

In Vitro Testing - Predictive of in vivo performance of ODPs?

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 **aaps**® Workshops

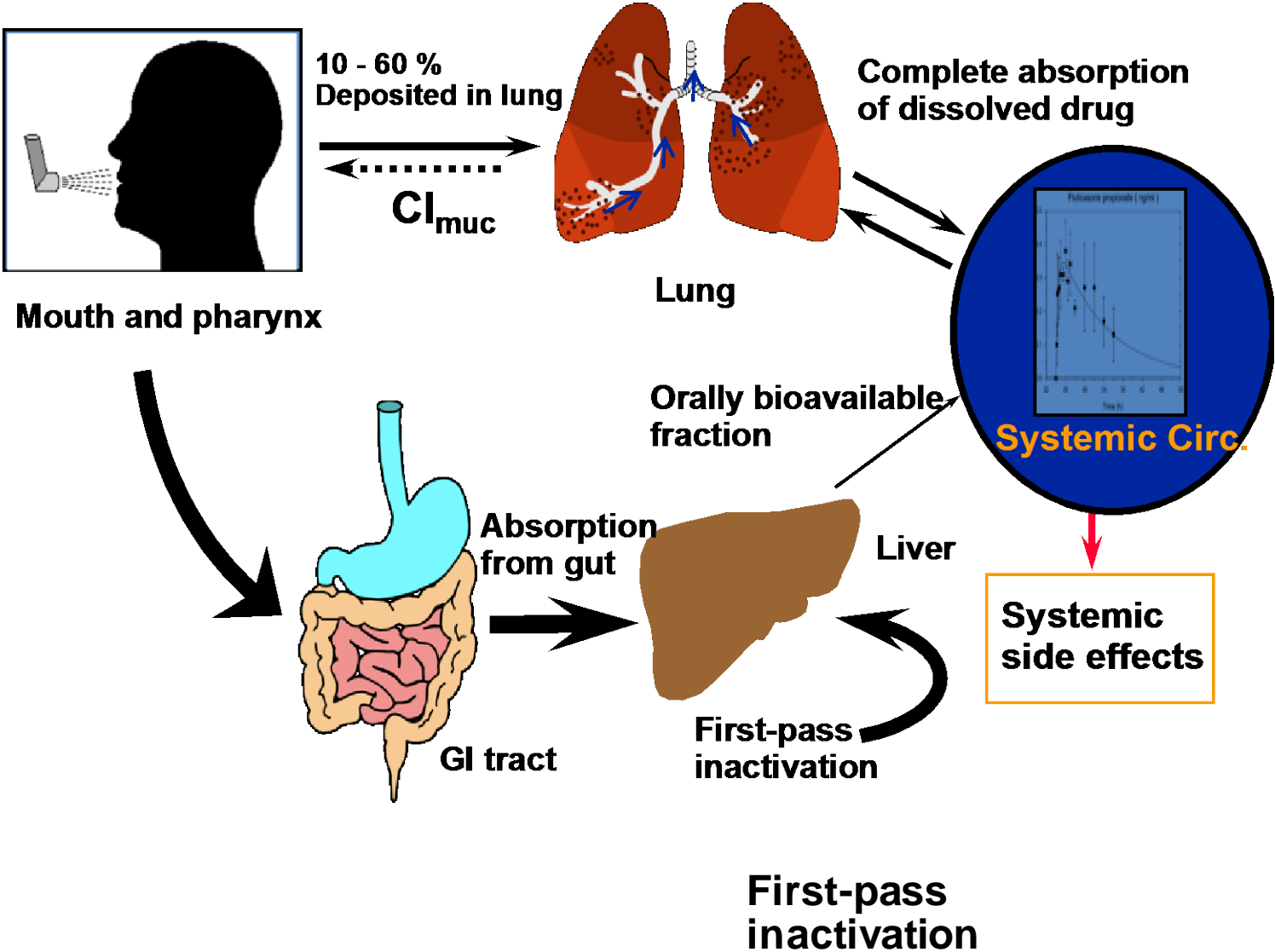
**AAPS/EUFEPS GLOBAL BIOEQUIVALENCE HARMONIZATION
INITIATIVE: 4TH INTERNATIONAL WORKSHOP**

DECEMBER 12-13, 2019 • BETHESDA, MD



UF

Pulmonary Delivery is rather Complex



Relevant Questions concerning pulmonary Bioequivalence

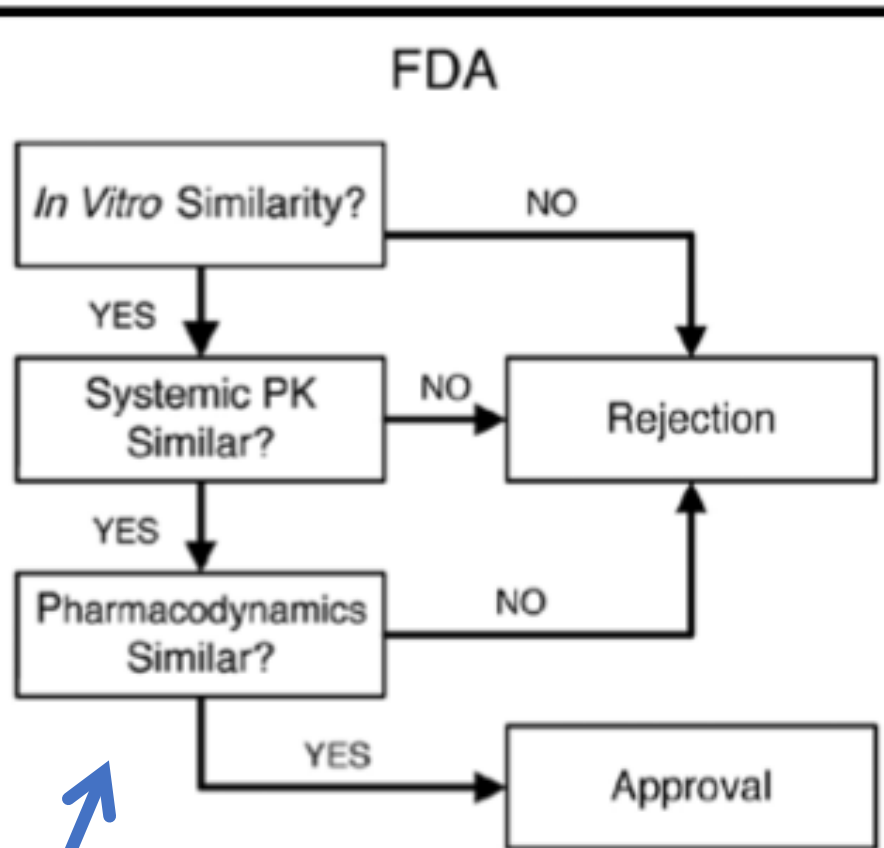
Pulmonary
Efficacy

Systemic
Safety

- What is the dose available to the lung?
- What is the regional distribution of the deposited dose?
- How long does the drug stay in the lung?

- What is the systemic exposure?

Current FDA Recommendation



• Alternative approaches are needed

- *In vitro* studies
- Pharmacokinetic studies for assessing lung equivalence

- expensive, risky,
- Can often not differentiate between doses

Bioequivalence: What needs to be shown?

- Same dose available, deposited



Ex throat dose ; ISM ? - PK

- Same regional deposition

Cascade impactor ? - PK ?

- Same post-deposition fate

- Dissolution

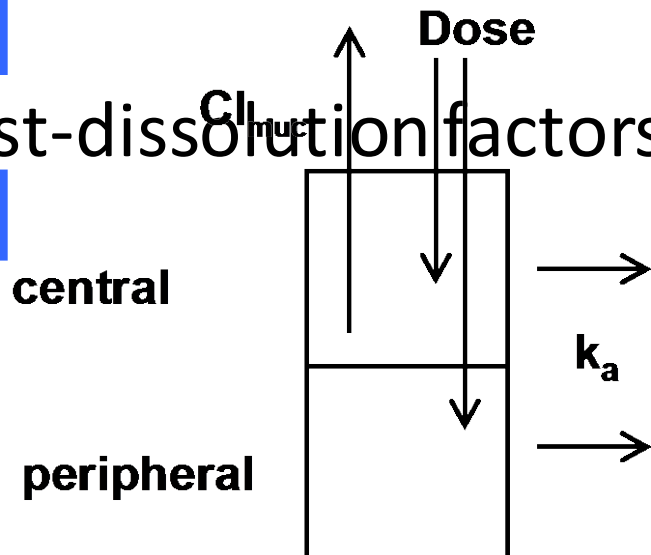


Dissolution Tests ? - PK

- Post-dissolution factors (not relevant?)



Cell culture ? - PK



More central deposition:

- Mucociliary clearance: Lung dose ↓ : AUC ↓, C_{mac} ↓
- Thicker membranes: k_a ↓ : C_{mac} ↓

FDA DPI Contract: Formulation Work

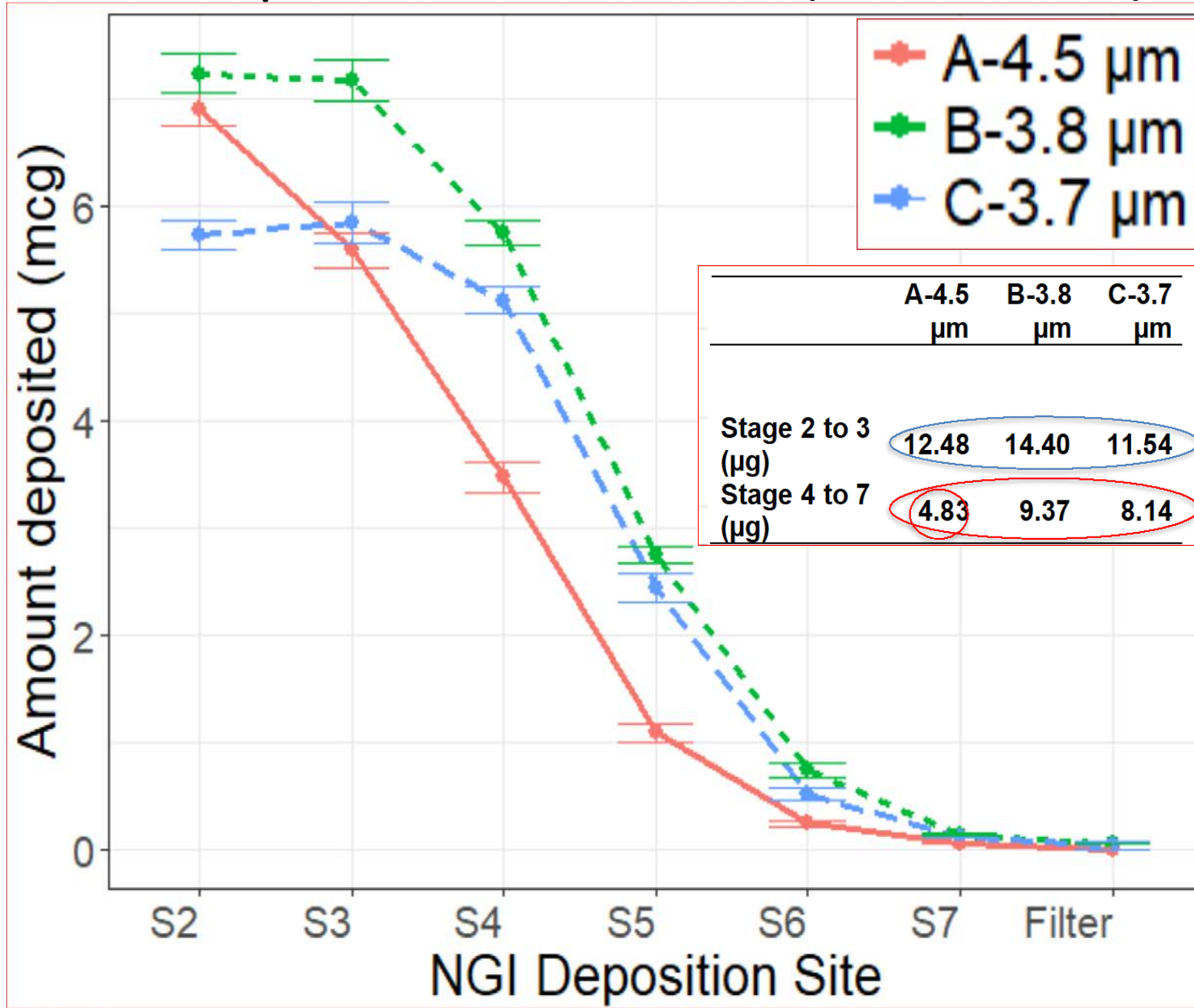
(Dr. Jag Shur, Robert Price, Univ of Bath)

Three formulations only differing in lactose fines (MMAD)

Product Name	Formulation (% w/w)	Lot Number
Fluticasone Propionate DPI (Active)	FP: 0.80	C-3.7 μ m
	Respitose SV003: 96.72	
	Lactohale LH300: 2.48	
Fluticasone Propionate DPI (Active)	FP: 0.80	A-4.5 μ m
	Respitose SV003: 79.36	
	Lactohale LH201: 19.84	
Fluticasone Propionate DPI (Active)	FP: 0.80	B-3.8 μ m
	Respitose SV003: 89.28	
	Lactohale LH230: 9.92	

Goal of study: Can PK detect differences in regional deposition?

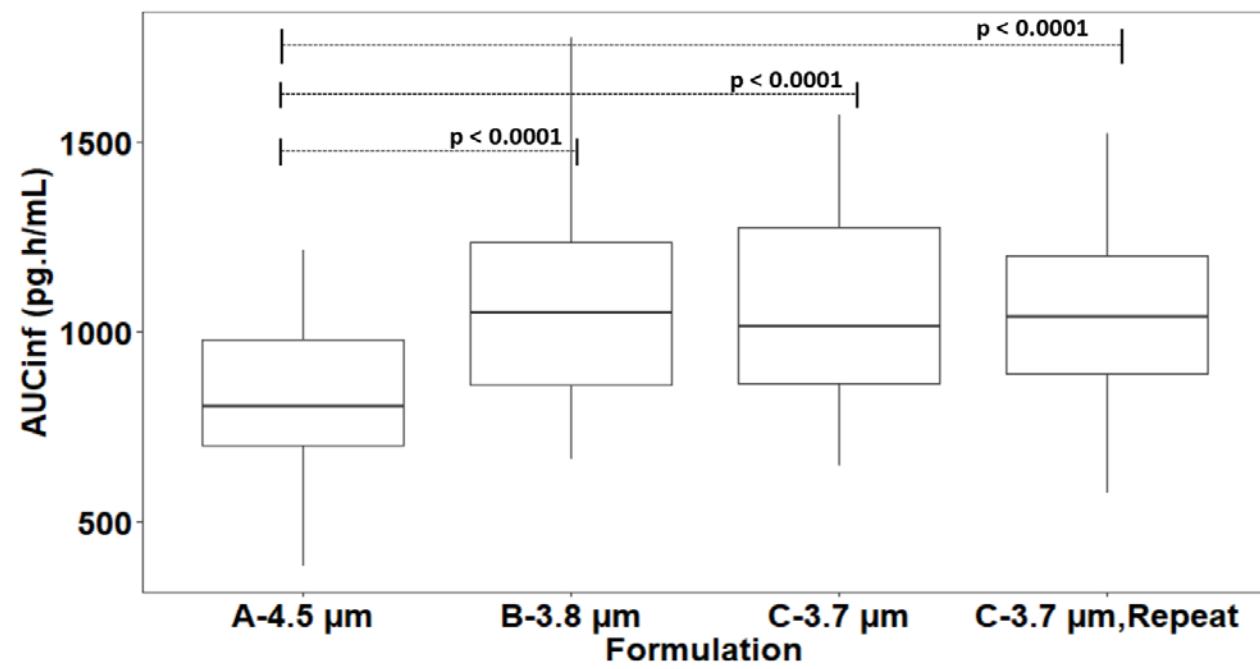
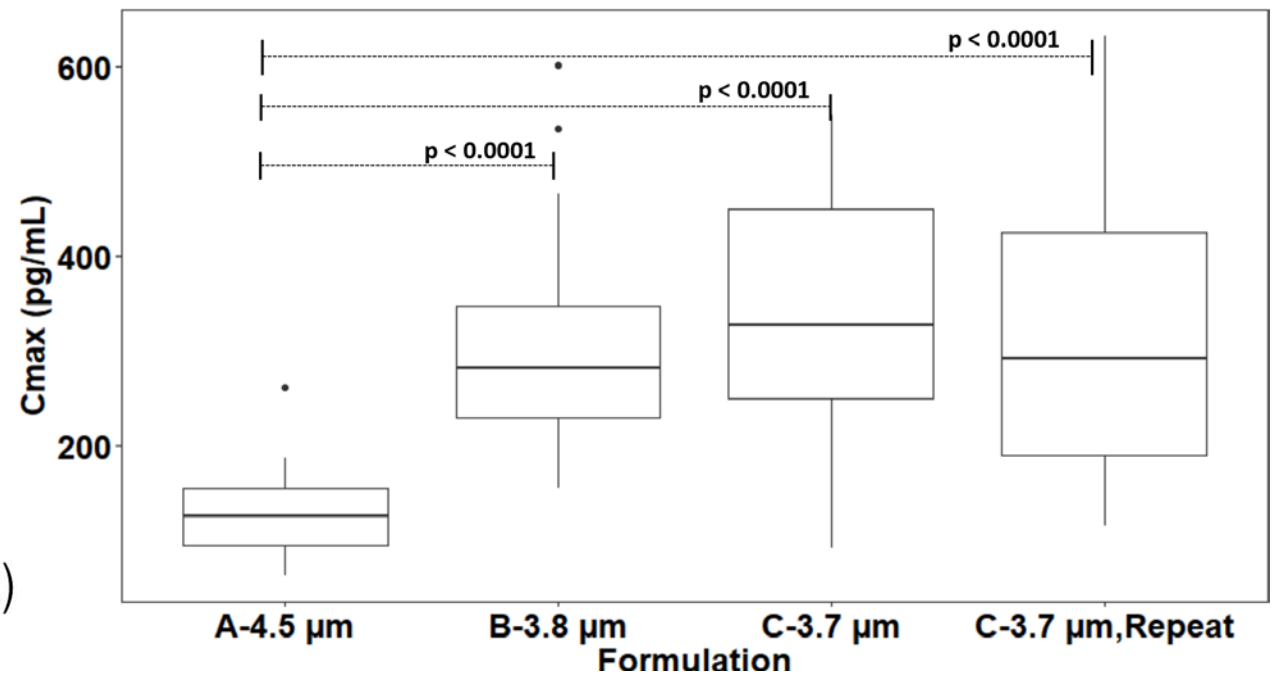
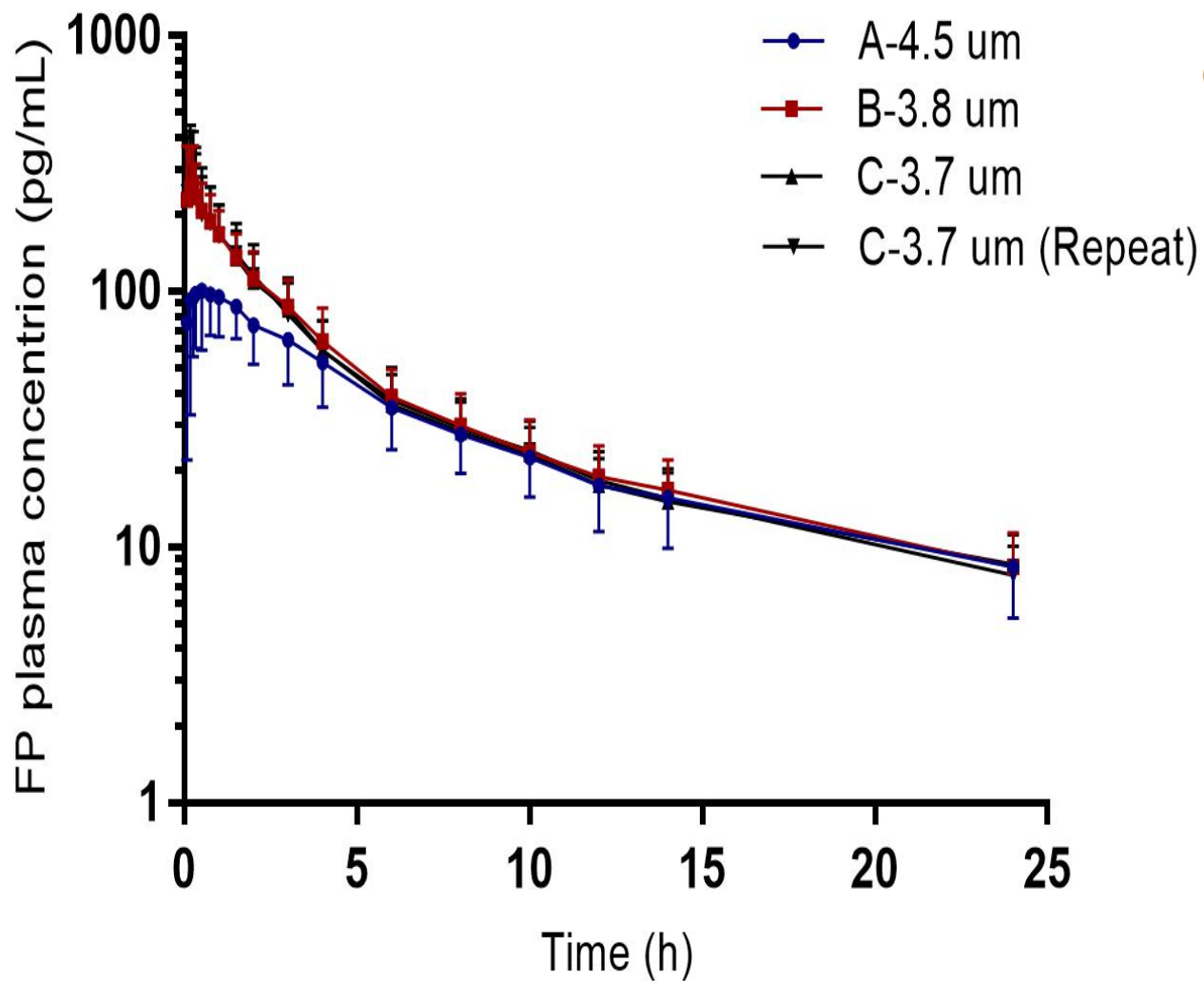
Cascade Impactor Studies (USP-NGI)



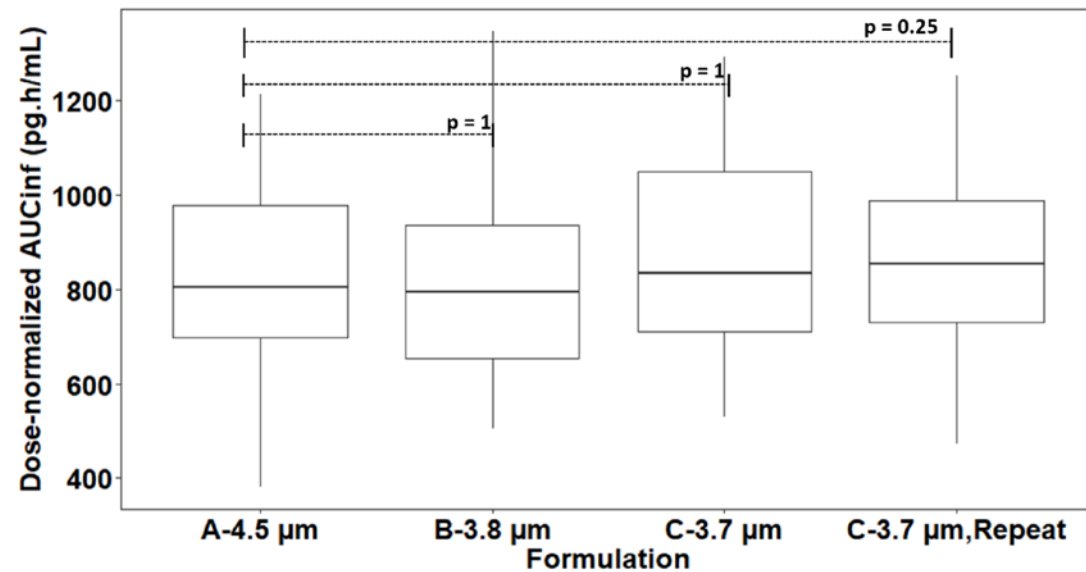
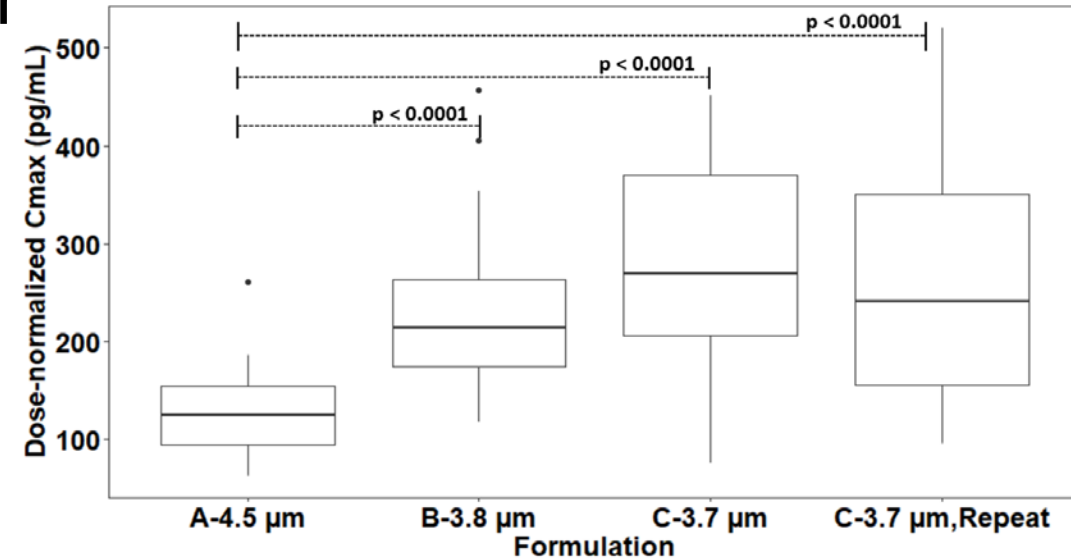
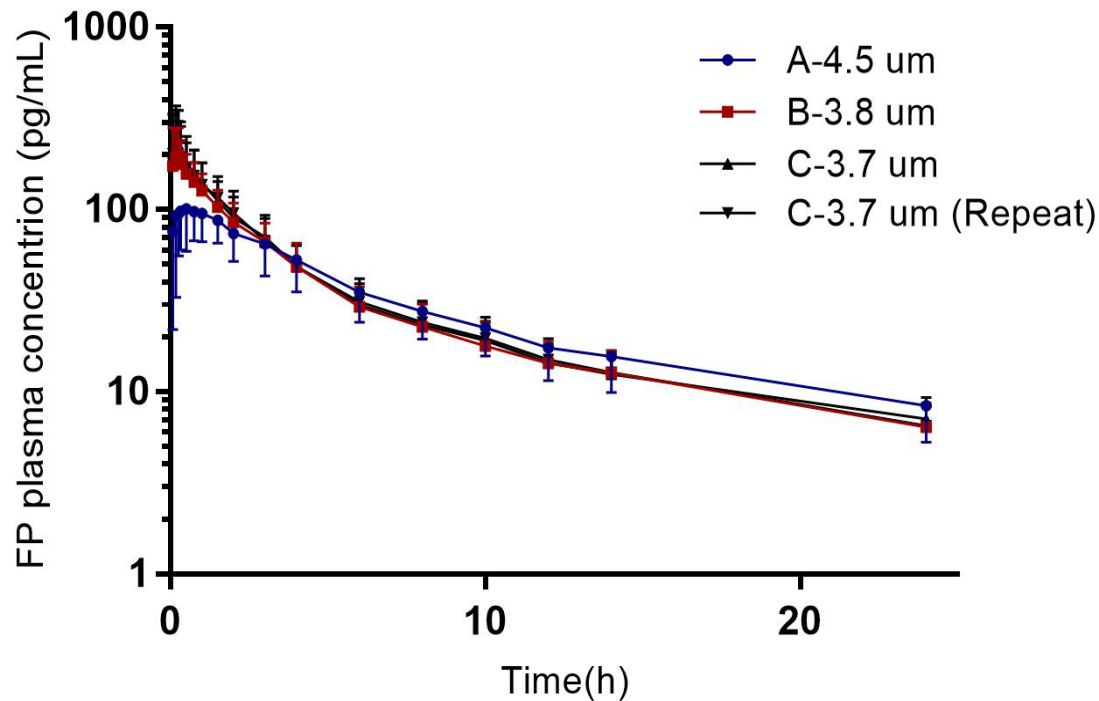
PK Study Design

- 4-way, cross-over, double blind (24 subjects)
- Dose: 5 * 100 µg
- Non-compartmental Analysis
- Compartmental Analysis (population-PK)
- PBPK based evaluation of popPK results

Before dose normalization



After the ex-throat dose normalization



AUC after dose normalization: bioequivalent

Cmax after dose normalization : lack of bioequivalence

Indicating differences in regional deposition?

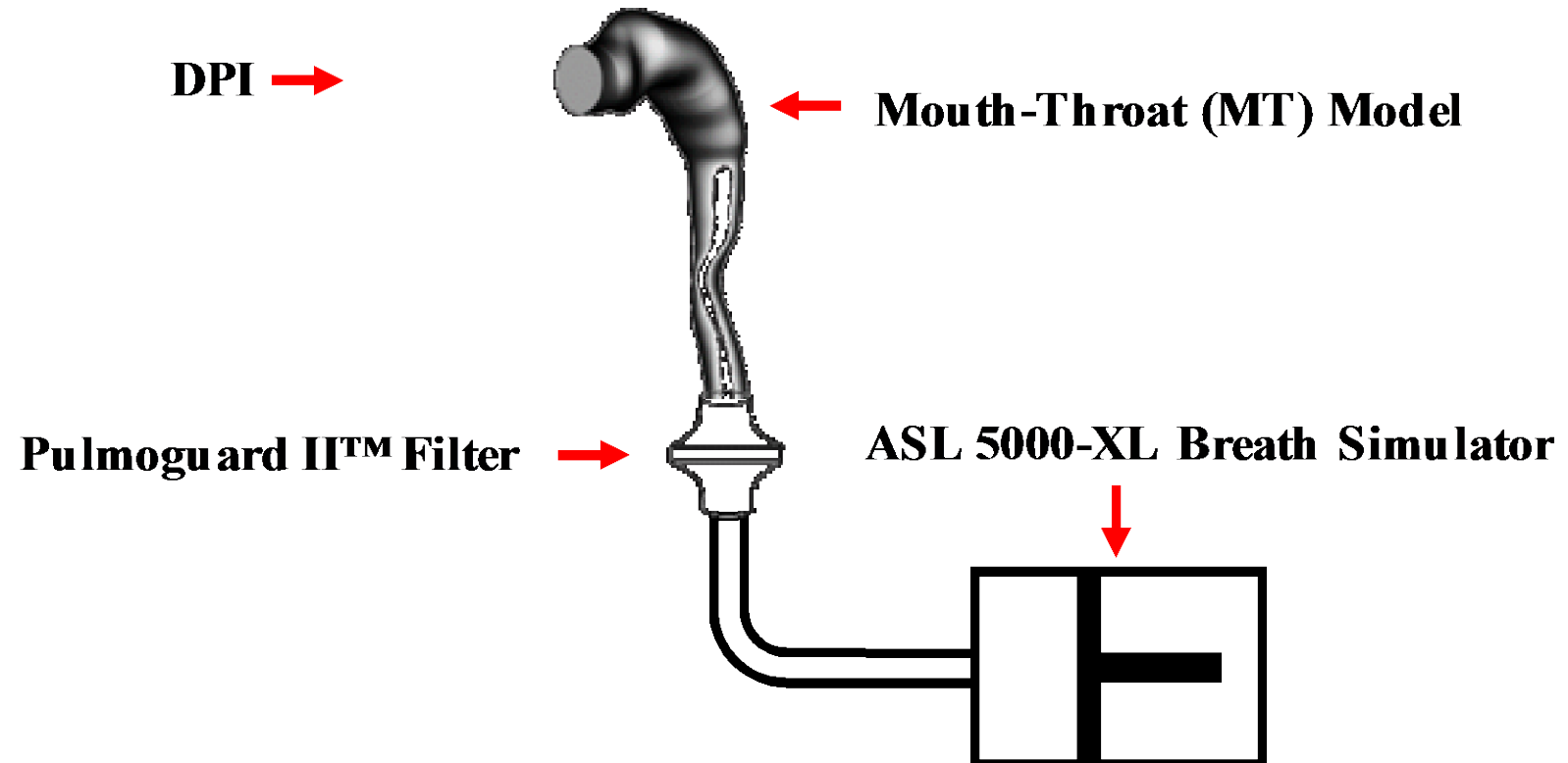
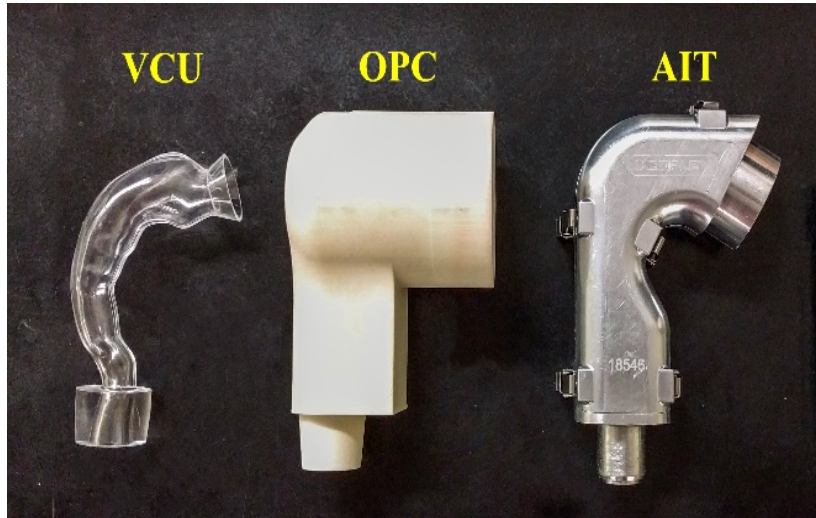
Relevant in vitro Studies

- Pulmonary Dose
 - Anatomical throats
- Regional Deposition
 - Standard USP ACI/NGI studies
 - Anatomical throats/cascade impactor studies
- Absorption Rates
 - Dissolution Rates

Relevant in vitro Studies

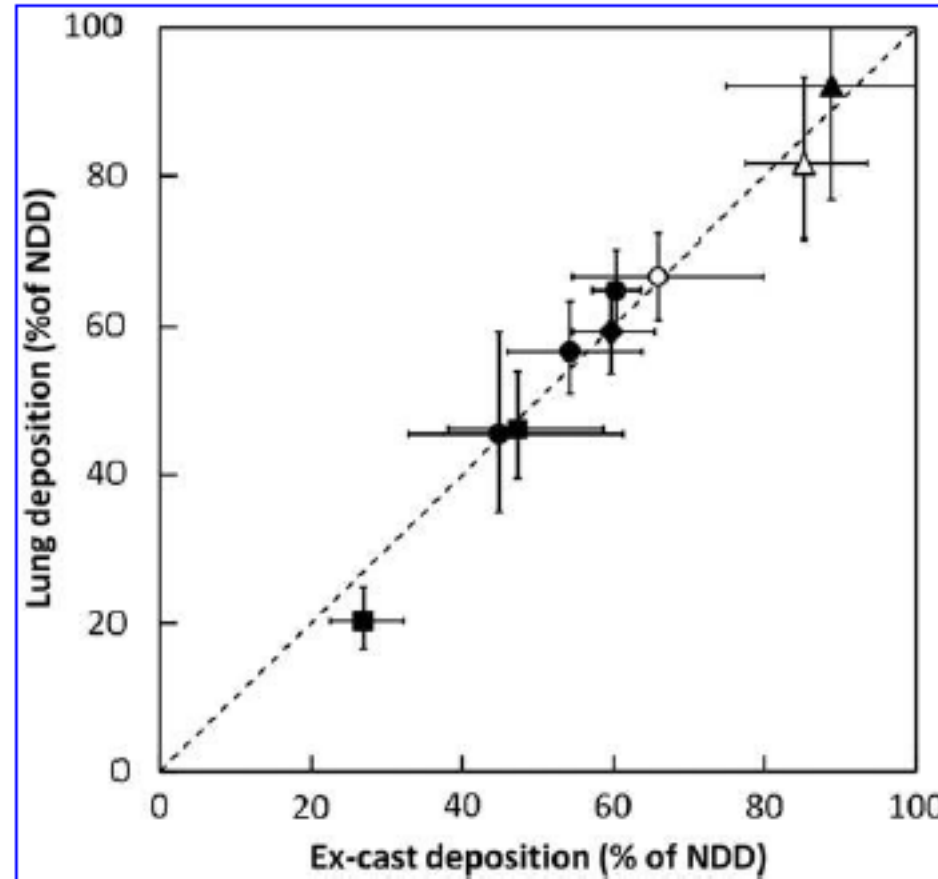
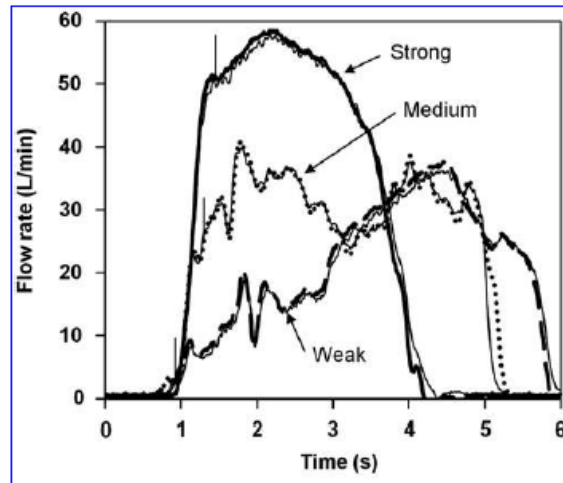
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Lung Dose: in vitro



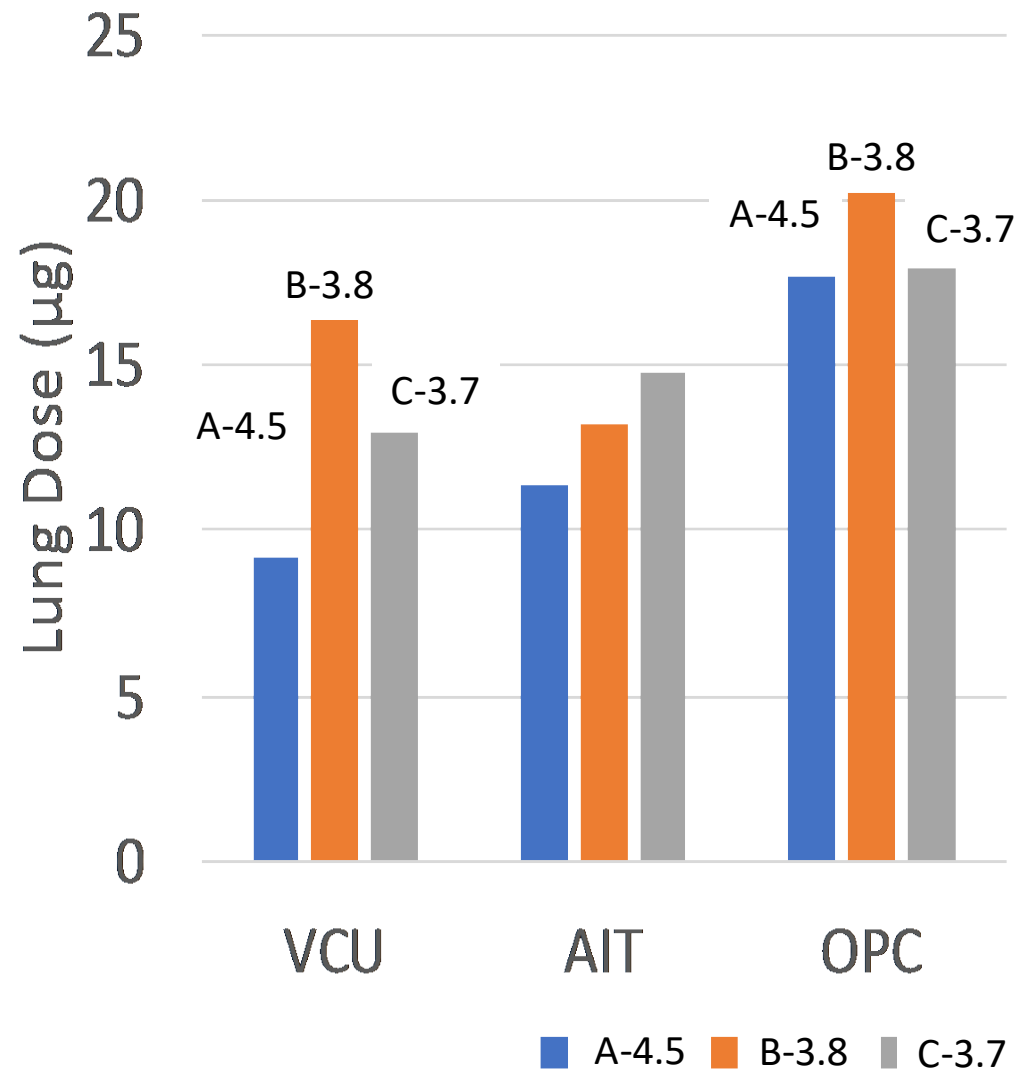
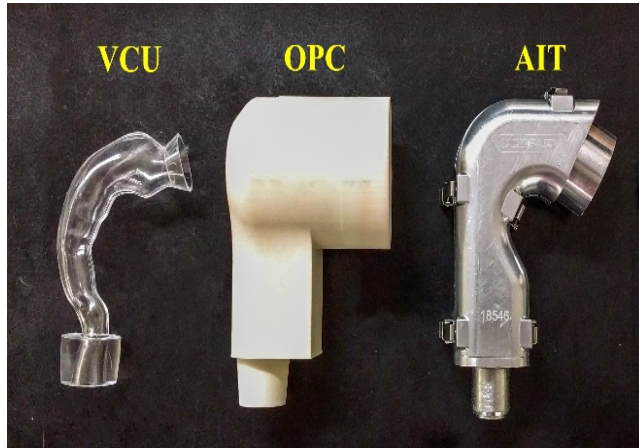
Lung deposition: in vitro/in vivo

Anatomical throat
Typical breathing pattern
ex-throat dose (filter or NGI)



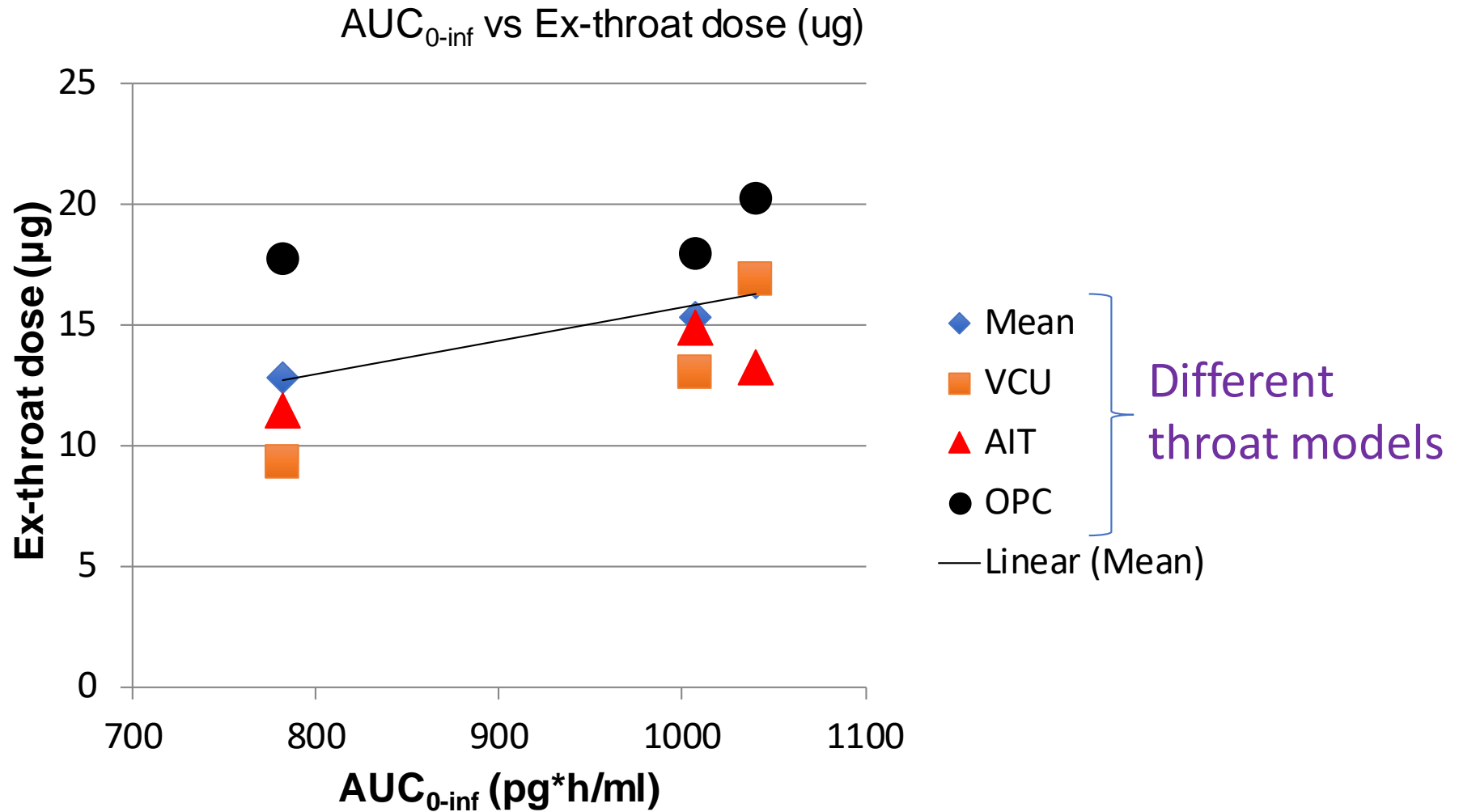
Further validation necessary

Comparison of 3 Throats



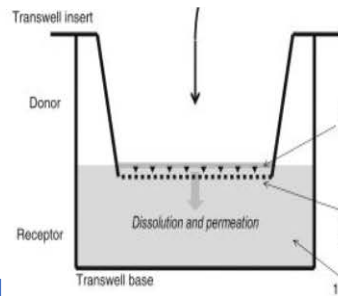
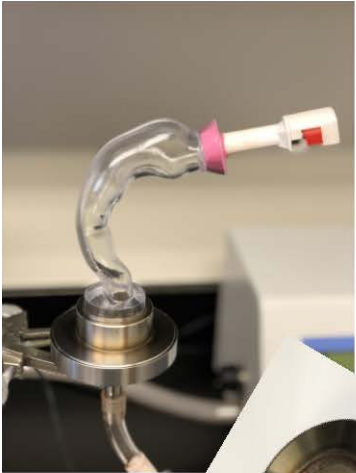
LD differs
Rank order differs

In vitro/ in vivo Correlations

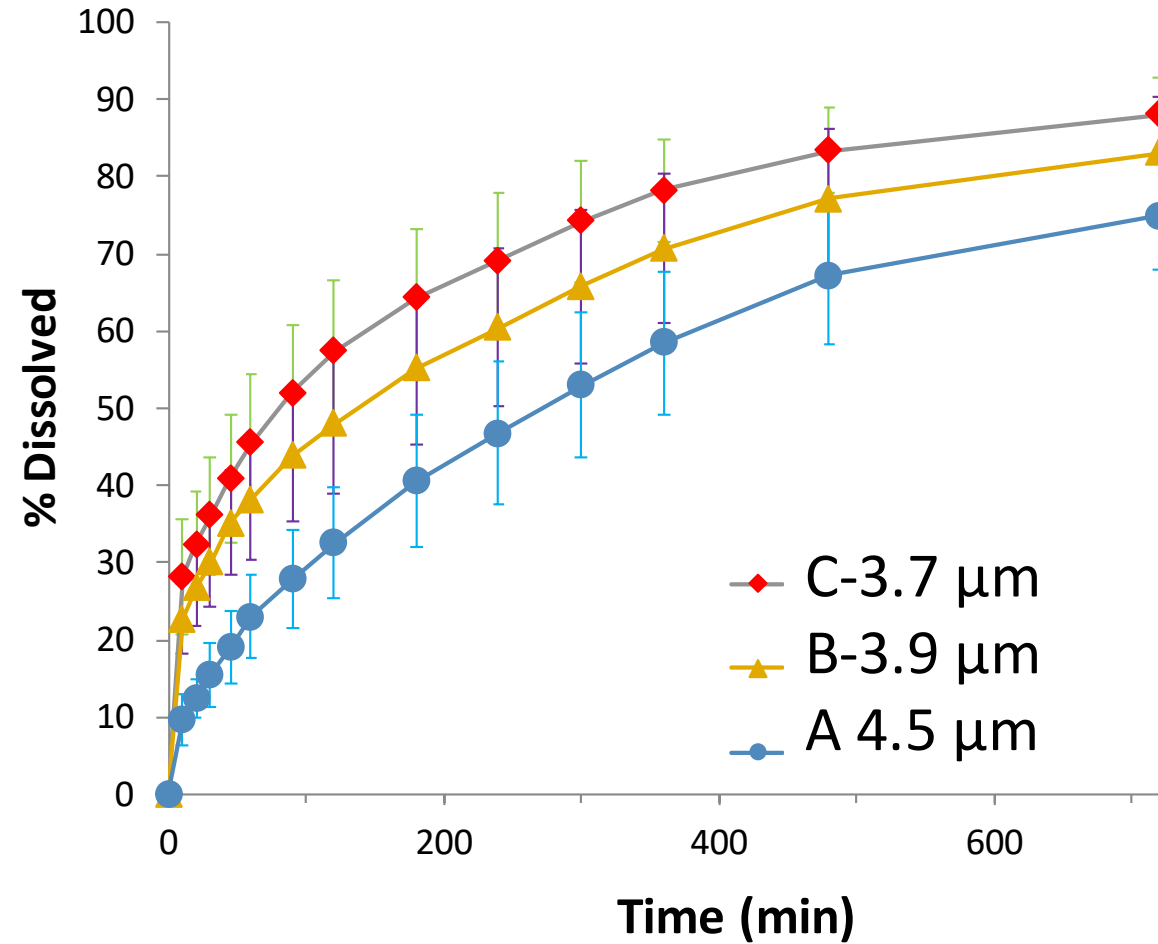


Dissolution

In vitro methods: Dissolution rate and in vivo absorption rates

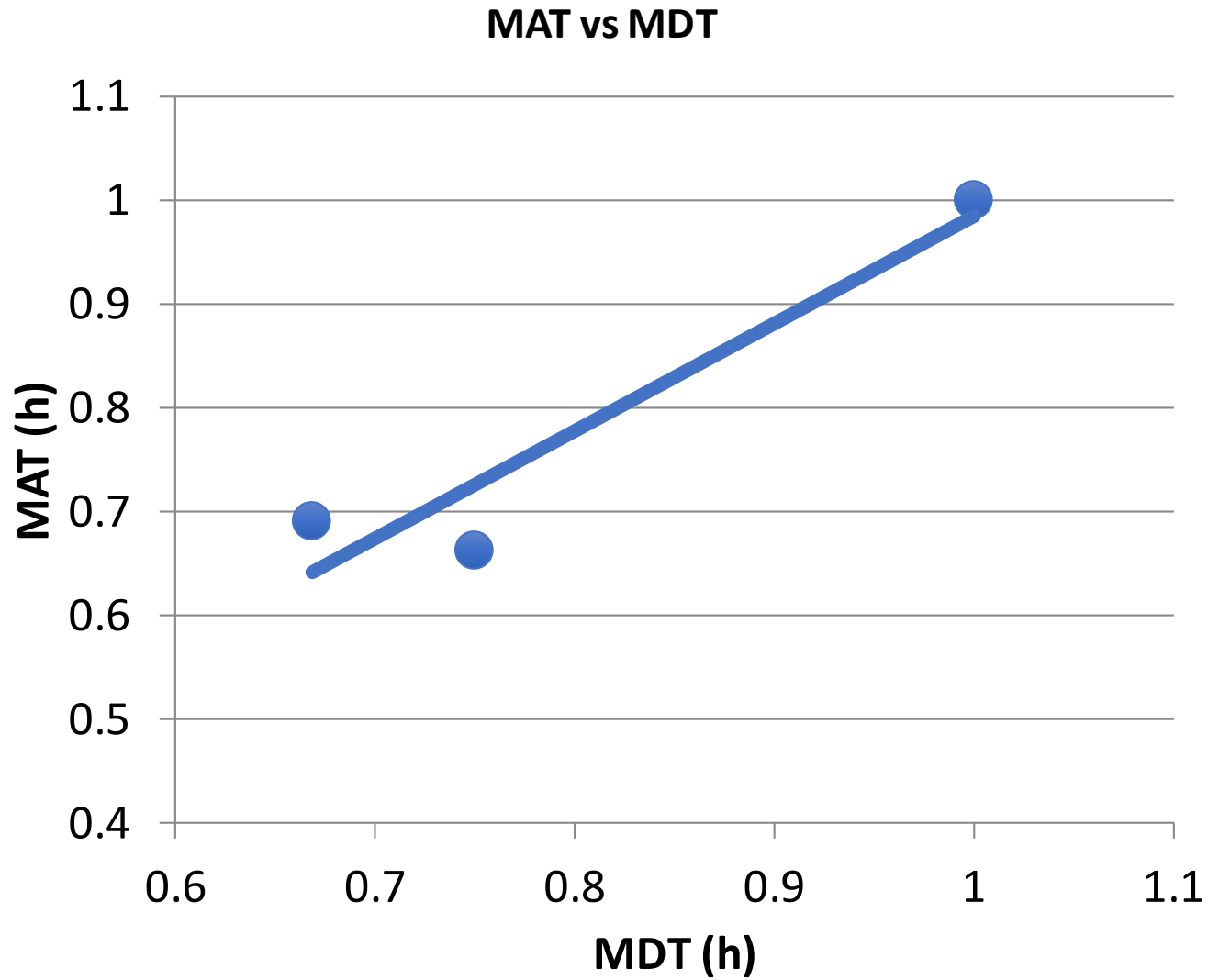


Arora, D., (2010)

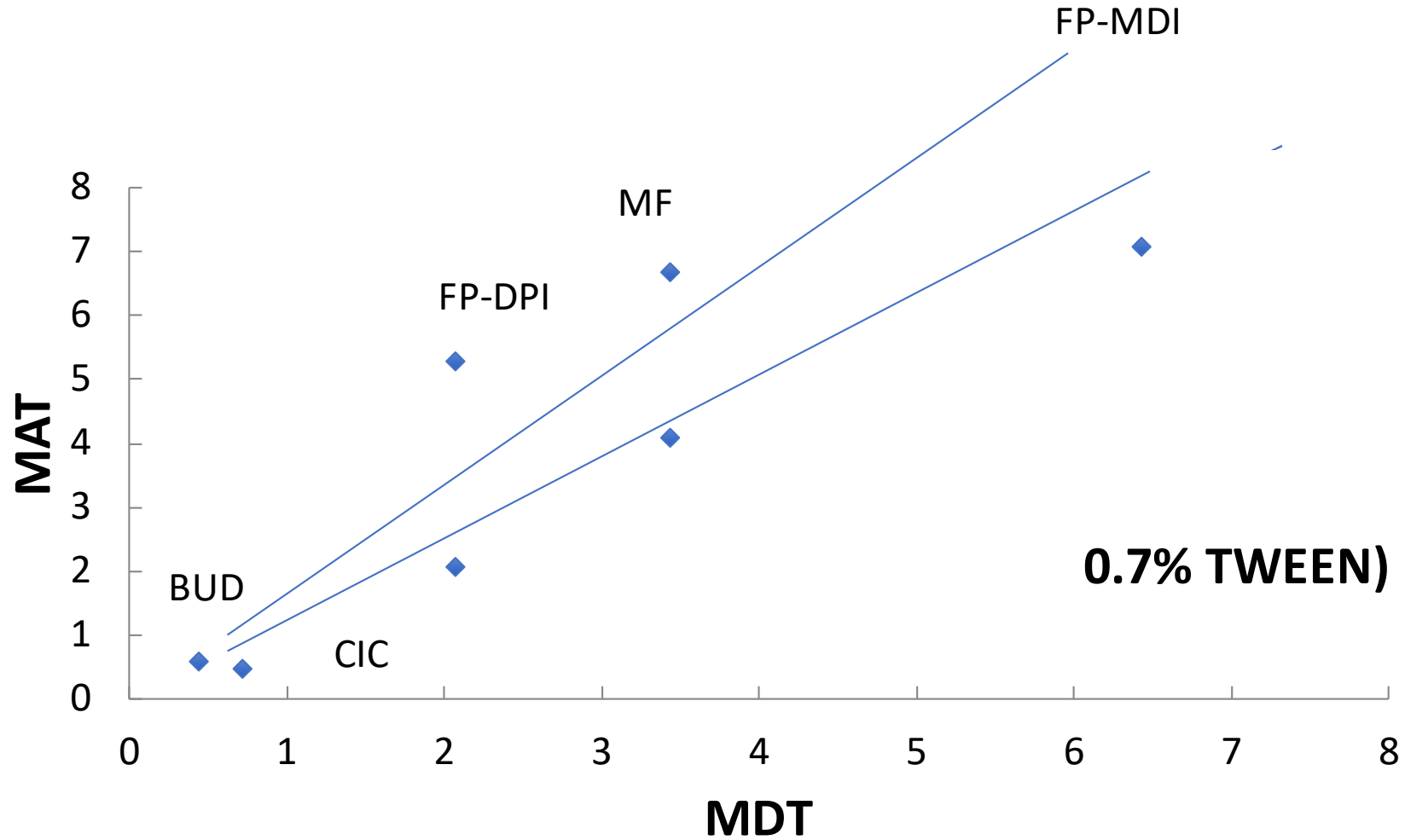


Formulation	Parameter	Value
A-4.5 μm	MDT	15.4 hrs
B-3.9 μm	MDT	13.3 hrs
C-3.7 μm	MDT	10.3 hrs

MAT (PK) vs MDT



Correlation between MDT and MAT

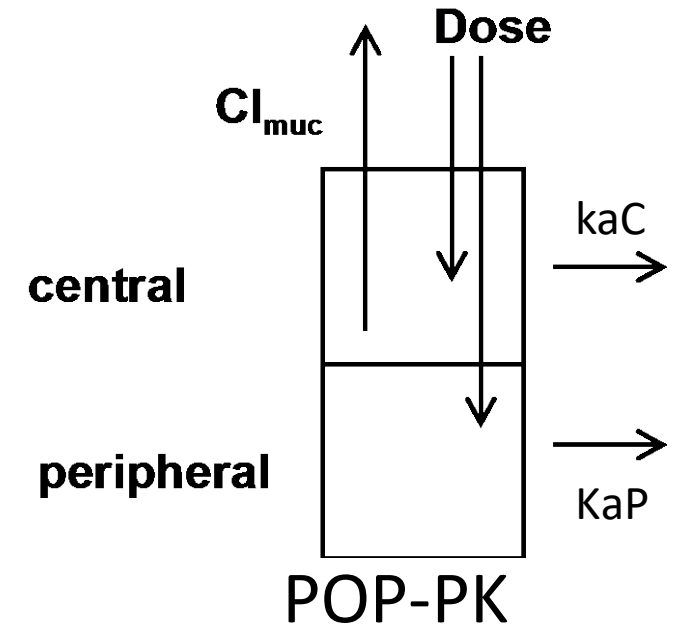


Correlation between MDT and MAT seems to exist

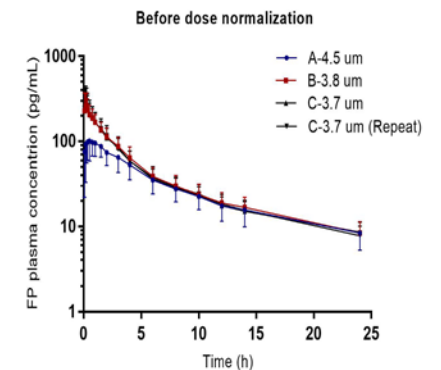
Regional Deposition

- NGI/Preludium
- CFD

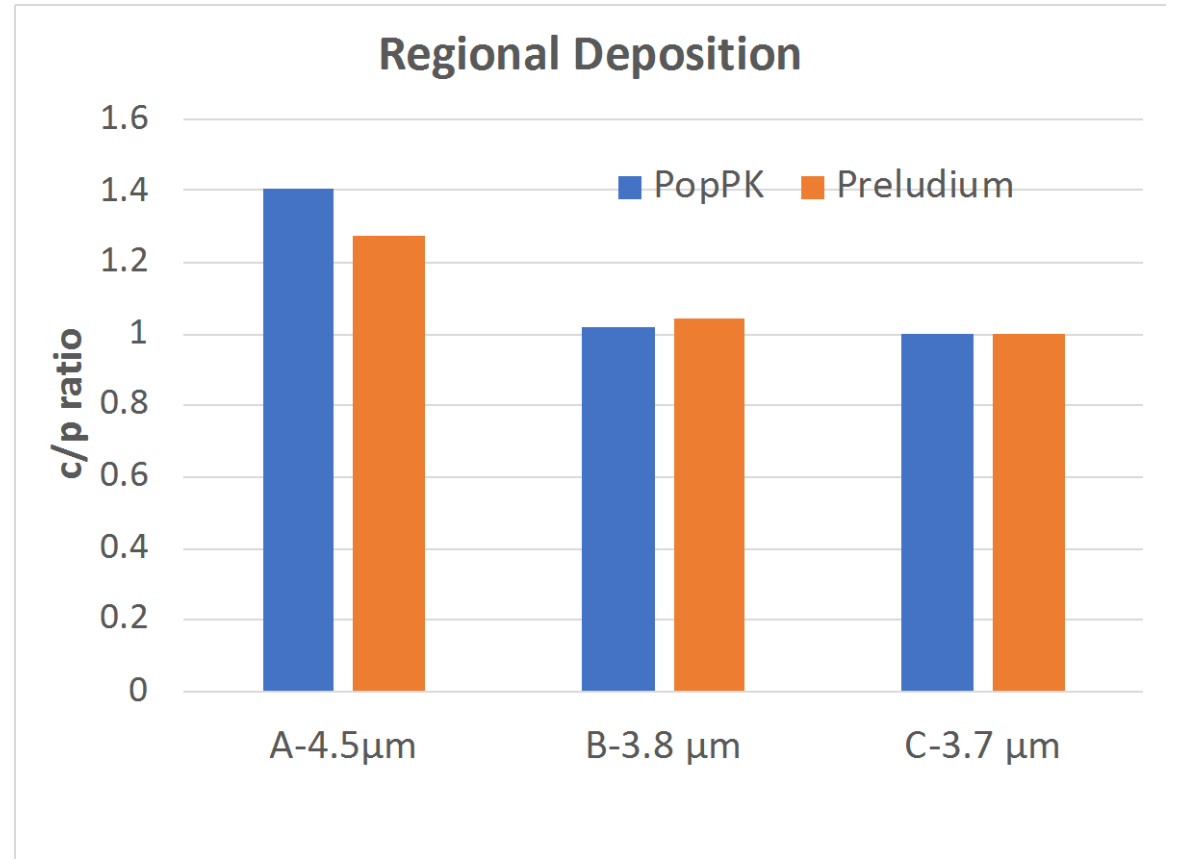
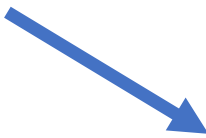
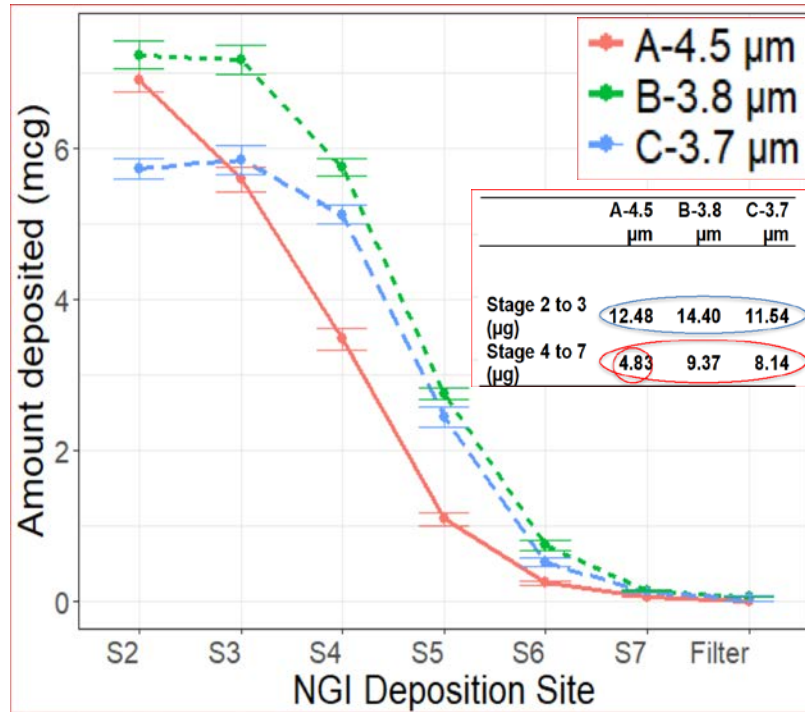
- Scintigraphy
- PK



	c/p	KaC h ⁻¹	kaP h ⁻¹
A-4.5	0.84	0.065	0.52
B-3.8	0.60	0.082	1.1
C-3.7	0.59	0.084	1.11



Relationship between NGI based c/p ratios (using NCRP) with popPK based estimates.



Is C_{max} sensitive to c/p ratio?

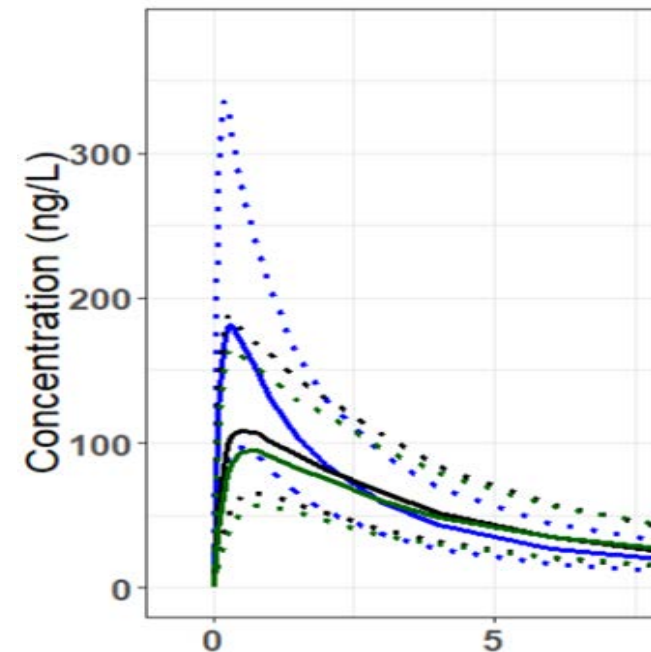
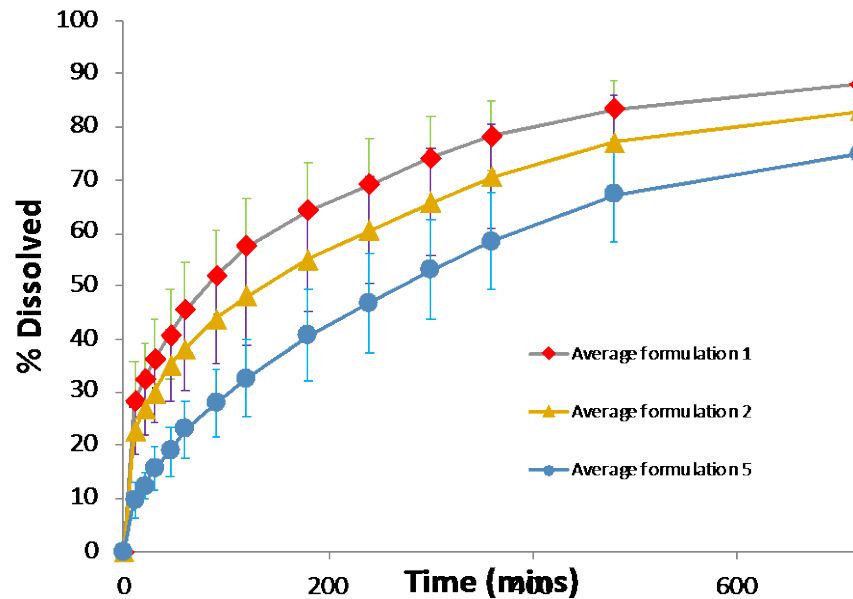
Differences in Dissolution Rate

	MDT (h)	Relative surface area
A-4.5 μm	19.2	0.5
C-3.7 μm	13.4	1

Integrate
in PBPK Model
Nernst-Brunner
Ficks Law

C_{max} , if only
dissolution differs

C_{max} ratio	Predicted	Measured
C/A	1.15	1.8



Summary

- In vitro method can provide information
 - Lung Dose
 - Dissolution
 - C/p
- PK is sensitive to: Dose, absorption rate, regional deposition
 - More work is necessary
- PK + in vitro provides "sufficient" detail on pulmonary fate of lipophilic corticosteroid (FP)

Study teams



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