Ocular Pharmacology – An Introduction

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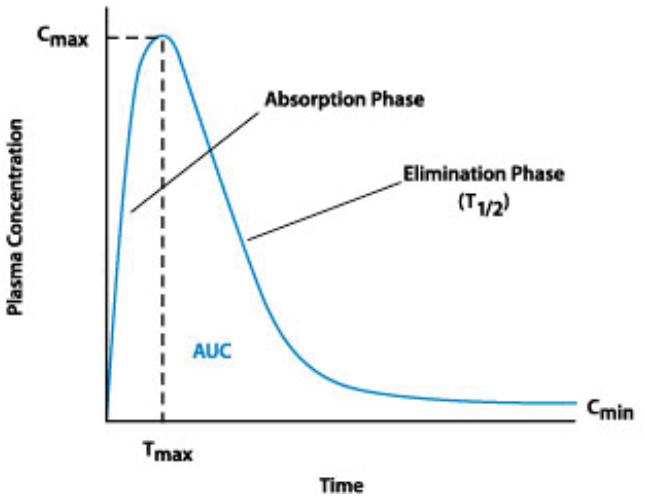
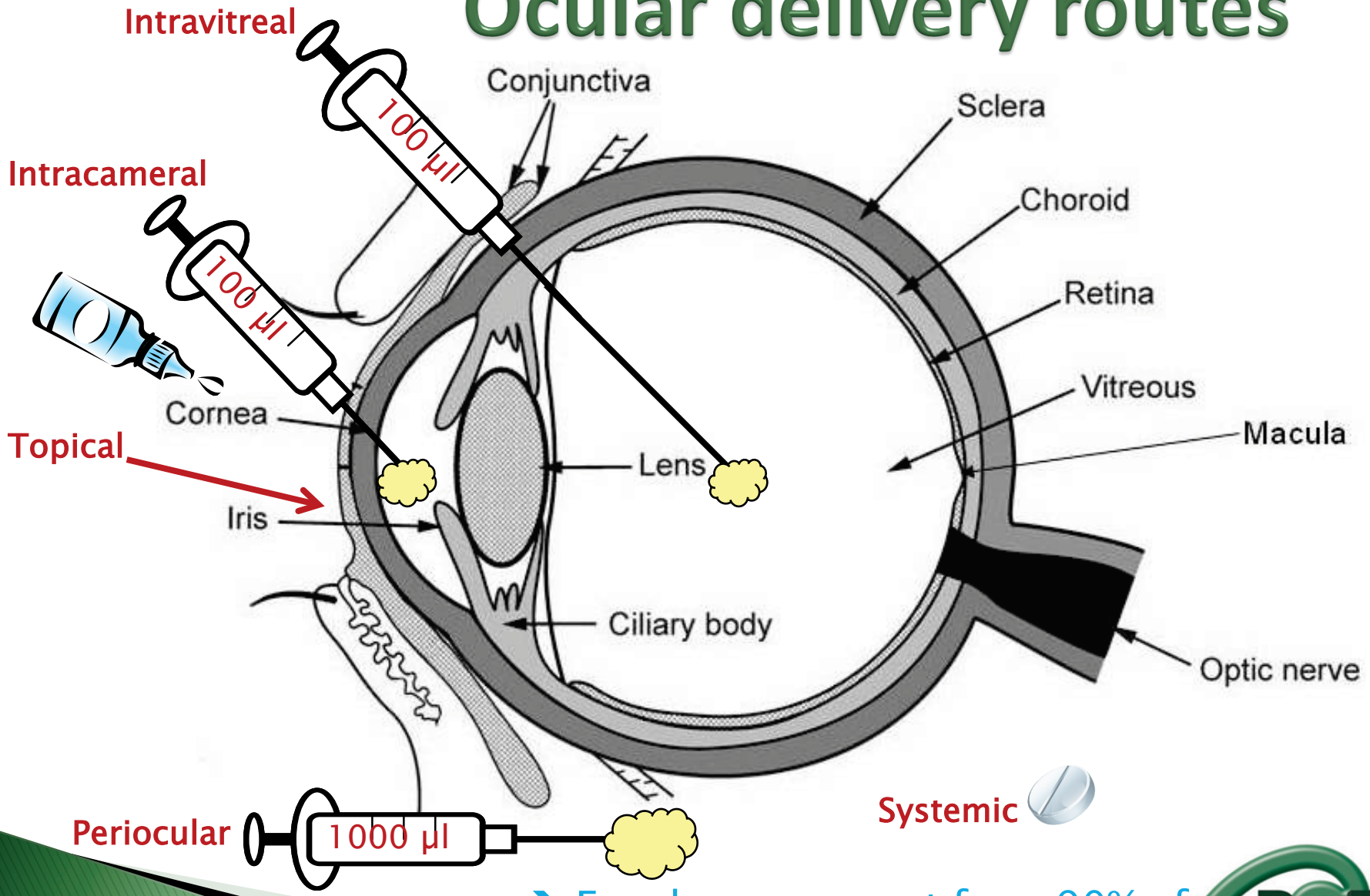
Pharmacokinetics *vs.* Pharmacodynamics

- **Pharmacokinetics**: What the body does to the drug
  - **ADME:** **A**bsorption
    Distribution
    Metabolism
    Elimination
  - Parameters: c_{max}, t_{max}, $t_{1/2}$, AUC, k



- **Pharmacodynamics:** What the drug does to the body
  - Pharmacological effect ➔ **This will be covered in detail in 5th year**

Ocular delivery routes



➔ Eye drops account for >90% of marketed ophthalmic preparations

Anterior Segment Diseases

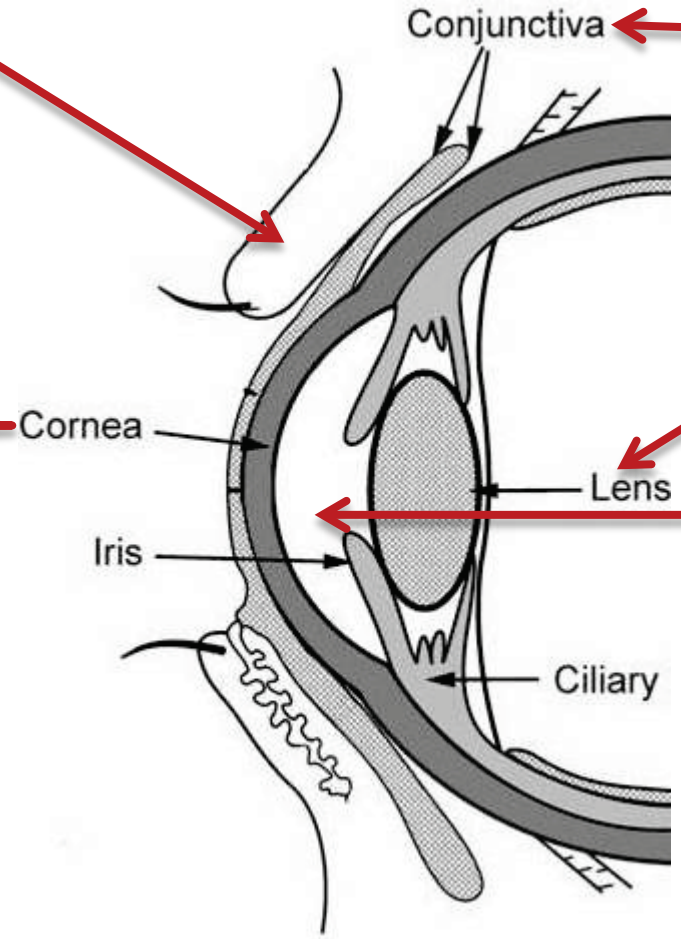
Blepharitis, styes
Hygiene, warm compresses, antibiotic eye drops

Dry eye
artificial tears

Keratoconus
riboflavin ➔ cross-linking

Corneal infections
anti-fungal/bacterial/viral eyes drops

Keratopathy
naltrexone, IGF



Conjunctivitis
artificial tears, antihistamines (allergic), antibiotics (bacterial)

Cataract
generally surgery

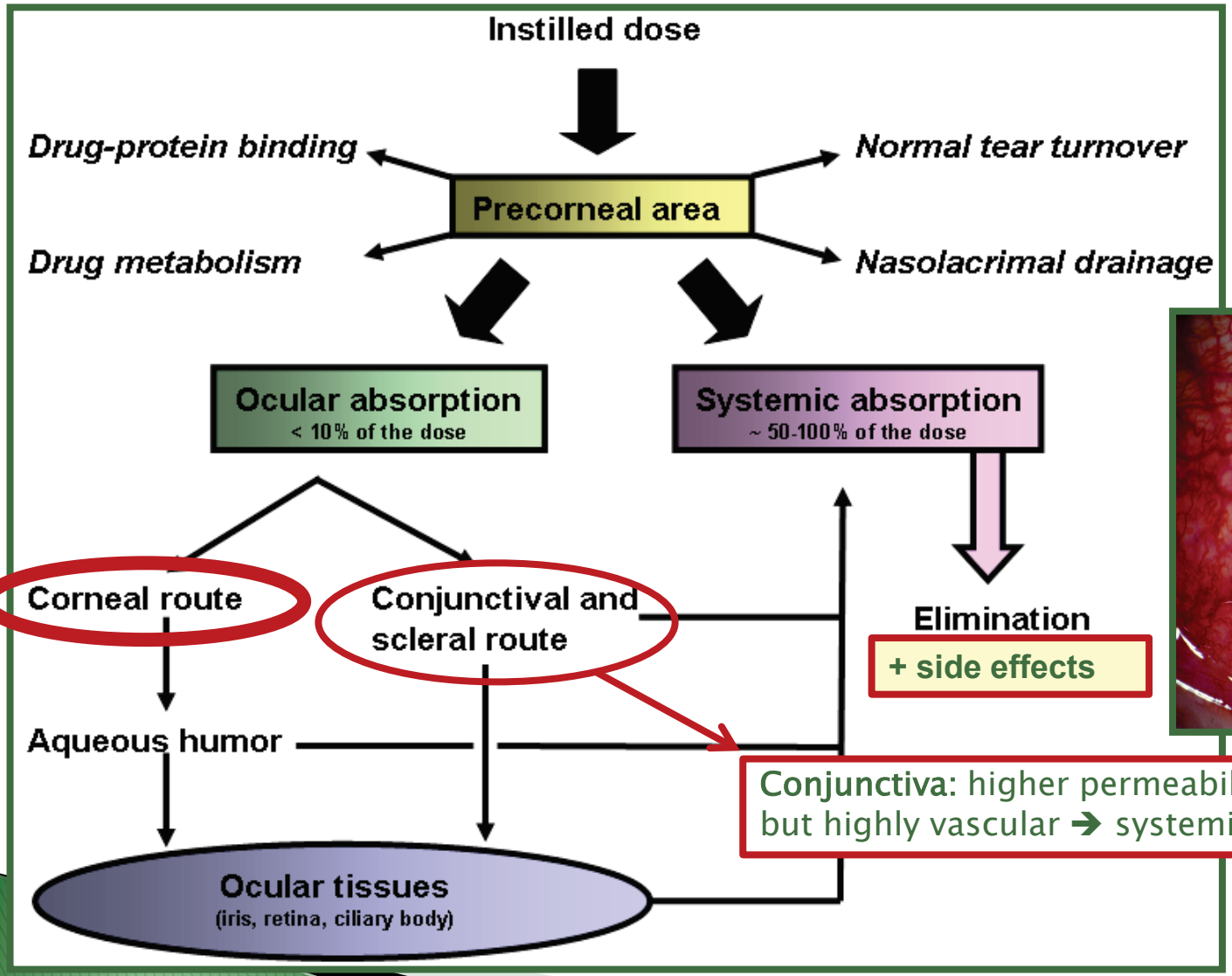
Glaucoma
Reduction of aqueous humor production (CAI, β-blockers, α_2-agonists); *increase of outflow* (PGA, parasympathomimetics, ROCK inhibitors);

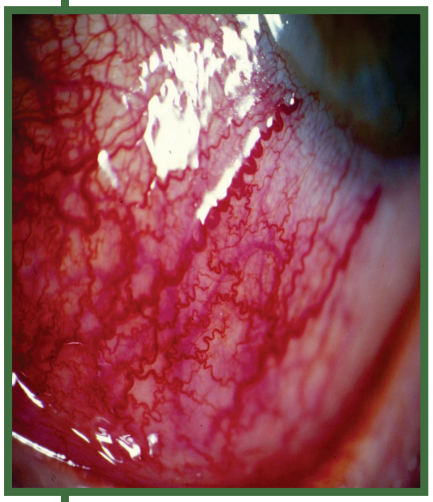
Topical ocular drug delivery

- ☺ Ease of application
- ☺ Direct application to target site
- ☺ Smaller drug dose required
- ☺ Rapid onset of action

- ☹ Contamination of drops
- ☹ Need for preservative → local toxicity
- ☹ Limited penetration and fast elimination
- ☹ Systemic absorption → side effects

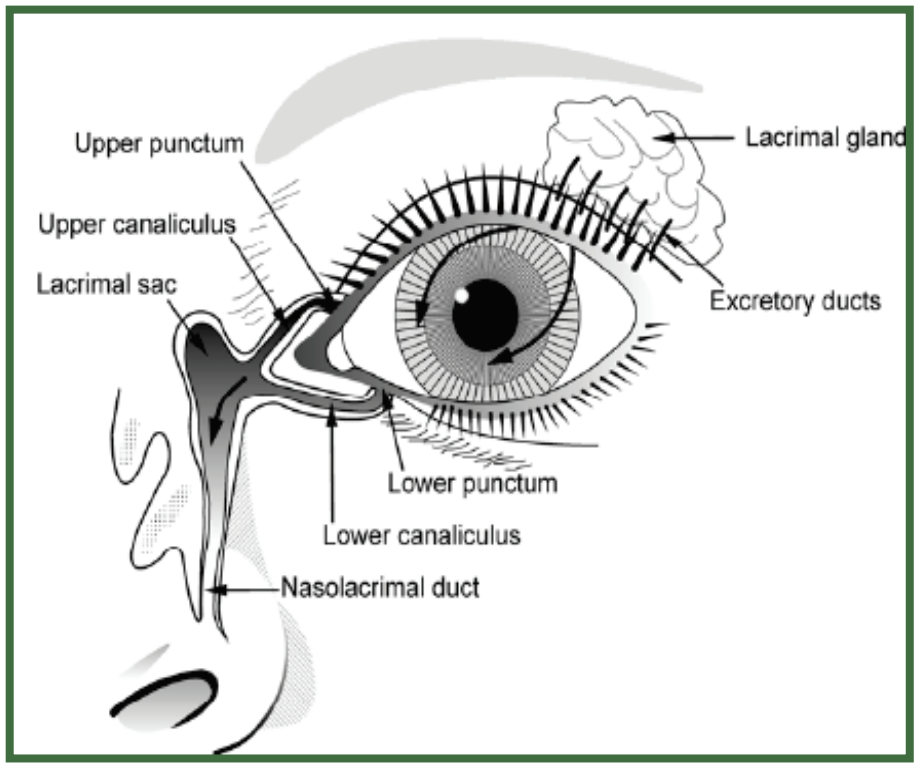
Pharmacokinetic considerations





Conjunctiva: higher permeability than cornea, but highly vascular ➔ systemic circulation

Nasolacrimal drainage

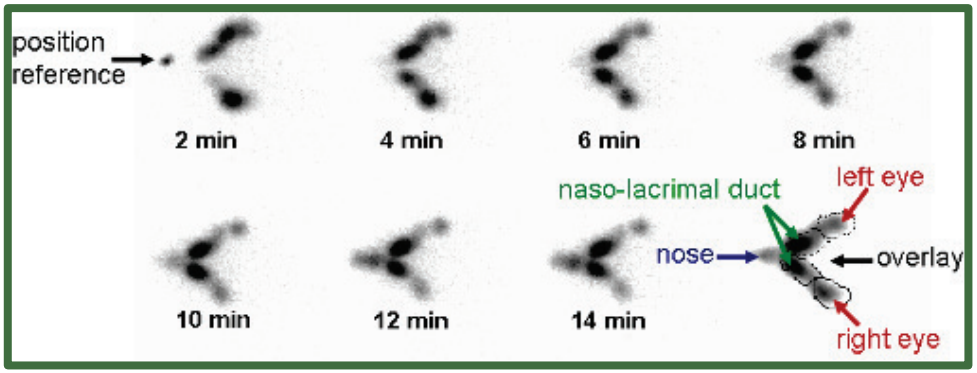


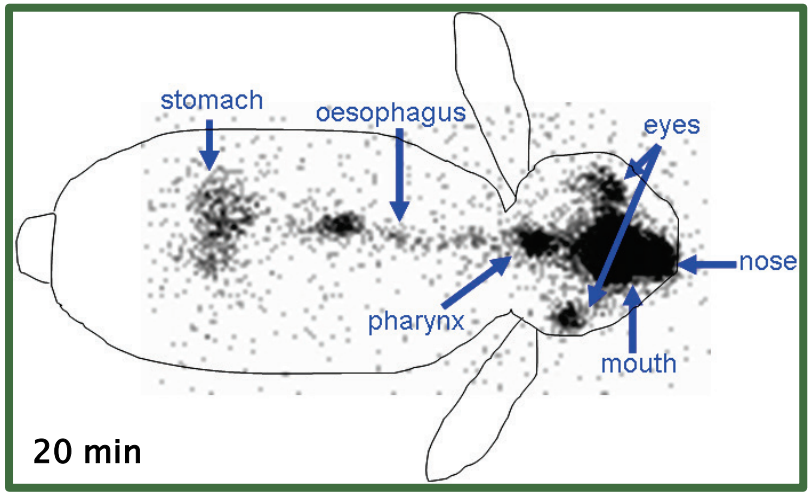
- Normal tear volume: 7-10 µl
- Lower lid can hold: < 30 µl
- Eye dropper delivers: 40-70 µl

- Tear fluid turnover doubles after eye drop application
  → **washout effect**

- **Reflex tearing** due to irritation (pH, foreign body sensation)

Nasolacrimal drainage





- > 80% of drug leaves via nasolacrimal duct
- High surface area and blood supply in nose
  ➔ **systemic absorption**

!

Application of >1 drop does **NOT** increase the effective ocular dose, but increases **systemic side effects** (β-blockers, steroids)

Eye drop application

- **Shake bottle** before use (suspensions!)
- Tilt head back and pull down lower lid
- Apply **one drop** into lower lid pocket
- **Close eyes** and **obstruct duct**
  - Normal blinking ➔ <10% of drug remains after 5 min
  - No blinking ➔ >50% of drug remains after 5 min
  - Nasolacrimal obstruction ➔ >80% of drug remains after 5 min
- Leave **5 min** between drops (washout effect)

Second drop washout effect

- If drug A is followed by drug B

  @ 30 sec: 50% of drug A is washed out

  @ 120 sec: 17%

  @ 5 min: 5%

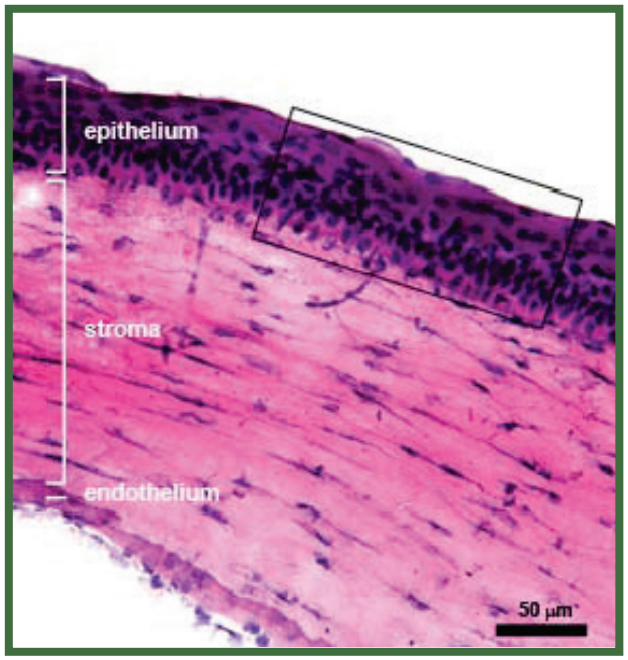
➔Leave **5 min** between drops

➔Combination rather than separate drops

=

BOTu

Transport barrier - Cornea



- Important mechanical barrier
- Main pathway for ocular penetration
- **Sandwich-like structure**
- Only drugs with MW <5kDa and logP of 10-100 can pass
- Thickness may affect drug permeation

Epithelium – lipophilic

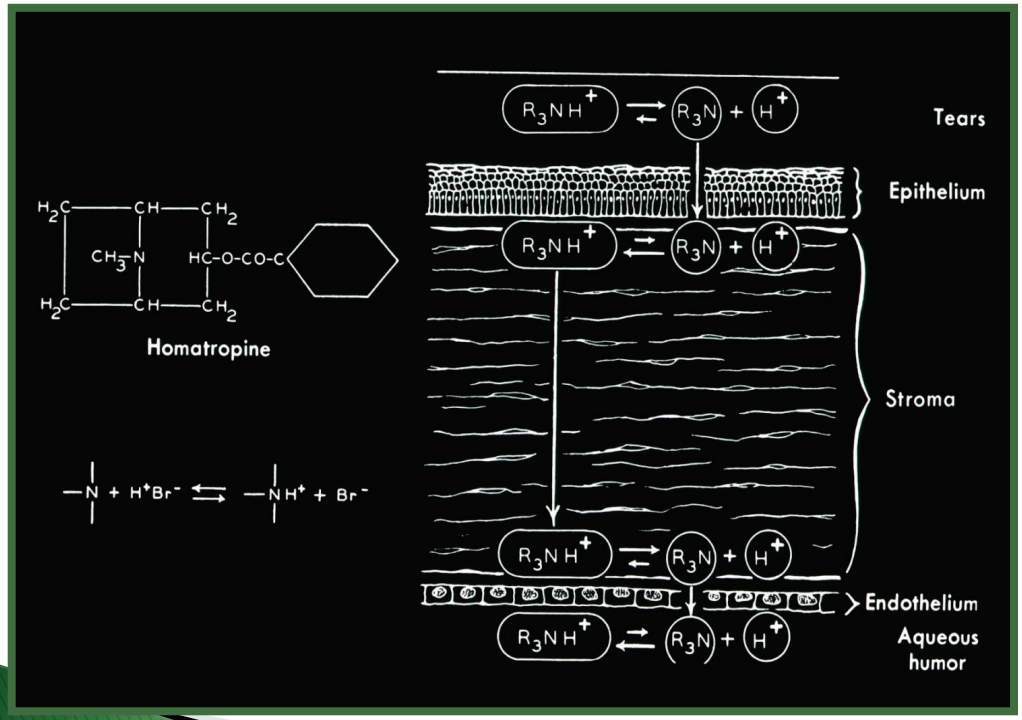
Stroma – hydrophilic

Endothelium – lipophilic

Transport barrier - Cornea

Henderson-Hasselbalch

$$pH = pK_a - log\frac{[unionised]}{[ionised]}$$

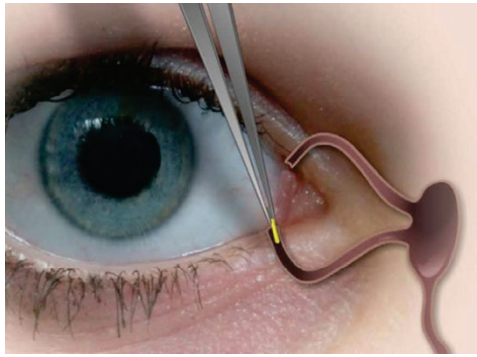


pK_a (homatropine) = 9.7

@ pH 7: ≥ 99% of drug in unionised form (lipophilic) ➔ can penetrate lipophilic epithelium

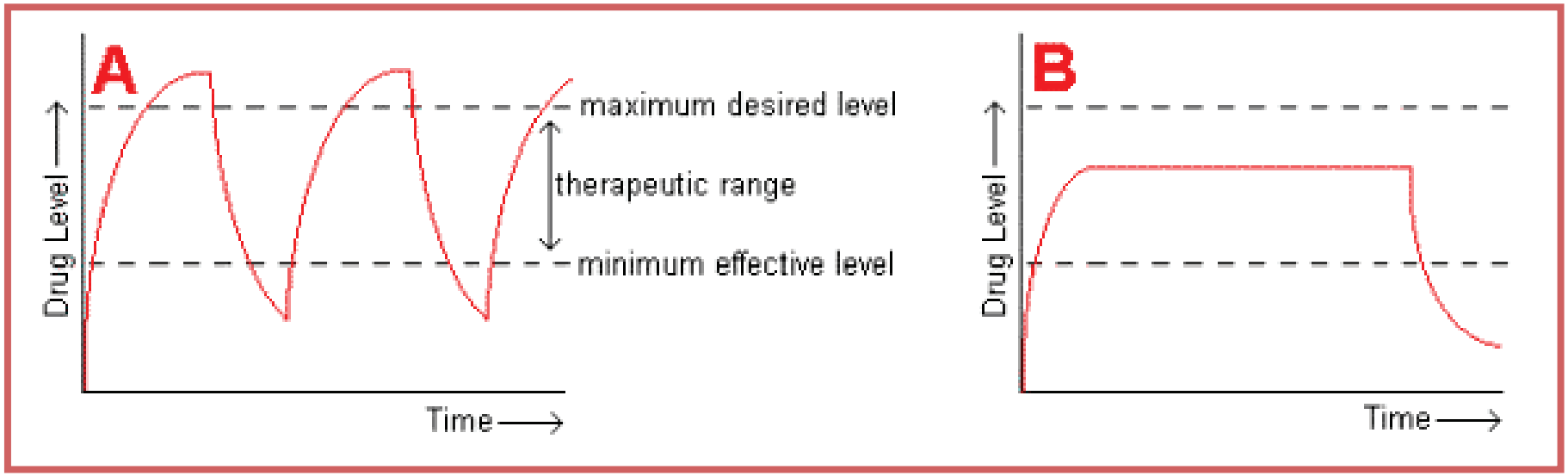
@ > pH 7 ➔ more ionised drug ➔ easily diffuses through hydrophilic stroma

Pulse entry



Drug-eluting punctum plug

A: Conventional eye drop
B: Controlled release formulation



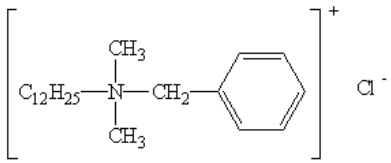
Frequent administration ➔ patient compliance↓

Is one drop the same as another?

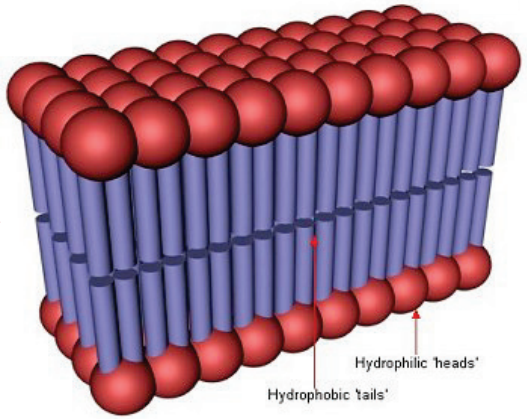
Generic equivalence

Two drops of the same drug concentration may <u>not</u> be bioequivalent due to:

- **pH** of formulation ➔ solubility/permeability (pKa)
- **Particle size** of drug in suspension ➔ drainage
- Addition of **preservatives** ➔ corneal permeability



Benzalkonium Cl (0.01%)



may increase drug absorption by 50%

<u>but:</u> may also cause toxicity/allergies

Ocular solutions

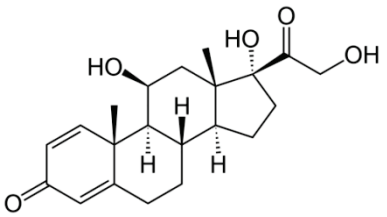
- **homogeneous mixture composed of only one phase**
- solute (drug) is dissolved in solvent (buffer)
- account for >90% of ophthalmic formulations
- β-blockers, PGA, α-agonists, CAI, some AB

☺ good stability
☺ easy to prepare
☺ low cost
☹ fast drainage ➔ limited residence time
☹ low drug permeability through cornea
☹ drug bioavailability generally <10%


"It appears to be a side effect of those herbal eye drops you've been using"

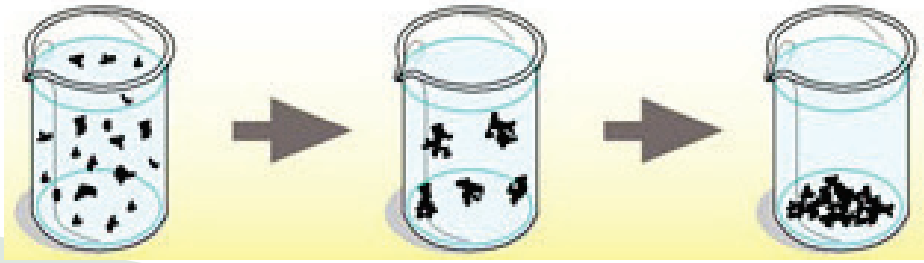
Ocular suspensions

- **heterogeneous mixture composed of <u>two</u> phases**
- internal solid phase (drug) is dispersed throughout the external liquid phase (buffer)
- steroids (Pred Forte, Maxidex, Flucon)



- ☺ reduced drainage as particles remain in lower lid
- ☺ prolonged residence time ➔ higher drug bioavailability
- ☹ high cost, sterilisation may cause physical instability
- ☹ particle size <10 µm ➔ foreign body sensation ➔ tearing
- ☹ particle aggregation/sedimentation

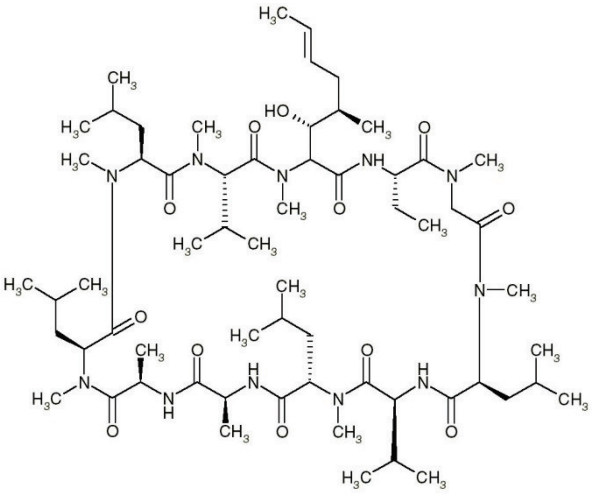
  ➔ **MUST** be shaken before use



Ocular emulsions

- **heterogeneous mixture of <u>two</u> immiscible liquids**
- water, oil and surfactant(s)
- Restasis (Cyclosporine A)

  glycerol, castor oil, Tween 80, water and NaOH



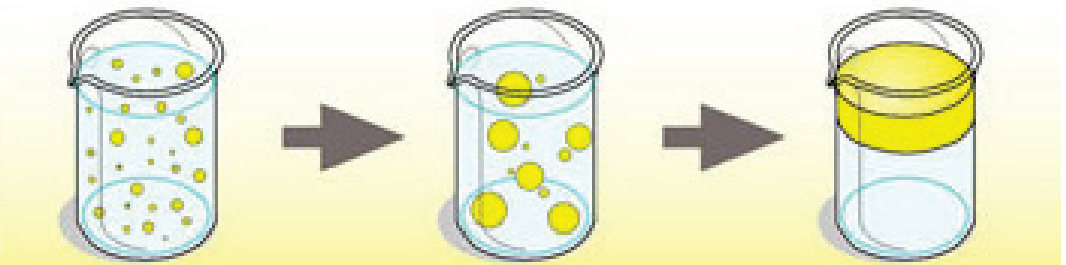
☺ suitable for oil soluble drugs

☺ lubricating nature

☹ contain surfactant(s) ➔ local toxicity

☹ low stability ➔ flocculation - coalescence - cracking

☹ high cost



Ocular ointments

- **semisolid preparation intended for external application**
- drug in hydrocarbon base (no water!)

☺ high viscosity ➔ reduced drainage

☺ no stinging upon application

☺ oily base ➔
- no dilution by tears
- no preservative required
- suitable for moisture sensitive drugs
- lubricating nature

☹ blurred vision ➔ application only at night time

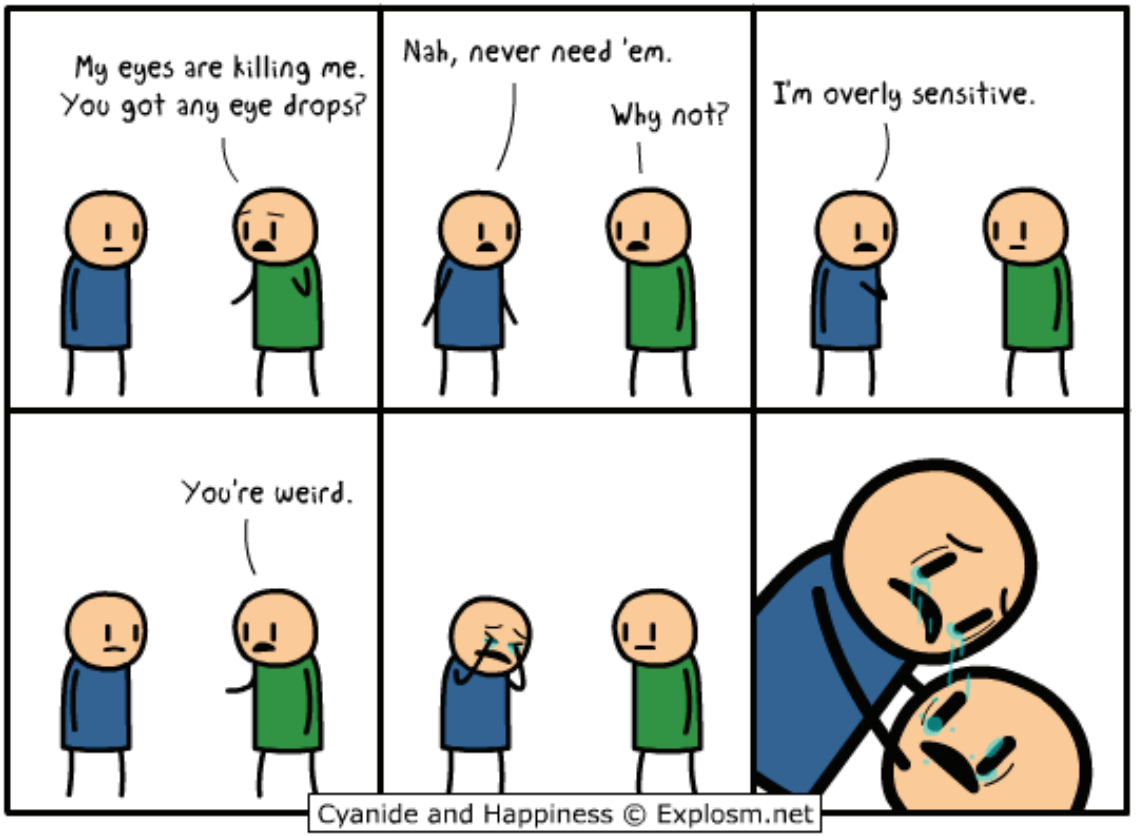
☹ greasy ➔ discomfort/irritation ➔ reflex tearing

10 things you need to know

1. Shake bottle before use ➔ suspensions!
2. Apply only one drop ➔ drainage ↓
3. Close eyes and obstruct duct ➔ drainage ↓
4. Leave 5 min between drops ➔ washout ↓
5. Two eye drops of the same drug concentration may not be bioequivalent ➔ efficacy, side effects

10 things you need to know

6. Topically applied drops can cause systemic side effects ➔ β-blockers, steroids
7. Preservatives can cause ocular toxicity and allergies
8. Ointments and suspensions exhibit longer drug action than drops ➔ drainage ↓
9. Use ointments only at night ➔ blurred vision
10. Corneal conditions may influence drug absorption


My eyes are killing me. You got any eye drops?
Nah, never need 'em.
Why not?
I'm overly sensitive.
You're weird.
Cyanide and Happiness © Explosm.net

Thank you