Drug Delivery: Beyond Eye Drops

Paul L. Kaufman, MD

Department of Ophthalmology and Visual Sciences
University of Wisconsin School of Medicine & Public Health
Madison, Wisconsin, USA
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Key considerations in drug delivery

✱ Manufacturable product
✱ Drug stability
✱ Drug bioavailability
✱ Product acceptance
  ✱ Convenience
  ✱ Compliance
Molecular delivery to the anterior segment

- **Topical drops**

- **Injections**
  - Anterior chamber
  - Trabecular meshwork
  - Intracanalicular

- **Intraocular, extraocular devices/implants**

- **Trans-scleral delivery**
  - Intrascleral/midscleral
Why sustained release?

- Addresses issue of compliance to daily eye drops
  - Takes the patient out of the equation
  - Can’t miss a daily dose

- Provides a steady level of drug without fluctuations
  - Lower Cmax may enable higher total exposure with lower adverse events
  - May provide more stable control

- Local delivery may have advantages
Extended Drug Delivery Options

- Biodegradable microspheres and nanoparticles
  PLGA, etc
- Solid implants
  Non biodegradable (Retisert)
  Biodegradable
- Thermoreversible gels (cross linked hydrogels)
- Atrigel
- Multivesicular and small unilamellar liposomes
- Lipid derivatized drugs
- Iontophoresis
Why do we want devices?

- Protect the drug product from the environment
- Provide local delivery and targeting
- Make therapy easier for the patient or physician
  - Reduce burden of treatment
- Alter pharmacokinetics or pharmacodynamics
  - Sustained release
  - Reduce Cmax to reduce adverse events
Poly(lactic-co-glycolic acid)/poly(lactic acid) microspheres can release timolol maleate for over 3 months.

Scanning electron micrograph (SEM) showing the morphology of 20% (w/w) timolol maleate loaded PLGA 503H microspheres. Scale bar size: 50 mm. Volume-weighted mean diameter from Coulter Multisizer®418.94.3 mm (meanSD).
In which patients would the use of a sustained release device be appropriate?

❖ How would you select patients as candidates for a sustained release device?
  ❖ Known compliance problems?
  ❖ Patients in which ineffective therapy would have a greater impact?
At what stage of clinical management would the use of a sustained release device be appropriate?

球星 Would you use a device as first line treatment?

球星 Would you need experience with a topical version of a new drug in order to feel comfortable implanting it?
The sustained release device and multiple therapies

• What about a patient requiring a combination of 2 drugs?
  – Would you consider using a SR device that was available for one of the drugs, even though the need for daily drops for the other would remain?

• Would use of the first available SR implant preclude the use of others?
  – If several therapies are available in SR form, would use of the first available mean that you would not put in a second?
Prodrugs are bioreversible derivatives of drug molecules and are designed to be therapeutically inactive until enzymatic and/or chemical bioreversion. In vivo bioreversion generates an active parent drug, which can then exert a desired pharmacological response.

Cholkar et al, J Ocular Pharm and Therap, 2012
Drug delivery system slowly releases measured doses of glaucoma medication that then disperses throughout the eye, providing a convenient way to treat glaucoma without eye drops. This method of drug delivery can control high internal eye pressure (IOP), which can damage the optic nerve. The technology currently is undergoing FDA clinical trials.
Brightfield microscopy image of a single solid stainless-steel microneedle used for intrascleral and intracorneal drug delivery shown next to a U.S. penny for size comparison. Inset: magnified view of the needle, which is 500 μm in length and 45° in tip angle.

In vivo delivery from fluorescein-coated microneedles showed anterior chamber fluorescein concentrations that were 60 times greater than those achieved by topical application without microneedles, in rabbits. No measurable inflammatory responses were caused by microneedle insertion.

Solid metal microneedles measuring 500-700um, coated with pilocarpine were inserted into rabbit corneas in vivo resulting in rapid constriction of the pupil.

Potential delivery vehicle for agents targeting the trabecular outflow and other pathways.

Microneedles can be coated with compounds ranging from small molecules (fluorescein) to proteins (bovine serum albumin) to plasmid DNA.

Delivery of compounds via microneedles inserted into the cornea or sclera may minimize corneal toxicity issues.
PGs trigger MMP gene transcription changes within the sclera

PGs can directly trigger MMP gene transcription changes within the sclera. These changes support a role for increased MMPs in the enhancement of uveoscleral outflow that occurs after topical treatment with latanoprost. Fifteen human eye bank eyes were studied.

Increased MMP mRNA in human sclera organ cultures after a 24-hour exposure to 100 nM PGF2 (A) or 100 nM latanoprost acid (B). Increases are relative to expression of each MMP in corresponding vehicle-treated cultures (dashed line). The second number above each data set indicates the total number of donor eyes represented in the data set; the first number indicates the cultures in which expression was increased. Each measurement represents the mean of triplicate determinations.

MMP-3 in PG vs Non-PG Treated Monkey Eyes

- **Ciliary Muscle**
  - Vehicle
  - PGF$_{2\alpha}$-IE

- **Iris**
  - Vehicle
  - PGF$_{2\alpha}$-IE

- **Sclera**
  - Vehicle
  - PGF$_{2\alpha}$-IE
Collagen Type I

Mean Optical Density (OD Units ± SD)

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Vehicle</th>
<th>PGF2α-IE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciliary Muscle</td>
<td>0.00</td>
<td>0.02</td>
</tr>
<tr>
<td>Iris Root</td>
<td>0.04</td>
<td>0.06</td>
</tr>
<tr>
<td>Sclera</td>
<td>0.04</td>
<td>0.06</td>
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Scleral permeability changes induced by PGs

Compared to tracer movement across untreated scleral cultures, exposure to PGF(2alpha), 17-phenyltrinor PGF(2alpha), or PhXA85 each increased scleral permeability in a dose- and time-dependent manner. Twenty-three pairs of human eye bank eyes were studied.

Scleral permeability after PGF2α exposure. Permeability determined by the transscleral movement of 10- (A), 40- (B), or 70-kDa (C) dextrans across treated sclera. Data presented as mean ± SD (x10-6 cm/sec). *P < 0.05 by Student’s-Newman-Keuls test.
Molecular delivery to the posterior segment

- Intravitreal, subretinal, or peribulbar injection
- Intraocular, via anterior segment administration (uveoscleral outflow)
- Trans-scleral via peribulbar implantable device
- Intraocular, via posterior segment implantable devices
  - Biological - cell based
  - Mechanical - polymer based
- Topical drops (seriously!)
Fig. 1. Example of intraocular drug delivery systems for vitreoretinal disorders (adapted from Kunou et al., Sakurai et al., and Okabe et al. with permission; Iluvien™ image courtesy of Alimera Sciences, I-vation™ TA image courtesy of SurModics Inc.).
Subconjunctival micro/nanospheres

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Particle Size (µm)</th>
<th>Theoretical Loading (% w/w)</th>
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</thead>
<tbody>
<tr>
<td>Bud-PLA Nano</td>
<td>0.345 ± 0.002</td>
<td>25</td>
</tr>
<tr>
<td>Bud-PLA Micro</td>
<td>3.6 ± 0.1</td>
<td>9</td>
</tr>
<tr>
<td>Cele-PLGA Micro</td>
<td>3.6 ± 0.6</td>
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Non-biodegradable implants in clinical practice or in the late developmental phase

- **Vitrasert** (ganciclovir intravitreal implant) for cytomegalovirus retinitis
- **Retisert** (fluocinolone acetonide intravitreal implant) for non-infectious uveitis
- **Iluvien** (fluocinolone acetonide intravitreal implant) for diabetic macular edema
- **NT-501 or 201** (a polymer implant containing human retinal epithelial cells genetically modified to secrete ciliary neurotrophic factor) for non-neovascular (dry) age-related macular degeneration and/or retinitis pigmentosa
- **I-vation** (triamcinolone acetonide intravitreal implant) diabetic macular edema

Kuno, Drugs Aging 2010; 27 (2): 117-134
Realities of implant technology

**Size**

**Erodability and removal**
- For micro- and nanoparticles, drug release often parallels the erosion of the device
- The life of larger “bioerodable” devices can extend beyond drug release
  - Retisert patients often have more than one retisert device in place (no benefit in removing old devices until the pars plana becomes crowded)

**Limit on ocular ‘real estate’**
- Once-yearly treatment of a glaucoma patient may mean 20-30 devices
- Implantation site usually can be used only once
Invasiveness
What are the practical aspects?

- All physicians can prescribe drops, but can all implant a device?
- Tradeoffs for convenience, invasiveness, duration of action
- What would be the impact on patterns of clinical practice
  - How long is the procedure?
  - See patients more often/less often?
- What are the risk/benefit issues
The neurotrophic factor hypothesis is based on the observation that neurons compete for limited amounts of target-derived neurotrophic factors that are required for their survival. Neurons that successfully compete for these factors survive, whereas less competitive neurons die. In glaucoma, neurotrophic deprivation caused by obstruction of retrograde axonal transport may be involved in RGC death.
Murine nerve growth factor (NGF) administered topically to the eye rescues RGCs from apoptosis in rats

RGCs express nerve growth factor (NGF) receptor (TrkA). NGF binding to TrkA up-regulates Bcl-2 protein, which protects cells from apoptosis by preventing caspase activation (21, 23).

Intravitreal NGF delivery to the retina and optic nerve is crucial to the survival of RGCs and NGF is known to be responsible for functional recovery of the retina following ocular ischemia and hypertension in animal models. An ophthalmic solution of NGF administered topically to the ocular surface has been shown to reach the retina and optic nerve where it is biologically active.

Encapsulated Cell Technology (Neurotech)

6 mm in length and consists of genetically-modified human cells packaged in a semi-permeable hollow fiber membrane with a suture loop at one end to anchor the implant to the sclera. The implant is surgically placed in the vitreous body. The implant is sutured in a manner that allows for its retrieval when desired. The surgical procedure is performed as an outpatient procedure in about 25 minutes.
Encapsulated Cell Technology (Neurotech)

- ECT is a unique technology that allows for the sustained, long term delivery of therapeutic factors to the back of the eye.
- ECT implants consist of cells that have been genetically modified to produce a specific therapeutic protein and are encapsulated in a semi-permeable hollow fiber membrane.
- The cells continuously produce the therapeutic protein which diffuses out of the implant at the target site.
Surface modified nanoparticulate carriers may be used to accommodate a wide variety of active compounds, including poorly water soluble drugs.

Drugs can be coupled to nanocarriers that are specific for cells and/or organs.
Nanoparticles - small polymeric colloidal particles with a therapeutic agent either dispersed in the polymer matrix (nanosphere) or encapsulated in polymer (nanocapsule).

Dendrimers - mono dispersed symmetric macromolecules built around a small molecule with an internal cavity surrounded by a large number of reactive end groups.

Microemulsions - dispersions of water and oil with surfactant and co-surfactant in order to stabilize the interfacial area.

Liposomes - small artificial vesicles of spherical shape that can be produced from natural phospholipids and cholesterol. They can encapsulate drugs inside the cavity or between the bilayers depending on the hydrophilicity or the hydrophobicity of the drug.

CDs - a group of cyclic oligosaccharides, capable of forming inclusion complexes with many drugs.
Figure 6. Flatmount RPE-choroid complex at 4 months after a single intravitreous injection of Rh NPs showing the RPE cells still filled with the engulfed fluorescent NPs (arrowheads). Diffusion of free Rh (nonaggregate red staining) was also observed (inset). N, nucleus.
Structural improvement after normal mouse peripherin/Rds (NMP) nanoparticle delivery

Transferred NMP leads to structural rescue of the rds\(^{+/−}\) phenotype.

Light micrographs (top rows) and electron micrographs (bottom rows, \(n=3−5/group\)) from the temporal side of rds\(^{+/−}\) eyes were examined. After P5 (A) or P22 (B) injection, moderate ultrastructural rescue is detected in the OSs of nanoparticle-injected eyes (arrows) at PI-30; significant ultrastructural improvement in OSs of nanoparticle-injected eyes is apparent by PI-120. OS discs are properly aligned and flattened, and improved OSs do not exhibit the swirl-like structures typical of the rds\(^{+/−}\). IS, inner segment layer; RPE, retinal pigment epithelium. Scale bars = 10 µm.

Cai, FASEB J. 2010
DNA nanoparticles can be used to deliver RNA (for RNA interference) to diseased tissues

Nanoparticle formulations typically contain a segment of DNA or RNA (circular or linear) which is compacted with a polycationic polymer.

Delivery of compacted DNA nanoparticles to the target yields medium to high transfection efficiency and may be a useful vehicle for gene therapy.

Insert capacity of compacted DNA/RNA nanoparticles is up to 20 kb.

The size has a typical range of 10–100 nm in diameter.

Small particles are taken up at the cell surface and trafficked to the nucleus within a short period of time.

Nanoparticles can be engineered to be highly cell specific.
Targeted Administration into the Suprachoroidal Space Using a Microneedle for Drug Delivery to the Posterior Segment of the Eye

Microneedle for SCS injection. Low-magnification view of a microneedle at the end of a syringe (A) and high-magnification comparison of a microneedle (left) to the tip of a 30-gauge hypodermic needle (right). Scale bars: 5 mm (A) and 500 lm (B).

Histological cross-sections of rabbit eye tissue after SCS administration of 10 lm fluorescent particles. A brightfield (A) and fluorescence (B) microscopy image of particles 2 months after a SCS injection. The particles can be distinctly located in the lower sclera or choroid layers of the eye. The inset shows a blow up of the boxed region where individual particles can be seen. Scale bar: 100 lm.

Canaloplasty

iTrack ophthalmic microcatheter with illuminated beacon tip.

Ultrasound image of the canal following viscodilation.

siRNAs are short, double-strand RNA oligomers consisting of 21 to 23 base pairs, with one strand being complementary to part of the mRNA of the fusion protein. siRNAs can either be introduced into the cell (e.g. by way of electroporation) or be expressed in the cell as small hairpin RNAs (shRNAs). The latter will then be processed into siRNA in the cytoplasm. In the cytoplasm, one strand of the siRNA will become part of what is known as RNA-induced silencing complex (RISC), which is then able to bind to suitable mRNAs. RISC is now able to cleave these mRNAs and digest or inhibit their translation (Figure: Prof. Heidenreich).
Effects of glucocorticoid receptor (GR) short-interfering RNA (siRNA) perfusion on the expression of dexamethasone-induced genes [myocilin (MYOC) and cornea-derived transcript factor 6 (CDT6)] in intact human trabecular meshwork in organ cultures. The delivered naked siRNA was functional, inhibiting not only the targeted gene (GR) but also the downstream effectors (MYOC, CDT6).
siRNA delivery to mammalian cells using layered double hydroxide nanoparticles

Fig. 8. Knockdown of ERK2 upon LDH mediated delivery of anti-MAPK1(ERK2) siRNA to HEK293T cells. Cells were seeded in 12 well plates at 5 10^5 cells/well 24 h prior to transfection. Transfection complexes were prepared in cell culture medium 15 min prior to transfection and added to the wells after the original medium in each well was replaced with fresh medium (RPMI-10%FCS). Cells were harvested and lysed in RIPA buffer at the indicated timepoints (controls were harvested after 24 h). Cell lysates were analyzed by SDS–PAGE and subsequent Western Blot analysis using anti-ERK2 antibody (raised in rabbit) as primary antibody and anti-rabbit antibody (raised in goat, HRP-conjugated) as secondary antibody. After exposure and development of the X-ray film, WBs were stripped and reprobed with anti-beta-tubulin (raised in rabbit) as loading control. Films were scanned and analyzed using ImageJ software [47]. Results shown are averages of two independent experiments performed as duplicate, normalized to the growth control.
Better outcomes for patients

- Better drugs
- Better drug delivery
- Reduction in adverse events
- Better compliance & persistence
- Easier for patient
- Take the patient out of the equation