


Ocular and Nasal Drug Delivery



December 1st 2015

Ocular Drug Delivery

- Ocular administration of drug is associated with the need to treat ophthalmic diseases such as:

1. Bacterial, fungal and viral infections of the eye or eyelids.
2. Allergic or infectious conjunctivitis or inflammation.
3. Elevated _____ _____and glaucoma.
4. _____eye syndrome.

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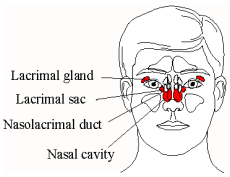
Lacrimal system



- Tears
  - normal volume=____ µl
  - non-blinking eye=__ µl
  - blinking eye ~ 10 µl
  - drop volume ~ 50 µl
- Tears are drained from the lacrimal lake by two tubes (lacrimal canaliculi) onto the nose.

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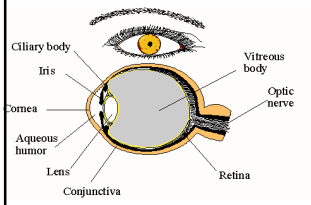
The Eye & Fate of absorption



- Drug **mainly** diffuses through cornea (membrane barrier) into the eye.
- Absorption may happen through sclera or conjunctiva. Very limited because penetrated drug is absorbed by general circulation.

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Fate of Drug

- *removal by the naso-lacrimal apparatus*
  - When reflex tearing causes volume to exceed ____ µl.
  - GI tract: Potential systemic effects, salty/bitter taste.
  - superficial adsorption by drug through the conjunctiva: rapid removal by peripheral blood vessels.
  - Ocular absorption is < ___% of administered dose.

Repeated administration

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Limitation of Ocular Bioavailability

1. Physiological Factors:
   1. Protein binding tears contain 0.6-2.0 protein. disease state.
   2. Drug metabolism enzymes such as lysozyme
   3. Efficient Naso-Lacrimal drainage
   4. Inflow and outflow of lacrimal fluids i.e. continuous washing.
   5. Limited surface area for absorption.
2. Physicochemical Characteristics of the drug
   1. Particle size
   2. Lipophilicity
   3. Solubility
3. Formulation factors: see slide 13

❖ Ophthalmic suspensions, gels and ointments mix with lacrimal fluids readily than do low viscosity solutions and thus remain longer in the cul-de-sac enhancing drug bioavailability.

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Ophthalmics

- Ophthalmic preparations are sterile products essentially free from foreign particles, suitably compounded and packaged for instillation in to the eye.
- The following dosage forms have been developed:

1. Ophthalmic solutions
2. Ophthalmic suspensions
3. Ophthalmic ointments
4. Ophthalmic inserts

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Ophthalmic Solutions

- **Sterile, free from foreign particles**
- Eye dropper bottles
- One drop only , not two or three.
- What is recommended when more than 1 drop is to be administered?

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Suspensions

- **Aqueous** formulations containing **solid** particles.
- The particle size must be kept to a minimum to prevent _____of the eye.
- Use of the micronized* form.
- How does a suspension increases duration of action compared to solution?

Ointment

- Keeps the drug in contact with the eye _____ than suspensions.
- Most ophthalmic ointment bases are a mixture of petrolatum and mineral oil have a melting point close to body temperature.
- Nonirritating and free from grittiness.
- Use of micronized form of the ingredients.

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Ocular Control Release System: Inserts

Non-erodible

- **Ocusert®** is a nonerodible device.
- First controlled release topical dosage form marketed in US by Alza in 1975.
- Delivers pilocarpine for several days in the treatment of glaucoma.
- A soft and flexible elliptical membrane designed to be placed in the cul-de-sac
- Advantage:
  - Steady levels for 7 days intraocular pressure (IOP)
  - vs. qid dosing from drops
- Disadvantage:
  - Cost.
  - Not Comfortable.

Erodible

- **Lacrisert®** is an erodible device. Alza
- Controlled erosion of the polymer matrix
- Poorly soluble, high-MW compounds
- q.d. or b.i.d. for moderate to severe dry eye syndrome
- 5 mg of hydroxypropylcellulose (anhydrous) in a rod shape
- Placed in cul-de sac.
- Advantage:
  - Controlled release
- Disadvantage:
  - Floats.
  - Not comfortable.

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Ophthalmic Dosage Form

	Advantage	Disadvantage
Solution	Convenience	Loss of drug by drainage
Suspension	Best for drugs with low dissolution, longer contact time than solution.	Loss of drug by drainage though less than solution. Irritation potential due to particle size. (best use micronized)
Ointment	Enhanced contact time	Poor patient compliance, blurred vision
Inserts	Prolonged release for several days (controlled release)	Discomfort, cost

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Uses of Ophthalmic products

1. Anti-inflammatory agents
2. Antibiotic/Antimicrobial
3. Antiviral Agents
4. Astringents
5. Beta-adrenergic blocking agents
6. Local anesthetics
7. Miotics
8. Mydriatics
9. Topical Protectants
10. Vasoconstrictors

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FORMULATION FACTORS TO CONSIDER

- Sterility and Preservation
- Iso-tonicity
- Buffering
- Viscosity and Thickening agent.
- Antioxidants

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Why sterilization?

- Contaminated ophthalmic formulations may result in eye infections that could ultimately cause blindness.
- *Most dangerous organism Pseudomonas aeruginosa.*
- Laminar flow hood.
- Filtration.
- Packaged in sterile containers.

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Sterilization

- Suspensions should not be filtered .Why?
- Obviously, ointments cannot be filtered.
- Ointment Individual ingredients are sterilized separately.
- Formulated using aseptic techniques.

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Preservatives

- Inhibit development of microorganisms.
- Low concentration.
- Multi-use containers → preserved

1. *Benzalkonium chloride*
2. *Thiomerosal*
3. *Chlorobutanol*
4. Polyquat (polyquaternium -1)
5. *Methyl- and propylparaben*

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Isotonicity

- Isotonic solutions do not damage tissue or produce pain
- Important for comfort.
- Tonicity Adjusting Agents:
  - NaCl
  - Mannitol
  - Glycerin (1%)
  - Propylene glycol (1%)
- Lacrimal fluid has tonicity of normal Saline =_____.
- 0.6 to 2.0% is acceptable.

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Why use of buffer?

1. To reduce discomfort to the patient.
2. To ensure drug stability.
3. To enhance aqueous solubility of drug.
4. To control the therapeutic activity of drug substance.
5. To maximize preservative efficacy.

❖ Physiologic pH of blood and tears is approximately 7.4= Optimum pH.
❖ Appropriate pH prevent corneal damage is 6.5 to 8.5.

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Viscosity

1. ↑ retention time
2. ↓ the drainage rate
3. ↑ ocular bioavailability
4. Have lubricant effect

- Cellulose derivatives (e.g. hydroxypropylmethyl-and methylcellulose)
- polyvinyl alcohol.
- Disadvantages: Crust formation and transient blurring

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Antioxidants

- Used to delay or prevent deterioration of the drug
- Examples:
- Sodium metabisulfite
- Ascorbic acid
- Edetic acid

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Packing

Eye Drops	Eye Ointments
• Plastic dropper bottles. • low-density polyethylene (LDPE) • 5,15, and 30 ml.	• small collapsible tube • Usually tin • 3.5 g

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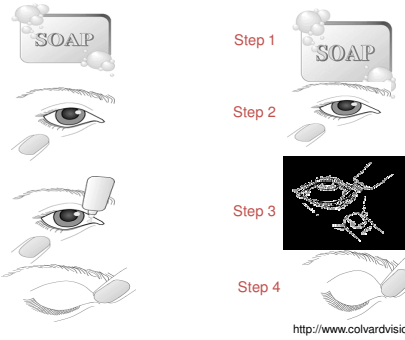
Patient consultation
How To Use Ophthalmic Drops & Ointments



http://www.colvardvision.com/ophthalmology

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Nasal Drug Delivery

- Local: nasal route is used for local acting drugs.
- Systemic: nasal route used for systemic absorption due to the high vasculature of the nasal cavity.
- Central Nervous System (targeted drug delivery): nasal route may also be used for delivering drugs to central nervous system via nasal mucosa.

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Limitation of Nasal Drug Delivery

1. Physiological Factors:
   1. Drug metabolism by nasal enzymes
   2. Short retention time.
   3. Limited surface area for absorption.
2. Physicochemical Characteristics of the drug
   1. Particle size 10-50 µm
   2. Lipophilicity
   3. Solubility
   4. Partition coefficient
3. Formulation factors:
   1. pH
   2. Viscosity

Most commonly used dosage form is drug solution. Also suspensions, gels and ointments.

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Advantage and Disadvantage of Nasal Drug Delivery

Advantage	Disadvantage
Bypass first pass metabolism and GI enzyme	Local irritation
Rapid absorption of drugs across nasal membrane	Short retention time
Used for local, systemic and potentially delivery to central nervous system	Pathologic condition such as allergy or colds alter drug nasal bioavailability
Non invasive Ease and convenience	
Lower dose = lower side effects	
Non-invasive	

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Approaches to enhance nasal drug delivery

1. Structural modification:
2. Salt or ester formation
3. Formulation design such as
   1. Surfactant: to modify permeability of nasal mucosa.
   2. Addition of bioadhesive/ mucoadhesive excipients to increase residence time. Microcrystalline cellulose.
   3. Choice of formulation: Gel formulation allows the drug to stay in contact longer with nasal tissues. E.g Zicam nasal gel

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FORMULATION FACTORS TO CONSIDER

- Preservation: same preservatives as in ophthalmic products.
- Iso-tonicity: isotonic to nasal fluids equivalent to 0.9% sodium chloride
- Buffering to pH of nasal fluid 5.5-6.5.
- Viscosity and Thickening agent.
- Antioxidants

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Therapeutic class of drugs

1. Corticosteroids
2. Antiviral
3. Antibiotics
4. Antifungal
5. More recently, vaccines e.g Live Attenuated Influenza Vaccine [LAIV] (The Nasal Spray Flu Vaccine)

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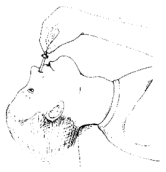
Patient consultation
How To Use Nasal Drops & sprays

- To minimize risk of contamination use by one person only.
- Patient is advised to blow the nose gently and was hands with soap.
- Patient should lie down, tilting head back.
- Instill prescribed number of drops.
- Patient to remain in the same position to allow spread in the nose.



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Nasal Spray

1. To minimize risk of contamination use by one person only.
2. Patient is advised to blow the nose gently and was hands with soap.
3. Hold head upright, insert the nose piece into nostril pointing slightly backward.
4. Close other nostril.
5. Spray the prescribed no of sprays while sniffing.

Google images

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