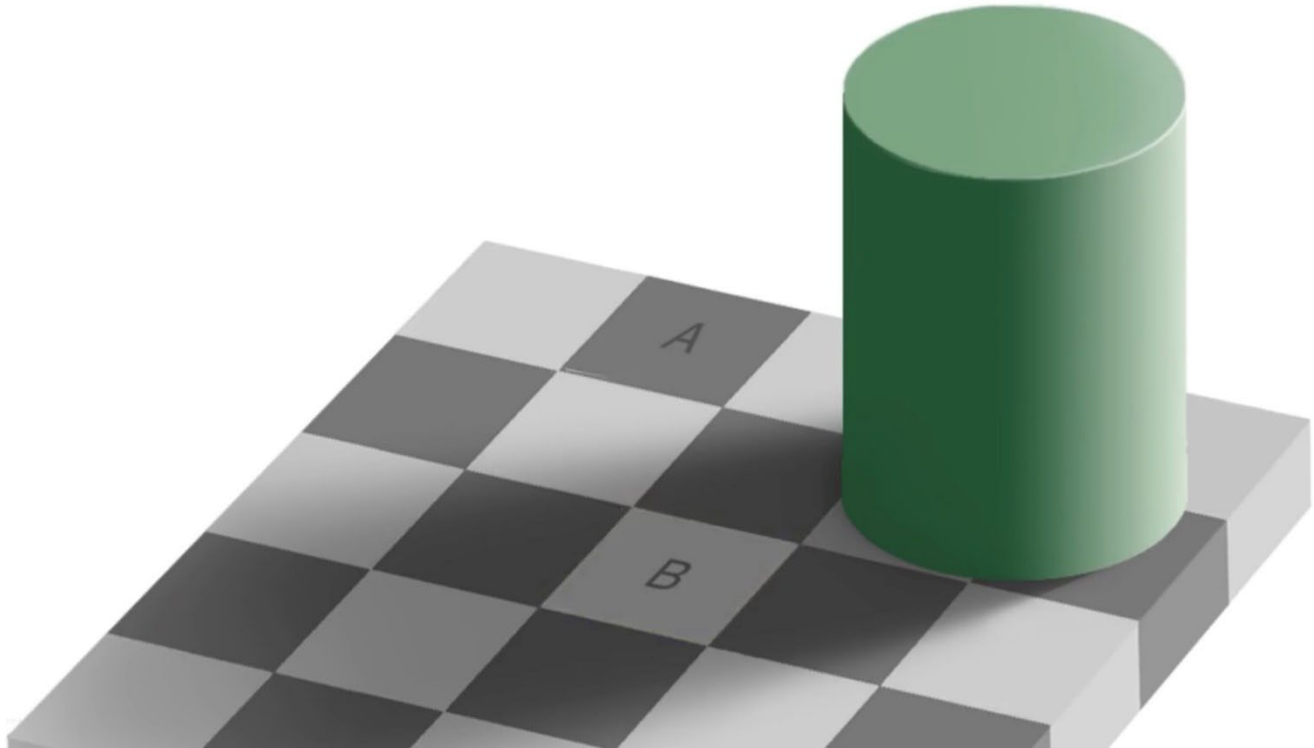
Seeing the Options: Challenges and Strategies in Developing IVRT Methods for Ophthalmic Products

Xiaoming Xu, Ph.D.

Office of Pharmaceutical Quality Research
Office of Pharmaceutical Quality
CDER | U.S. FDA

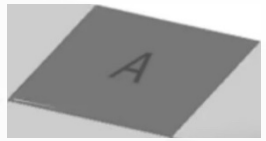
Perception Dilemma

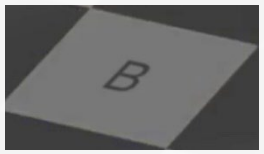
Is **A** the same as **B**?



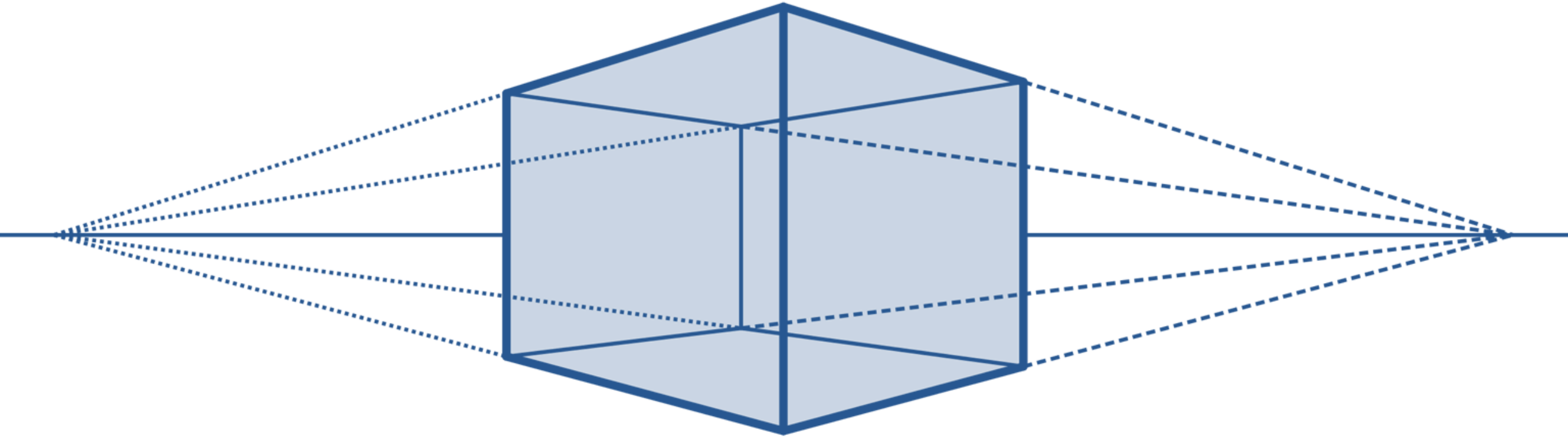
Perception Dilemma

Is **A** the same as **B**?





Perspective Limitation



https://commons.wikimedia.org/wiki/File:Normalperspektive_zwei_Fluchtpunkte.svg

Purpose of an IVRT: The Why

- Product development (formulation screening, product understanding)
- Quality control (batch-to-batch consistency)
- Bioequivalence (sameness)
- In lieu of in vivo test (IVIVC, Post-approval supplements)

Challenges in IVRT for Complex Ophthalmics

- Variable release characteristics, depending on dosage form
- Generally, lack of understanding in drug release mechanism
- The need to separate the particles from “released” drug
- Physiological constrains such as short ocular residence time, contrasting long IVRT duration
- Challenging to demonstrate the method is discriminative (against formulation and process changes)

A Good IVRT is:

Reproducible

- **Precise**
  e.g., low CV%
- **Robust**
  e.g., against minor disturbance to method

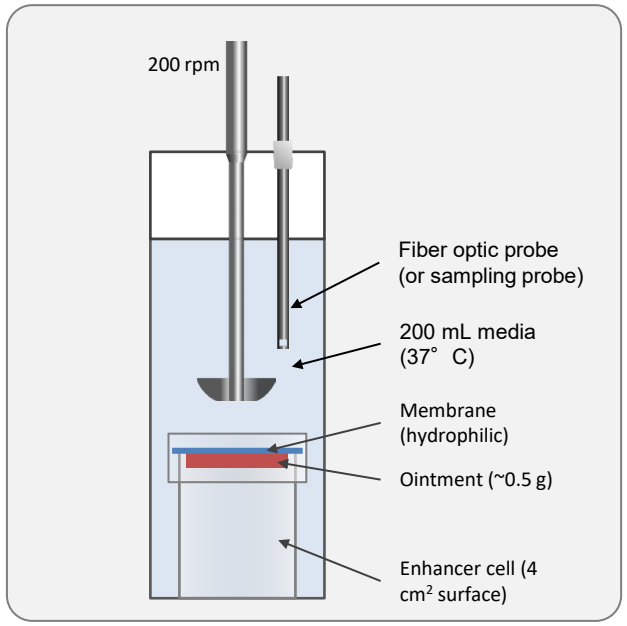
and

Discriminatory

- **Sensitive**
  e.g., known changes in quantity like sample with 25%, 50%, 100% drug loading
- **Selective**
  e.g., able to detect differences in sample if CQAs changed, such as particle size

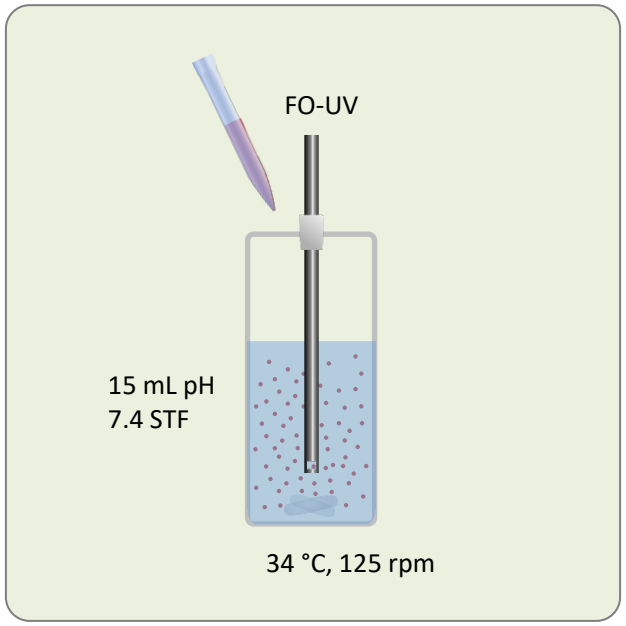
Three Examples

Ointment



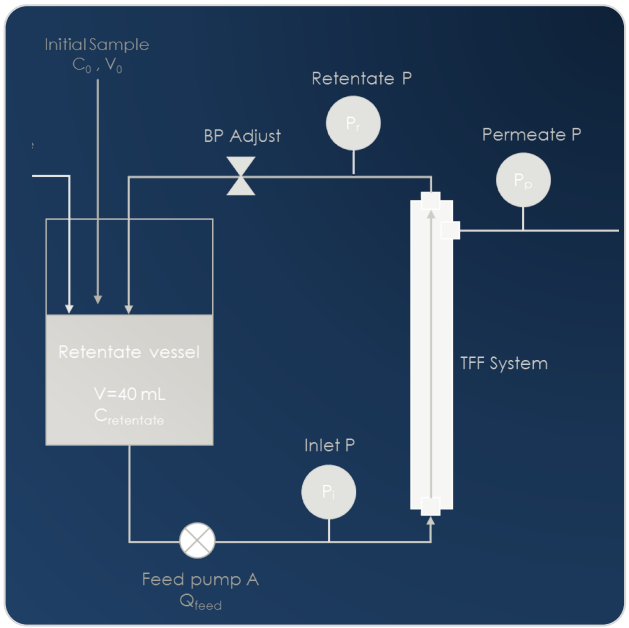
- Long release duration (hours)
- Compendial setups available (common)
- **A new kinetics theories** (Transient-Boundary vs. Higuchi)

Suspension



- Rapid release (under sink-condition) or
- Slow release when membrane separation technique is used (e.g., dialysis)
- Developed **Non-sink condition method** to capture rapid release (within seconds) and achieve discriminatory power

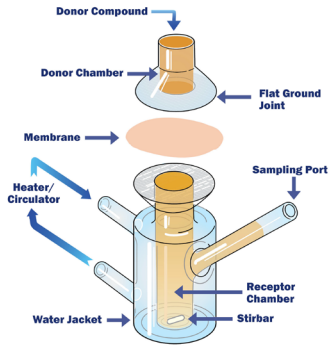
Emulsion



- Most complex (multiphasic: rapid and slow components)
- Membrane separation is almost always used but has severe limitations
- Developed **New method** to capture the multiphasic behavior (however, may be years away from usage)

Example 1: Ointments

Vertical diffusion cell (VDC) A,B,C



Immersion cell

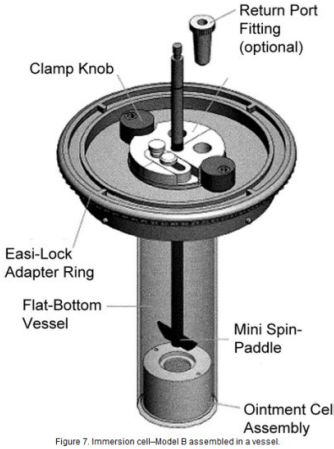


Figure 7. Immersion cell–Model B assembled in a vessel.

USP 4 with semisolid cell

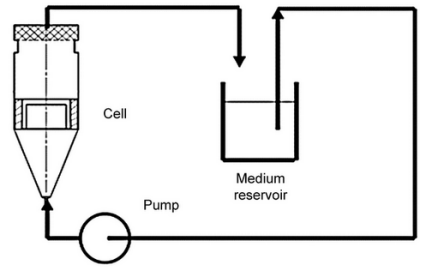
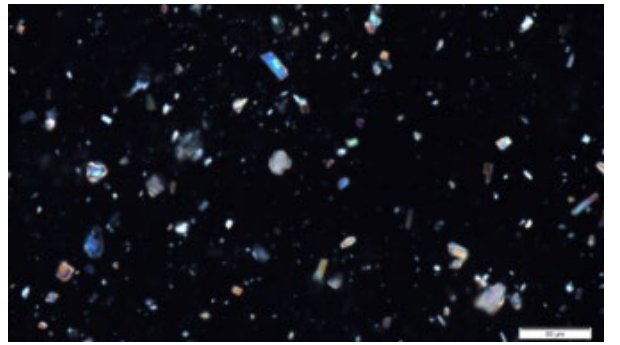
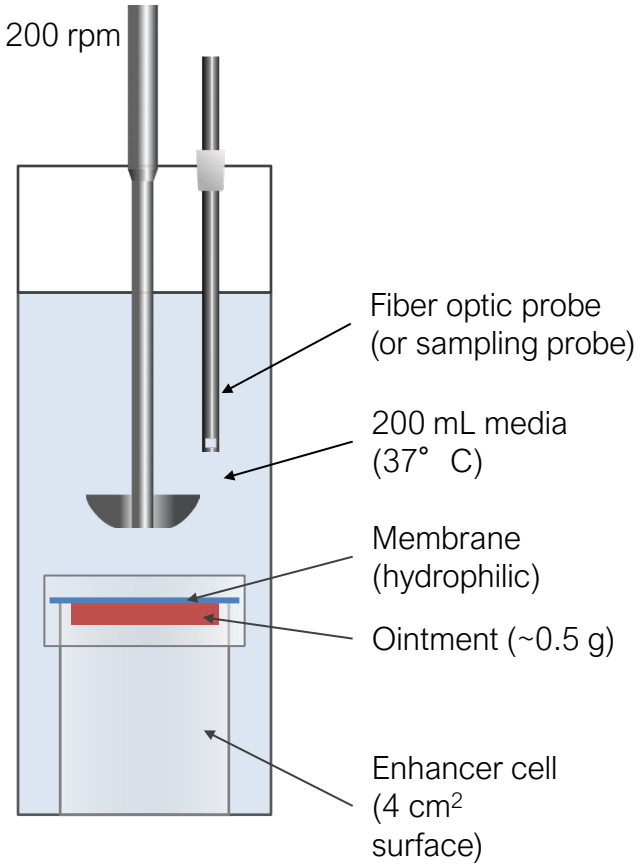


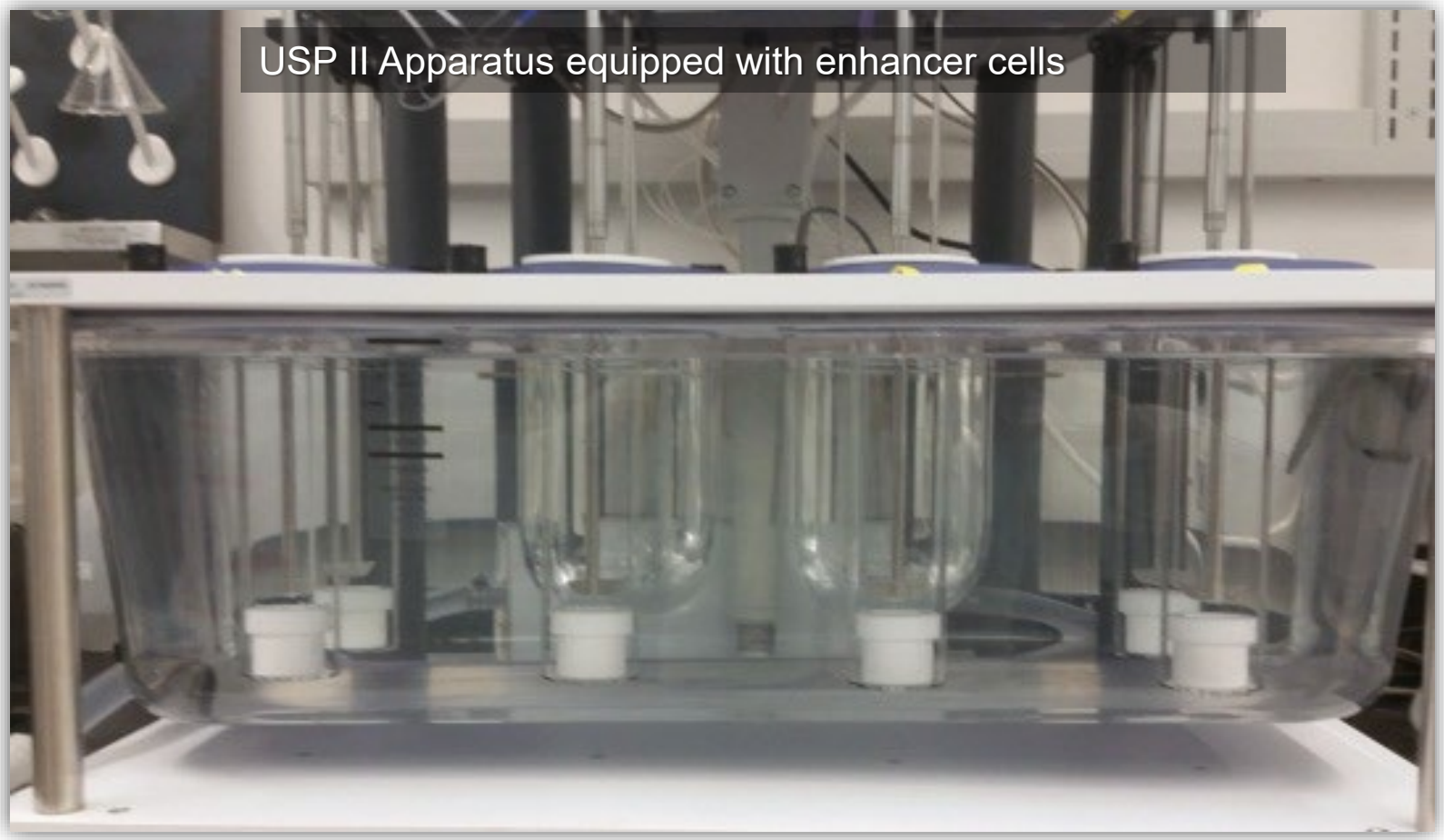
Figure 10. Closed system configuration.



- Acyclovir ophthalmic ointment, prepared in-house
- Oleaginous base (i.e., only petrolatum)
- Acyclovir remains as solid particles (not soluble in petrolatum)
- Three setups recommended by USP (for semisolids)
- Recommend to fit Higuchi release, and using T/R ratio to compare reference and test product (8^{th} and 29^{th} percentile)

IVRT for Ointments Using Immersion Cells

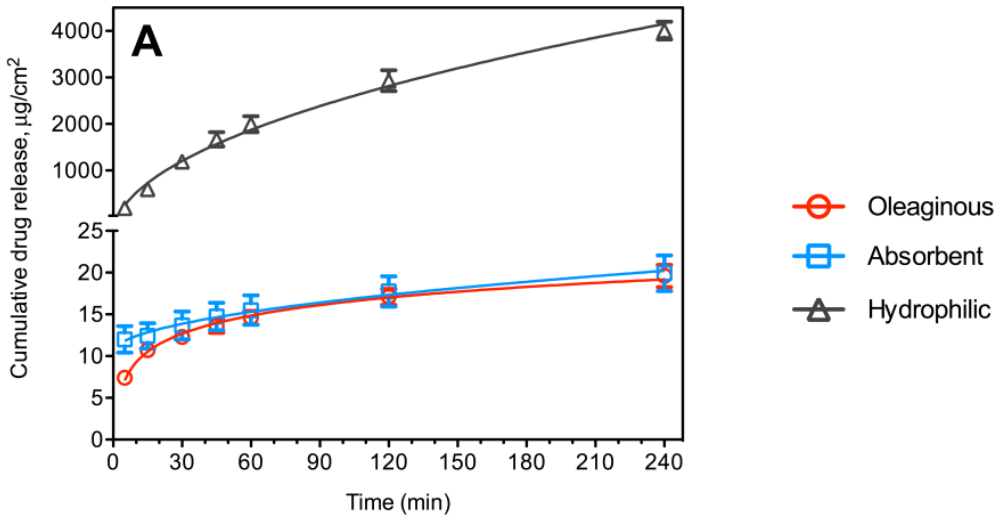




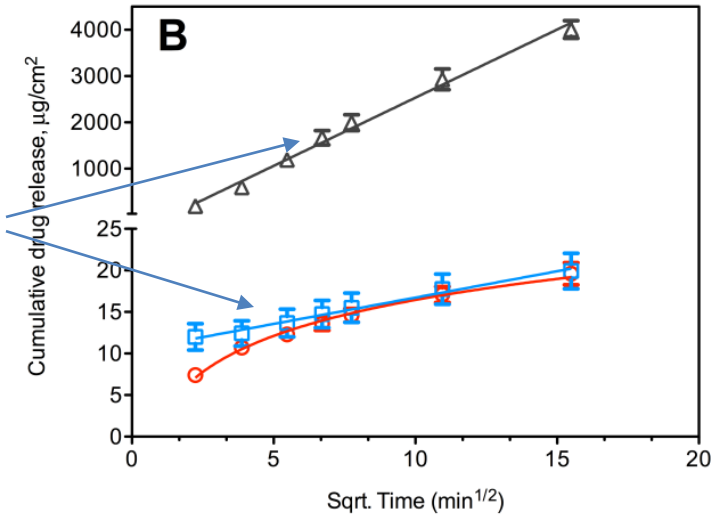
X. Xu, et al. 2015. Formulation and process factors influencing product quality and in vitro performance of ophthalmic ointments. International Journal of Pharmaceutics. 493 (1-2), pp. 412-425.

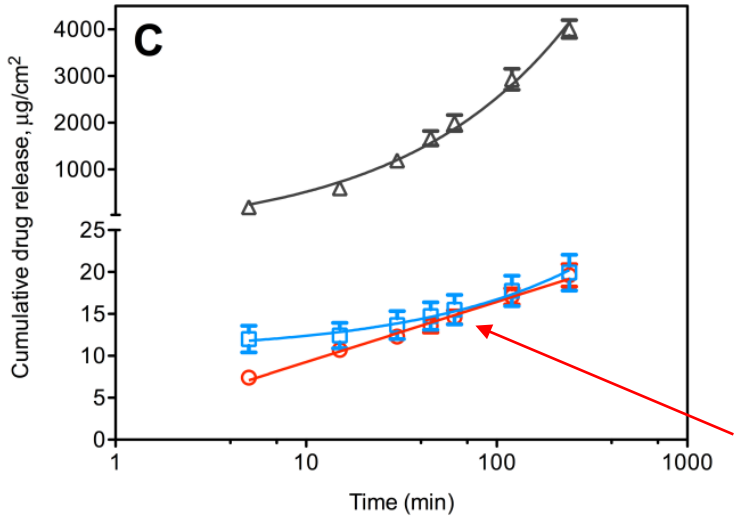
Acyclovir Release From Three Types of Ointment Bases

(A) Cumulative drug release per unit area in linear time scale; (B) Cumulative drug release per unit area plotted against square-root of time; and (C) Cumulative drug release per unit area in logarithm-time scale. (4% w/w drug loading, pH 7.4 PBS, 37° C, n=6)



Higuchi release



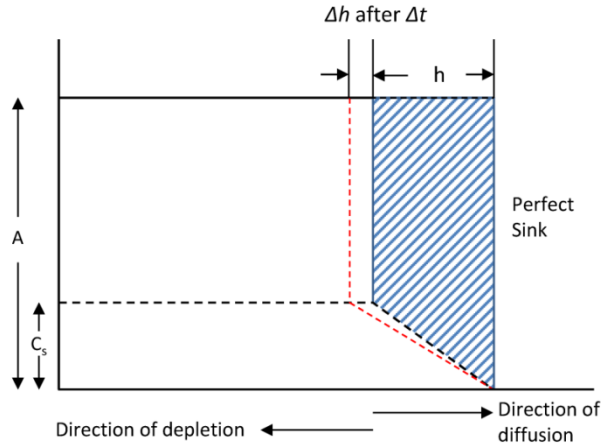


Logarithm-time! Why ???

X. Xu, et al. 2015. Kinetics of Drug Release from Ointments: Role of Transient-Boundary Layer. International Journal of Pharmaceutics. 494 (1), pp. 31-39.

A New Transient-Boundary Layer (TBL) Theory

Higuchi theory



Inward moving boundary

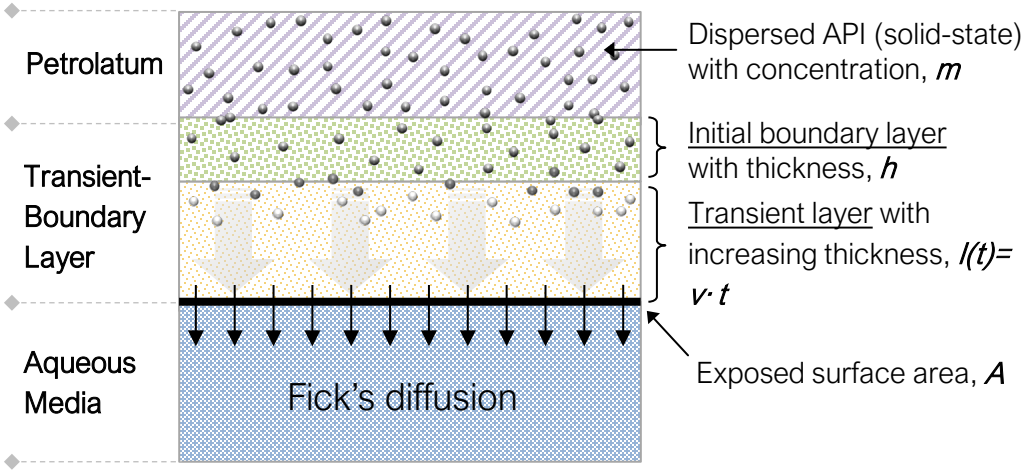
$$\frac{dQ}{dt} = \frac{D(C - C')}{h}$$

$$\frac{dQ}{dh} = A - \frac{C_S}{2}$$

$$Q_{aq} \propto \sqrt{t}$$

vs.

TBL theory



Outward expanding boundary

$$\frac{dQ_{aq}}{dt} = K \cdot \frac{1}{t}$$

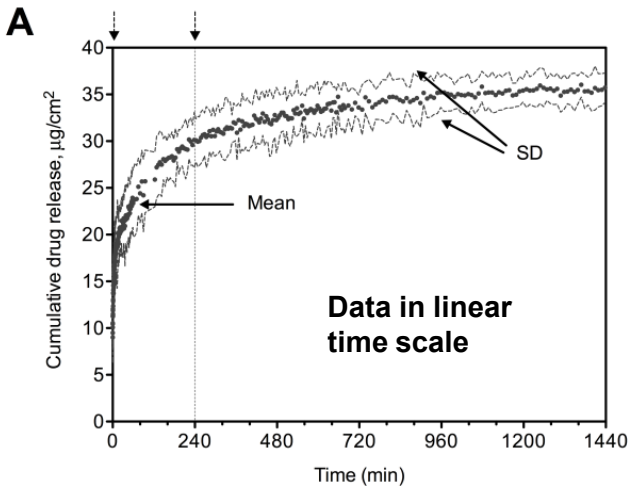
$$Q_{aq} = K \cdot \ln(t) + Q'$$

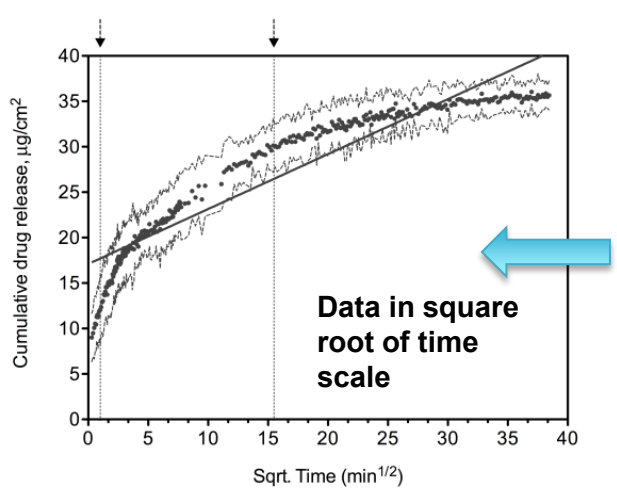
where $K = \frac{P \cdot m \cdot h \cdot A}{v}$

$$Q_{aq} \propto \ln(t)$$

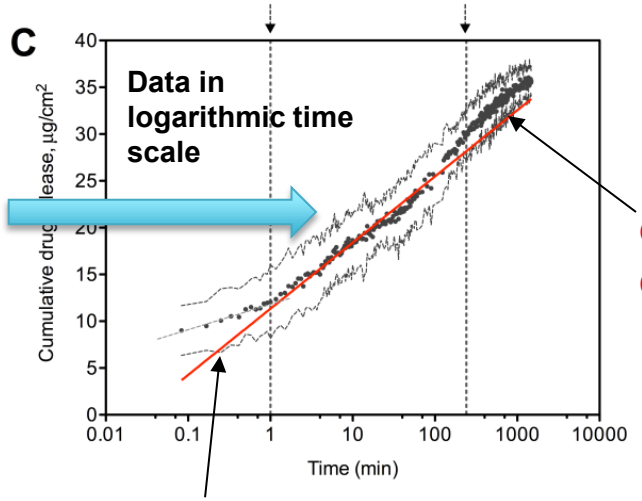
X. Xu, et al. 2015. Kinetics of Drug Release from Ointments: Role of Transient-Boundary Layer. International Journal of Pharmaceutics. 494 (1), pp. 31-39.

Evidence of Logarithmic-time Dependent Drug Release





Does not follow Higuchi square-root time law



Follows Logarithmic-time scale

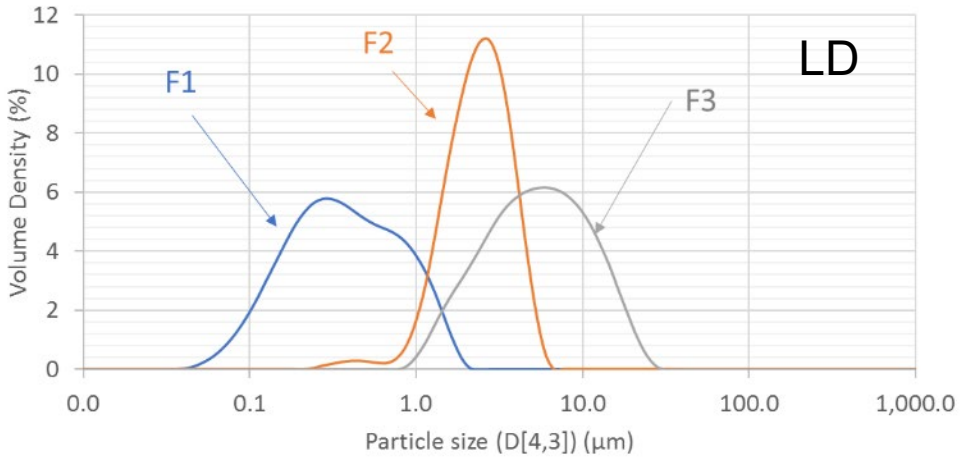
depletion of ointment

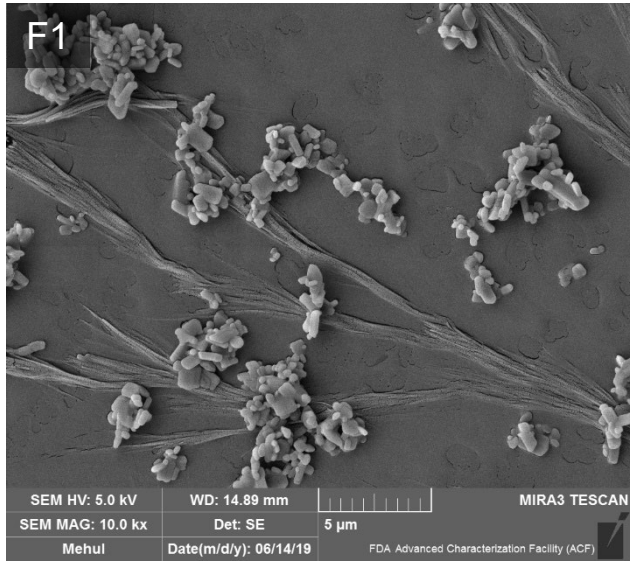
Equilibration phase

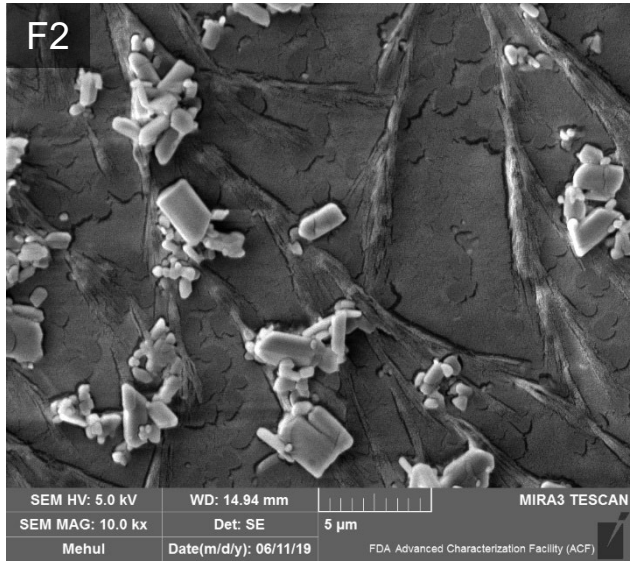
X. Xu, et al. 2015. Kinetics of Drug Release from Ointments: Role of Transient-Boundary Layer. International Journal of Pharmaceutics. 494 (1), pp. 31-39.

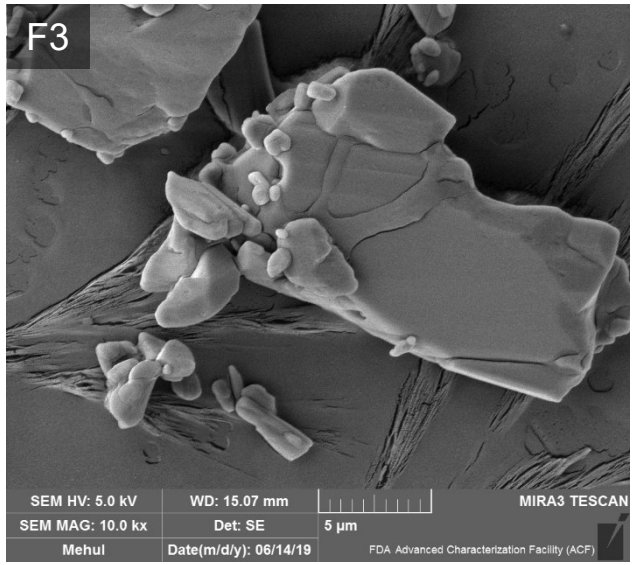
Example 2: Suspensions

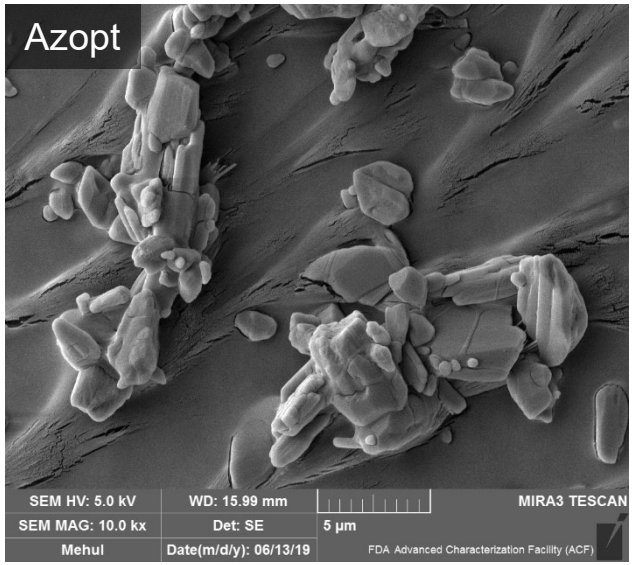
- Brinzolamide ophthalmic suspensions
- Prepared in-house with **varying PSDs** (relative to the RLD)
- Expected to have **different** dissolution rates
- It is desired that IVRT to be discriminatory in terms of PSD, possibly supporting in vitro BE approach





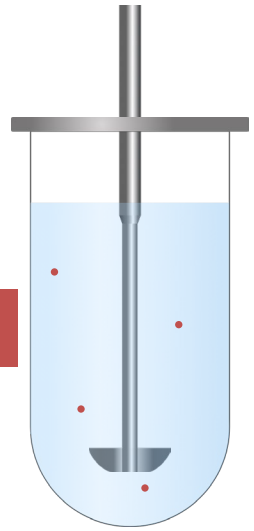




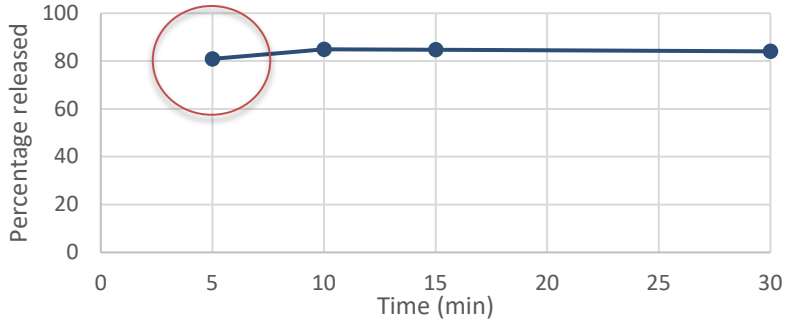


How to improve discrimination?

Option 1: USP 2 (900 mL)

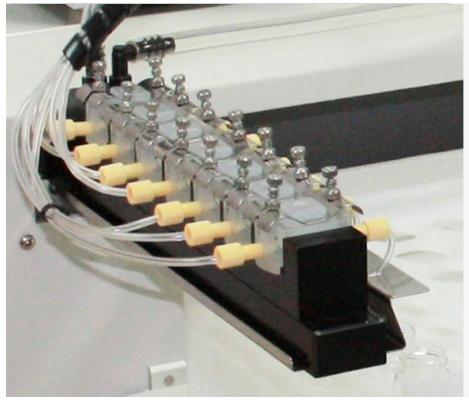


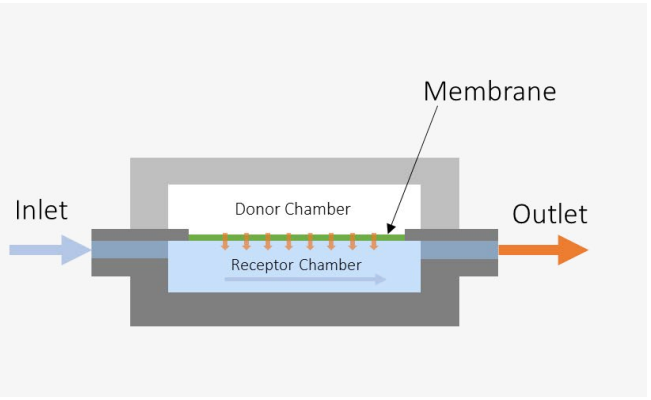
Sink-condition!

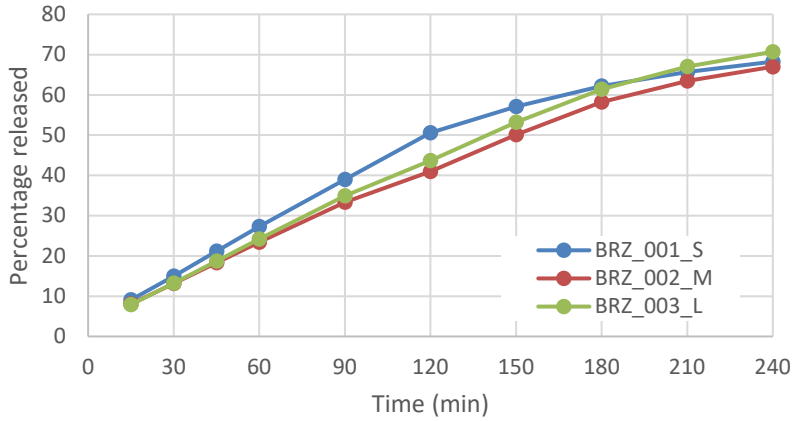


Release too fast, all formulation dissolves nearly identically

Option 2: VDC (0.45 um membrane)

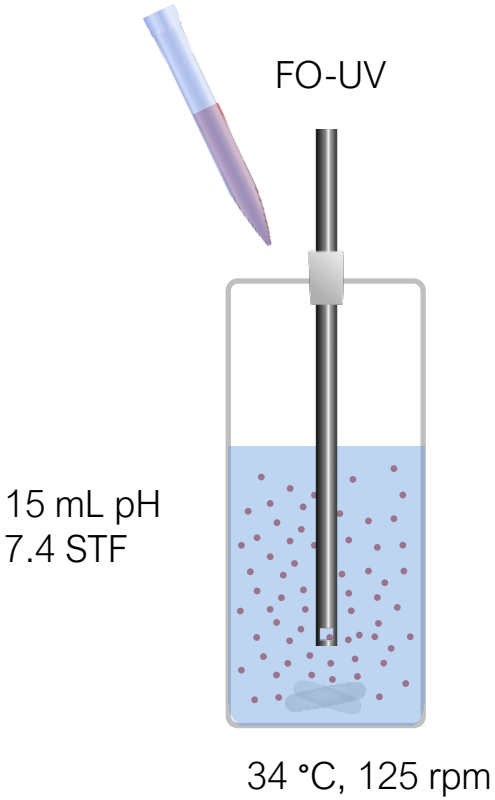




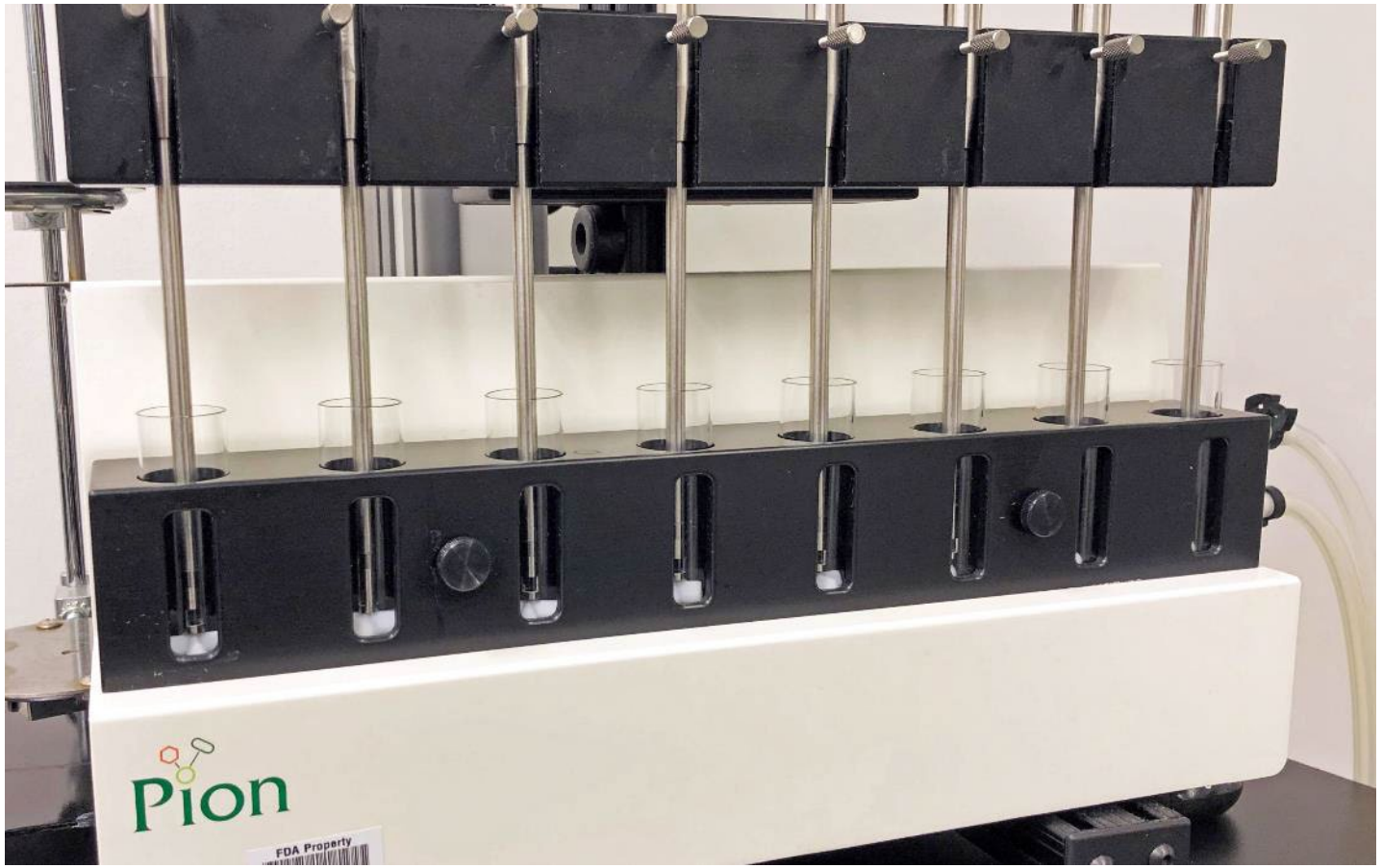


Release slowed down (by membrane), but no discrimination

How to improve discrimination? (cont.)



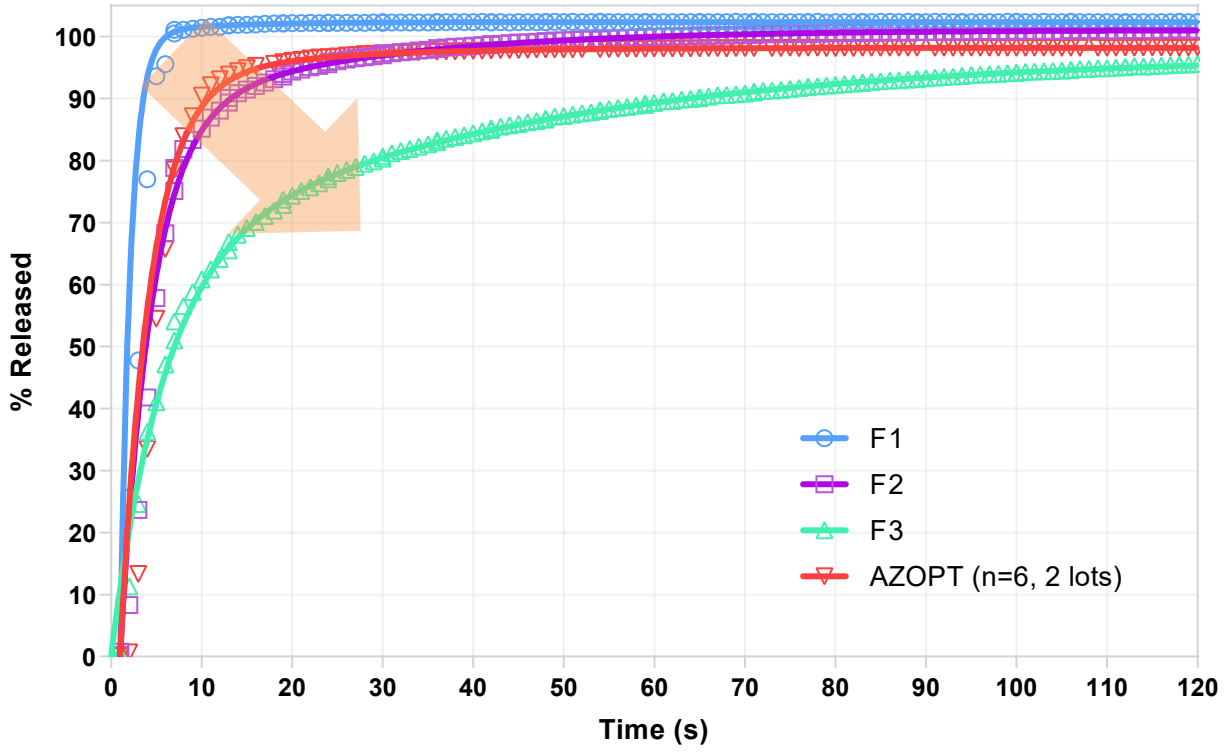
1 non-sink condition
(just like in the eye)

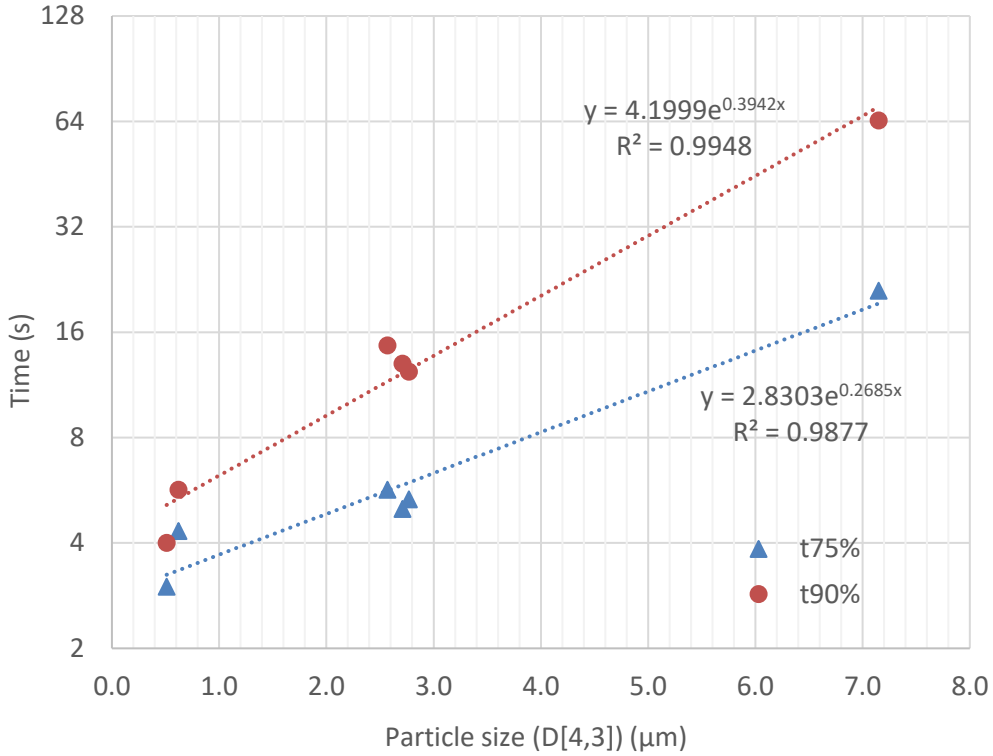


2 Continuous monitoring

A. Vo, et al. In vitro physicochemical characterization and dissolution of brinzolamide ophthalmic suspensions with similar composition. International Journal of Pharmaceutics (2020), 588, 119761.
https://doi.org/10.1016/j.ijpharm.2020.119761

Discriminatory IVRT for Suspensions

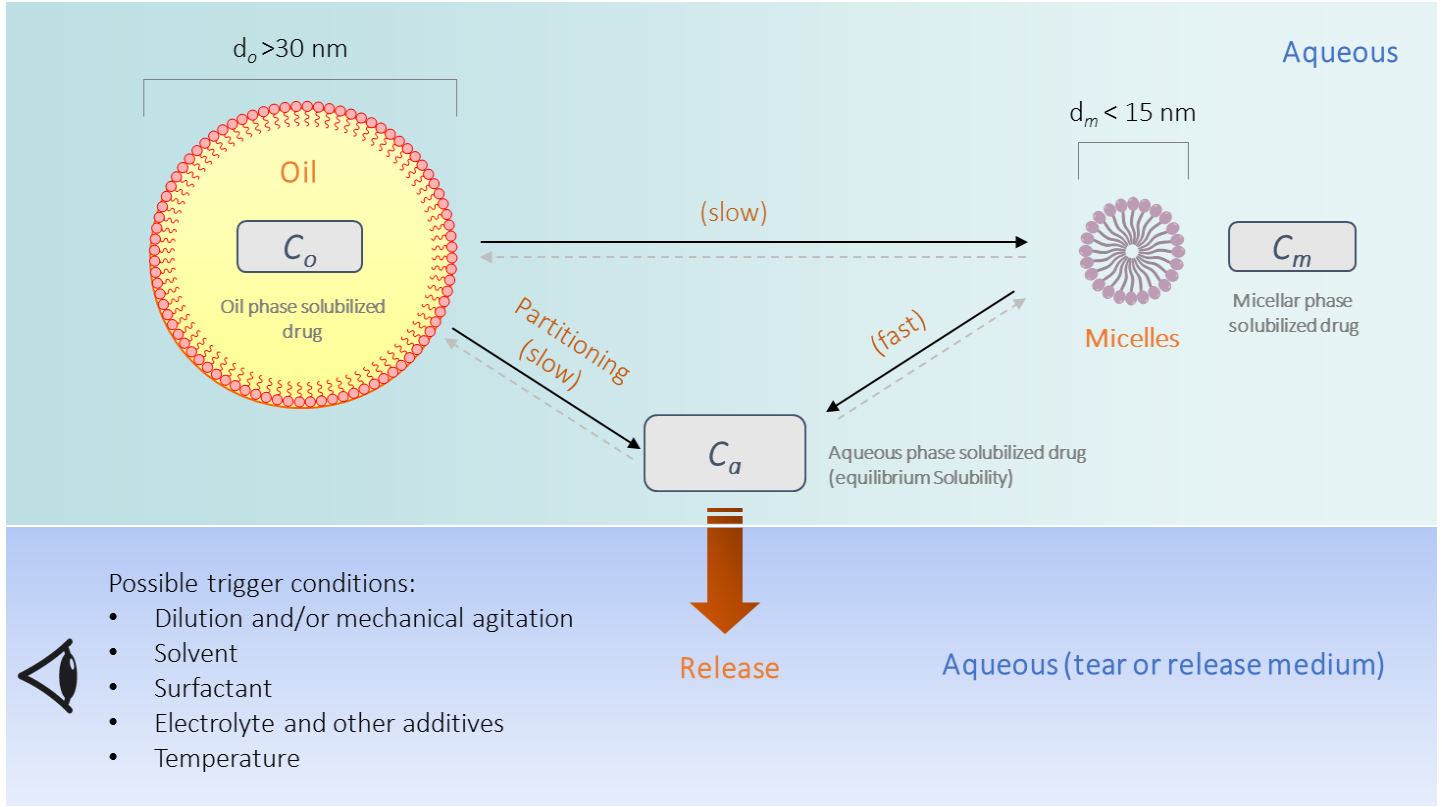


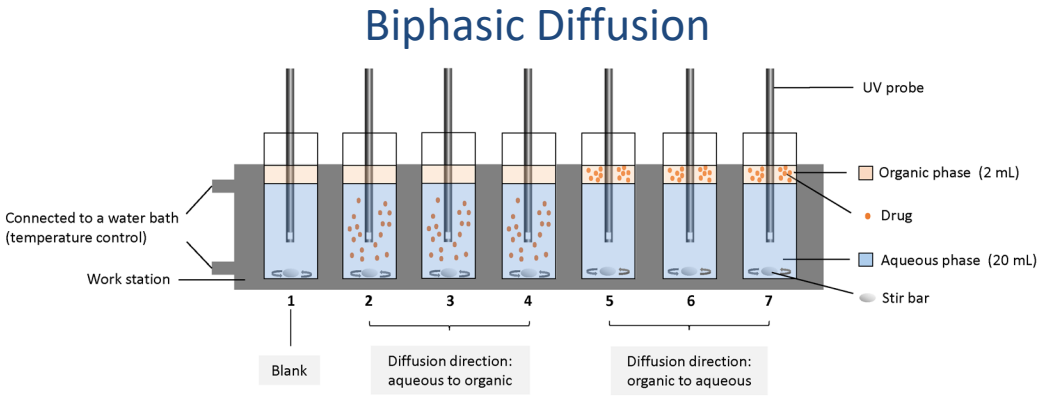


- Nano- suspensions completes dissolution within 6 seconds
- Micron- suspensions dissolves in 2 min
- Good correlation (r^2>0.9) between dissolution rate and the PSD

A. Vo, et al. In vitro physicochemical characterization and dissolution of brinzolamide ophthalmic suspensions with similar composition. International Journal of Pharmaceutics (2020), 588, 119761. https://doi.org/10.1016/j.ijpharm.2020.119761

Example 3: Emulsions





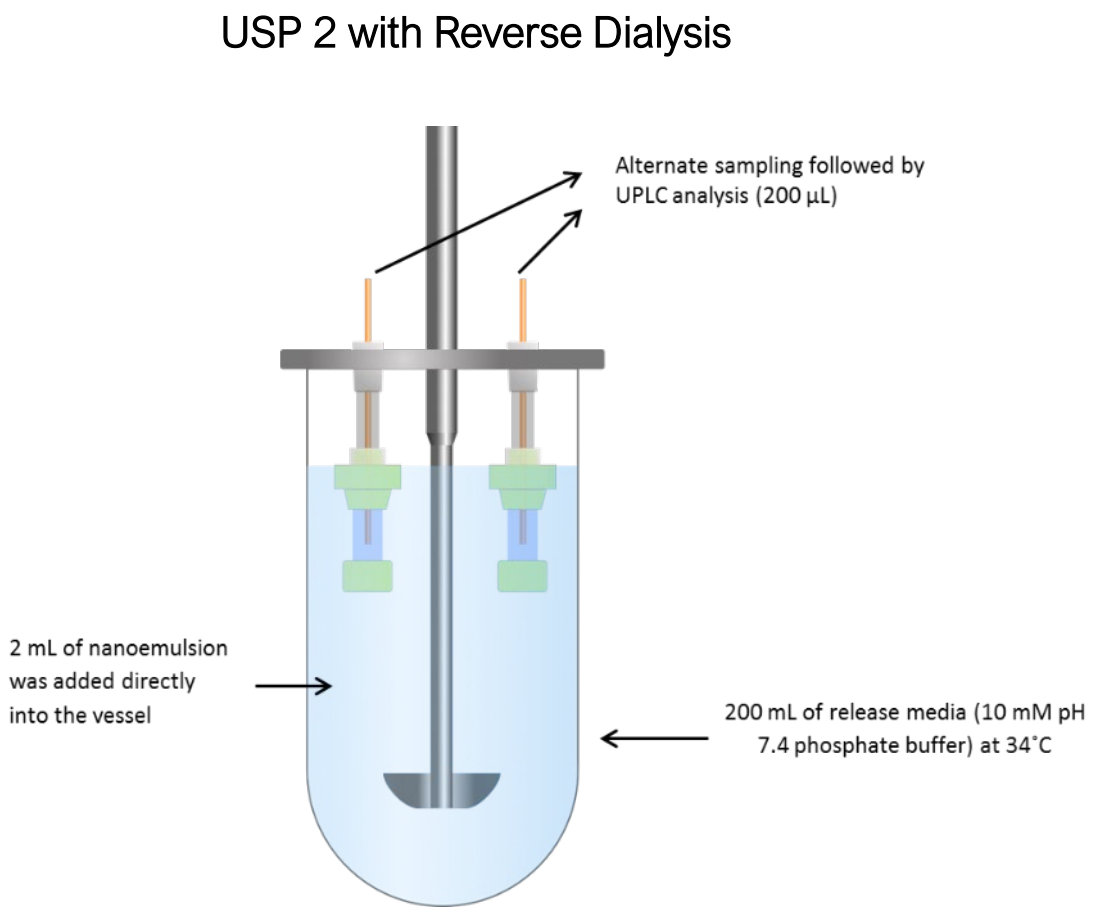
$t_{1/2}$ is approximately 12 min

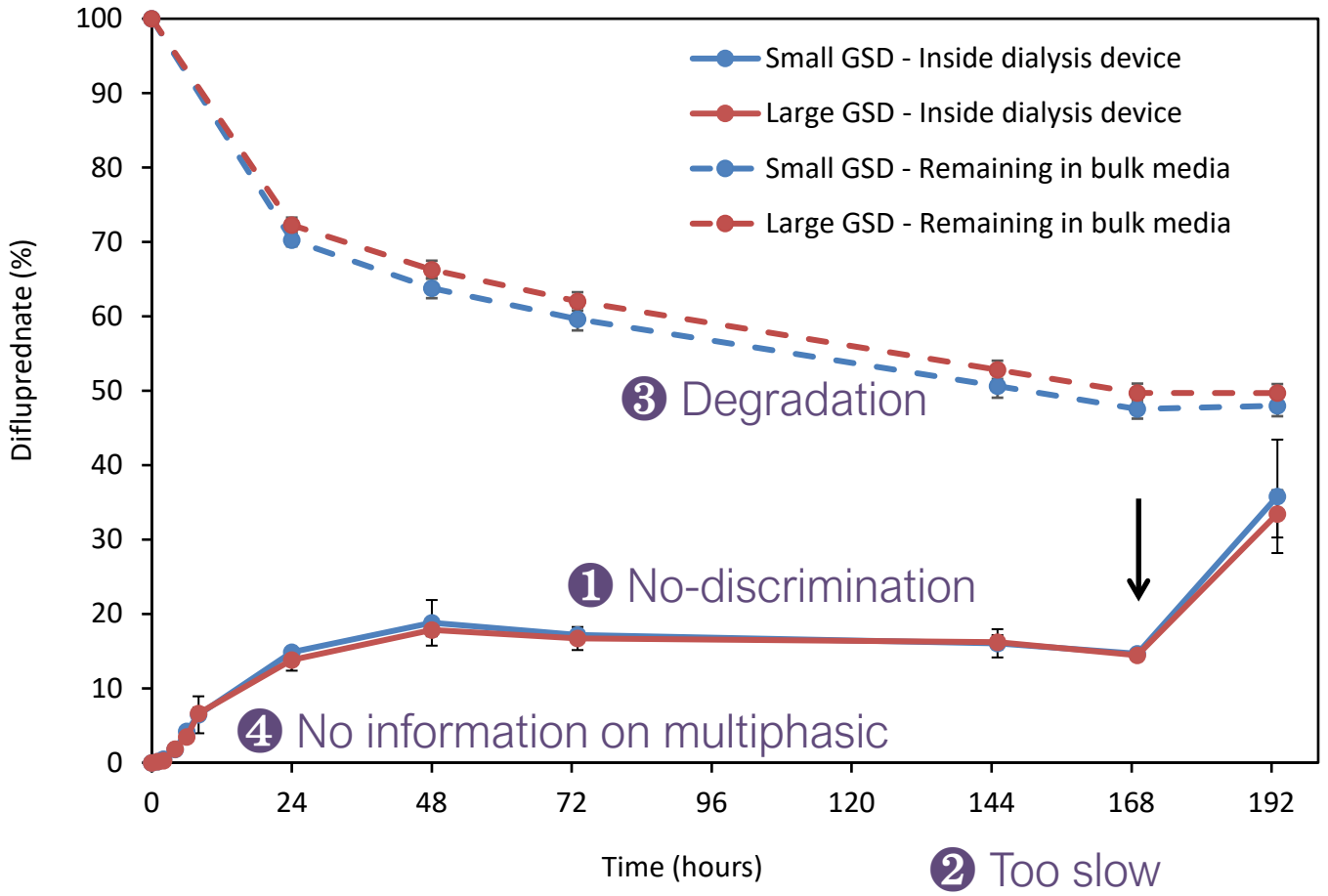
Q: How to separate the released drug (at the relevant time scale)?

Y. Dong et al. Journal of Controlled Release (2019), 313, 96-105

Y. Dong et al. Journal of Controlled Release (2020), 327, 360-370

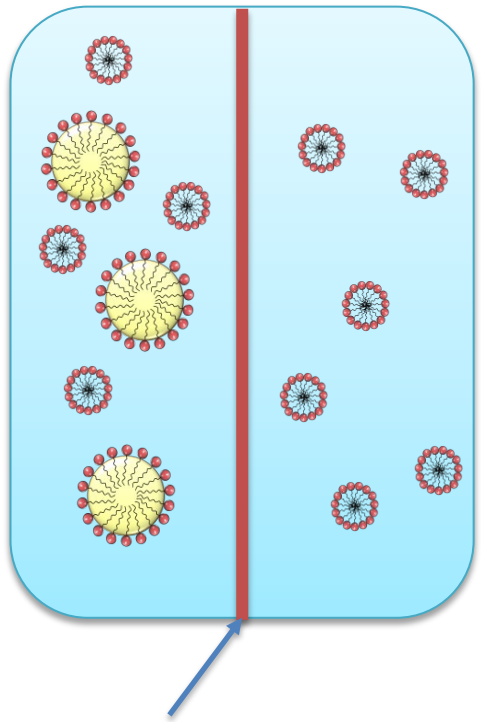
IVRT by (Reverse) Dialysis: A Typical Example

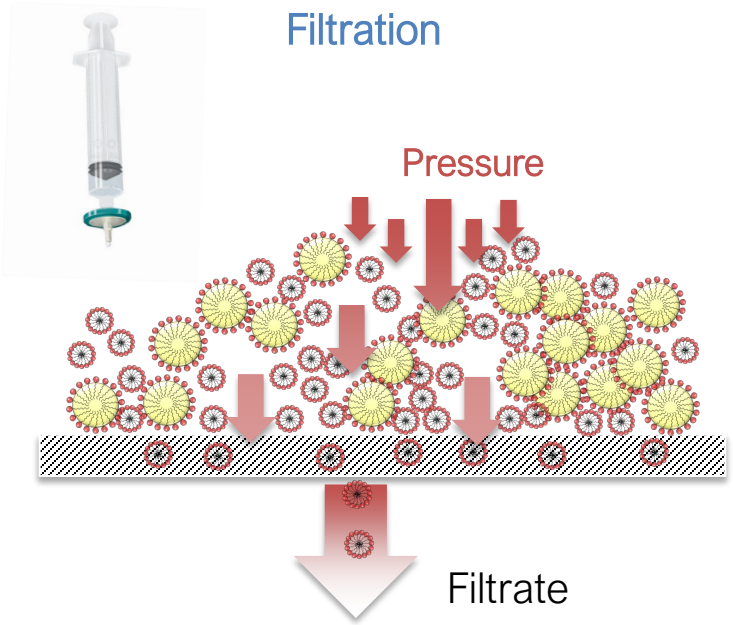


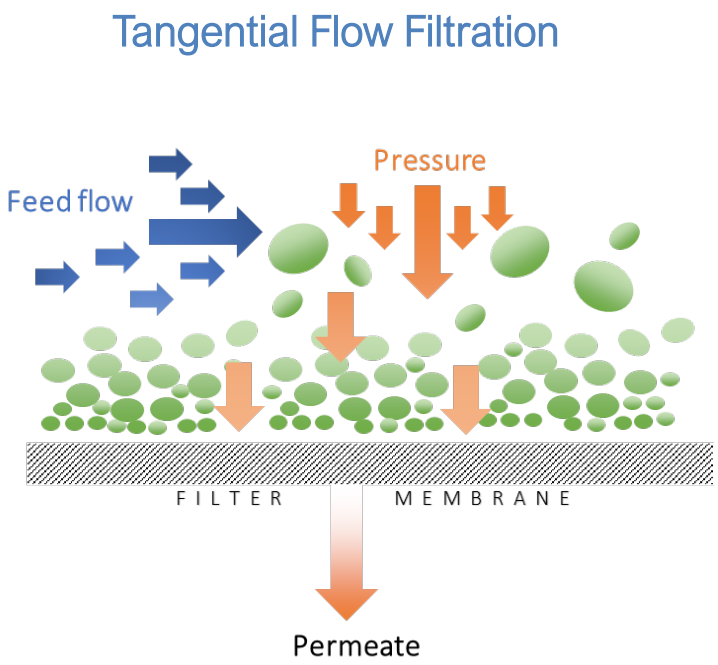


D. Patel et al. Adaptive Perfusion: An In Vitro Release Test (IVRT) for Complex Drug Products. Journal of Controlled Release (2021), 333, pp.65-75.

Filtration, Instead of Diffusion



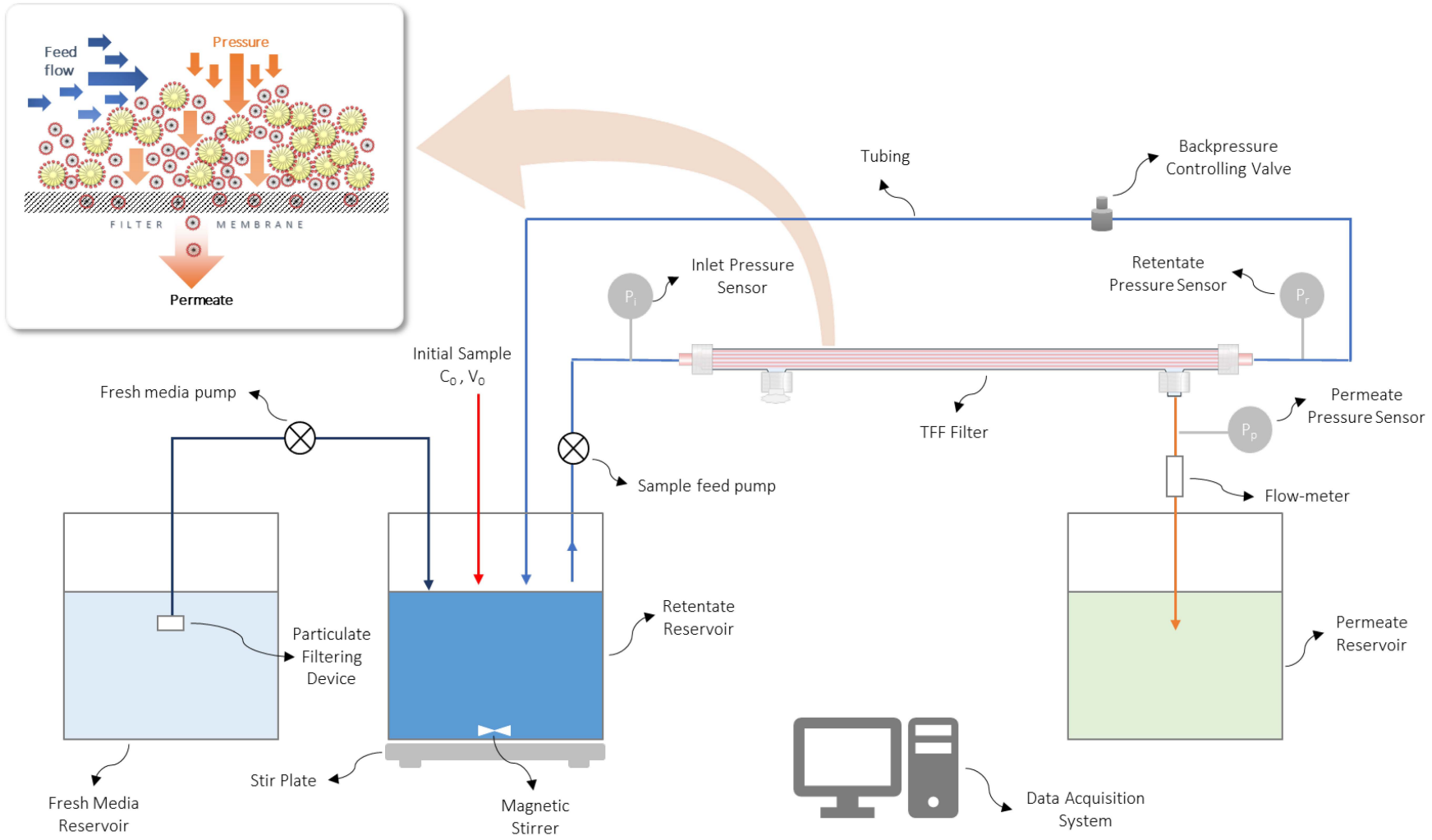




- Pressure driven
- Controllable flow by filtration
- Separation based on membrane size

- Tangential flow, thus avoiding build up at the membrane surface (swept away by flow)

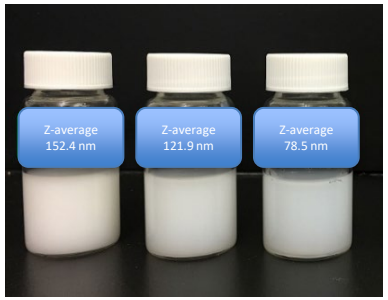
Schematic Diagram of Adaptive Perfusion

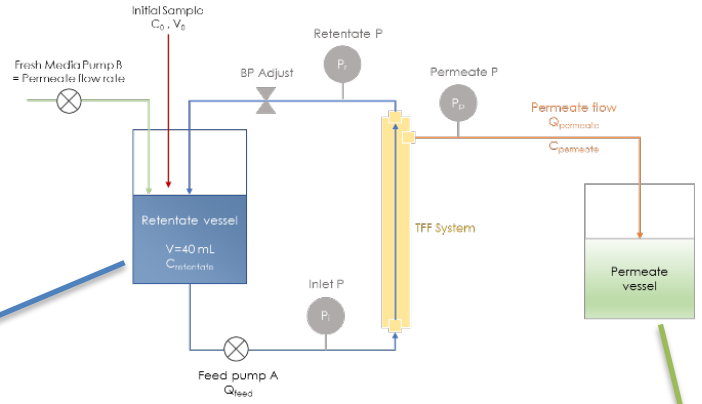


D. Patel et al. Adaptive Perfusion: An In Vitro Release Test (IVRT) for Complex Drug Products. Journal of Controlled Release (2021), 333, pp.65-75.

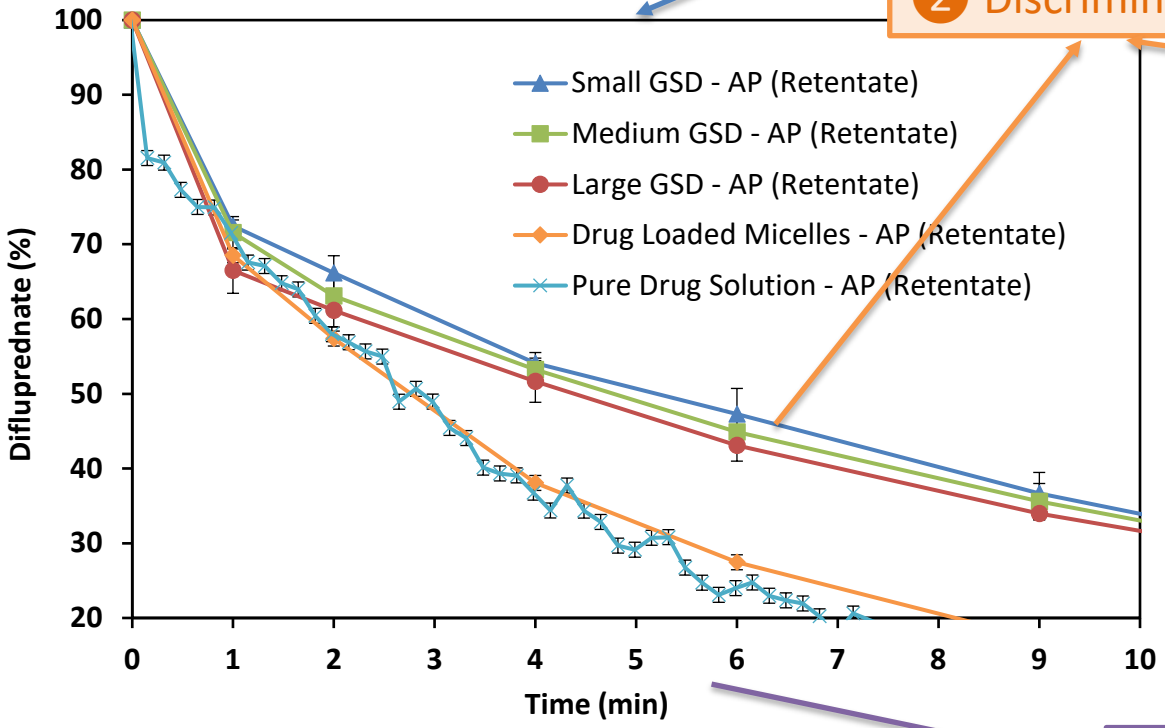
Where we started…

Results

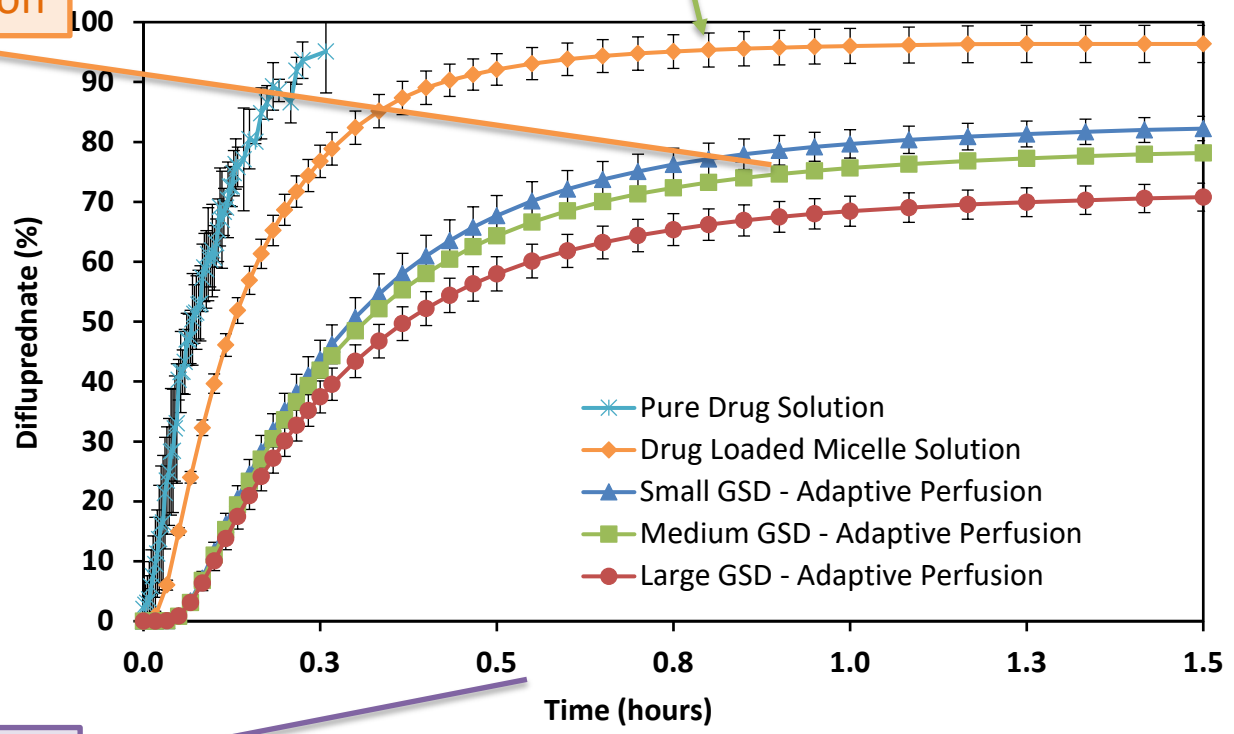




Retentate Concentration Profile (n=3)



Permeate Concentration Profile (n=3)



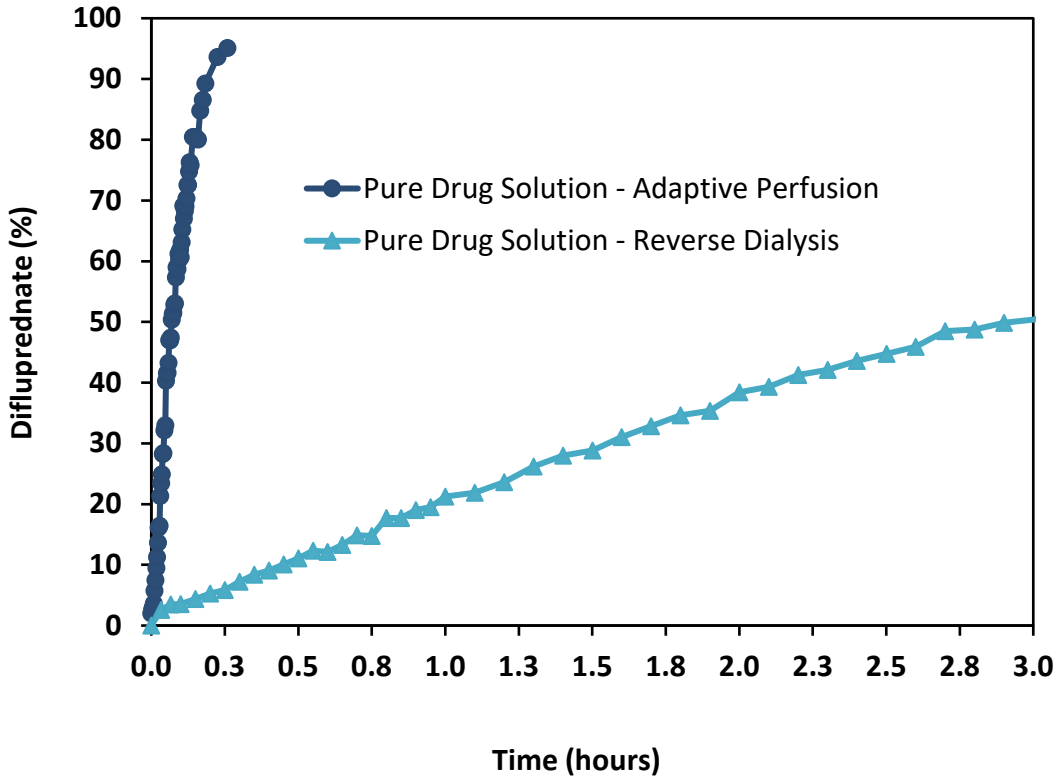
2 Discrimination

1 Fast

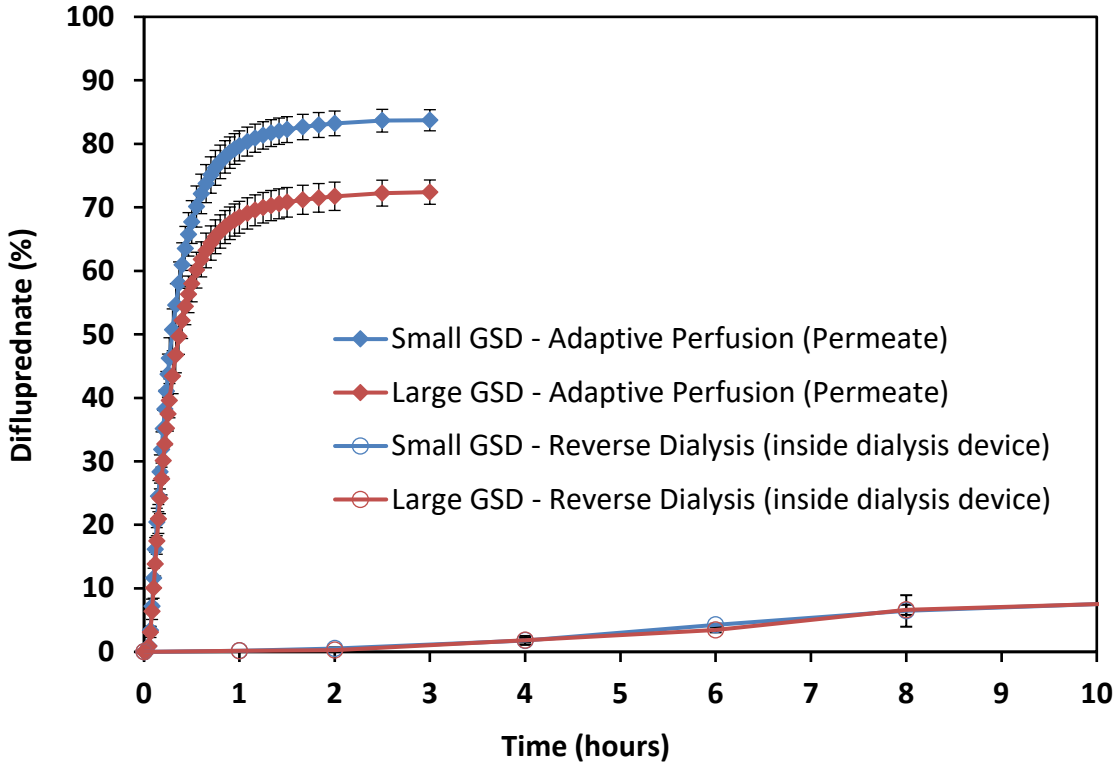
D. Patel et al. Adaptive Perfusion: An In Vitro Release Test (IVRT) for Complex Drug Products. Journal of Controlled Release (2021), 333, pp.65-75.

New vs. Old

Pure Drug Solution (n = 3)

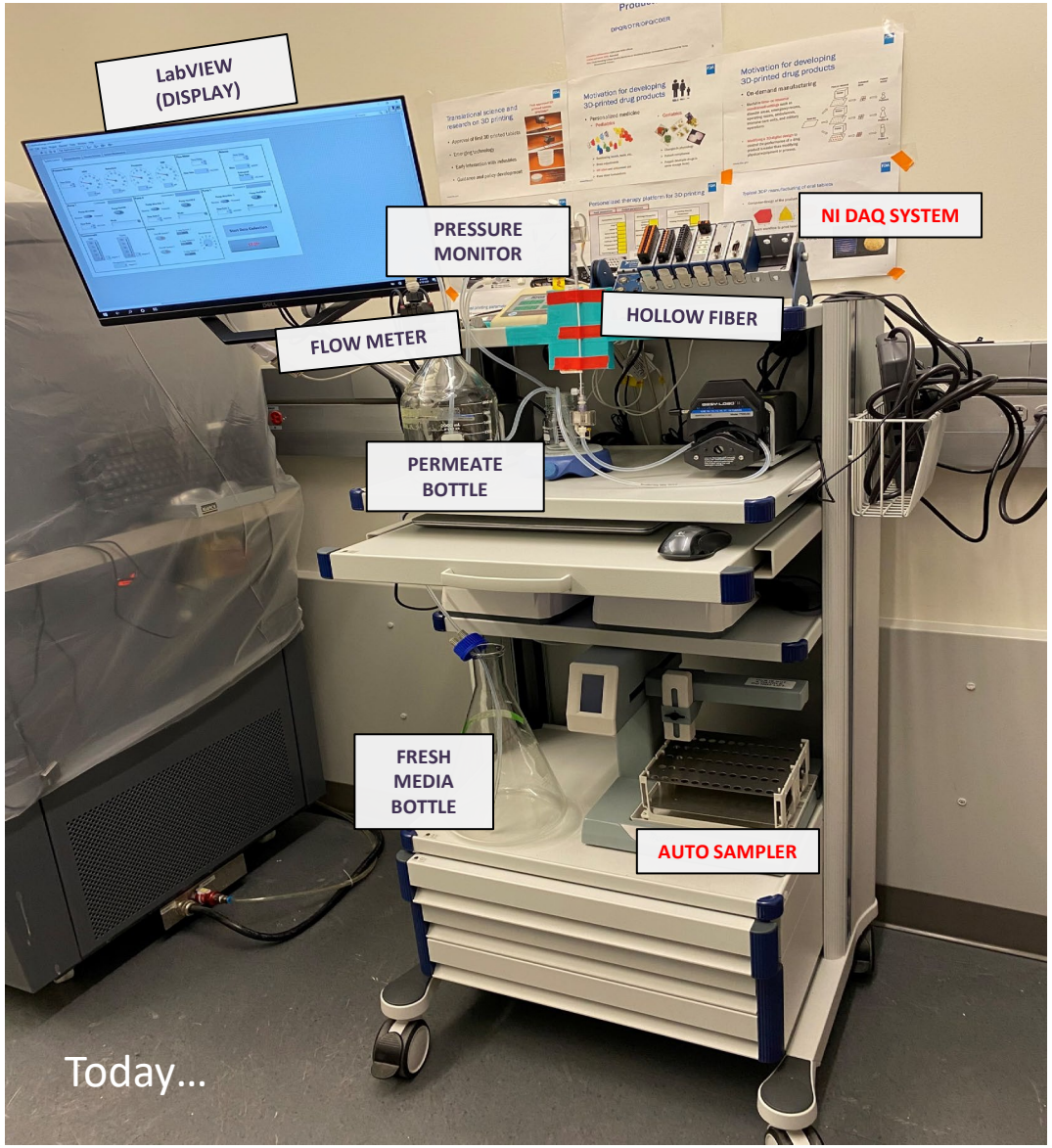


Small and Large GSD nanoemulsions (n = 3)

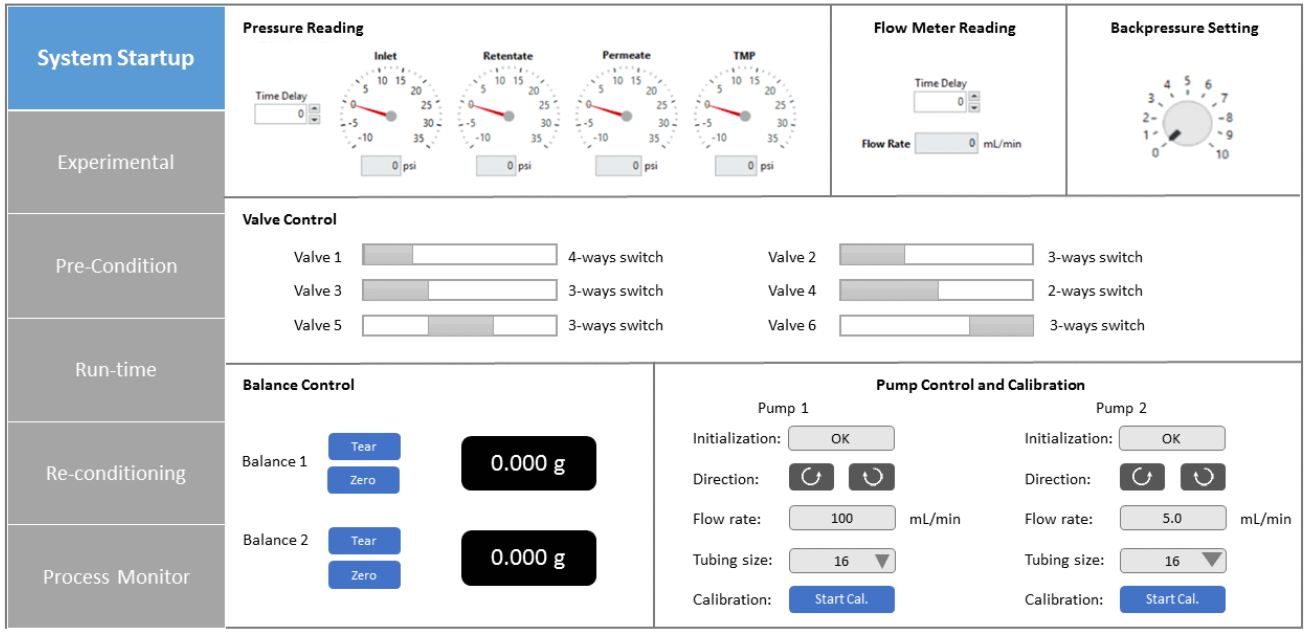


D. Patel et al. Adaptive Perfusion: An In Vitro Release Test (IVRT) for Complex Drug Products. Journal of Controlled Release (2021), 333, pp.65-75.

Future: A Turnkey Solution

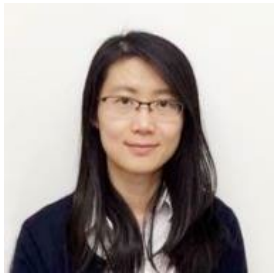


Custom Designed Control Interface

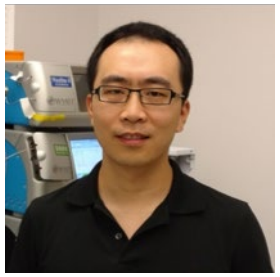


Acknowledgement

Deval Patel



Yixuan Dong



Haiou Qu

Anh Vo

Ying Zhang

Dongkai Zhu

Jungeun Bae

William Smith

Rokon Zaman

Other FDA Collaborators:

- Leanna Hengst
- Robert Hunt
- Manar Al-Ghabeish
- Muhammad Ashraf
- Xin Feng
- Naresh Pavurala
- Darby Kozak
- Stephanie Choi
- Yan Wang
- Jiwen Zheng
- Asif Rasheed
- Patricia Onyimba
- Bing Cai

Thank you