

The development of newer, more sensitive diagnostic techniques and therapeutic agents renders urgency to the development of more successful ocular delivery system. Potent immuno suppressant therapy in transplant patients and the developing epidemic of Acquired Immuno Deficiency Syndrome (AIDS) have generated an entirely new population of patients suffering from virulent uveitis and retinopathies.

Uveitis is an inflammation of middle vascular tunic of the eye (uveal tract). It is a specific organ disease frequently considered being autoimmune. Uveitis can occur as an ocular manifestation of a variety of autoimmune diseases such as juvenile rheumatoid arthritis, Reiter's syndrome, and inflammatory bowel diseases and sarcoidosis. When associated with Behcet's disease uveitis frequently leads to blindness.

Uveitis can be treated with topical or systemic steroids but frequently recurs after discontinuation of therapy. Complications of topical steroids use include cataract formation, poor wound healing, toxicity to corneal epithelium and increased intra-ocular pressure. Complications arising from systemic administration of steroids are varied and often extremely unpleasant. To overcome the disadvantages of steroid administration (both topical and systemic) in the treatment of uveitis, non-steroidal anti-inflammatory drugs such as indomethacin have been investigated. In recent years, cyclosporin and cyclosporin A has been used to treat some forms of uveitis.

Cyclosporin is an effective secondary agent in the treatment of uveitis. Usually reserved for patients with advanced bilateral disease despite high doses of prednisolone, its main effect is on the recruitment and activation of T cells. It is believed to act by interfering with interleukin 2 (I-2) in the activation of T cell genes. Although CD4 lymphocytes are the main target, CD8 cells are also suppressed. Systemic administration is usually through the oral route as a suspension. Some of the most common side effects at a dose of 10 mg/kg include paraesthesias and hyperaesthesia (40%), hypertension (24%), epigastric burning (20%), hypertrichorism and gingivitis (20%).

Cytomegalovirus (CMV) is the most common cause of viral retinitis in patients with AIDS, affecting approximately 25% of the patients. If left untreated blindness inevitably results. Intravenous Ganciclovir and Foscarnet are effective in the treatment of CMV retinitis, but require frequent intravenous dosing. Serious dose-limiting side effects are associated with both drugs necessitating a two-week period of induction therapy.
followed by indefinite lower dose maintenance therapy. Retinitis normally reactivates while patients are on maintenance therapy with either drug, with a mean reactivation time of 56 days for Ganciclovir and 59 days for Foscarnet. Other problems associated with systemic administration include sepsis related to permanent indwelling catheters of long infusion times.

Intravitreal Ganciclovir injections provide a higher intraocular drug concentration than systemic therapy and reduce systemic exposure to the drug. The intravitreal half-life of Ganciclovir in the human eye necessitates frequent injection (at least once each week) to maintain therapeutic levels in the eye. Repeated intravitreal injections have an attendant risk of cataract formation, retinal detachment, cystoid macular edema, progressive retinal toxicity and endophthalmitis.

The main approaches investigated in treatment of uveitis and CMV retinitis using sustained release ophthalmic formulation to internal structures of the eye are;

**INTRAVITREAL ADMINISTRATION THROUGH NOVEL DELIVERY VEHICLES**

**Approaches for uveitis**

Intravitreal injections of cyclosporine have been used in the rat model to treat EAU (experimental autoimmune uveitis) without significant blood levels. However, the intraocular half-life of cyclosporine would require multiple weekly injections, making such a delivery impractical. Other studies in rabbits have demonstrated that intravitreal administration of 100 μg of cyclosporine is non-toxic to retinal structures.

**Approaches for CMV retinitis**

Although the intravenous administration of ganciclovir is used for the treatment of bilateral CMV retinitis and control of CMV infection of other sites, the high toxicity levels of this route has necessitated the search for direct placement of a device in the vitreous.

Akula et al. have studied treatment of CMV retinitis with intravitreal injections of liposome-encapsulated ganciclovir (GCV) in a patient with AIDS. To overcome the risk to and poor tolerance by end stage patients, GCV was encapsulated in liposomes, to increase the intravitreal retention of the drug, thereby decreasing the frequency of injections. The right eye of the patient was injected with liposome encapsulated GVC and the left eye served as the control, receiving intravitreal free GVC. The right eye showed no retinal hemorrhages or detachment; but vision declined initially, stabilizing later. Weekly examination showed neither progression of CMV retinitis nor new lesions in the right eye, but the left eye showed reactivation of CMV retinitis.

A single application of 20% aqueous solution of GCV by trans-scleral Iontophoresis (1.0mA for 15 minutes) in rabbit eyes gave a vitreal/retinal level of GVC at 74±17 μg/ml at 2 hours as determined by HPLC. At 24 hours after iontophoresis, the vitreal/retinal level was above the therapeutic level at 4.2±0.6 μg/ml. At 72 hours, there were still detectable levels in the vitreous(retina). Thus trans-scleral iontophoresis is able to deliver effective dose of GCV into the vitreous and multiple applications of iontophoresis should be examined as a possible means of CMV treatment.

The intraocular safety and the antiviral treatment efficacy of the sustained lipid pro-drug of GVC, 1-o-hexadecyl propanediol-3-phospho-GVC (HDP-P-GCV) as an intra vitreal injectable drug system for CMV retinitis were evaluated by Cheng et al. HDP-P-GCV was formulated into liposomes. The antiviral activity was assessed by DNA reduction in vitro and intraocular safety was assessed by ophthalmoscopy, electrophysiology, and histology after intravitreal injections, with resultant intravitreal concentration of 0.2, 0.632, 1.12 and 2 mM. The treatment efficacy was evaluated by simultaneous intravitreal injection of HDP-P-GCV and Herpes simplex type I (HSV-I) or by intravitreal injection of HDP-P-GCV at various times before HSV-I intravitreal inoculation. The IC50 (in vitro) of HDP-P-GCV against HSV-I and human cytomegalovirus (H CMV) infected cell was 0.02 and 0.6 μM, respectively.

In rabbits, HDP-P-GCV dispersed evenly and maintained a good vitreous clarity at all doses except 2 mM final intravitreal concentration.

**INTRAVITREAL AND SCLERAL IMPLANTS**

In the area of ocular drug administration, important efforts concern the conception and design of new biodegradable implantable systems to interior parts of the eye to prolong the residence time. The use of implants,
which are solid devices to be placed trans-sclerally by
minor surgery represent possibilities to achieve
increased residence time. The use of biodegradable
polymeric devices offers certain advantages over more
conventional formulations. If drug release kinetics can
be controlled, target tissue concentration of the drug
can be maintained in the therapeutically appropriate
range and harmful side effects associated with intravit-
real and intravenous administration can be reduced.
Continuous long-term administration can eliminate
the discomfort associated with multiple dosing and
improve patient compliance.

These potential advantages must be viewed in light of
the disadvantages that if it does not biodegrade, the
device may require surgical removal. The implanted
polymer must be biocompatible, causing no tissue irri-
tation, and if it is biodegradable its breakdown prod-
ucts must be non-toxic. The device must be adequately
designed to eliminate possible dumping of the dose.
There are also problems associated with the removal or
the shutting off of release from the implant.

Implantable intravitreal devices slowly release medica-
tion into the vitreous cavity. The device is a small res-
ervoir of drug with a polymer coating that control the
release rate. They have the potential to ameliorate a
variety of chronic infections or inflammatory ocular
diseases.

An implant has been designed for the long term intrav-
itreal release of cyclosporine A. It bypasses the sys-
temic circulation avoiding the side effects associated
with cyclosporine A, while administering therapeutic
doses of the medication to the eye over an extended
period of time. The implant consists of a drug pellet
coated with silicone attached to a poly vinyl alcohol
(PVA) anchor strut. This design has been used to create
implants that can release the drug at several rates,
depending on the material used to coat the drug pellet.
Experimental studies have shown that devices releasing
cyclosporine at a rate of 1.3µg / day can achieve intrav-
itreal levels over a 6 month period of 500 ng/ml, or 5
times the therapeutic level needed to suppress T-cell
activation.\textsuperscript{40, 46} Systemic doses of at least 5 mg/kg are
usually necessary to achieve intravitreal levels of 100
ng/ml.\textsuperscript{47}

Scleral implants of indomethacin with sodium alginate
carrier were evaluated in uveitis induced rabbit eye-
model. The pharmacodynamic studies showed a
marked improvement in the various clinical paramete-
ers; congestion, keratitis, flare, clot, aqueous cells and
synechias, in the implanted eye when compared to the
control eye in the rabbits.\textsuperscript{48}

Devices giving zero order release of GCV was
implanted intravitreally first in rabbits and then in
eight patients with AIDS associated CMV retinitis as
part of phase I clinical trial.\textsuperscript{49} Steady state intravitreal
GCV levels were obtained and elimination rate con-
stants were calculated assuming first order pharma-
coknetics. Normalizing for retinal surface area,
distribution volume and anatomic volume, the retinal
elimination rate constants were found to be 0.017 cm\textsuperscript{-2}
hr\textsuperscript{-1} in rabbits and 0.015 cm\textsuperscript{-2} hr\textsuperscript{-1} in humans.
The study indicated that rabbit eye could serve as a good
model for studying IV pharmacokinetic and suggested
a common elimination mechanism, which may be
trans vitreal.

Smith et al\textsuperscript{50} developed devices that release GCV at
rates of 2µg/ h and 5µg/ h in-vitro. When implanted
into the vitreous of rabbit eyes, mean intravitreal GCV
levels of 9mg/L and 16mg/L were maintained for
more than 80 and 42 days, respectively. The devices
were found to be well tolerated and may prove useful
in the clinical management of CMV retinitis in
patients with AIDS.

A surgically implantable device for sustained intravit-
real release of GCV was reported.\textsuperscript{51} The device deliv-
ered GCV intraocularly over approximately 4 to 5
months. Eight patients with AIDS and associated
CMV retinitis were recruited as part of phase 1 study.
Thirteen eyes with active CMV retinitis underwent
surgical implantation of the GCV device. All eyes
showed resolution of the CMV retinitis; none showed
progression. Surgical complications included mild vit-
reous hemorrhage, astigmatism and suprachorodial
placement of the device.

A randomized controlled clinical trial to assess the
safety and efficacy of a 1µg/h GVC implant for the
 treatment of CMV retinitis in AIDS patients was con-
ducted.\textsuperscript{52} Patients with previously untreated peripheral
CMV retinitis were randomly assigned either to imme-
tiate treatment with GCV implant or to deferred treatment. Standardized fundus photographs were taken at 2-week intervals and analyzed in a masked fashion. The GCV implant was found to be effective for the treatment of CMV retinitis.

Morley et al\textsuperscript{53} reported their surgical experience in replacing empty GVC implants in patients with AIDS related CMV retinitis. Nine eyes in eight patients received two or more implants and the average time before a second implant was needed was 6 months. CMV retinitis was controlled in all patients except one. Three patients required intermittent intravenous exogenous anti-CMV therapy, one for persistent CMV retinitis and two for systemic CMV infection. Visual acuity of 20/40 or better was maintained in five of eight patients, despite a long standing history of CMV retinitis.

**Summary**

Routes and problems of drug administration in uveitis, retinopathies:

**Intravenous and intravitreal injections**
- Frequent Administration
- Poor drug penetration into ocular tissues
- Dose related bone marrow depression
- Cataract formation
- Retinal detachment
- Endophthalmitis
- Reactivation

**Intravitreal non-erodible implants, Liposomes**
- Extended duration of drug release, but surgical implantation under general anesthesia.
- Device removal necessary
- Visual disturbances
- Low drug loading and poor physico-chemical stability of Liposome

**Iontophoresis (very limited investigation)**
- One iontophoretic application is effective for only 48-72 hours.
- Only institutionalized patients eligible
- Possible iontophoretic burns on long term usage

**Scleral implants**
- Displacement of device due to breaking of device.
- Drug release, if not well modulated, may result in multiple burst releases with short periods of slow release.

**Conclusions**

A surgically implantable device for sustained intra-vitreal release of drug can be achieved. The device delivers drug intra-ocularly over approximately 4-5 months and reaches effective intravitreal therapeutic concentration. They have the potential to ameliorate a variety of chronic infection or inflammatory ocular diseases. Most importantly biodegradable implants do not require removal after drug delivery. Additionally, adverse tissue reactions from the implanted polymers are ameliorated as the polymers biodegrade.

**References**


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