Ocular Drug Delivery
ACVO Basic Science Course

Brian C. Gilger, DVM, MS, Dipl. ACVO, Dipl. ABT
Professor of Ophthalmology
bgilger@ncsu.edu

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1. Selecting the correct pharmacologic agent
2. Achieve appropriate dose at the target ocular tissue
3. Select delivery method that does not damage healthy tissue

(Weiner & Gilger, Ocular Drug Delivery, Veterinary Ophthalmology 2010).
Topical application

Limited penetration (<5%)
Rapid tear washout
Poor patient compliance
Systemic administration

Limited/variable penetration
Potential for systemic toxicity

Topical application

Limited penetration (<5%)
Rapid tear washout
Poor patient compliance
Intravitreal injections

Increased risk of retinal detachment, hemorrhage, endophthalmitis, cataracts
Rapidly diluted
Repeat procedures necessary

Systemic administration

Limited/variable penetration
Potential for systemic toxicity

Topical application

Limited penetration (<5%)
Rapid tear washout
Poor patient compliance
**Intraocular implants**

*Increased risk of retinal detachment and intravitreal hemorrhage*
*Invasive*

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**Intravitreal injections**

*Increased risk of retinal detachment, hemorrhage, endophthalmitis, cataracts*
*Rapidly diluted*
*Repeat procedures necessary*

---

**Systemic administration**

*Limited/variable penetration*
*Potential for systemic toxicity*

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**Topical application**

*Limited penetration (<5%)*
*Rapid tear washout*
*Poor patient compliance*
When considering drug delivery methods

* Three important aspects
  1. Duration of drug delivery needed
  2. Intended tissue target
  3. Owner or patient compliance
Challenges to Ocular Drug Delivery

- Highly sensitive ocular tissues
- Tissue barriers to drug penetration:
  - Lipophilic corneal epithelium
  - Hydrophilic corneal and sclera stroma
  - Conjunctival lymphatics
  - Choroidal vasculature
  - Blood-ocular barriers.
Ocular Drug Delivery

- Formulation considerations for ocular drugs
- Review pharmacology of topically applied drugs
  - Corneal penetration
- Practical methods to increase drug penetration
- Alternative methods
  - Drug devices, injections
- Advances in ocular drug delivery
Ocular formulations must fulfill the essential requirements of safety, stability, manufacturability, and bioavailability. Special attention to formulation factors that may affect ocular tolerability and safety, such as listed in table:

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Drug characteristic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appearance</td>
<td>color, clarity, particulate, and precipitate tests</td>
</tr>
<tr>
<td>pH</td>
<td>pH between 4–8 (most marketed products 5-8)</td>
</tr>
<tr>
<td>Osmolality</td>
<td>160 to 480 mOsm/kg (0.5–1.5 % NaCl conc.)</td>
</tr>
<tr>
<td>Active ingredients</td>
<td>95-105% of label claim</td>
</tr>
<tr>
<td>Insoluble particulate</td>
<td>No more than one particle &gt;300um/ml</td>
</tr>
<tr>
<td>Sterility</td>
<td>Sterile</td>
</tr>
<tr>
<td>Bacterial endotoxin</td>
<td>&lt;0.5 EU/ml</td>
</tr>
<tr>
<td>Packaging</td>
<td>No interactions with packaging; intact package integrity</td>
</tr>
</tbody>
</table>
General Features of Ocular Drug Delivery

- **Ocular formulations**
  - **Solutions**
    - **Adv:** dose uniformity, ease of manufacturability and often provides better bioavailability.
    - **Disadv:** rapid clearance and a short precorneal residence time after instillation
  - **Suspensions**
    - Coarse dispersion of insoluble solid particles of a drug
    - **Adv:** provide higher bioavailability by prolonging residence time of formulations in precorneal area
    - **Disadv:** The particle size 95% <10 um to avoid foreign body sensation
General Features of Ocular Drug Delivery

* Ocular formulations
  * Ointments
    * Sterile semisolid
    * Typically involves a combination of mineral oil and white petrolatum.
    * Adv: better product stability; better bioavailability due to longer residence time of the formulation, and dilution effect due to tear is marginal and low nasolacrimal clearance
    * Disadv: Messy, difficult to apply? Blurred vision?
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Basic Ocular Pharmacology

- First order kinetics
  - The rate of elimination depends on drug concentration
Basic Ocular Pharmacology

First Order

Toxicity

Therapeutic

Sub-therapeutic

Repeat Dose

Dose
Basic Ocular Pharmacology

- Zero order kinetics
  - Elimination independent of time
  - Elimination is independent of drug concentration

![Graph showing zero order kinetics](image)
Basic Ocular Pharmacology

Therapeutic

Toxicity

Sub-therapeutic

First Order

Zero Order

Repeat Dose
Basic Ocular Pharmacology

Toxicity

Therapeutic

Sub-therapeutic

Repeat Dose

First Order

Zero Order

Controlled Release
Topical Ocular Medications

- The main route of topical drug entry to the anterior chamber is penetration through the cornea.
- Peak concentration in aqueous humor is typically 20 to 60 minutes.
- “Lag time” – time from drug application to appearance in AH
In general, the amount of drug penetrating the cornea is linearly related to its concentration in the tear film.
Commercially available topical medications dispense a range from 25.1 to 70 μL (average drop size of 39 μL).

Tear volume
- Human = 7–9 μL (turnover rate of 0.5–2.2 μL/min).
  - Palpebral fissure “holds” 25-30 μL
  - Complete turnover in 10 min
- Horse = 230 μL (rate 33 μL/min)

Application of topical drop causes increase in tear volume and rapid reflex blinking.

Remainder is drained into systemic circulation via nasolacrimal duct or overflow onto face.
Because of these properties, only 7 to 10% of a topical dose of medication ever reaches the anterior chamber.

The remainder exits with the tear film through the nasolacrimal system, is deposited on the eyelids, or metabolized by enzymes in the tears and surface tissue.

Systemic absorption of some drugs can be significant.
Patel et al., Syst Rev Pharm 2010; 2:113-120

Flowchart:

- Instilled dose
  - Tear evaporation
  - Corneal absorption
  - Conjunctival absorption
  - Poor corneal permeability
  - Preocular area
    - Tear turnover
    - Drug metabolism
    - Protein drug binding
    - Nasolacrimal drainage
  - Drug loss
  - Low bioavailability

- Ocular absorption (<7-10% of the dose)
  - Corneal route
    - Aqueous humour
      - Ocular tissues (iris, retina, ciliary body etc)
  - Conjunctival and scleral route

- Systemic absorption (~50-100% of the dose)
  - Minimum
    - Aqueous humour
    - Lachrymal glands
    - Pharynx
    - GIT
    - Skin
  - Maximum
    - Nose
    - Conjunctiva
  - Elimination
Properties of Corneal Drug Penetration

- The cornea is essentially a multilayered sandwich
  - fat (epithelium)
  - water (stroma)
  - fat (endothelium)
Properties of Corneal Drug Penetration

- The epithelium is the major barrier to absorption, especially for hydrophilic medications.
Properties of Corneal Drug Penetration

- The corneal stroma is a major barrier for lipophillic drugs.
Penetrate through the cornea by passive diffusion via either transcellular or paracellular pathway. Partition coefficient (log P) of the drug molecule has significant impact on drug penetration through cornea. The partition coefficient measures how hydrophilic or hydrophobic a chemical substance is. Compounds with log P between 1 and 3 show maximum corneal penetration.

Reddy et al 1996
Topically Applied Drugs

- Molecular weight / size of the drug molecule cutoffs
  - Cornea approx. 500 Da
  - Conjunctiva approx. 40 kDa
  - Sclera approx 150 kDa
  - Therefore, higher molecular weight molecules would more likely be absorbed in conjunctiva and sclera compared to cornea.
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Practical methods to increase topical drug penetration

- Prolong the topical contact time of the drug.
  - vehicles with increased corneal contact time
    - gels, ointments, emulsions, or biodegradable inserts
  - Increase viscosity
  - Instill drug in a contact lens (30-70% water)

\[ \uparrow \text{viscosity} = \]
\[ \uparrow \text{retention} = \]
\[ \uparrow \text{residence time} = \]
\[ \uparrow \text{amount of drug absorption} \]
Topical Route of Administration

- **Ophthalmic solutions / suspensions**
  - If desire a higher conc. of drug in eye - instead of giving more drops at one time:
    - Increase frequency of administration
      - (wait 5 minutes between drops)
    - Use higher concentration of drug
      - (watch for toxicity / irritation)
    - Improve ocular penetration
      - (remove epithelium)
Methods to increase topical drug penetration

- Prolong the topical contact time of the drug.
  - vehicles with increased corneal contact time
    - gels, ointments, or biodegradable inserts.
  - Increase viscosity
  - Instill drug in a contact lens (30-70% water)

- Alter the epithelium
  - Damaging the epithelium can reduce the barrier properties of the epithelium.
Methods to increase topical drug penetration

- Alter the epithelium
  - Damaging the epithelium
    - Corneal scraping
    - Epithelial debridement
    - Certain topical medications contain preservatives or surfactants that increase penetration
      - E.g., Benzalkonium chloride
Methods to increase topical drug penetration

• Choose a medication that will stay on the cornea

• Improve penetration by altering epithelium

• Bypass barriers
  • Subconj injection
  • Intraocular injection
  • Ocular implants
Route of Administration of Ophthalmic Medications

* Subconjunctival Injections
  * Bypass ocular barriers!
  * Great ocular penetration
  * Most aqueous soluble IV meds well tolerated
  * Can give up to 0.25 cc
  * Use with caution, esp steroids
    * Once injected - cannot reverse
    * Only for those animals that cannot be treated frequently

Subconjunctival injections
Route of Administration of Ophthalmic Medications

* Intraocular injections
  * Risky due to toxicity of many drugs
  * Gentocin used to destroy eye in chronic glaucoma
    * 20 to 35 mg of gentocin (0.25-0.30 cc of 100mg/ml)

24 hours post injection 10 mg
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Sustained Drug Delivery Devices

- Sustained release of medication
- To ocular surface and intraocularly
- Canine KCS, equine IMMK
General Features of Ocular Drug Delivery

- First Order
- Zero Order
- Controlled Release

Toxicity

Therapeutic

Sub-therapeutic

Repeat Dose
Sustained Drug Delivery Devices
Matrix-Reservoir Implant

Projected release duration: 3.18 years

Release Rate [μg/day]

Time (Days)
Sustained Release Drug Delivery

- Equine uveitis
- Canine KCS
- Effective delivery of medications to the suprachoroidal and episcleral space is feasible
Can a local injection into the SCS reach the retina?
Single injection (latex) reached 40-50\% of ocular posterior segment.

Intracameral implant of travaprost
Commerciafly available sustained ocular drug delivery devices

- Ozurdex: dexamethasone/PLGA
- Retisert: Flucinolone
- Envisia (ENV 515XR)
  - Travaprost
- Bimatoprost SR (Allergan)
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Advances in ocular drug delivery

- Thermosensitive, biocompatible, hydrogels
- Advanced implant technologies
- Mesenchymal stem cells
  - Would healing and immunomodulation
- Gene therapy
  - Gene replacement
  - Gene addition studies
- Iontophoresis
Methods of Ocular Drug Delivery

A. Topical application
   passive diffusion device (Visudyne®)

B. Topical iontophoresis
   (EyeGate® II)

C. Sub-Tenon’s injection:
   1. Solutions
   2. Suspensions
   3. Others: solids, fibrin sealants, nanoparticles

D. Unidirectional episcleral implant

E. Hollow microneedles:
   Suprachoroidal injection

F. Solid coated microneedles:
   Intrapapillary depot

G. Free floating intravitreal implant:
   1. Iluvien™ (formerly Medidur®): non-biodegradable
   2. Ozurdex™ (formerly Posurdex®): bioerodible

H. Scleral-fixated intravitreal implant (Ratisan®)

1. Scleral-fixated intravitreal implant; helical design (I-valent®)

J. Intravitreal injection:
   1. Solutions
   2. Suspensions
   3. Varsana™ (a proprietary biodegradable formulation)

Thermosensitive hydrogels

Pentablock Copolymers
PTSgel, 31-G Needle, into 37°C

Video clip for 103GH
Rabbit Ocular Tolerability & Histology

Ocular Histopathology - PTSgel

7 days

16 WEEKS

H&E

100X

400X
In vivo Degradation Intracamereral (Area)

Anterior chamber of the eye (intracameral)

50μL of 20% 10GH PTSgel
31 gauge needle
n=3

Conclusion: Drug release parallels degradation in vivo
Modulation of IgG Release – *In vivo* (113GH) Subcutaneous Delivery

IgG in saline

IgG in 10% 113GH

IgG in 20% 113GH

**Xenogen IVIS imager**

ROI Mean +/- SD

NIR-IgG in BSS
NIR-IgG in 10% 113GH
NIR-IgG in 20% 113GH

200ug NIR-IgG in 200 uL volume; N=3 mice/group; 31 gauge needle for subcutaneous injection
Iontophoresis

EyeGate Applicator
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