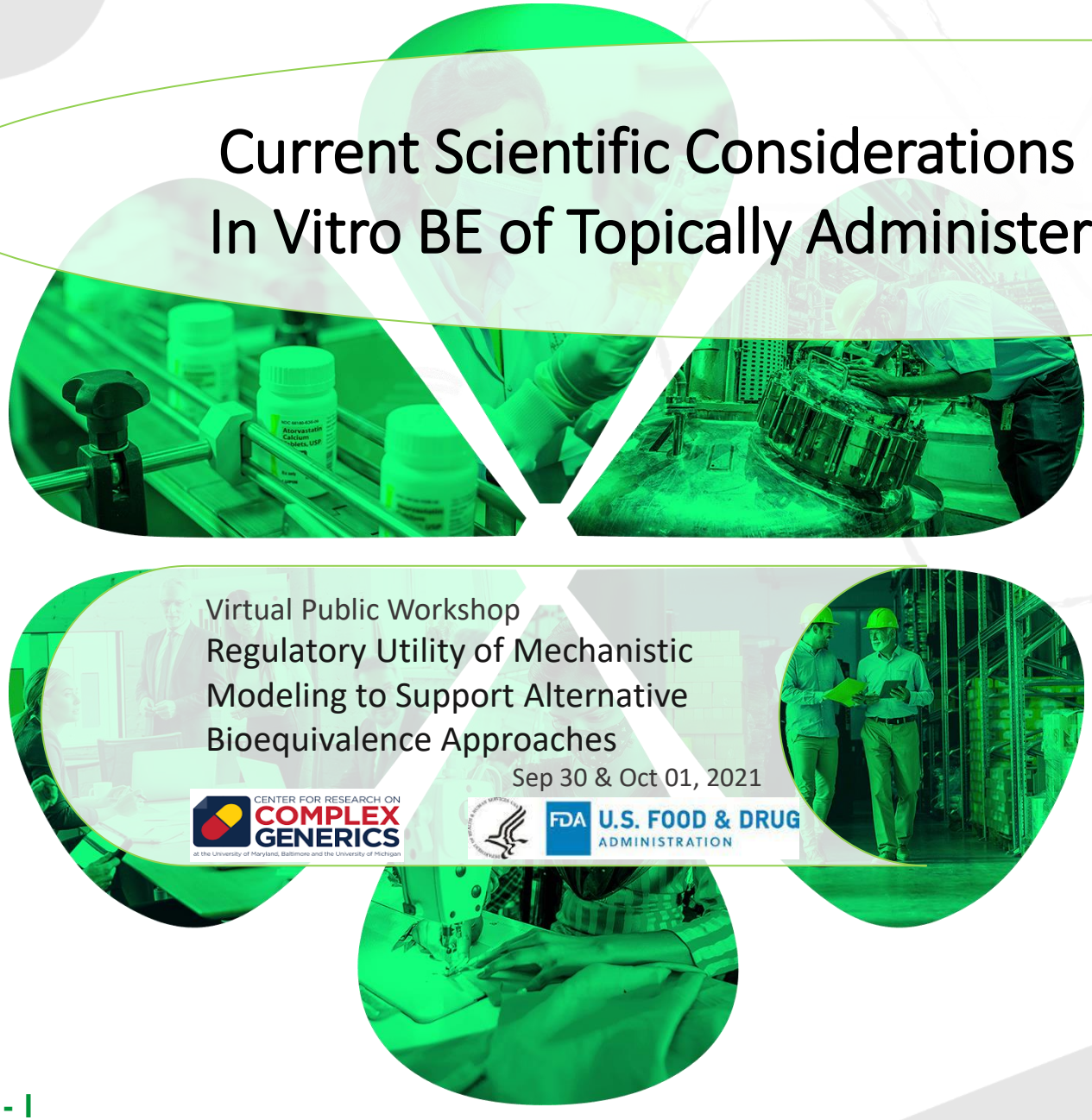
Current Scientific Considerations in Modeling for In Vitro BE of Topically Administered Ophthalmics



Virtual Public Workshop

Regulatory Utility of Mechanistic Modeling to Support Alternative Bioequivalence Approaches

Sep 30 & Oct 01, 2021

CENTER FOR RESEARCH ON COMPLEX GENERICS
at the University of Maryland, Baltimore and the University of Michigan

FDA U.S. FOOD & DRUG ADMINISTRATION

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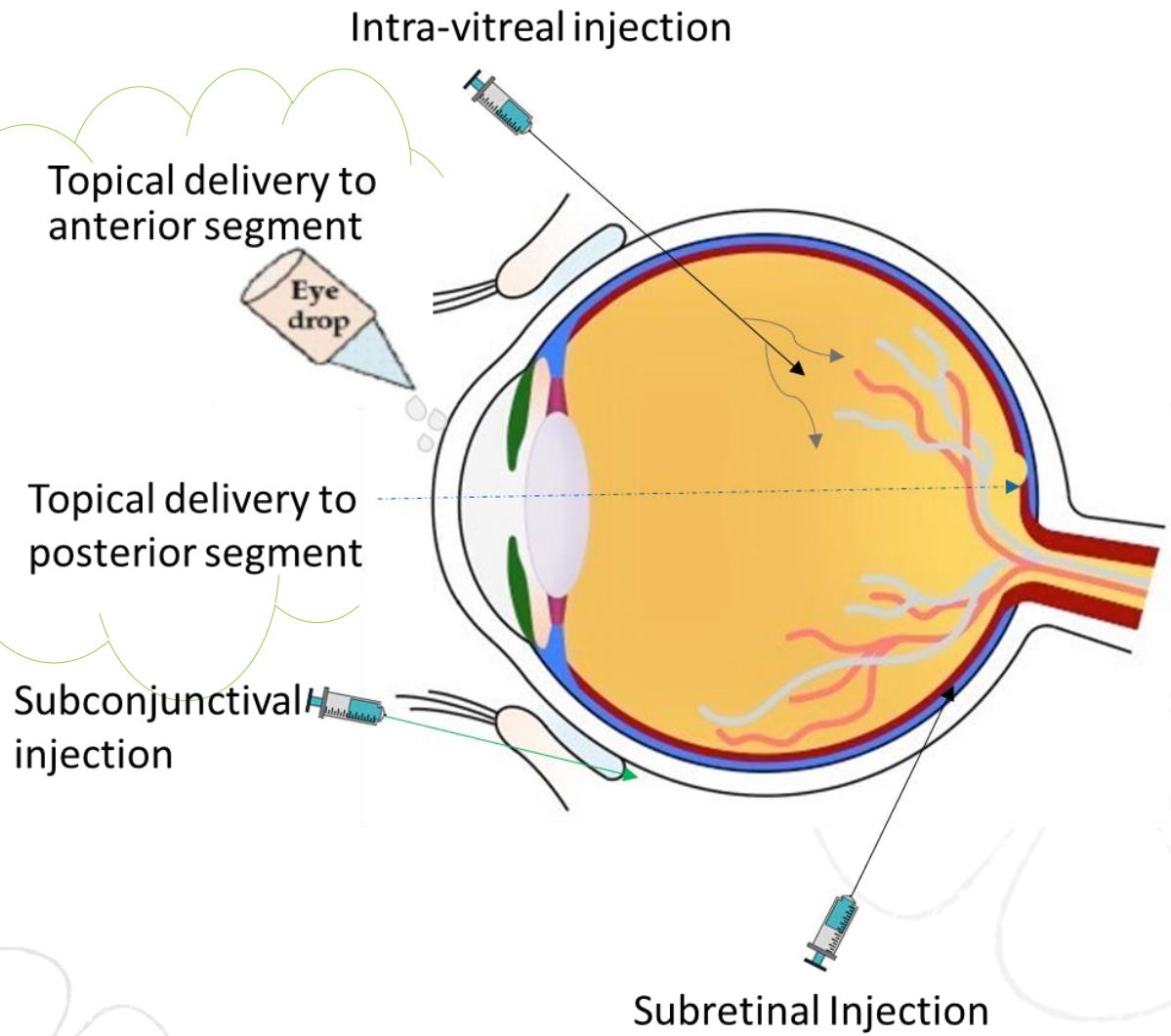
Class - I

Disclaimer

The opinions expressed in the presentation are solely those of the presenter and do not represent the statements or opinions of Lupin Limited.

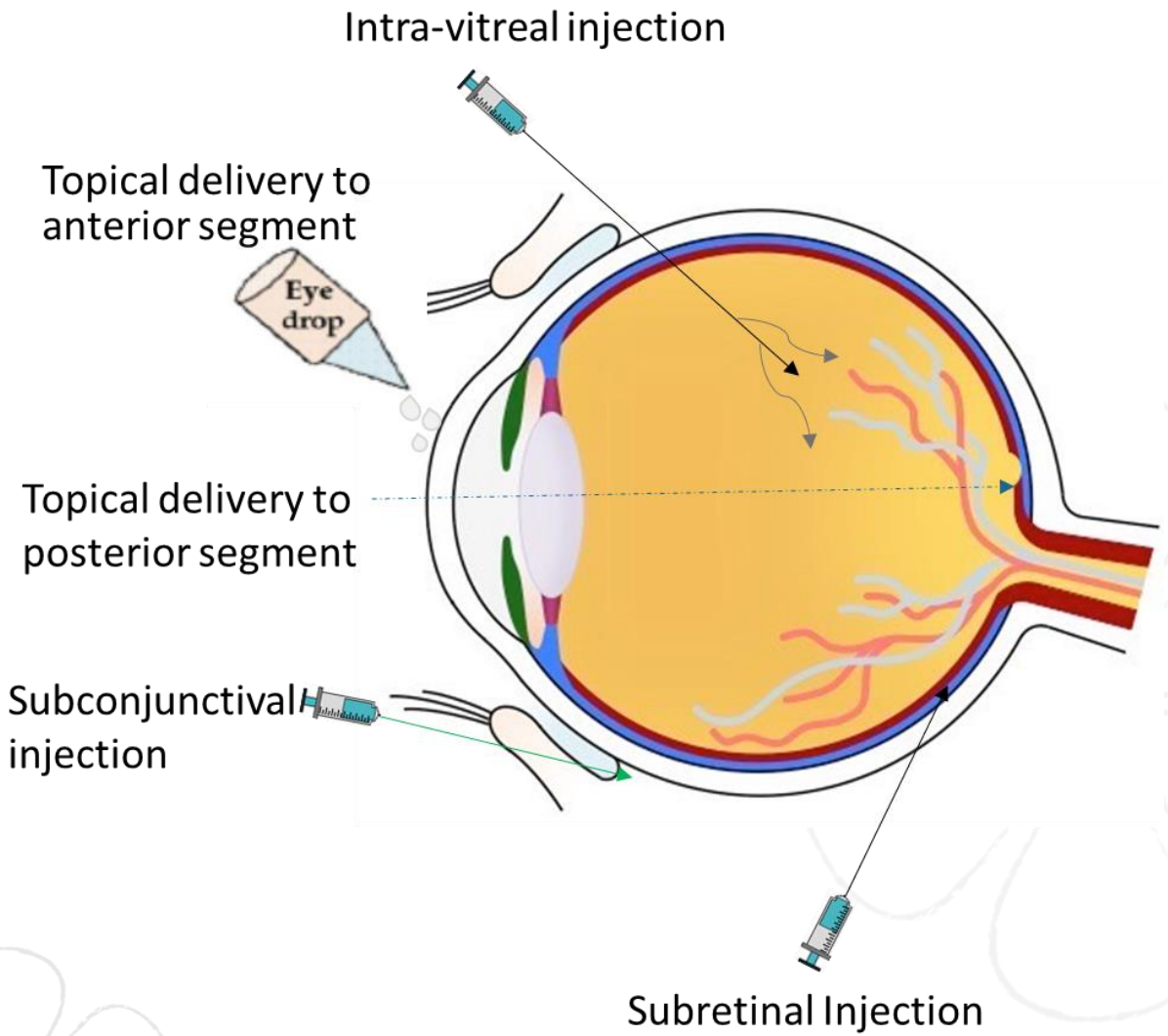
Agenda

- Topical drug delivery to eye- Examine the constraints
- Formulation variables influencing barriers to drug diffusion in the precorneal (tear-film) & corneal space- Ophthalmic suspensions & emulsions
- Scientific considerations to establish In-vitro BE for topical ophthalmic delivery

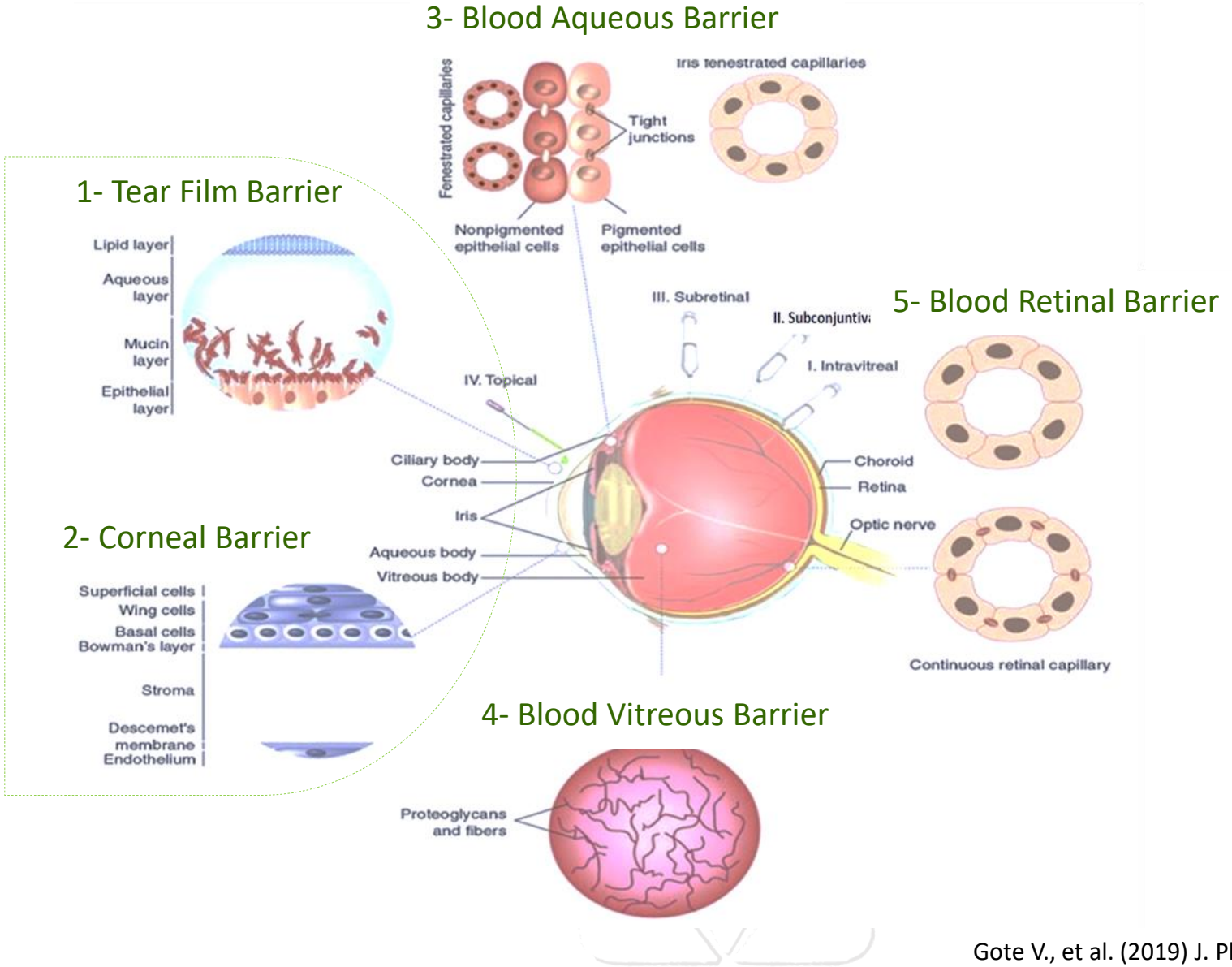


Background

- Eye is a specialized sensory organ; relatively secluded from systemic access
- Ability of dosage form to circumvent the protective barrier of eye without causing irreversible tissue damage
- Ocular disposition kinetics of ophthalmic drugs used on humans are incomplete or totally unknown; Mostly based on empirical models developed based on animal studies
- Topical ocular drug delivery most popular but severely constrained
- Less than 5-10 % of the topically applied dose is absorbed into anterior chamber

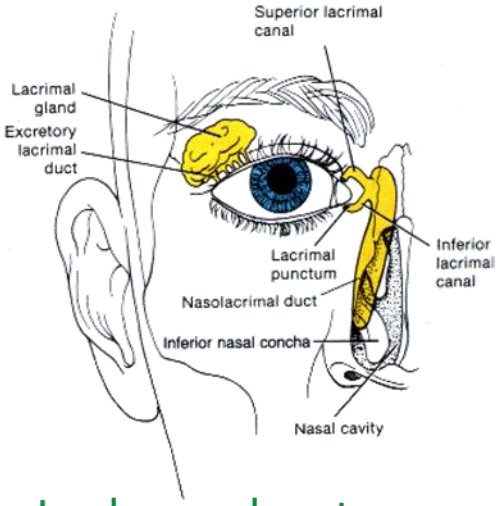


Anatomical & Physiological Barriers to Ocular Drug Availability



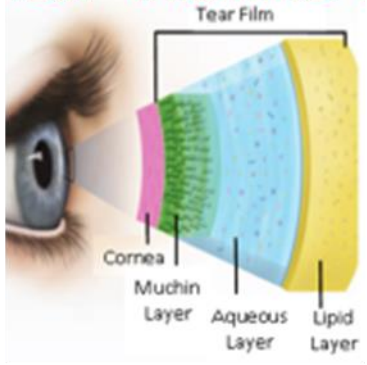
Gote V., et al. (2019) J. Pharmacol. Exp. Ther., 370 (3) 602-624

Tear & Corneal Barrier



Lachrymal system

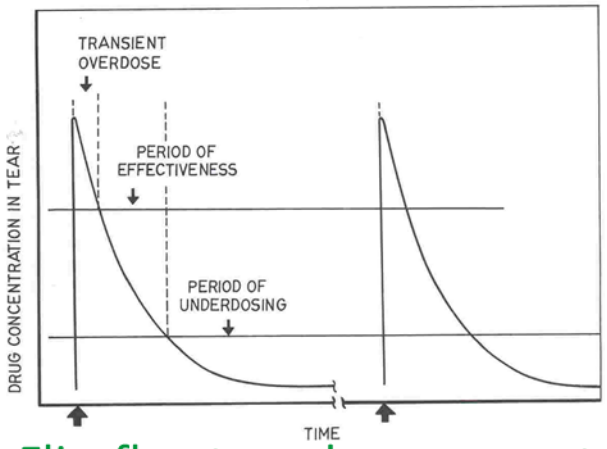
Tear- Trilaminar film



Thickness: 3 µm

Protect & lubricates eye

Washes away foreign particles



Flip-flop tear drug concentration profile

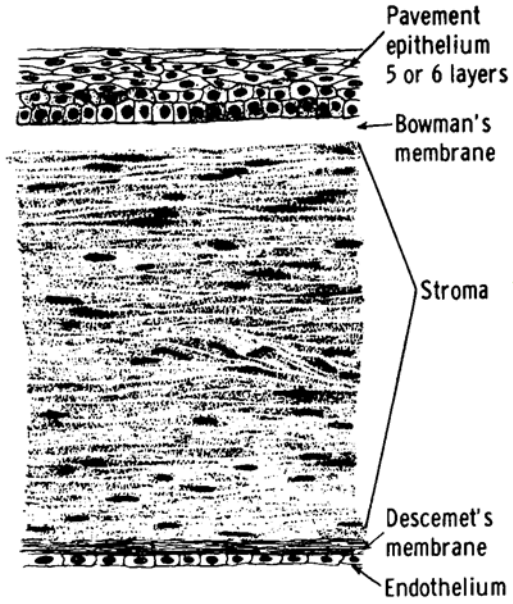
Normal volume of tears: 7 µl

Blinking eye can accommodate a volume of up to 30 µl without spillage

Drop volume: 25-50 µL

Tear-turn over ~ 16 %/min

Cornea



50-60 µm thick; highly hydrophobic; barrier to invasion by foreign substances; holds tear to anterior surface of the eye

400-500 µm thick; highly hydrophilic; gives physical strength and optical transparency

5-6 µm thick; hydrophobic; ensures active fluid transport through mitochondria, vesicles and ion pumps

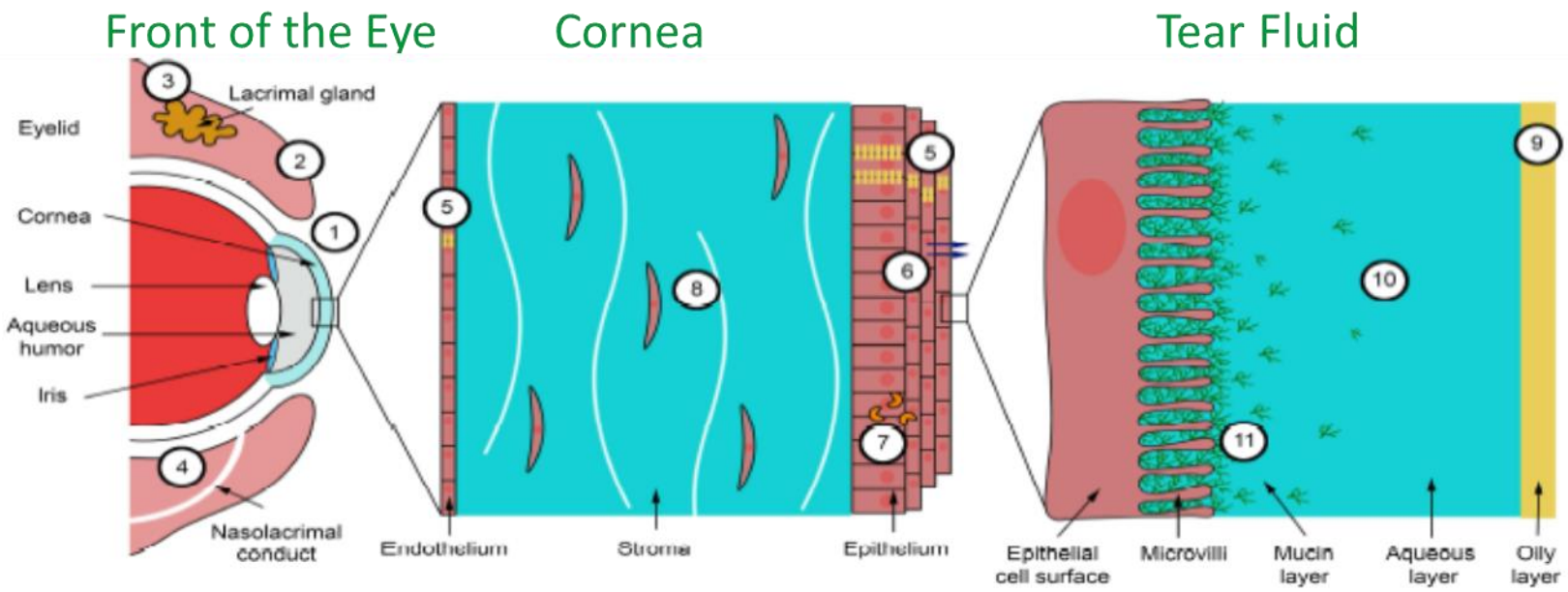
Diameter: 11.5 mm;

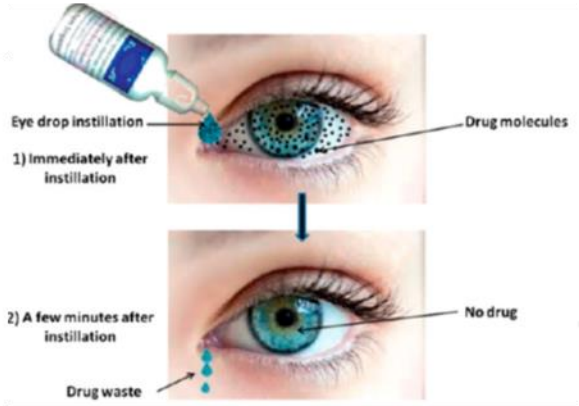
Anterior corneal surface radius of curvature: 7.8 mm;

Total corneal and conjunctival surface area: 16 cm^2

Summary of Impact of Static & Dynamic Barriers

(Topical Solution, Suspension, Emulsion & Ointment)





Less than 5-10 % of the topically applied dose is absorbed into anterior chamber

1- Low precorneal volume
2- Reflex Blinking (Drainage)
3- Tear fluid production (16%/ min)
4- Nasolacrimal drainage (Systemic absorption)

5- Tight junction
6- Drug efflux pumps
7- Drug- degrading enzymes
8- High water content (Barrier to hydrophobic drugs)

9- High lipid content (Barrier to hydrophilic drugs)
10- High water content (Barrier to hydrophobic drugs)
11- High mucin content (Electrostatical repulsion)

Pictorial representation adapted from- Jumelle C., et al. (2020) J. Control. Rel., 321, 1-22

Ophthalmic Suspension- Factors Influencing Drug Release & Absorption

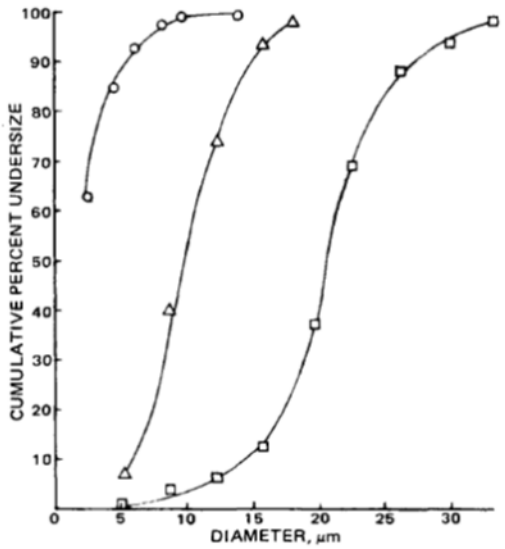
Process Variables
- Mill type/ Micronization tech.
- Bead size & quantity
- No. of milling cycle

Critical Quality Attributes
- Drug particle size distribution (PSD)*
- Dispersion viscosity

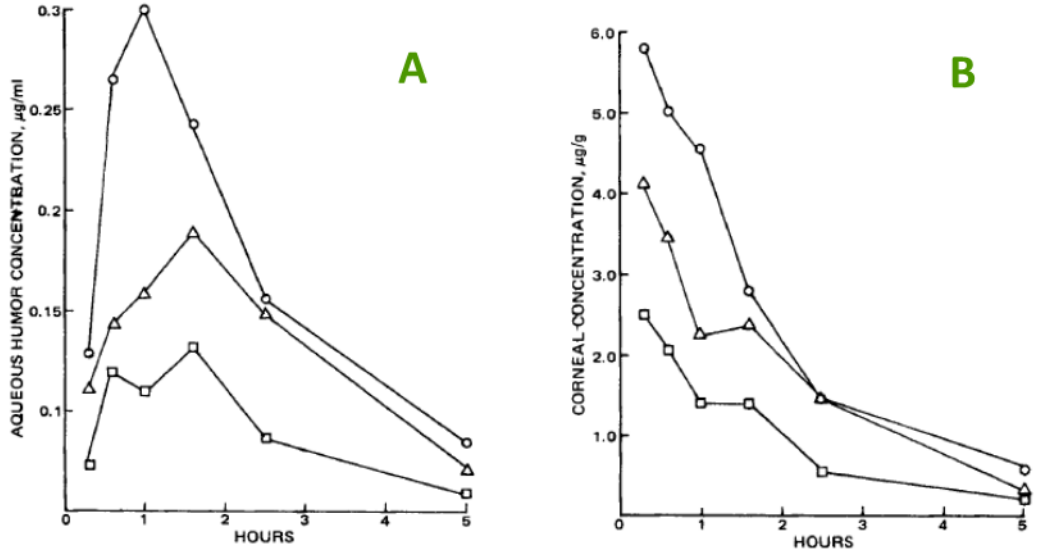
*SPAN describes the breadth of PSD

Performance Parameters
- Suspension physical stability
- Ocular surface retention
- Drug release characteristics

Effect of PSD (Dexamethasone Ophthalmic Suspension)



Particle size distribution of dexamethasone suspension



Mean dexamethasone concentration in (A) aqueous humour and, (B) corneal button of rabbit suspensions having different mean PSD

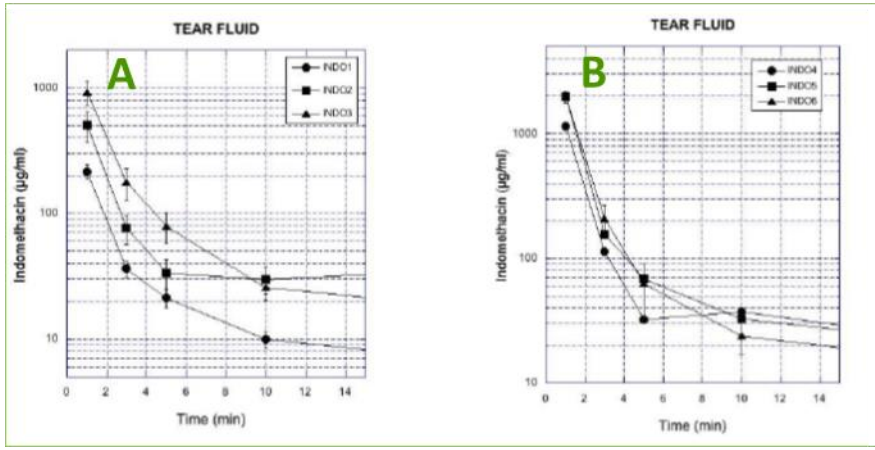
Increase in PSD decreases the rate and extent of drug penetration into the corneal membrane & aqueous humour thereby decreasing ocular bioavailability

Schoenwald RD. & Stewart P. (1980) J. Pharm. Sci. 69(4): 391-394

Ophthalmic Suspension- Factors Influencing Drug Release & Absorption

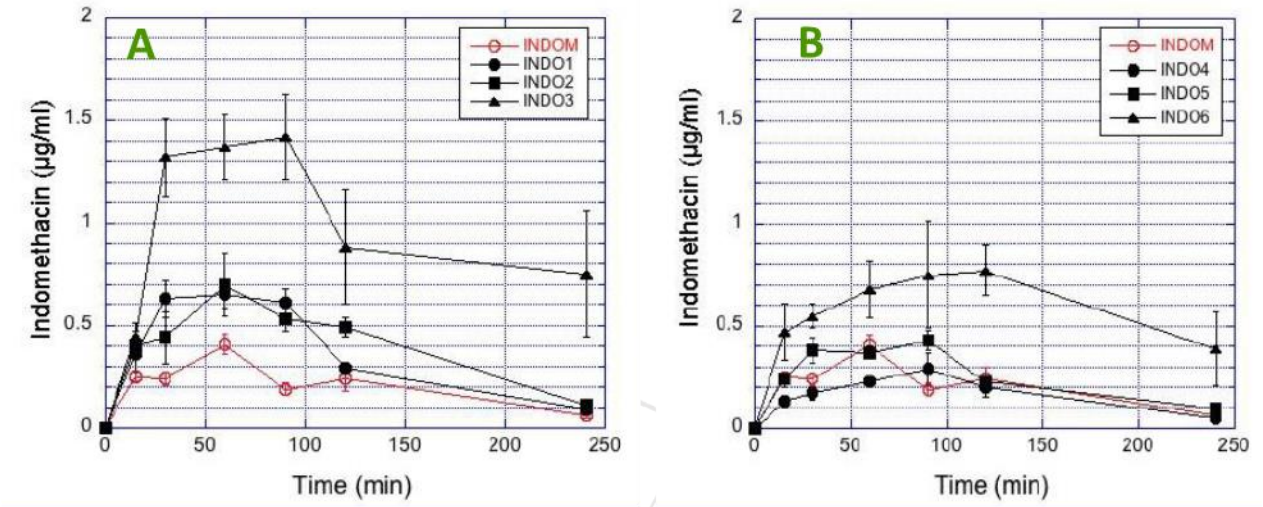
Effect of Viscosity and Particle Size (Indomethacin Ophthalmic Suspension)

Sample	Particle Size	d_{50} (µm)	Viscosity	Viscosity (mPa.s)
INDO1	Small	0.43	Low	~ 1.3 (HPMC E5)
INDO2	Small	1.33	Medium	~ 7 (HPMC 4000)
INDO3	Small	0.37	High	~ 15 (HPMC K35M)
INDO4	Large	3.23	Low	~ 1.3 (HPMC E5)
INDO5	Large	3.50	Medium	~ 7 (HPMC 4000)
INDO6	Large	3.12	High	~ 15 (HPMC K35M)



Mean concentration of indomethacin in rabbit tear fluid after instillation of the suspension (A) Small particles (INDO01-INDO03) & (B) Large particles (INDO04-INDO06)

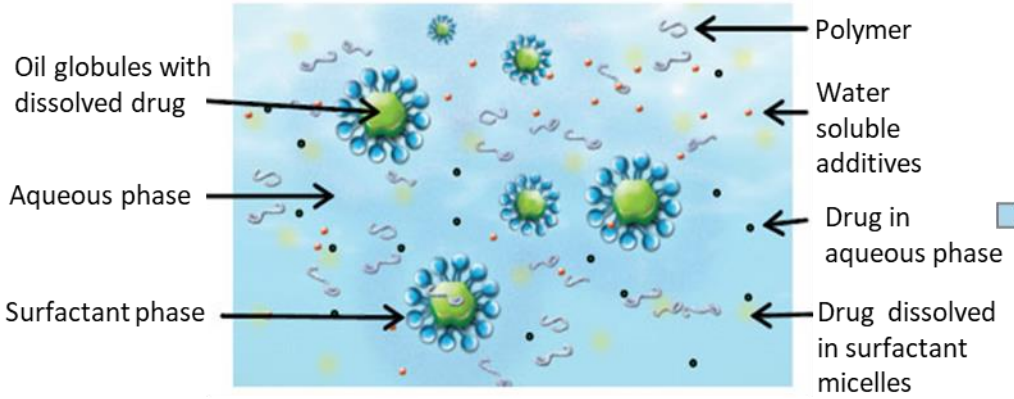
Mean concentration of indomethacin in rabbit aqueous humour after instillation of the suspension (A) Small particles (INDO01-INDO03) & (B) Large particles (INDO04-INDO06)



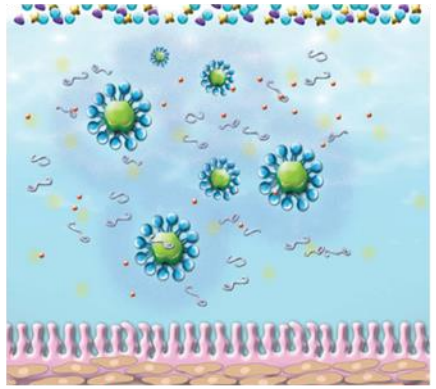
Drug particle size and dispersion viscosity of indomethacin suspensions affect rate and extent of ocular bioavailability

Toropainen E., et al. (2021) Pharmaceutics. 13: 452

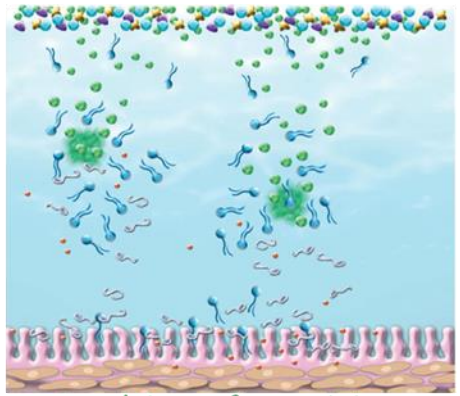
Ophthalmic Emulsions- Phenomenon at Ocular Surface



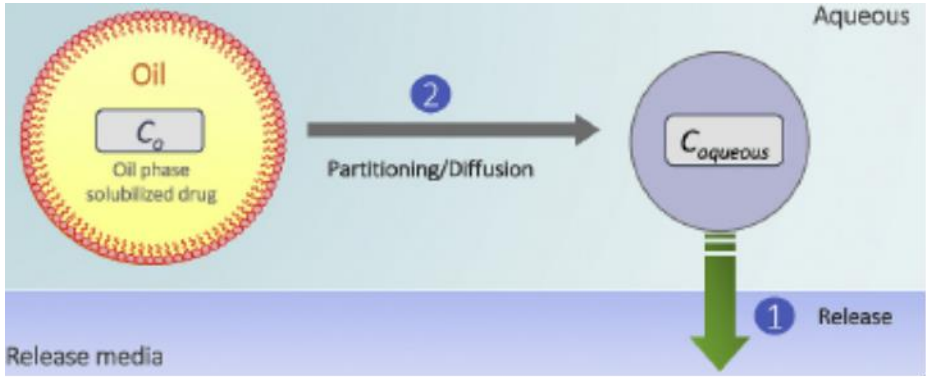
Microemulsion components in the formulation

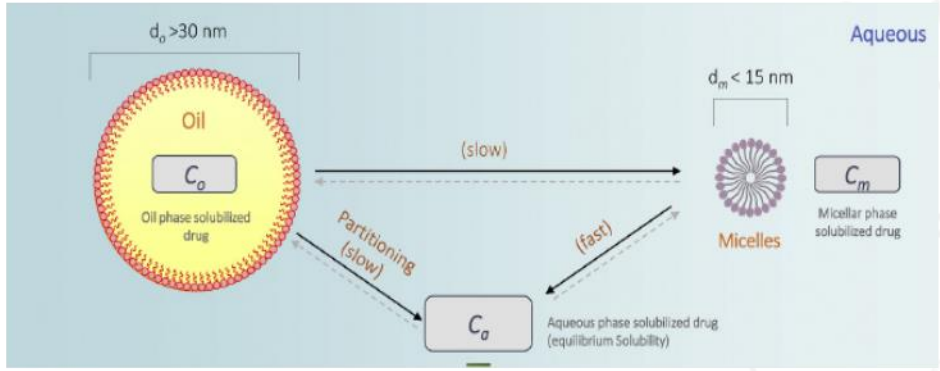


Emulsion in tear film (Site of first application)



Emulsion after mixing with tear film





Drug diffusion/ partition into aqueous phase is key to drug release (biphasic release in tear or IVRT medium)

Biphasic release profile – Initial rapid release caused by drug diffusion from aqueous phase including micelles to bulk media; followed by a slower release due to drug diffusion from oil globules

Gore A., et al. (2017) GaBI Journal. 6(1):13-23
Dong Y., et al. (2020) J. Control. Rel., 327, 360-370

Ophthalmic Emulsions- Factors Influencing Drug Release & Absorption

- Short residence time in the precorneal region
- Emulsion drop forms a thin film (~ 50 µm) on the ocular surfaces which rapidly depletes with time *(Lack of reservoir effect)*
- Biphasic release pattern *(in vitro & in vivo)*
- Effect of temperature on release pattern *(Eye surface temperature ~35 °C)*- Drug release to aqueous phase decreases in case of Cyclosporine but increases in case of Difluprednate emulsion

Factors impacting contact time in the pre-corneal region

Globule size distribution & surface area
Formulation viscosity
Surface interactions
Tear related (pH, osmolality)
Distribution of the drug in different phases in the formulation

Static responses

Factors impacting drug availability to ocular tissue vs. time (transfer)

Initial distribution
Release kinetics from globule phases
Tear turnover & dilution
Temperature impact

Kinetic responses

In vitro BE Considerations

- In vivo equivalence between two formulations is dependent on similarity of-
  - Static responses (Formulation factors impacting contact time in the ocular region & drug distribution in multiple phases of the emulsion/ dispersion)
    - Distribution of drug in different phases of the formulation- drug present in oil globules, micelles and the free drug (emulsion)/ solubilized fraction (suspension)
    - D50 & SPAN of globules (emulsion) / drug particles (suspension)
    - Viscosity as a function of applied shear
  - Kinetic responses (How formulation would respond to in vivo precorneal & corneal barriers)
- IVRT method-
  - Selection of IVRT apparatus
  - Selection of release medium and its volume
  - Sample volume
  - Selection of surfactant (SLS in comparison to other surfactants) & its concentration
  - Solubility enhancement of the drug and maintenance of sink condition
  - Temperature, rotation speed/ agitation

Summary

- Corneal & pre-corneal barriers present unique challenges to ophthalmic drug bioavailability from topical administration
- Ophthalmic emulsions & suspensions are complex formulations making it difficult to model drug delivery
- Goal of an ideal in vitro release technique-
  - Obtain in vitro release data in timeframe similar to the ocular residence time
  - Able to simulate the in vivo pre-corneal fluid dynamics

Thank You …

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