Bioequivalence Assessment for Complex Ophthalmic Products

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Session: Non-traditional Approaches to BE and Biosimilars and Application of Clinical Pharmacology to Minimize Barriers to Generic Drug Substitution

Biography and Contact Information

- Professor of Biopharmaceutics at University of Helsinki and University of Eastern Finland
- Research expertise in ocular drug delivery and pharmacokinetics
- Research published in more than 300 journal papers
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BARRIERS IN TOPICAL OCULAR DRUG DELIVERY

Drainage factors

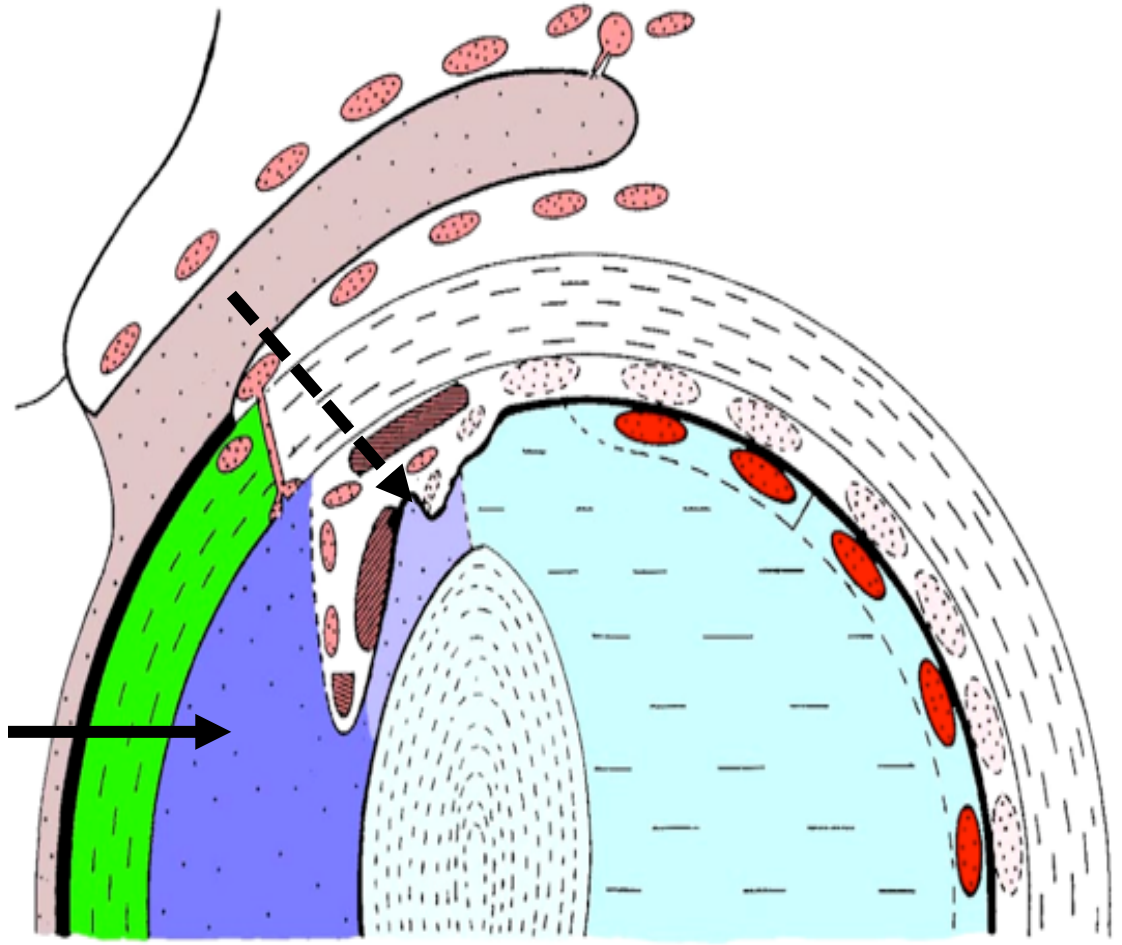
- Solution flow
- induced lacrimation
- Tear turnover

Non-corneal absorption

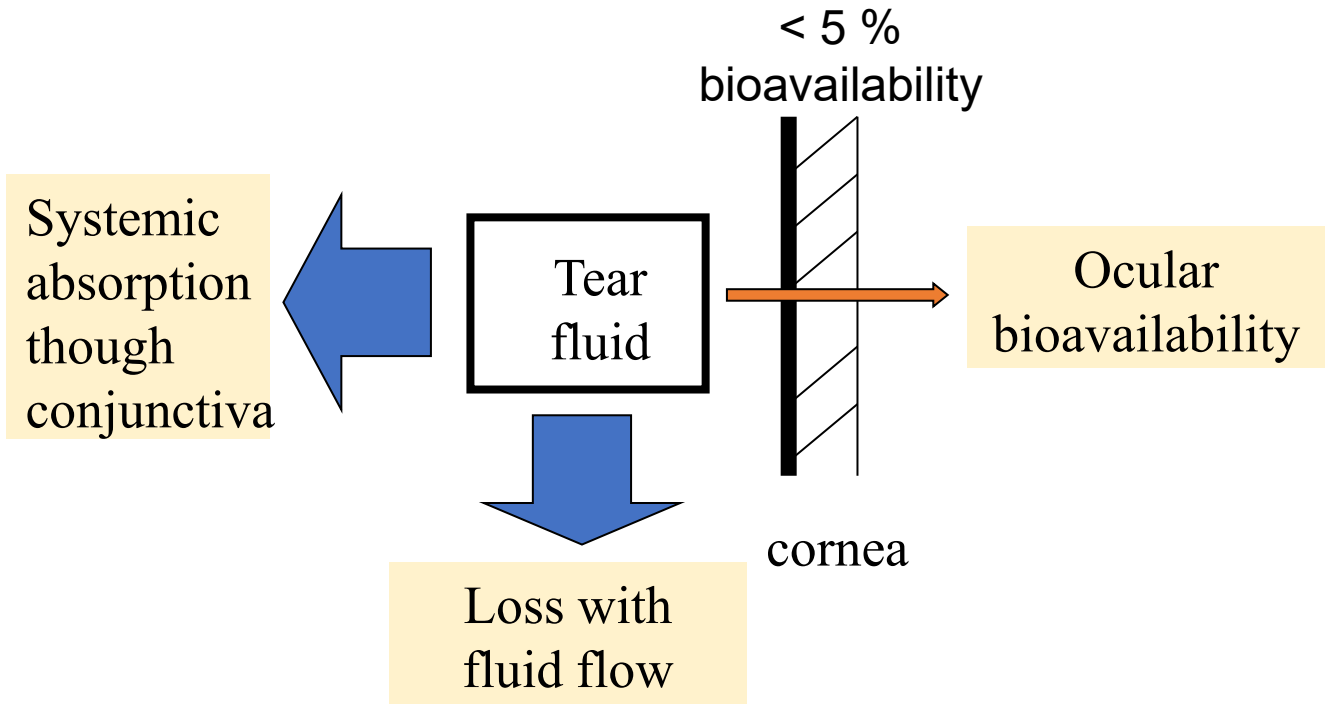
Tissue barriers

- Cornea
- Conjunctiva
- Sclera

Corneal Absorption



Ocular drug absorption



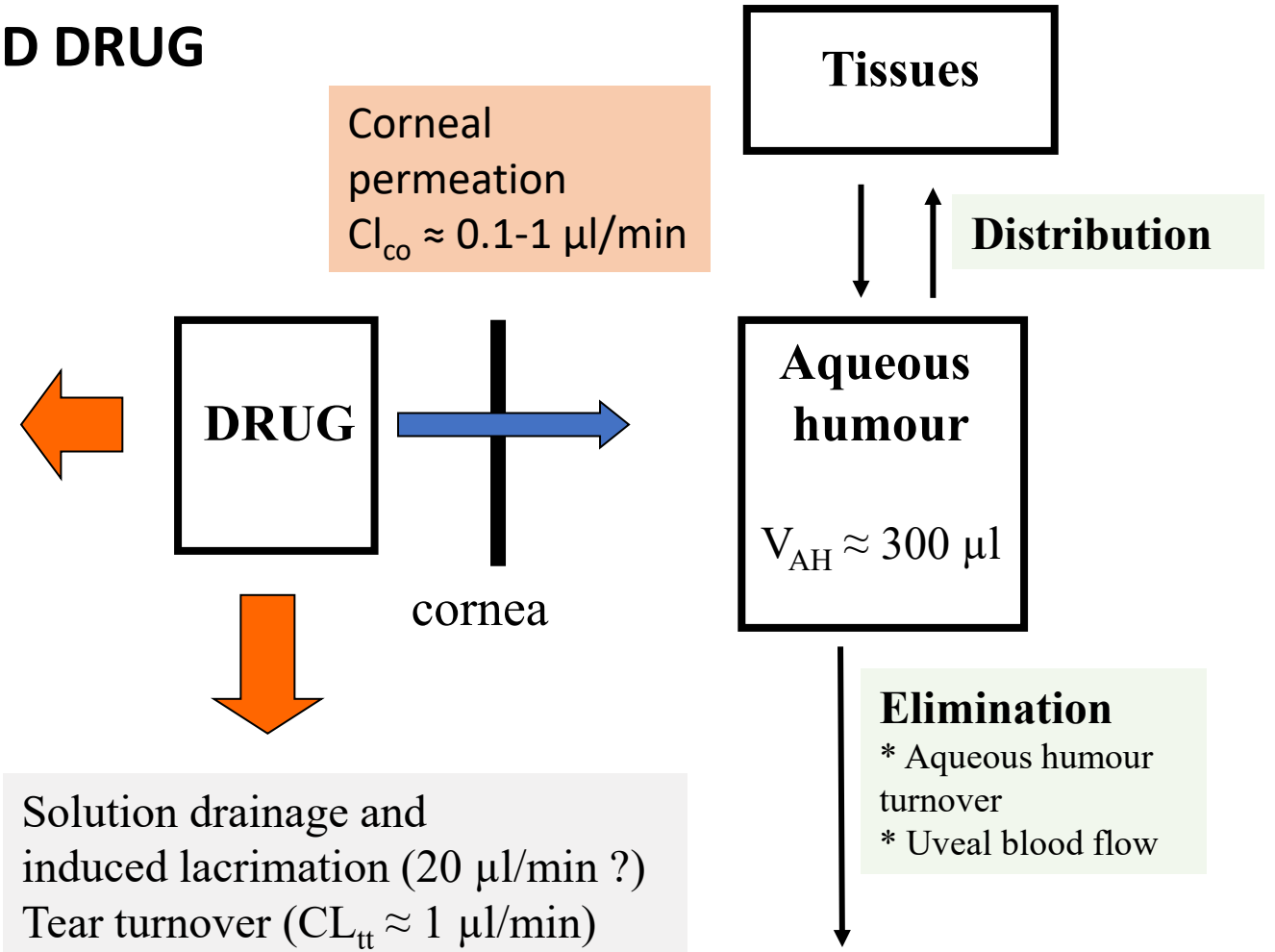
Permeation factors

- Biological barriers
- Drug
- Formulation

Contact time factors

- Tear flow
- Eye response to instillation
- Drug
- Formulation

FATE OF THE INSTILLED DRUG



Systemic absorption through conjunctiva
CL_{cj} ≈ 5-10 µl/min

Systemic BA often > 50%
Fast

CL = P x S
P = permeability
S = surface area

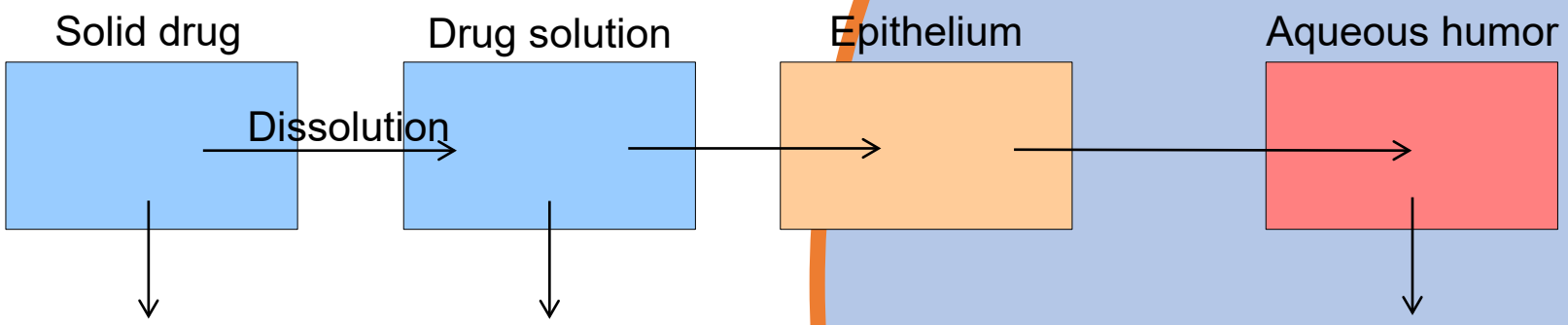
Permeation factors
Lipophilicity
Molecular size
pH
Preservative

Contact time factors
Osmotic pressure
pH
Viscosity

Complex formulations: suspensions, emulsions

- Physical chemical factors
  - Particle size distribution
  - Drug solubility
  - Viscosity / mucoadhesion
  - pH
  - Tonicity
- Impact of the factors on
  - Bioavailability
  - Bioequivalence
  - Efficacy and safety

Ocular suspensions



- **Tear flow**
  - Basal tear flow
  - Drainage of excess fluid
  - Induced lacrimation

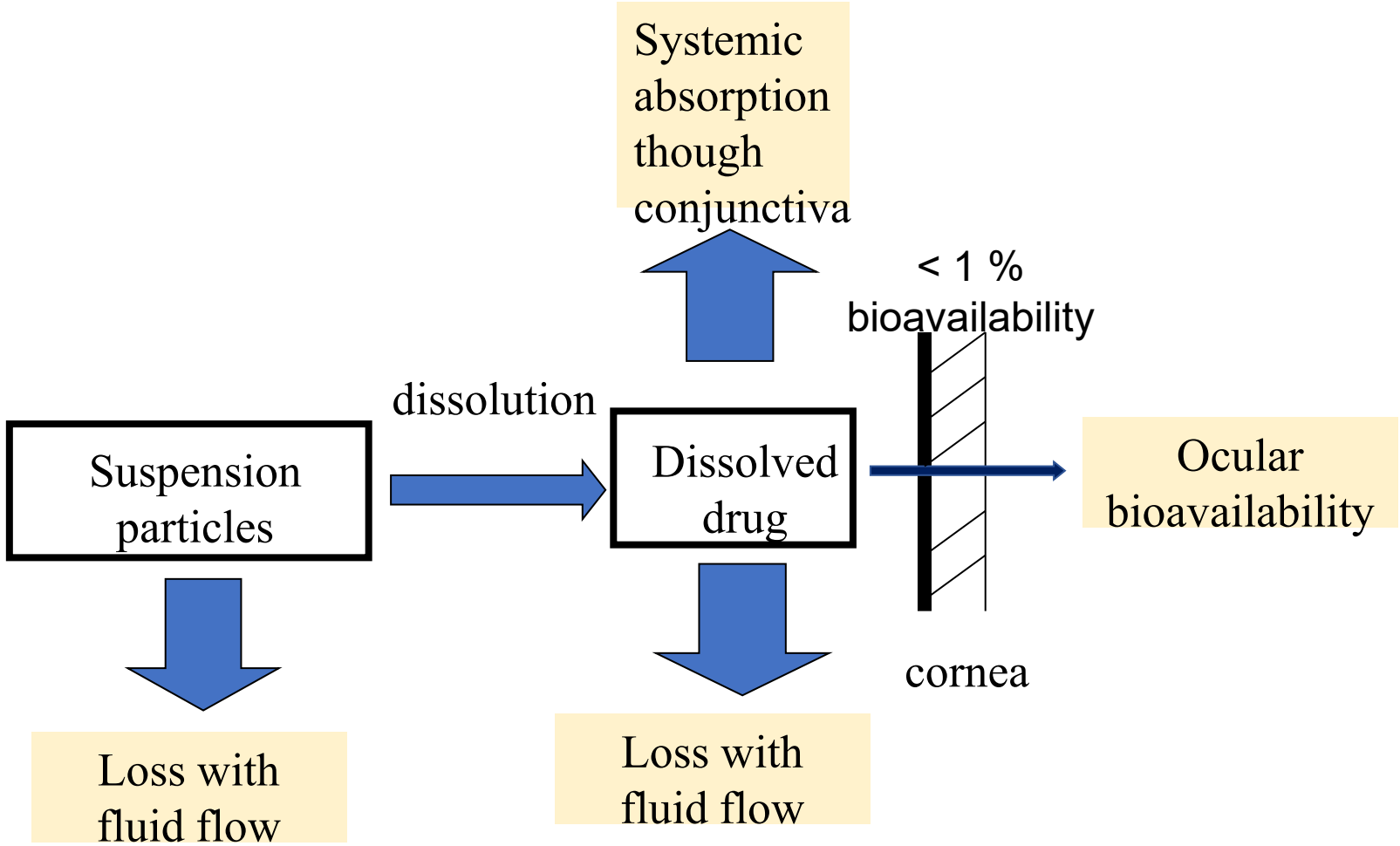
Cornea

ADDITIONAL FACTORS:

Dissolution rate

Particle retention on ocular surface

SUSPENSION KINETICS



Particle size effects

→ Contact time?

→ Dissolution rate?

Viscosity

→ Contact time?

Fluorometholone absorption from suspensions and solutions in rabbits

Drug concentrations in the aqueous humor:

Suspension > saturated solution

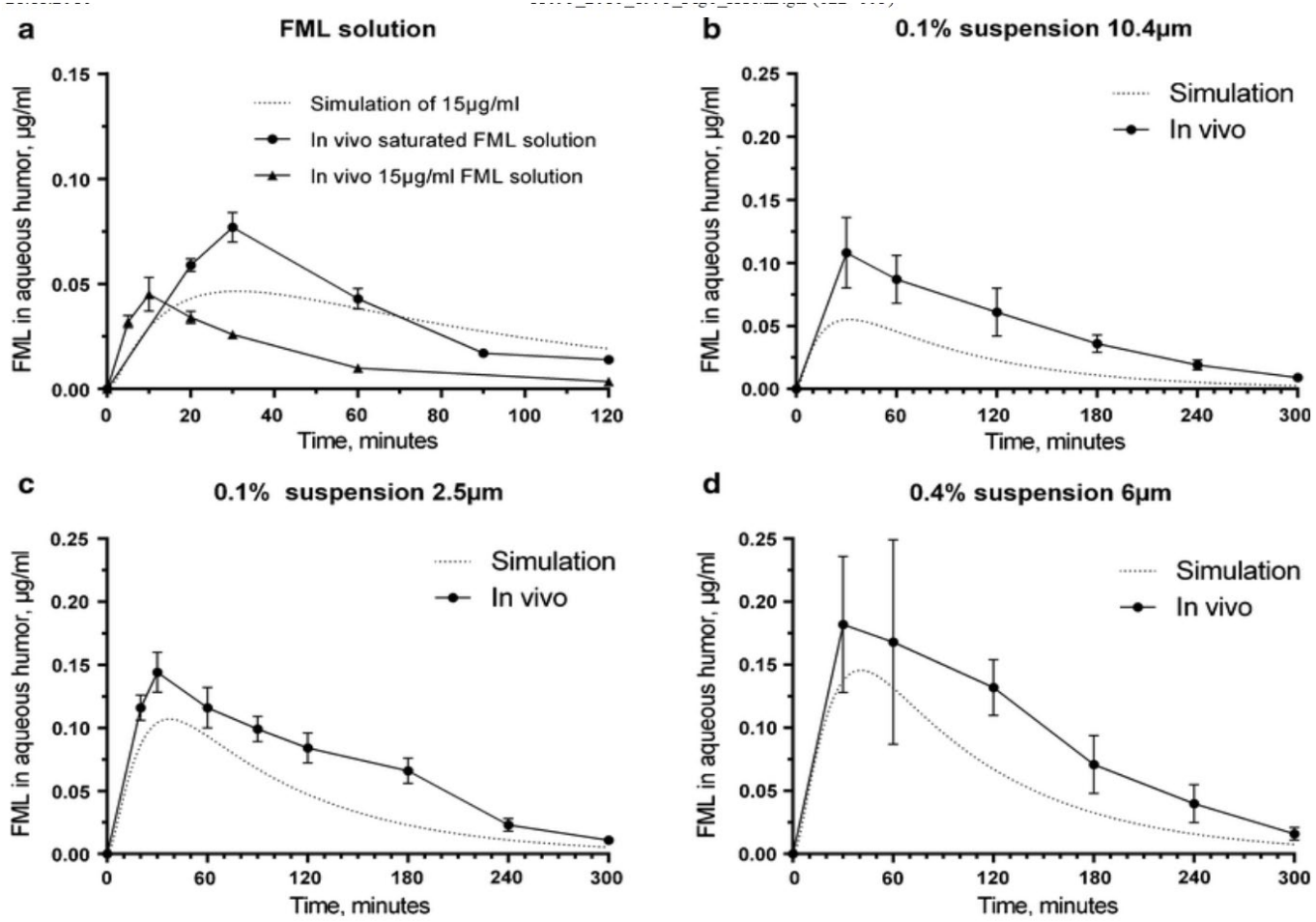
Particle size 2.5 µm > Particle size 10.4 µm

Concentrations increase less than proportionally with the dose (solution, suspension 0.1% and 0.4%)

Conclusions

Dissolution rate affects bioavailability

Drug dissolution takes place in the tear fluid, but only part of the drug dissolves

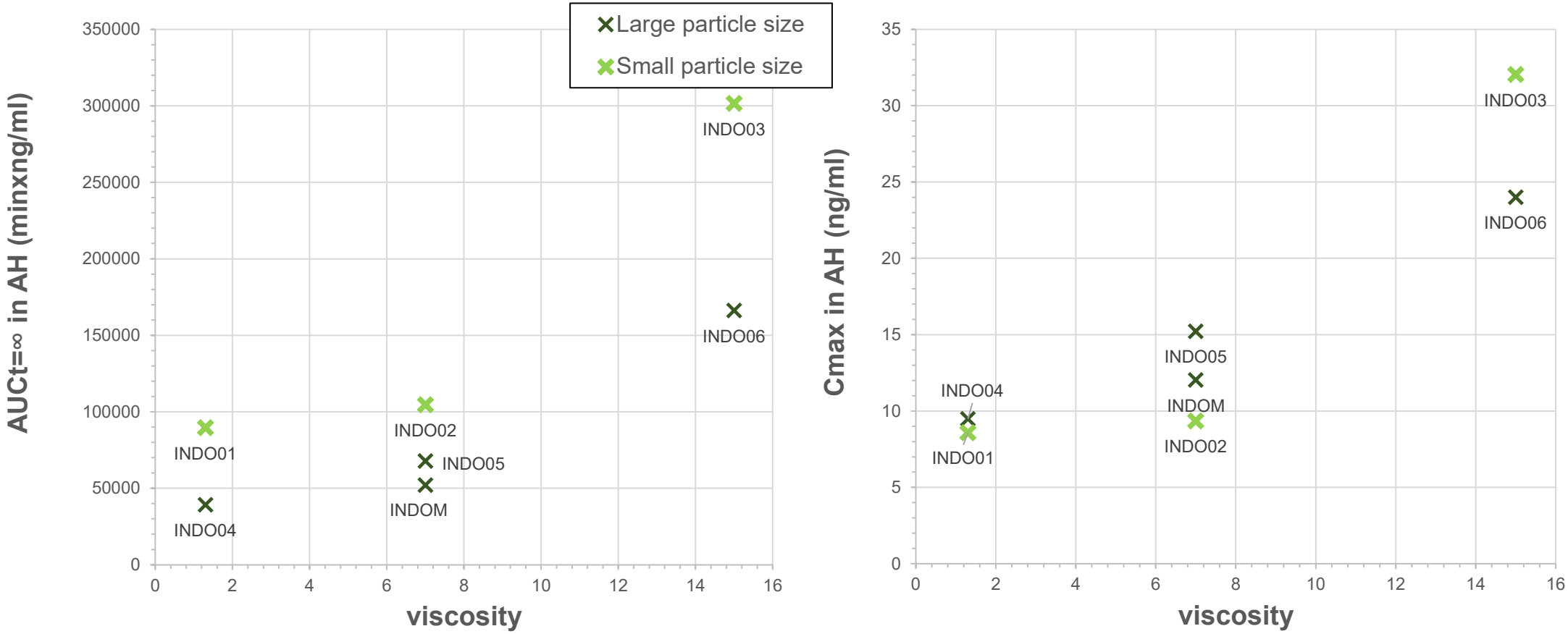


Tests with indomethacin suspensions

Sample	Particle size d(0.5) µm	Calculated viscosity (mPa s)	Osmolality mOsm/kg	pH
INDO1	0.43	≈ 1.3 (HPMC ES)	241	5.80
INDO2	1.33	≈ 7.0 (HPMC4000)	239	5.90
INDO3	0.37	≈ 15 (HPMC K35M)	239	5.84
INDO4	3.24	≈ 1.3 (HPMC ES)	241	5.82
INDO5	3.49	≈ 7.0 (HPMC4000)	242	5.89
INDO6	3.12	≈ 15 (HPMC K35M)	236	5.91
Commercial	5.58	≈ 7 (measured)	232	5.90

FORMULATION	***Particle size***	***Viscosity***
INDO 1	small	low
INDO 2	small	medium
INDO 3	small	high
INDO 4	large	low
INDO 5	large	medium
INDO 6	large	high
INDOM	large	medium

Indomethacin absorption to the aqueous humour in rabbits



Particle size shows about 2 fold differences in the AUC and smaller differences in C_{max}

Viscosity shows about 4 fold differences in AUC and 2-3 range of C_{max}

Ocular suspensions

- Dissolution takes place in the tear fuid
- Only part of the particles dissolve, most particles are removed from the ocular surface undissolved
- Dissolution properties do influence ocular bioavailability (impact of particle size)
- Increased viscosity increases contact time and ocular absorption

Current BE assessment

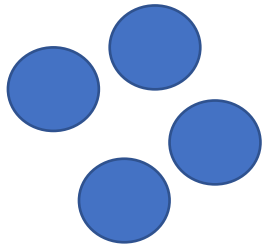
Drug concentrations from the aqueous humour of patients.

Sparse samples from many patients.

A lot of work - may prevent development of generic products

Need for new approaches

Dissolution and permeability tests



Suspension particles

dissolution

Lacrimal fluid

Free drug

Corneal absorption 0.1-1 µl/min

Aqueous humor

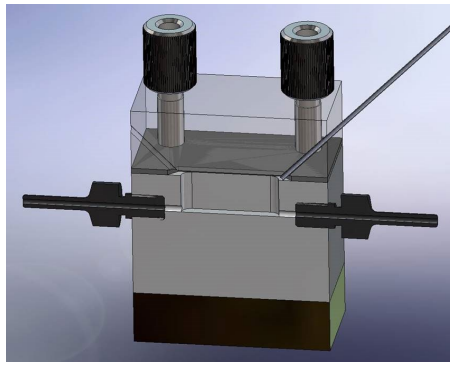
Drainage and Induced lacrimation 20 µl/min ?

Tear flow 1 µl/min

Conj. abs 5-10 µl/min

Free drug

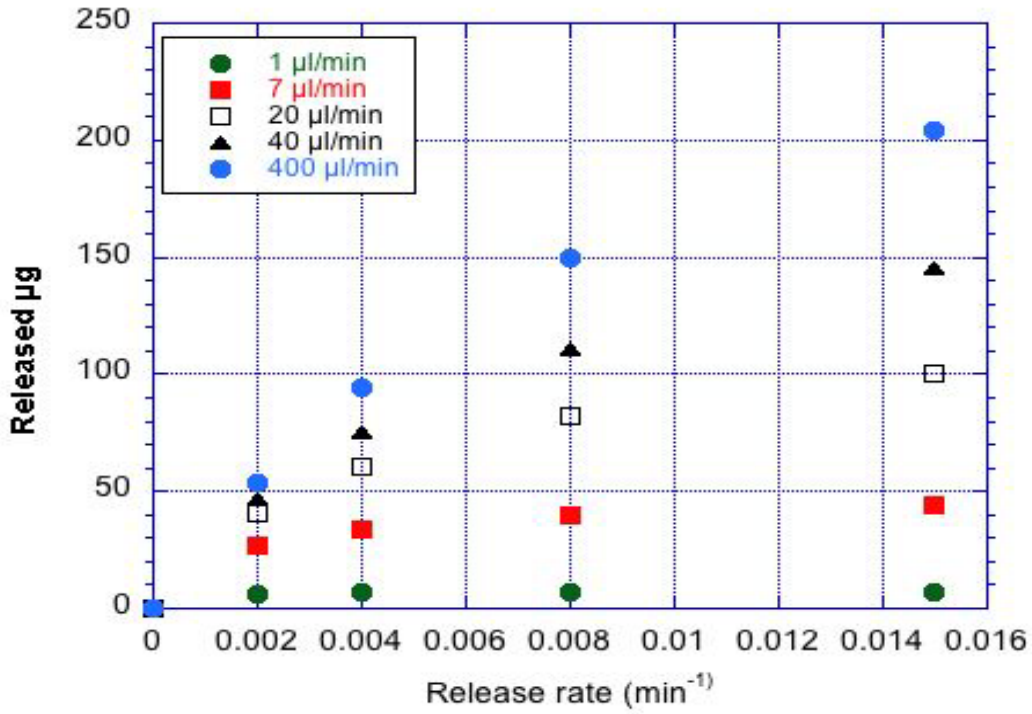
Blood circulation



Clearance factor in the dissolution test should mimic the situation
In the tear fluid → correct level of sensitivity on formulation factors.
Permeability and dissolution combined ?

Impact of drug clearance from tear fluid on the release rate

Simulations



Conclusions

In sink conditions release rate ranges over 7.5 fold.

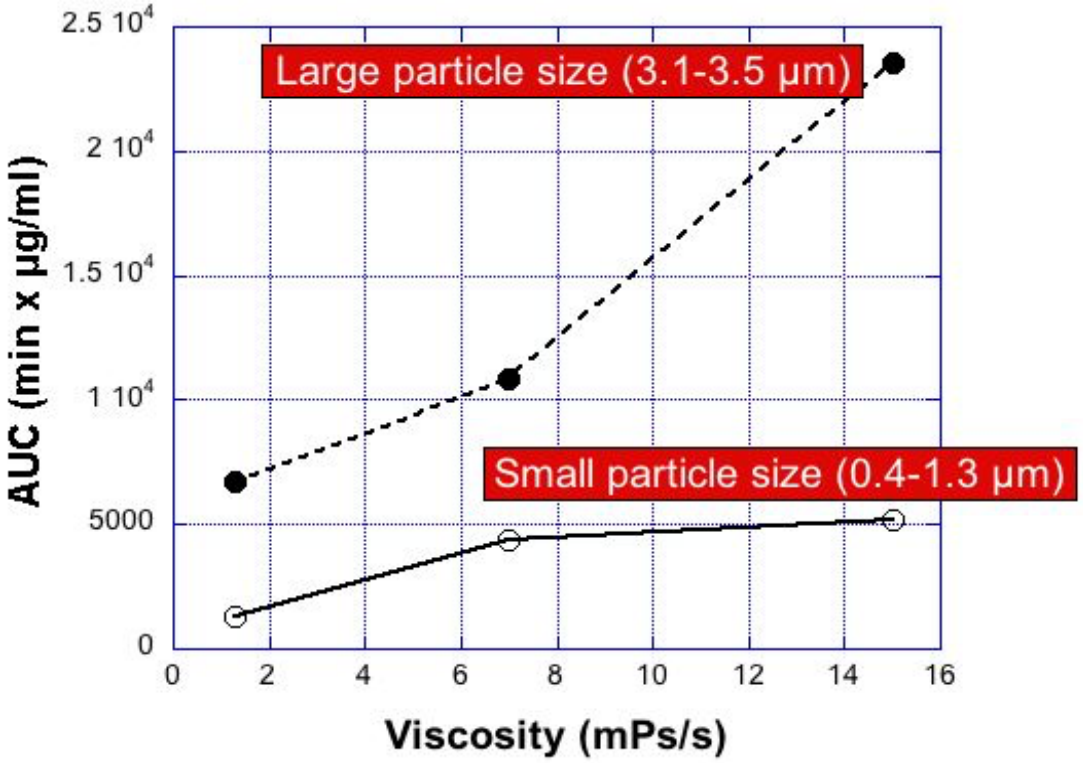
For the same formulations, dissolution rates range less than 7.5 fold under clearance conditions of tear fluid

For example,
CL = 1 µl/min → 1.1 fold range
CL = 20 µl/min → 2.5 fold range

Dissolution tests in sink conditions over-estimate the importance of dissolution rate

Impact of particle size and viscosity on contact time

AUC of indomethacin in rabbit tear fluid after instillation of a suspension



Increased viscosity

- Increases ocular surface contact time
- Increases bioavailability

Increased particle size

- Increases ocular surface contact time
- Decreases bioavailability

Dissolution of large particles is slower than that of smaller particles.

Lacrimal sampling: solution and suspension withdrawn.

Absorption is driven by the concentration of the dissolved drug.

Conclusions

- Pharmacokinetics of complex formulations is complicated
- Two main parameters that define bioequivalence are contact time and dissolution rate on the ocular surface
- Particle size and viscosity have impact on contact time
- Particle size has impact on dissolution rate
- Tear sampling of *dissolved* drug - suitable bioequivalence test ?
- Dissolution, permeation or contact time alone are not sufficient
- Simulation will be useful support to experimental work
- Species differences

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Questions

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