GastroPlus User Group Webinar
27th October 2021

PBPK Modeling of Pulmonary Drug Absorption: Challenges & Perspective

[1]University of Belgrade-Faculty of Pharmacy, Department of Pharmaceutical Technology and Cosmetology

[2]The Control Laboratory of the Agency for Medicinal Products and Medical Devices of Bosnia and Herzegovina

Sandra Cvijić[1]
Jelisaveta Ignjatović[1]
Amar Elezović[2]

Outline

- **Background** – PBPK modeling for orally inhaled drug products (OIDPs)

- **Case studies**

- Particles regional deposition
- Drug solubility
- Mucoadhesion/prolonged retention time in the lungs
- Dissolution rate

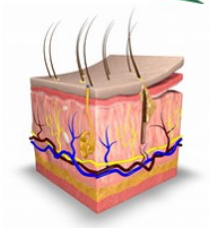
- **Remarks on PBPK modeling**

- Advantages
- Limitations/Future opportunities

Background

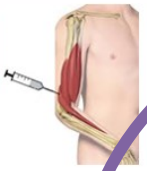
- Solutions, suspensions
- Lotions/gels
- Creams
- Ointments/pastes
- CR transdermal patches
- Subqutaneous IR/CR injections

TCAT™



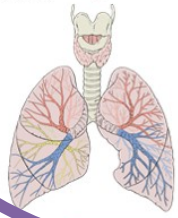
- IR/CR injections

Intramuscular model



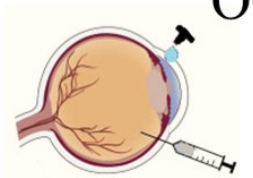
- Nasal solutions/powders
- Pulmonary solutions/powders
- Pulmonary infusion solutions/powders
- Intratracheal solutions/powders

PCAT™



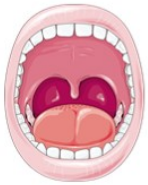
- Topical: eye drops/ointments
- Intravitreal: IR injections, CR implants
- Subconjuctival: CR implants

OCAT™



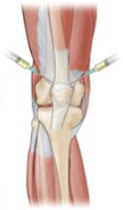
- Intraoral solutions/tablets
- Sublingual solutions/tablets
- Lingual sprays
- CR buccal patches

OCCAT™



Intraarticular model

- IR/CR injections



Additional dosage routes in GastroPlus™

Cvijić et al., 2021; doi: 10.5937/arhfarm71-32479

Background

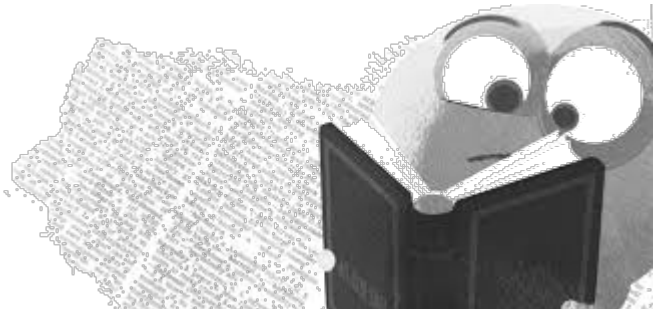
- Chaudhuri & Lukacova 2010. www.ondrugdelivery.com
- Wu et al. 2013, doi:10.4172/2329-9053.1000106
- Wu et al. 2016, doi: 10.1016/j.ijpharm.2016.08.064
- Backman et al. 2016, doi: 10.1089/jamp.2016.1306
- Salar-Behzadi et al. 2017, doi:10.1016/j.ijpharm.2017.08.124
- Vulović et al, 2018, doi: 10.1016/j.ejps.2017.10.022
- Zhang et al. 2018, doi: 10.1080/1062936X.2018.1518928
- Radivojev et al. 2019, doi: 10.1016/j.jddst.2019.05.047
- Idkaidek et al. 2020, doi: 10.1055/a-1325-0248
- Shi et al. 2021, doi: 10.1016/j.ajps.2020.12.001*
- Radivojev et al. 2021, doi:10.1016/j.ijpharm.2021.120893
- Miller et al. 2021, doi: 10.1007/s40262-021-01066-2

- Boger et al. 2016, doi:10.1002/psp4.12074**
- Boger and Wigstrom, 2018, doi:10.1002/psp4.12344
- Kannan et al. 2018, doi: 10.1002/cnm.2955
- Boger and Friden, 2019, doi:10.1089/jamp.2017.1436**
- Hassoun et al. 2019, doi: 10.1021/acs.molpharmaceut.8b01200
- Himstedt et al. 2020, doi: :10.3390/pharmaceutics12050408**
- Ruzycki et al. 2020, doi: 10.1007/s11095-020-02924-7

Literature

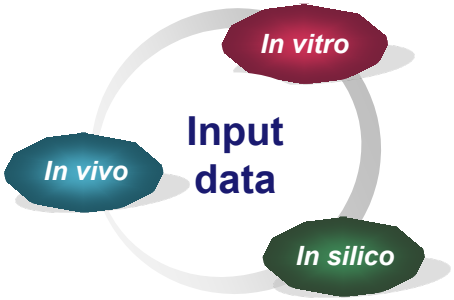
- Borghardt et al. 2015, doi: 10.1208/s12248-015-9760-6
- Backman et al. 2018, doi: 10.1016/j.ejps.2017.10.030

* rat physiology
** rat and human physiology



Background

Modeling strategy



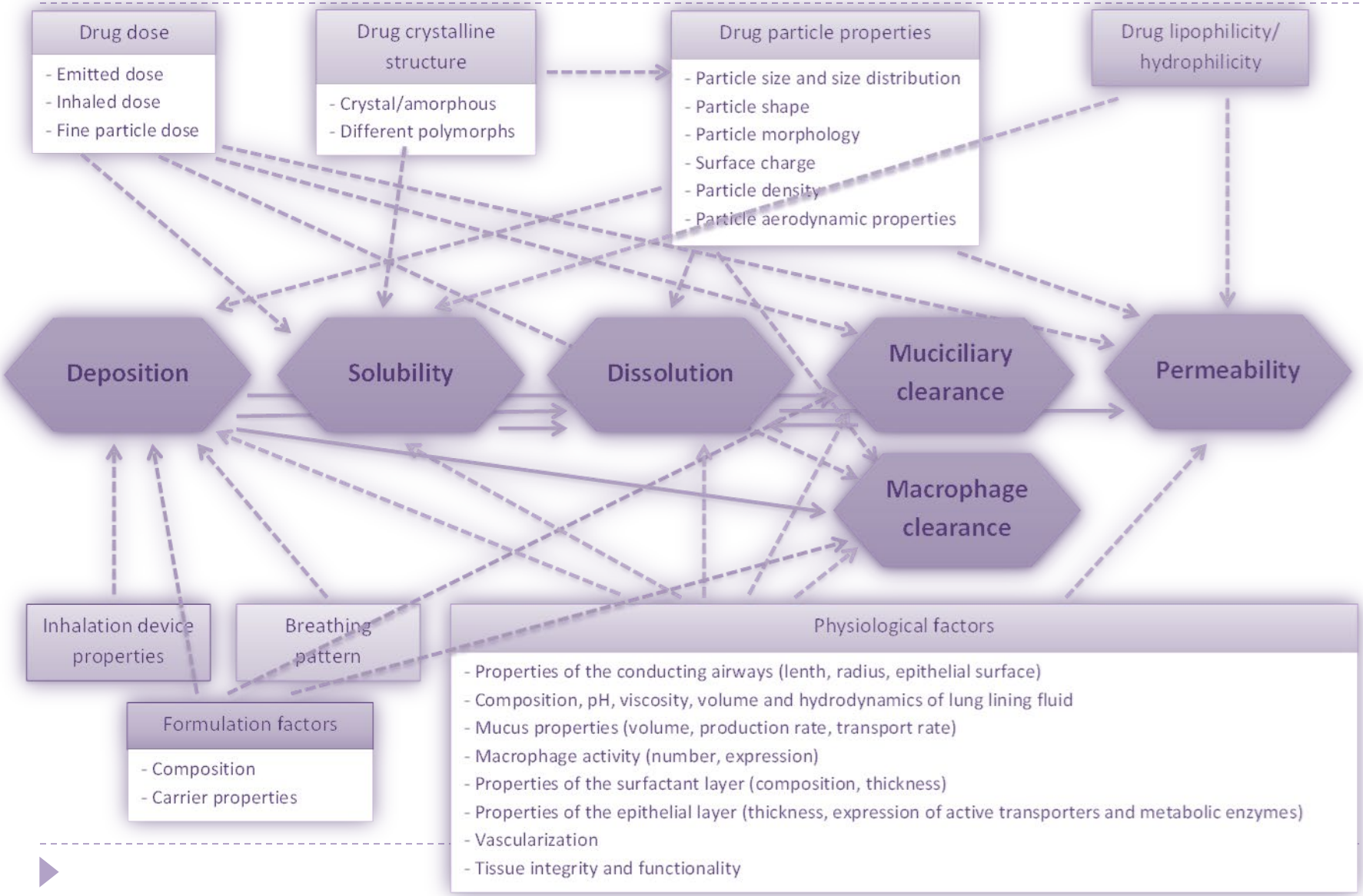
Model construction

- Data collection
- Parameters optimization
- Model validation

Model exploration

- Mechanistic interpretation of drug absorption pattern etc.
- Parameter sensitivity analysis
- Assessment of disease- and patient/population-related effects
- PK outcomes for different dosage forms/dosing regiments
- Virtual bioequivalence trials
- Guidance on formulation strategy
- Generation of data for regulatory applications

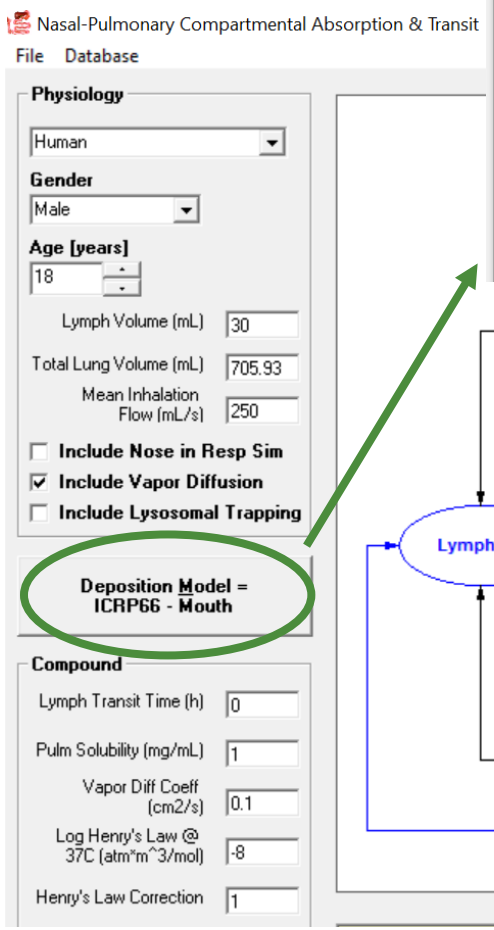
Background

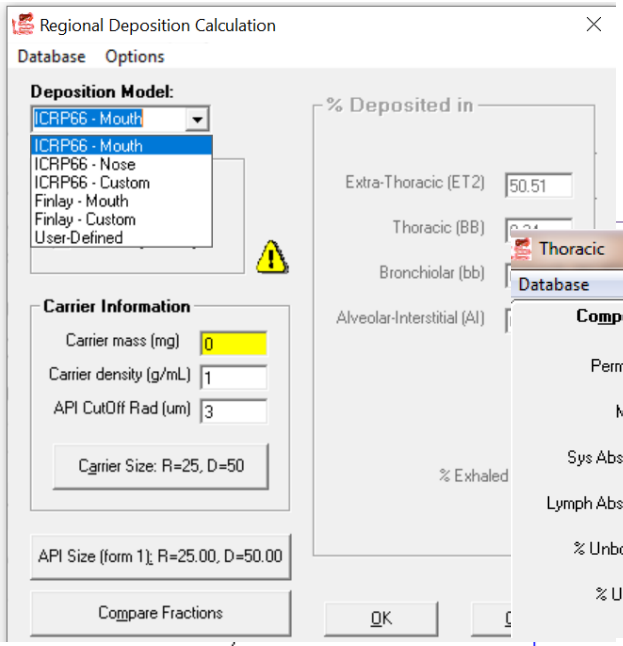


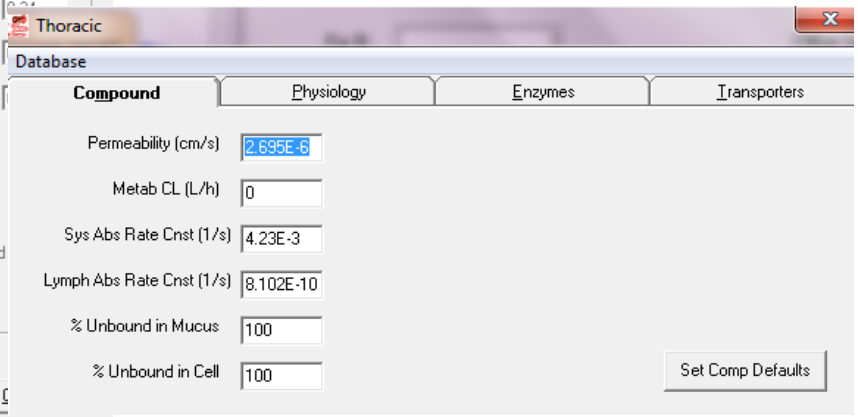
Velaga et al., 2018; doi: 10.1016/j.ejps.2017.09.002

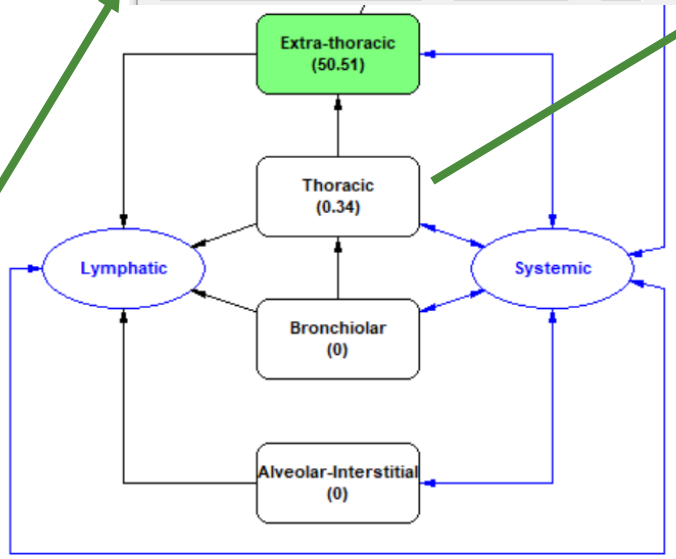
Background

- PCAT™ mode





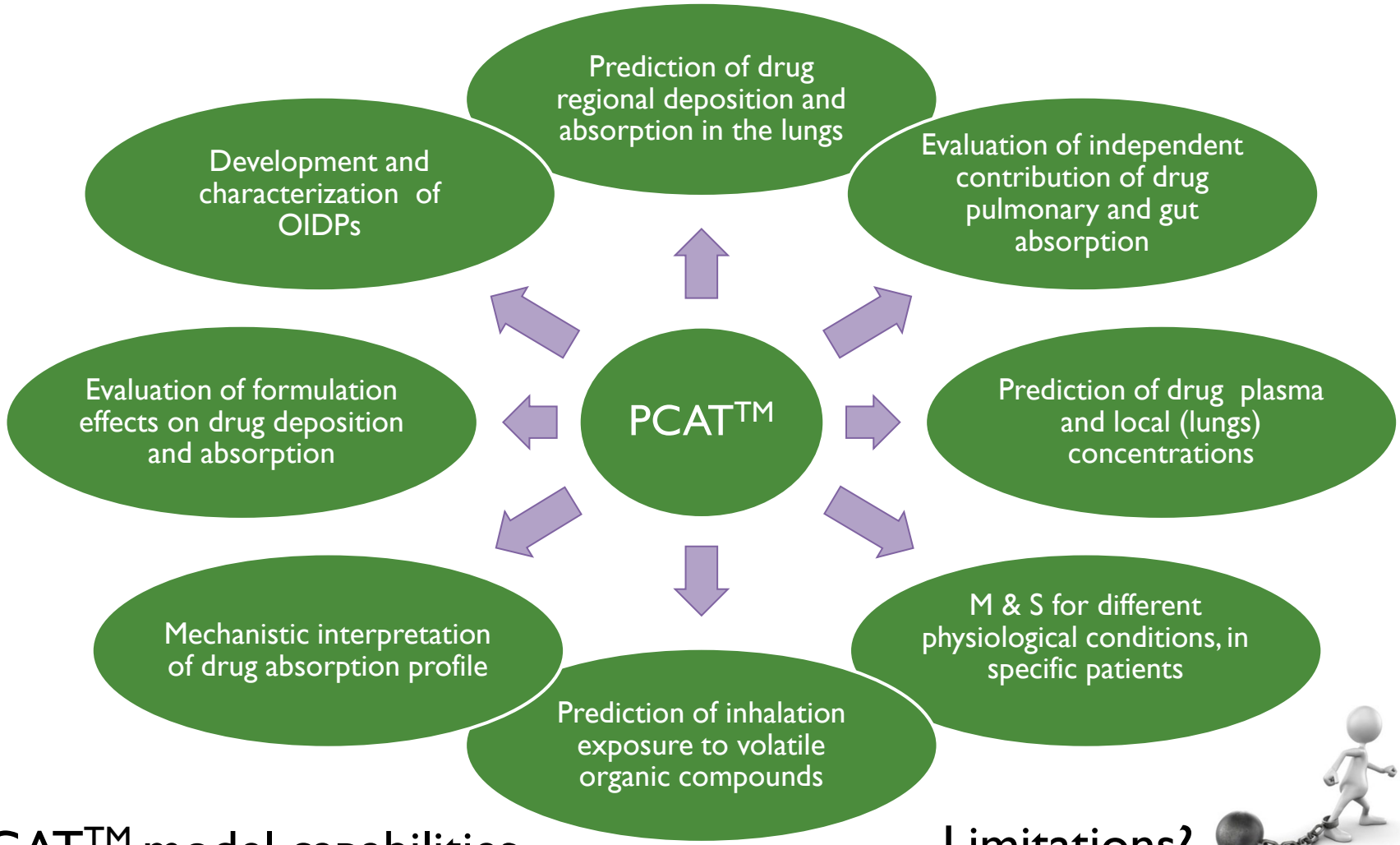




- **Input data - Physiology**
- Lung physiological parameters
- Deposition Model
- Mucociliary transit
- Dissolution/precipitation
- Absorption into pulmonary cells
- Non-specific binding
- Metabolism
- Transfer into the systemic circulation

https://www.youtube.com/watch?v=fnkbENLMGuY&t=458s

Background



PCAT™ model capabilities

Limitations?

Case study 1

- **Amiloride hydrochloride**
- Aerosolized amiloride improves mucociliary clearance in patients with cystic fibrosis
- Oral administration of amiloride does not provide effective concentration on the respiratory apical membrane, in contrast to the pulmonary drug delivery

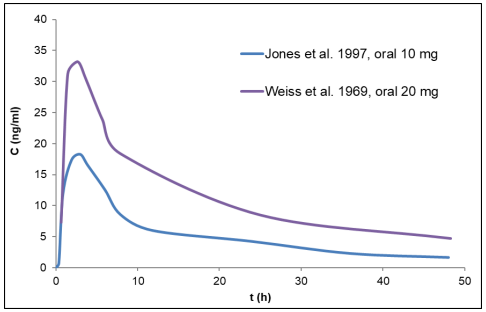
→ Important to understand disposition and concentration-time profile of aerosolized amiloride

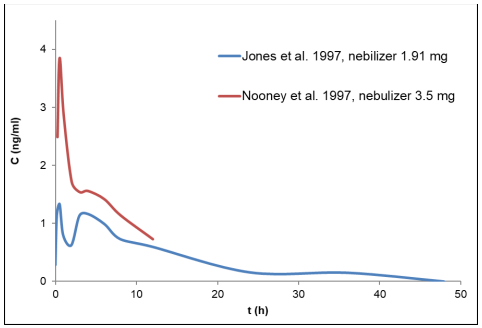
- Development and validation of amiloride-specific whole-body PBPK model for oral drug delivery
- Development and validation of the drug-specific model for pulmonary drug delivery (nebulized solution)
- Simulations of pulmonary drug delivery (model DPI formulations with amiloride)
- Assessment of the influence of formulation properties on the simulation outcomes

Vulovic et al, doi:10.1016/j.ejps.2017.10.022

Case study 1

- **Amiloride hydrochloride**
- BCS Class I/III drug
- pK_a 8.7 (weak base)
- Highly soluble (aqueous solubility 5.2 mg/ml)
- Poorly/highly permeable ($logP_{o/w}$ -0.3; P_{eff} 1.6 x 10^{-4} cm/s)
- Oral bioavailability about 50% (15-90%)
- Not metabolized in the liver
- Excreted unchanged in urine (via tubular secretion)





- After inhalation, amiloride enters the systemic circulation in two phases: quickly via the respiratory tract, and more slowly following oropharyngeal deposition, swallowing and GI absorption → double peak
- Amiloride is not metabolized by the airway epithelium

Vulovic et al, doi:10.1016/j.ejps.2017.10.022

Case study 1

Parameter	Value
Molecular weight	229.63 g/mol[a]
logD (pH 7.4)	-0.86[a]
pK_a	8.7[a]
Solubility (aq)	5.2 mg/mL[a]
Human jejunal permeability	1.6 x 10^{-4} cm/s[a]
Diffusion coefficient	8.864 x 10^{-6} cm^2/s[b]
Drug dose	10 mg; 20 mg; 1.91 mg; 3.5 mg[a]
Dose volume	250 mL[c]
Mean precipitation time	900 s[c]
Effective particle radius	25 µm[c]; 4 µm[a]; 4.88 µm[a]
Drug particle density	1.2 g/mL[c]
Blood/plasma concentration ratio	1[c]
Unbound percent in plasma	60%[a]
Body weight	70 kg
Renal clearance	25 L/h[d]
Unbound percent in enterocytes	5%[d]
Whole body PBPK model; optimized Kp values (multiplied by 3.5 scaling factor)	

[a]Literature values; [b]GastroPlus™ predicted; [c]GastroPlus™ default values; [d]Optimized values

GastroPlus™ software, ver. 9.0

Vulovic et al, doi:10.1016/j.ejps.2017.10.022

Case study 1

Model building – oral administration

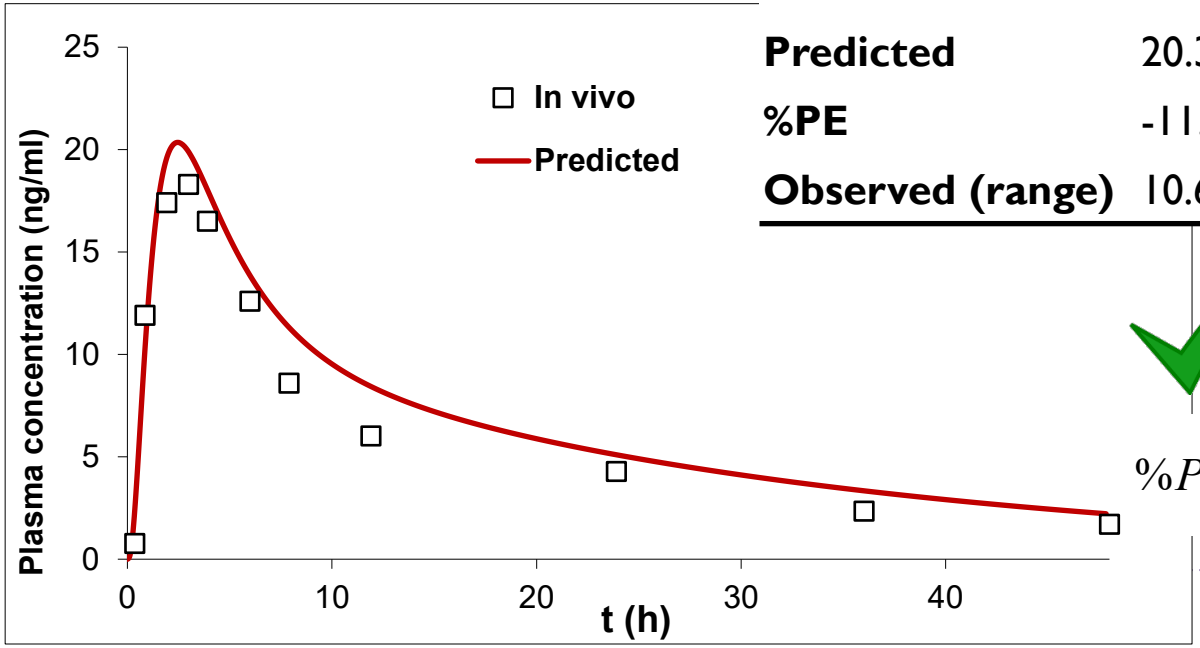
Oral (IR) solution 10 mg amiloride (Jones et al, Pharmacotherapy 1997;17(2):263-270)

Fasted state physiology (default values)

Drug-specific whole body PBPK model

- V_{ss} = 577.97 L (literature: 350 -
- $t_{1/2}$ = 16.021 h (literature: 15.3

Parameter	C_{max} (ng/ml)	t_{max} (h)	$AUC_{0-\infty}$ (ng h/ml)
Observed mean	18.30	2.99	323.64
Predicted	20.35	2.44	380.80
%PE	-11.20	18.39	-17.66
Observed (range)	10.6-30.6	2.0-4.4	160.0-390.0



$$\%PE = \frac{observed - predicted}{observed} \times 100$$

Vulovic et al, doi:10.1016/j.ejps.2017.10.022

Case study 1

Model building – pulmonary administration

Nebulizer solution 1.91 mg (ED) amiloride (Jones et al, Pharmacotherapy 1997;17(2):263-270)

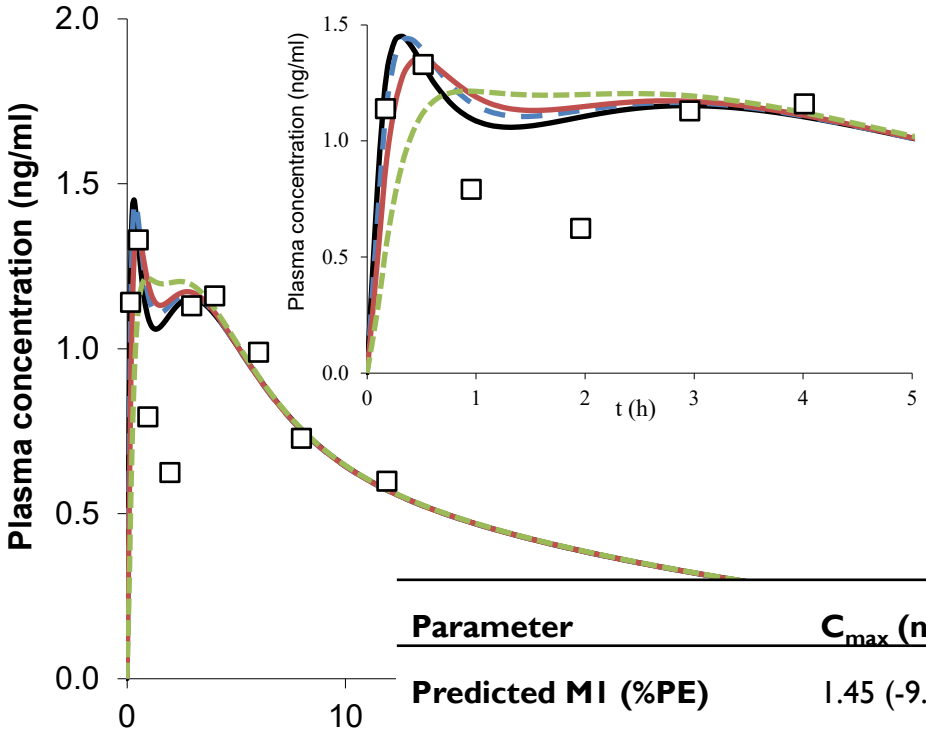
- Dosage form: PL Soln
- Particle size: 4 µm (MMAD)

Additional Dosage Routes/Nasal-Pulmonary

- Nasal Pulmonary Physiology (gender, age, lymph volume, total lung volume): default
- Deposition Model: ICRP66 Mouth; 100% swallowed from the extra-thoracic region
- **Gastric residence time: 0.25 h → 1 h**
- Compound (lymph transit time, pulm solubility (at pH 6.9)): GastroPlus default/predicted

Vulovic et al, doi:10.1016/j.ejps.2017.10.022

Case study 1



M1: Ka(p)=8.42 × 10^{-3} 1/s

M2: Ka(p) reduced by 25%

M3: Ka(p) reduced by 50%

M4: Ka(p) reduced by 75%

Parameter	C_{max} (ng/ml)	t_{max} (h)	$AUC_{0-\infty}$ (ng h/ml)
Predicted M1 (%PE)	1.45 (-9.02)	0.32 (38.46)	25.79 (-46.45)
Predicted M2 (%PE)	1.44 (-8.27)	0.36 (30.77)	25.79 (-46.45)
Predicted M3 (%PE)	1.35 (-1.50)	0.48 (7.69)	25.79 (-46.45)
Predicted M4 (%PE)	1.21 (9.02)	0.9 (-73.08)	25.79 (-46.45)
In vivo mean[a]	1.33	0.52	17.61
In vivo range[e]	0.10-3.20	0.30-0.70	3.20-32.00

Vulovic et al, doi:10.1016/j.ejps.2017.10.022

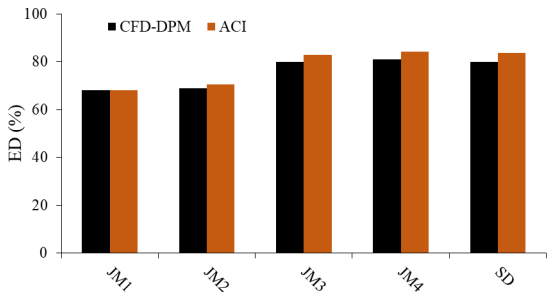
Case study 1

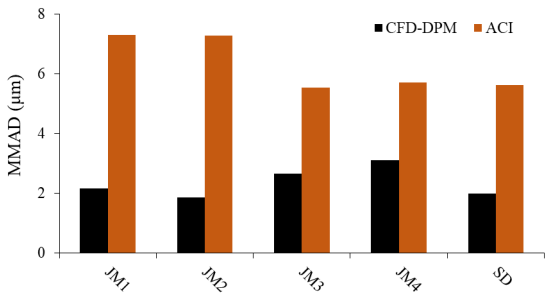
Model exploration

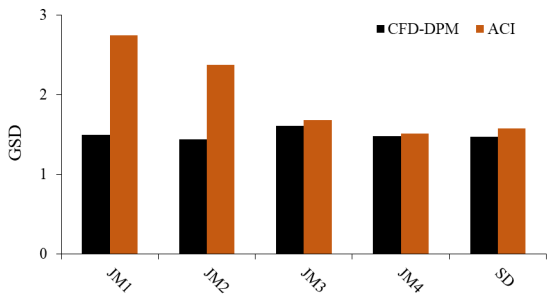
Amiloride dry powder for inhalation (DPI) (Djokic et al, Powder Technol. 2014;262:170-176)

- Jet-milled (JM) (process variables); Spray-dried (SD); Airflow = 28.3 l/min

Sample	Density (g/cm³)	ED (%)		MMAD (μm)		GSD (μm)	
		CFD-DPM	ACI	CFD-DPM	ACI	CFD-DPM	ACI
JM1	1.67	68.00	68.15	2.17	7.30	1.50	2.74
JM2	1.68	69.00	70.54	1.86	7.27	1.44	2.37
JM3	1.72	80.00	82.97	2.65	5.53	1.61	1.68
JM4	1.73	81.00	84.23	3.10	5.71	1.48	1.51
SD	1.71	80.00	83.74	2.00	5.61	1.47	1.58

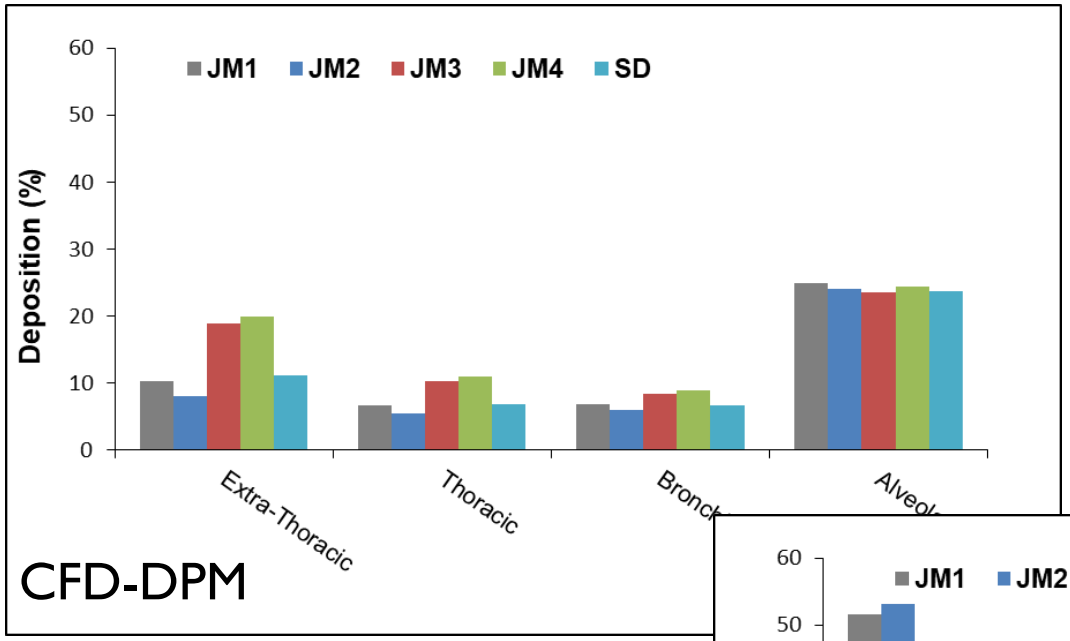




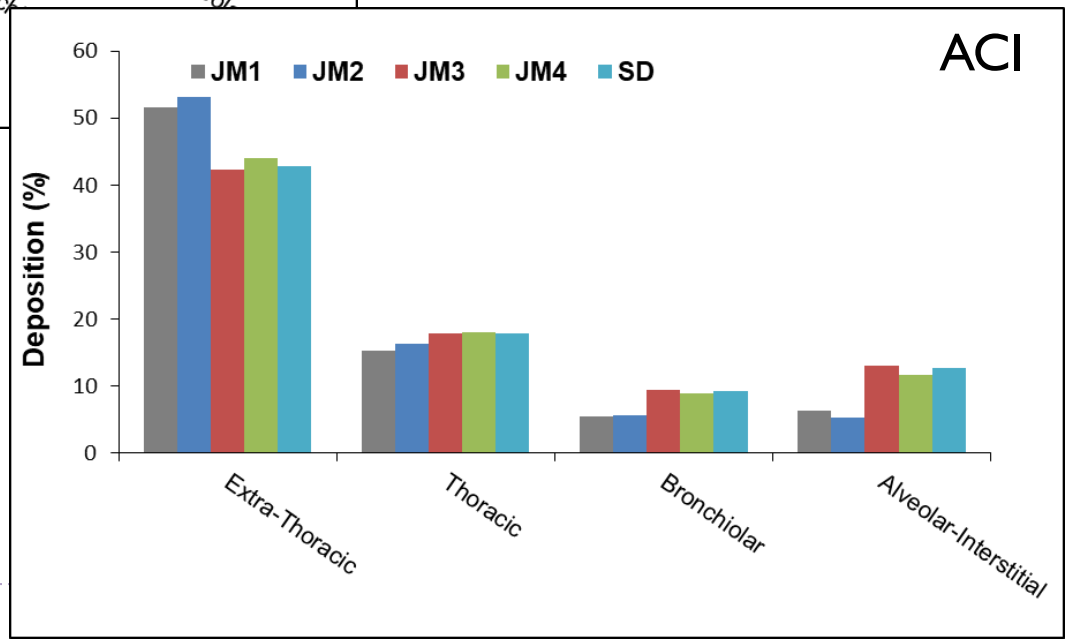


Vulovic et al, doi:10.1016/j.ejps.2017.10.022

Case study 1



- Potential of the combined CFD-PBPK approach to model inhaled drug bioperformance (?)



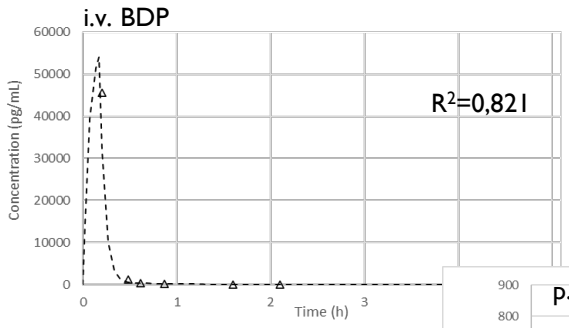
- (Bio)relevance of ACI data as inputs for PBPK modeling (?)

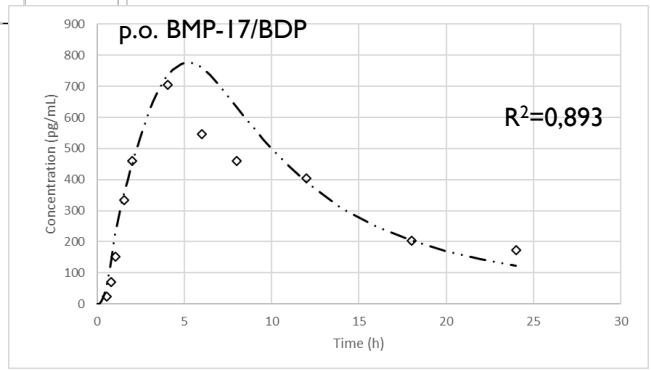
Case study 2

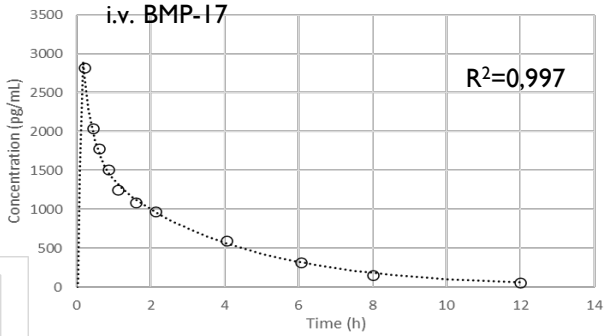
- **Atempts to assess particle size cut-off limits for PCAT™ modeling**

- **PBPK model for Beclomethasone dipropionate**
- i.v. model for BDP and BMP-17 and p.o. model for BMP-17/BDP "hybrid"

Daley-Yates at al. doi: 10.1046/j.0306-5251.2001.01374.x.







Elezovic et al, doi:10.1007/978-3-030-73909-6_74

Case study 2

	BDP	BMP
Mr (g/mol)	521.1[a]	465[a]
logP	1.3[b]	2.46[a]
pKa	-3.3(base) 13.85(acid)[a]	-3.3(base) 13.85(acid)[a]
Solubility (mg/mL @pH 7)	0.00208[b]	0.0457[d]
Diff.Coef. (cm^2/s $x10^{5)}$	0.75	0.6072
Vc (L/kg)	0.08[c]	3.725[c]
CL (L/h)	99.84[c]	136[c]
Dose (mg)	1000	892
f_{up} (%)	5[a]	
$t_{1/2}$ (h)	0.47	2.42
K_{12} (1/h)	0.741[c]	1.403[c]
K_{21} (1/h)	1.53[c]	1.997[c]

a – go.drugbank.com; b – pubchem.ncbi.nlm.nih.gov; c – PKPlus predicted (based on data from Daley-Yates at al. doi: 10.1046/j.0306-5251.2001.01374.x); d – Boobis doi: 10.1016/S0954-6111(98)90434-6

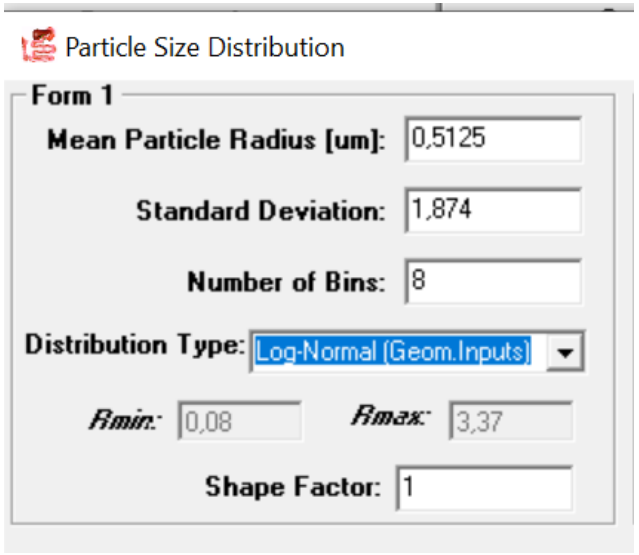
Case study 2

- Two pMDI products (P1 and P2) containing beclomethasone dipropionate
- Product specific parameters:

- Dose: declared dose ≠ <u>delivered dose</u> Initial Dose = Delivered dose

- Particle size: Mean Particle radius = ½ MMAD
  Standard Deviation = GSD

- Particle deposition ??



Elezovic et al, doi:10.1007/978-3-030-73909-6_74

Case study 2

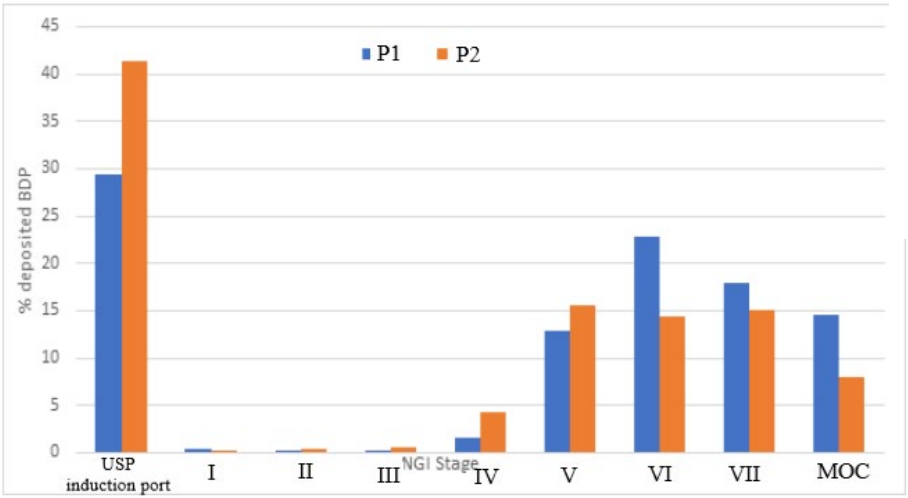
- PCAT™ integrated deposition models:

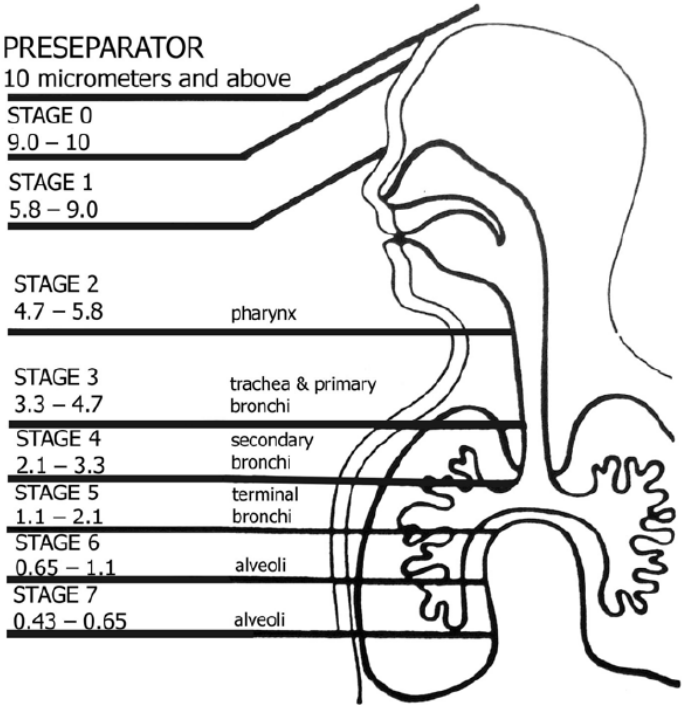
- ICRP66

- Finlay

- User defined

Aerodynamic assessment of fine particles:





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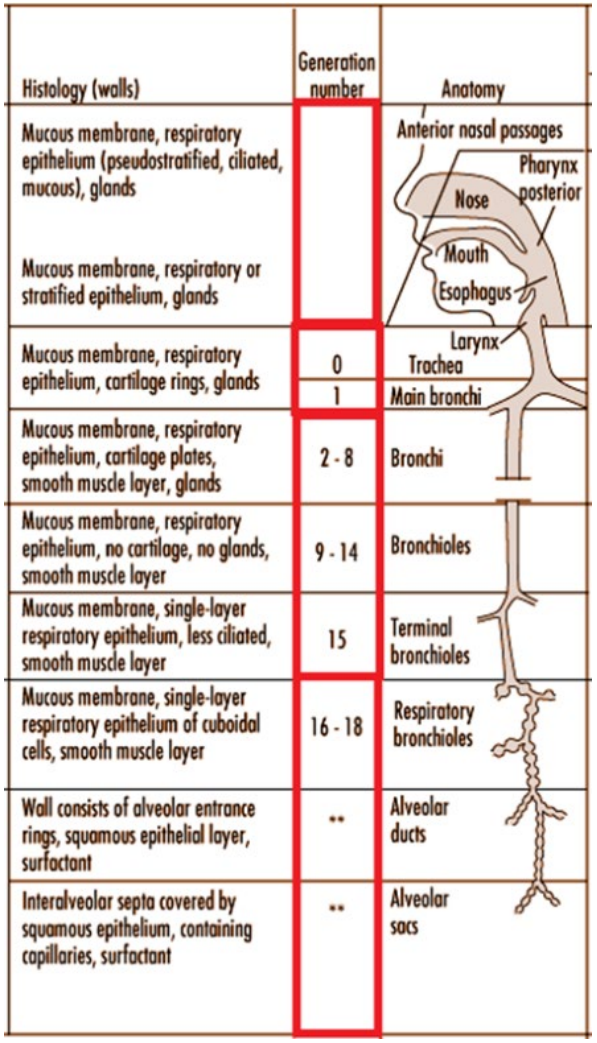
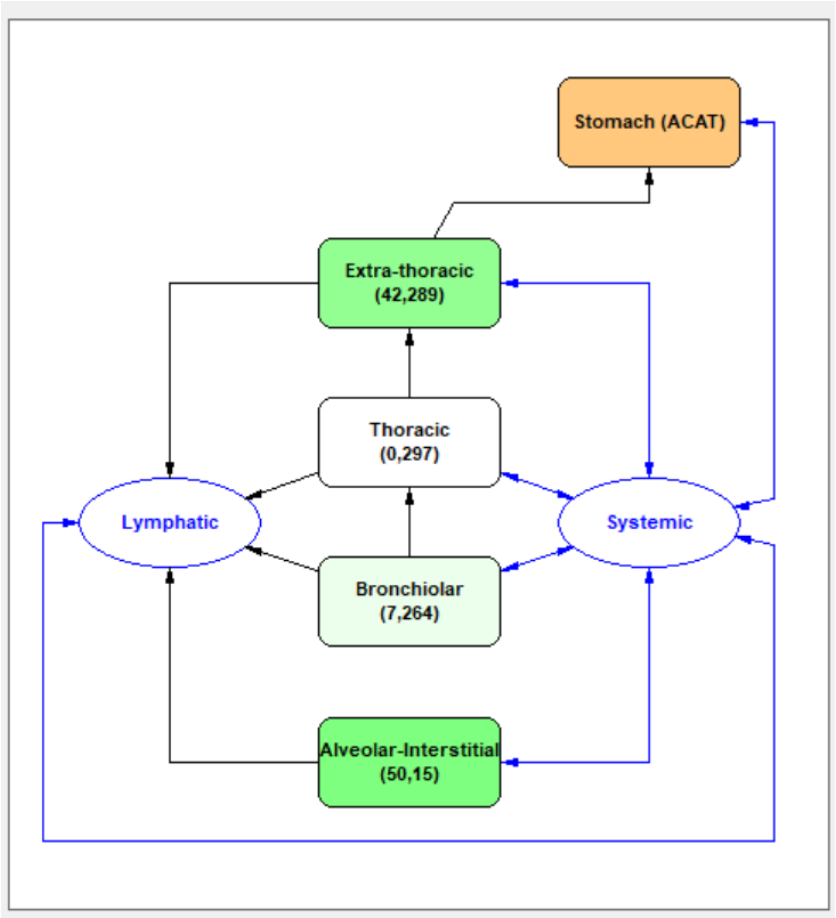
Case study 2





Elezovic et al, doi:10.1007/978-3-030-73909-6_74

Case study 2

- Aerodynamic particle size cut-off values for the regional lung deposition

Compartment	Aerodynamic particle size dimensions limit (µm)					
	-0.5	0	+0.5	+1	A1*	A2*
Alveolar-Interstitial (AI)	0 – 0.6	0 – 1.1	0 – 1.6	0 – 2.1	0 – 2	0 - 1
Bronchiolar (B)	0.6 – 3.2	1.1 – 3.7	1.6 – 4.2	2.1 – 4.7	2 – 4	1 – 3
Thoracic (T)	3.2 – 4.2	3.7 – 4.7	4.2 – 5.2	4.7 – 5.7	4 - 5	3 - 5
Extra-thoracic (ET)	4.2 - ∞	4.7 - ∞	5.2 - ∞	5.7 - ∞	5 - ∞	5 - ∞

* Mitchell & Nagel. doi: 10.14356/kona.2004010

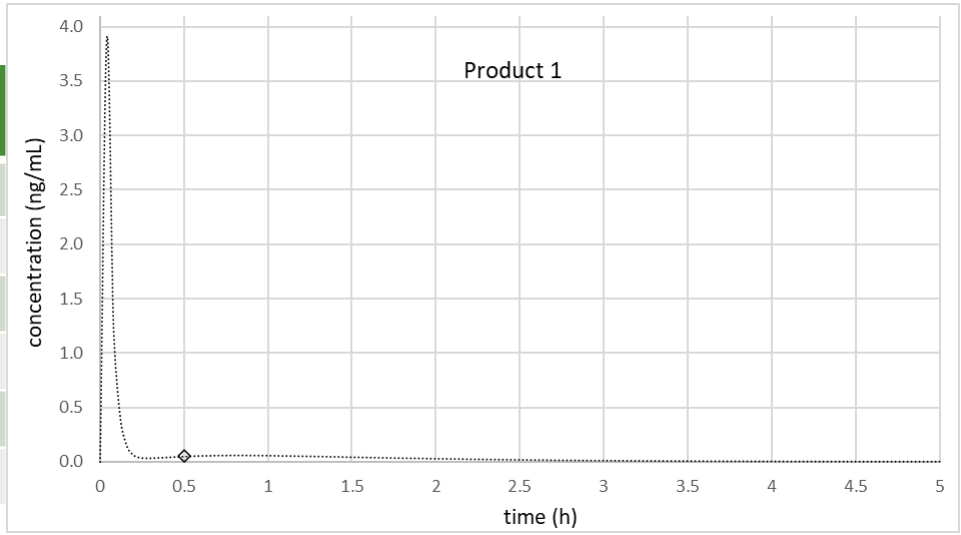
- Dose % calculated with Copley Inhaler Testing Data Analysis Software (CITDAS) v. 3.10 (Copley Scientific, Nottingham, UK)

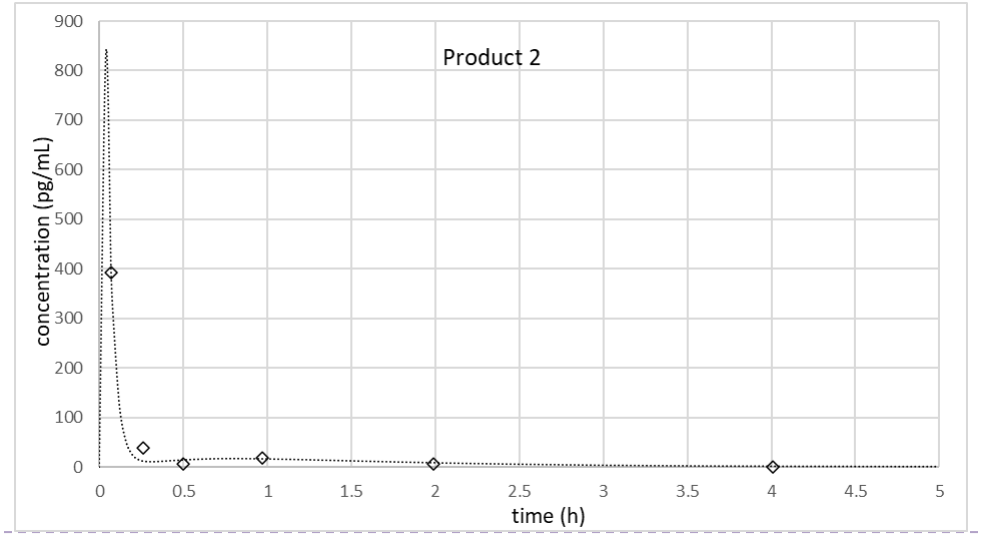
Elezovic et al, doi:10.1007/978-3-030-73909-6_74

Case study 2

RESULTS

Particle size grouping	Product 1 PE (%)	Product 2 R^2
-0.5	4.200	0.418
0	-2.580	0.877
+0.5	-0.940	0.984
+1	**0.400**	**0.988**
A1	**0.440**	**0.990**
A2	14.640	0.833





Elezovic et al, doi:10.1007/978-3-030-73909-6_74

Case study 2

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A2	14.640	0.833

Compartment	Aerodynamic particle size dimensions limit (µm)					
	-0.5	**0**	**+0.5**	**+1**	**A1**	**A2**
Alveolar-Interstitial (AI)	0 – 0.6	0 – 1.1	0 – 1.6	0 – 2.1	0 – 2	0 - 1
Bronchiolar (B)	0.6 – 3.2	1.1 – 3.7	1.6 – 4.2	2.1 – 4.7	2 – 4	1 – 3
Thoracic (T)	3.2 – 4.2	3.7 – 4.7	4.2 – 5.2	4.7 – 5.7	4 - 5	3 - 5
Extra-thoracic (ET)	4.2 - ∞	4.7 - ∞	5.2 - ∞	5.7 - ∞	5 - ∞	5 - ∞

Two groupings with smallest errors are +1 and A1

- Both have particle size limits for Alveolar-Interstitial compartment in similar ranges of around 0-2 µm
- Limits for Bronchiolar compartment are relatively high – in range of 2-4 µm
- The selected distributions for Thoracic compartment have lower limit at around 4 µm while distribution with higher error have lower limits set around 3 µm

Suitable inputs correspond to higher values for particle size limits than initialy suggested for the *in vitro* measurements

Modeling results suggest increased particle deposition in the lower pulmonary compartments (AI and B)

The most adequate size distribution: A1 and +1

Elezovic et al, doi:10.1007/978-3-030-73909-6_74

Case study 2

Conclusion

MMAD and GSD may not be suitable inputs for PBPK modeling of particle deposition in the lungs (courser particles are not included in the calculations)

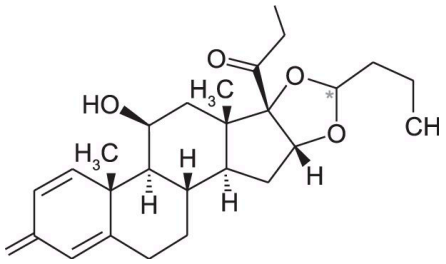
Percentual distribution of active substance in each of the respiratory compartments could improve quality of the *in silico* study results

Particle size groupings A1 and +1 are the most adequate to define deposition of beclomethasone dipropionate from pMDI products in the *in silico* model

Elezovic et al, doi:10.1007/978-3-030-73909-6_74

Case study 3

- **Budesonide - rat study**

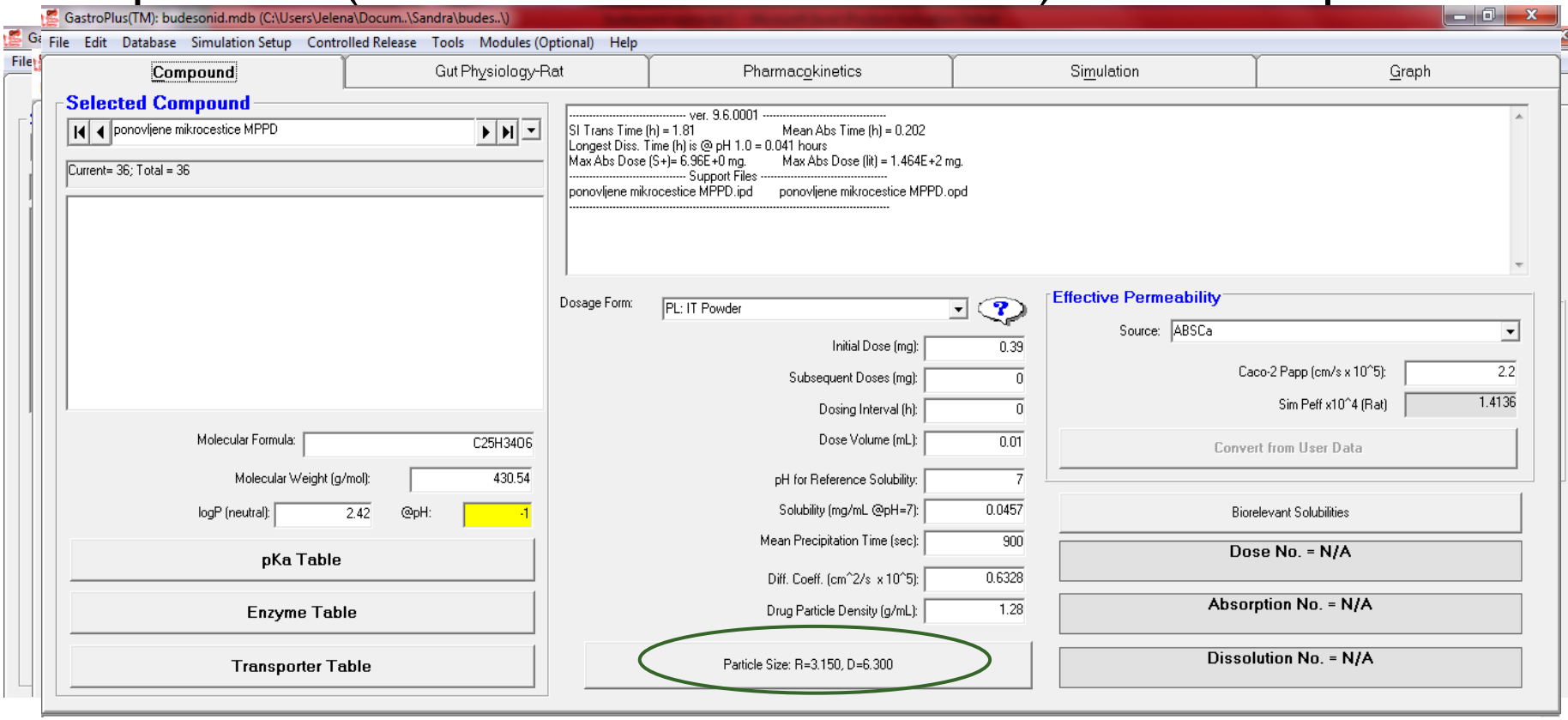


- Three formulations:
  1) Commercially available micronized BUD (Pulmicort®) mixed with coarse lactose as a carrier (BUD-PT)
  2) BUD nanocrystal suspension (BUD-NC)
  3) BUD nanocrystals embedded hyaluronic acid microparticles (BUD-NEM)
- BCS Class II drug
- pK_a 13.74 (base)
- Poorly soluble (aqueous solubility 0.0457 mg/ml)
- Highly permeable (logP = 2.42)

Liu et al, doi:10.1016/j.carbpol.2017.11.018

Compound

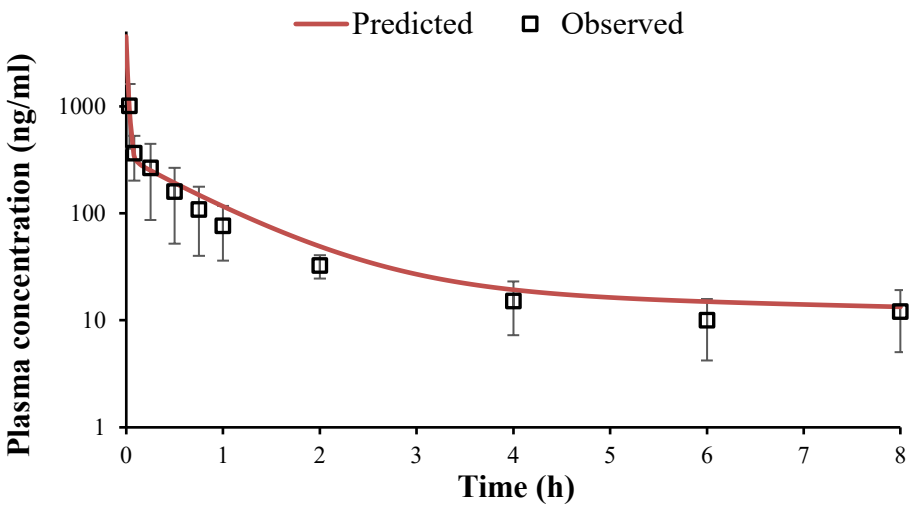
- IV bolus – model construction
- IT powders (BUD-PT, BUD-NC, BUD-NEM) – model exploration

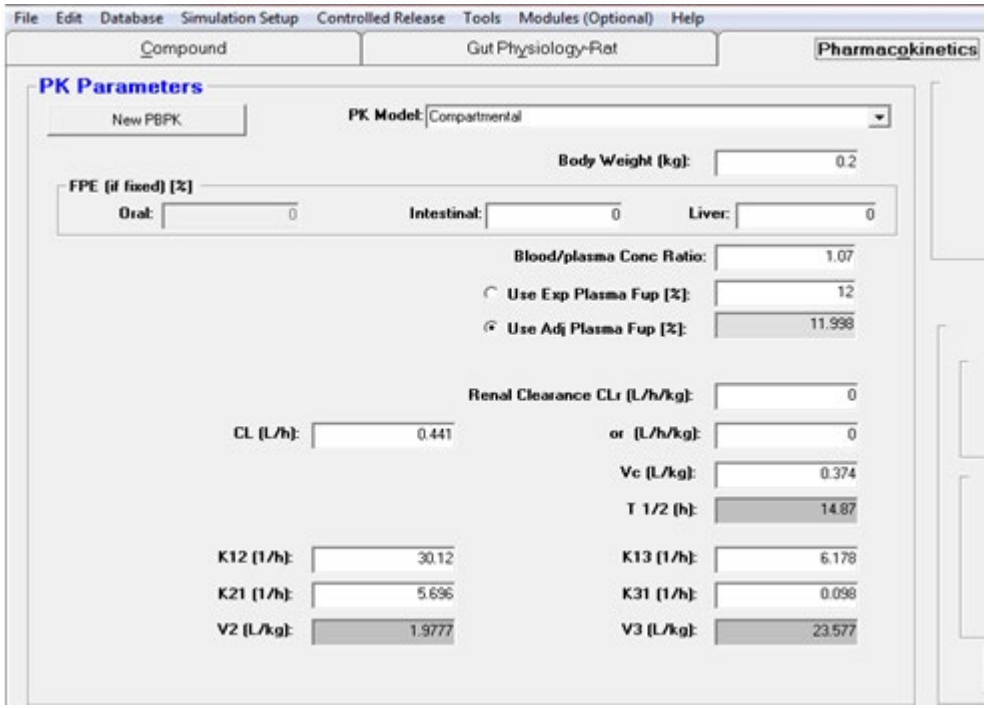


Geometric particle size to simulate drug dissolution: 2.32 (BUD-PT); 0.26 (BUD-NC); 6.30 (BUD-NEM)

Pharmacokinetics

- IV bolus
- PKPlus module
- Three-compartmental model

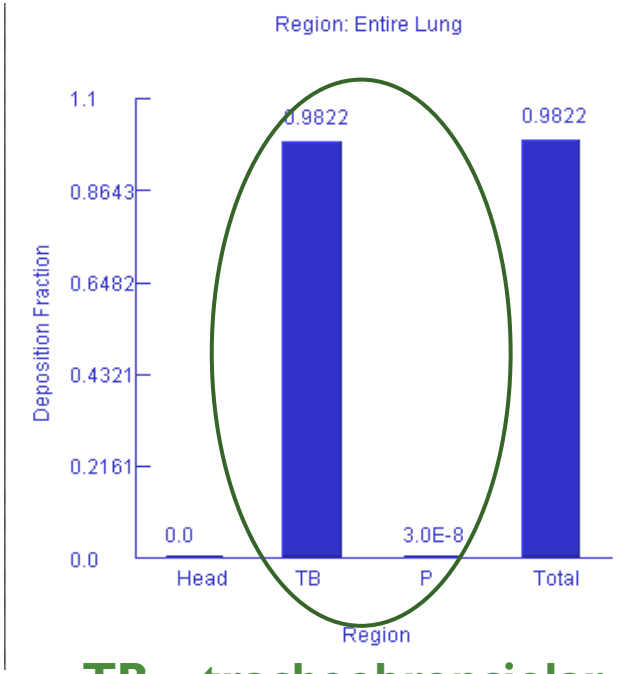




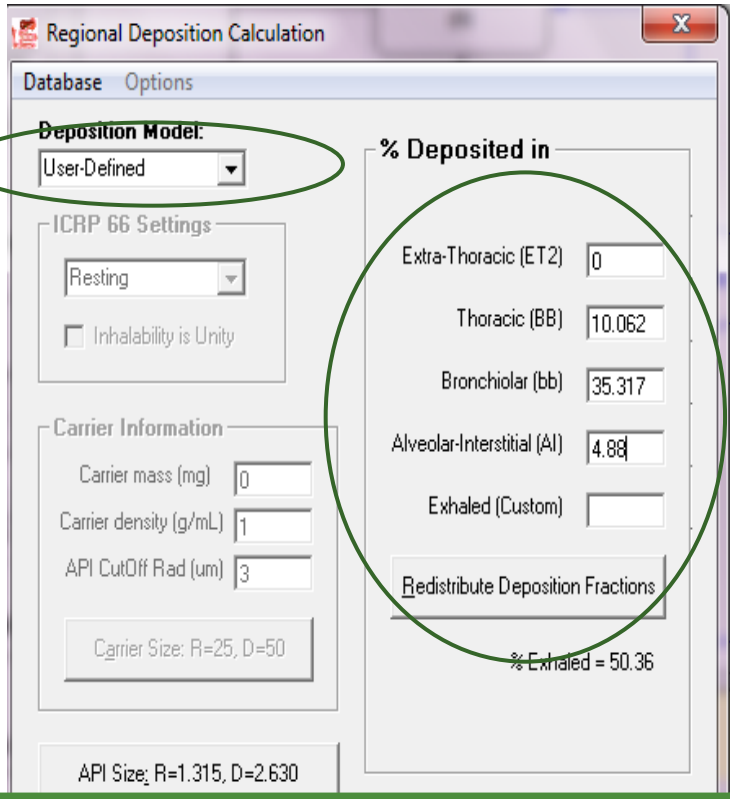
GastroPlus™ software, ver. 9.7

PCAT parameters

- D1 (*in vivo*) and D2 (*in silico*) deposition
- Multiple-Path Particle Dosimetry (MPPD)



TB – tracheobronciolar
P – pulmonary

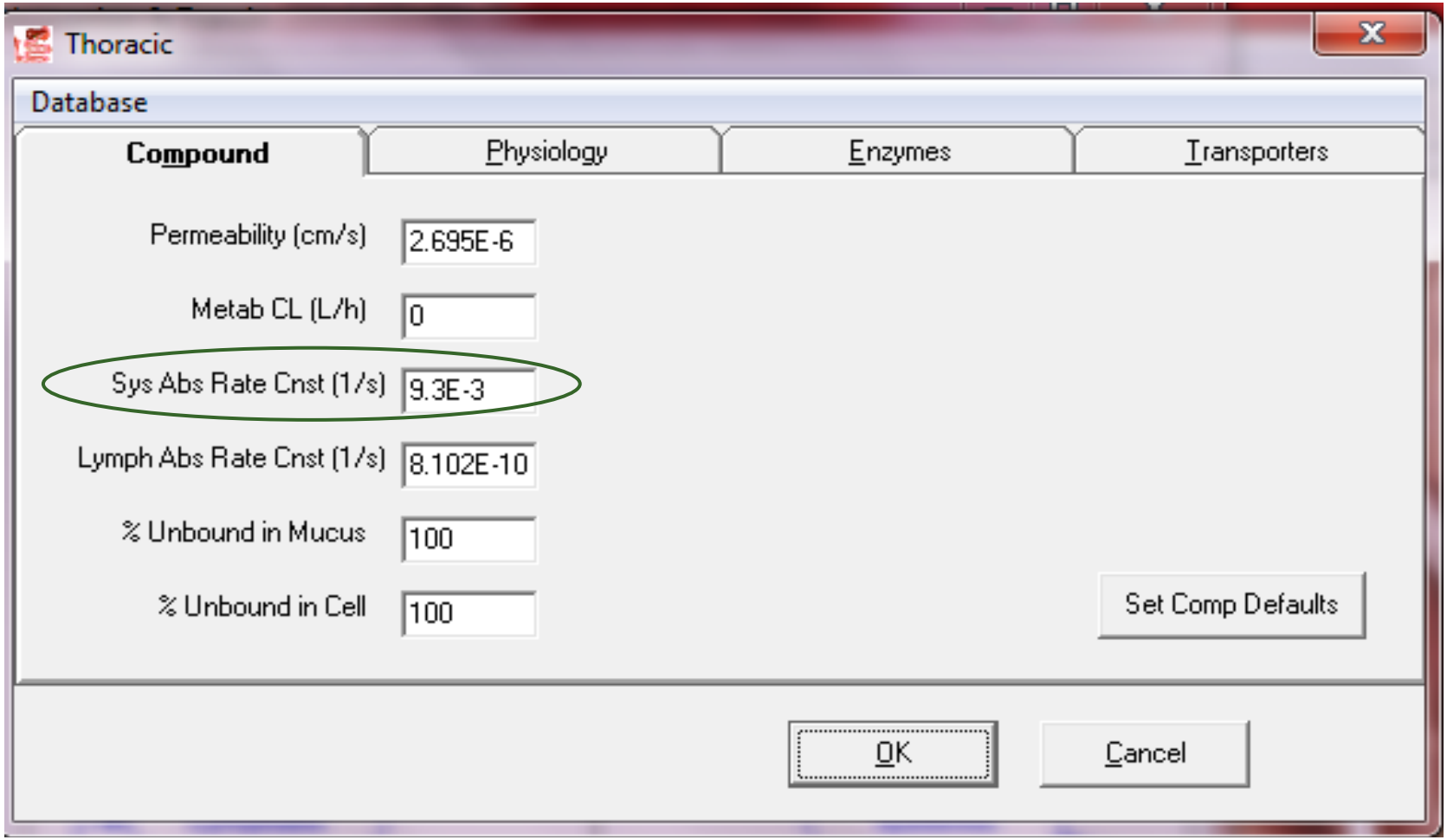


Formulation	MMAD (μm)	GSD
BUD-PT	2.63	1.97
BUD-NC	27.90	0.89
BUD-NEM	5.33	1.68

*droplet size of aerosolized BUD-NC, obtained by laser diffraction

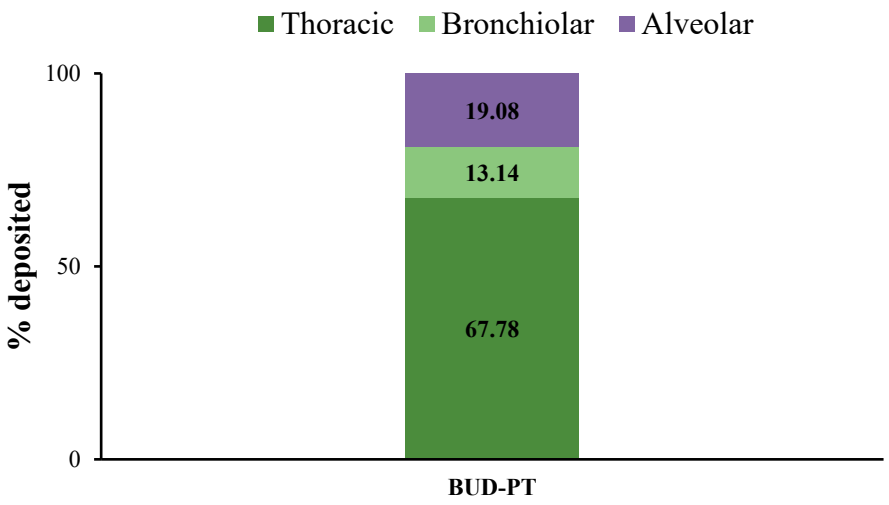
PCAT parameters

- Systemic absorption rate constant (thoracic, bronchiolar, alveolar)

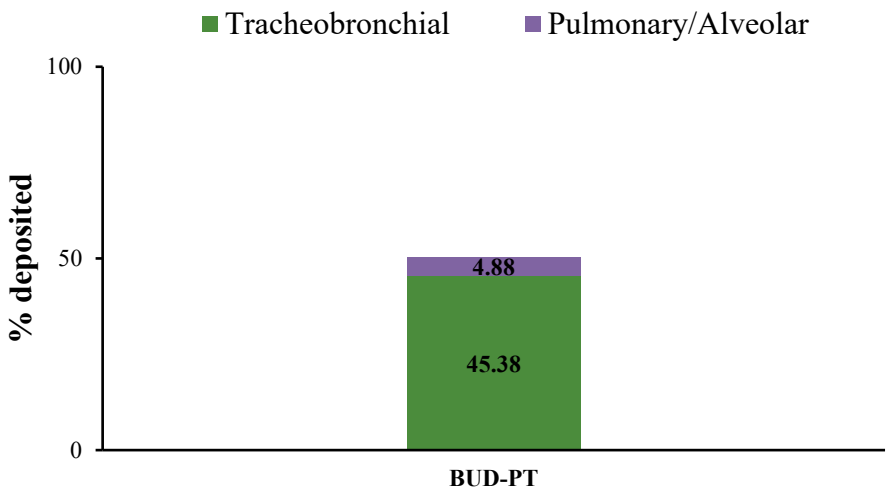


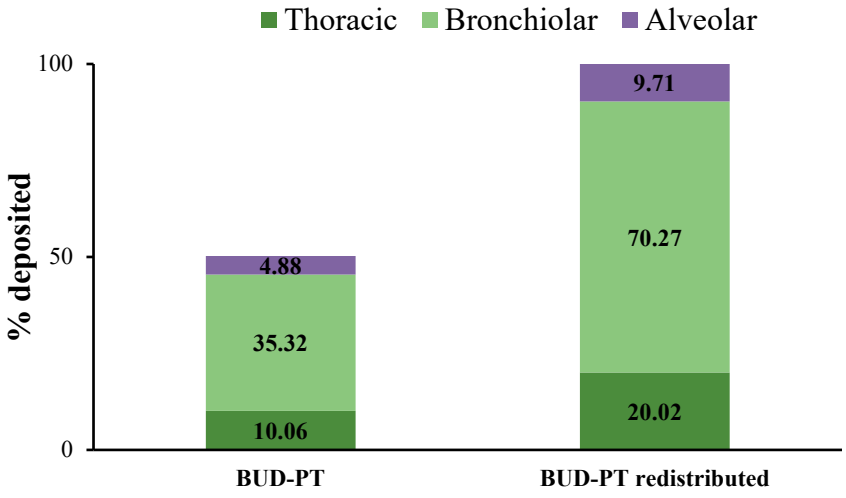
1. BUD-PT

- D1 (*in vivo*) deposition

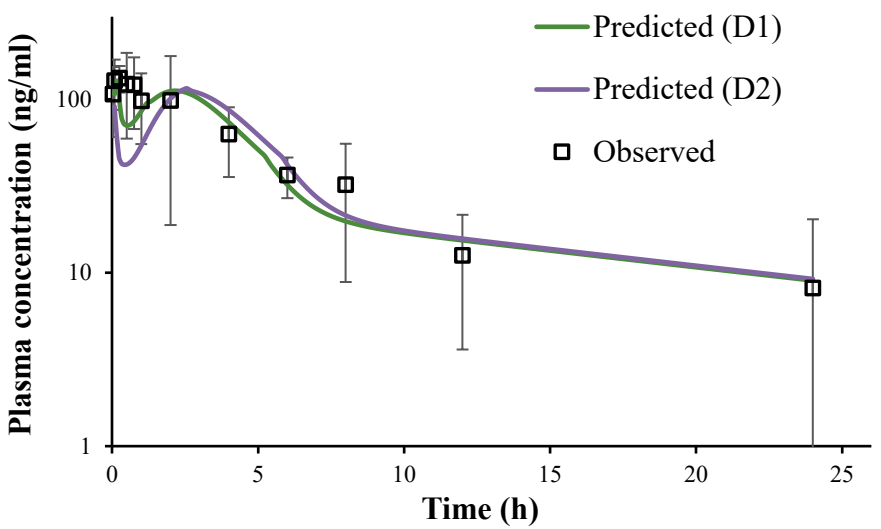


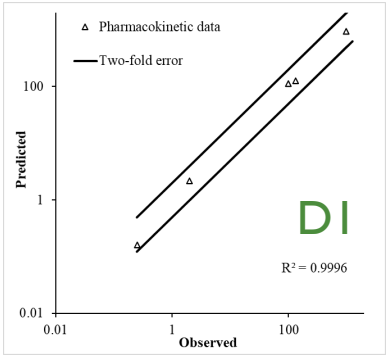
- D2 (*in silico*) deposition

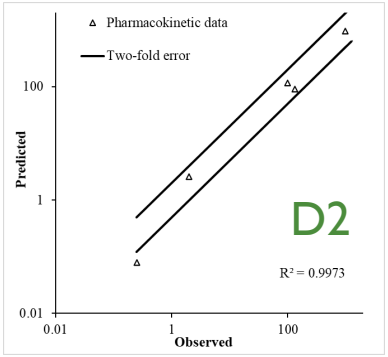


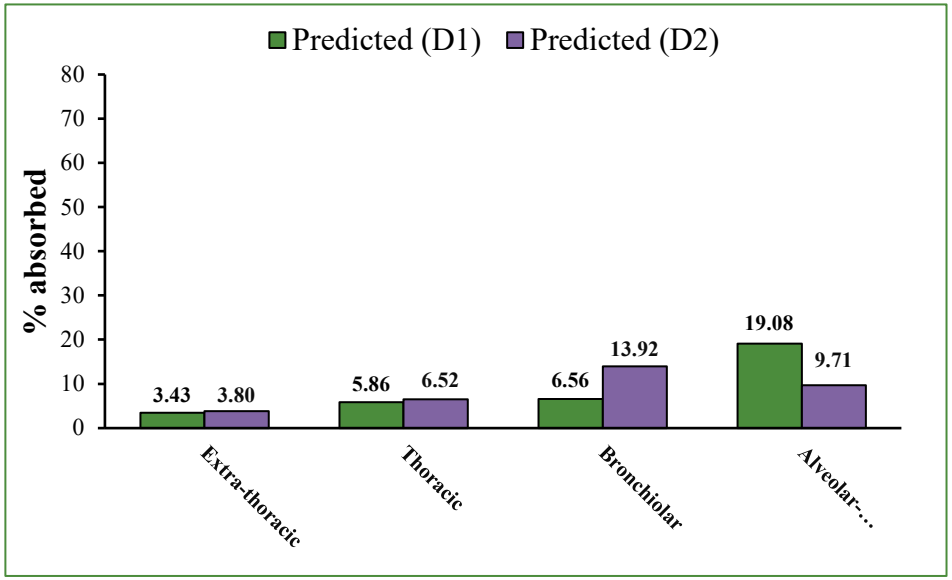


1. BUD-PT





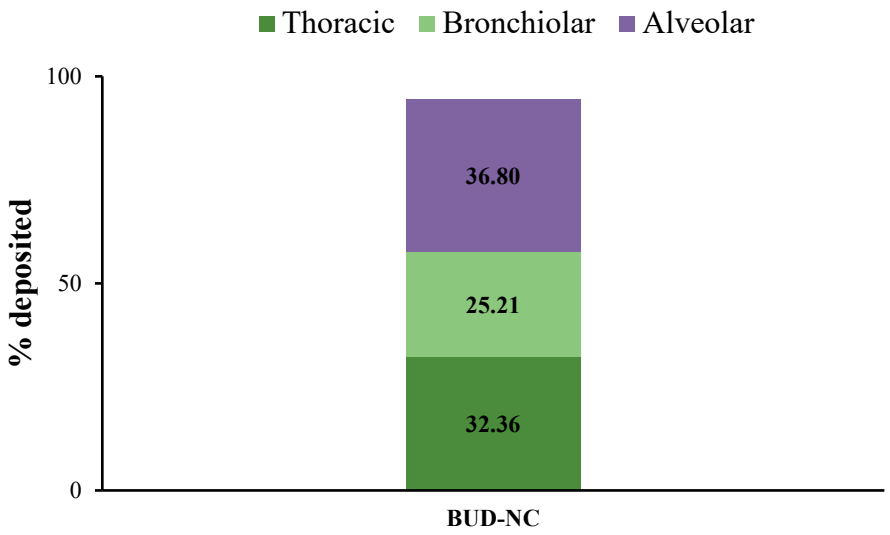




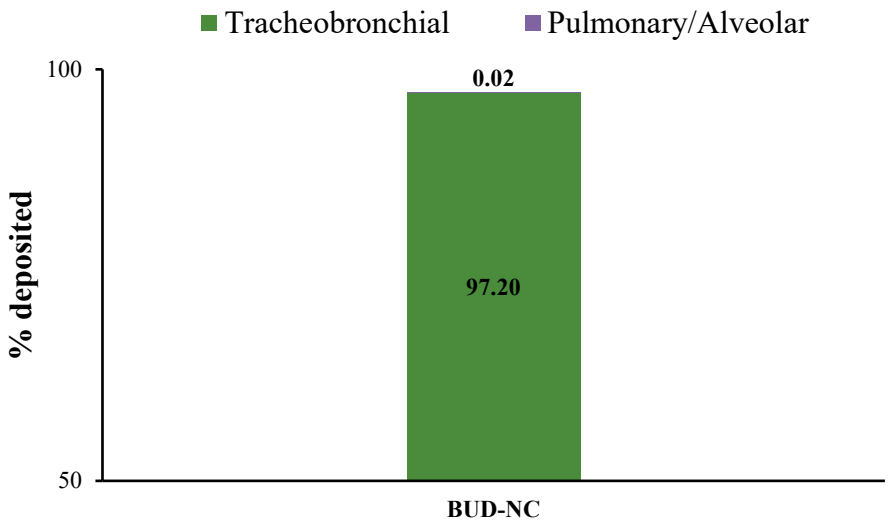
Shi et al, doi:10.1016/j.ajps.2020.12.001

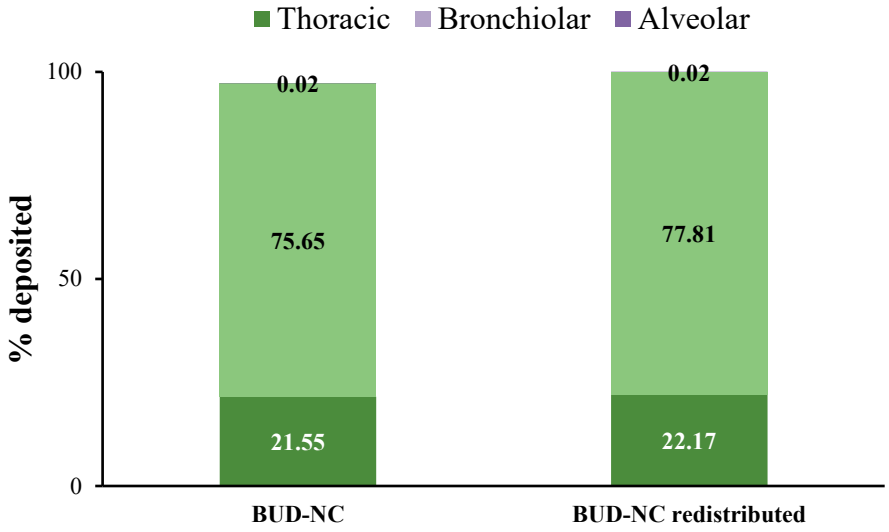
2. BUD-NC

- D1 (*in vivo*) deposition

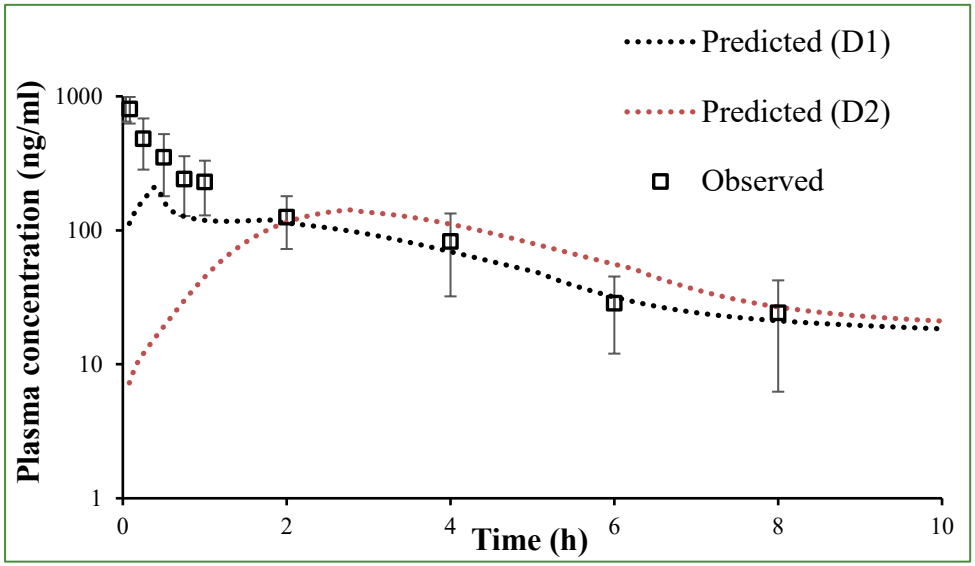


- D2 (*in silico*) deposition





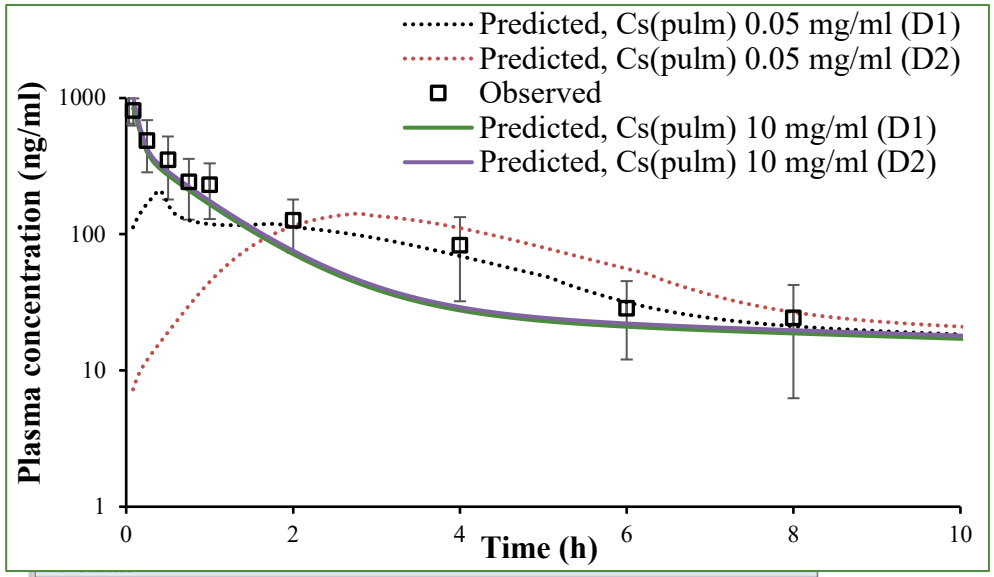
2. BUD-NC

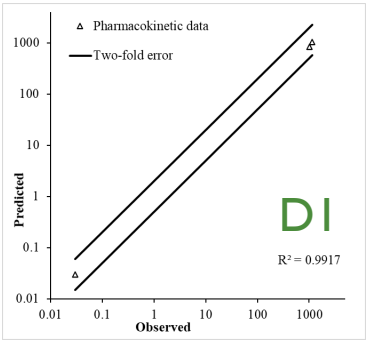


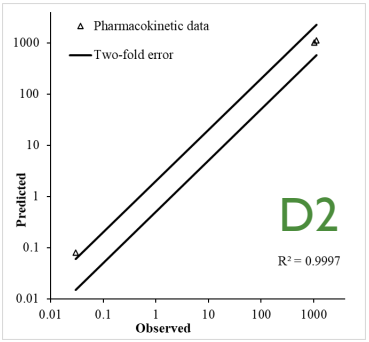
- Faster and more complete BUD *in vivo* dissolution from the nebulized nanosuspension → nanosize effect on drug particle dissolution and the presence of additional water in the nebulized droplets
- BUD nanosuspension behaves more like solution?
- Nanocrystals/nanoparticles possess increased surface to volume ratio in comparison to larger particles → increase in drug dissolution rate

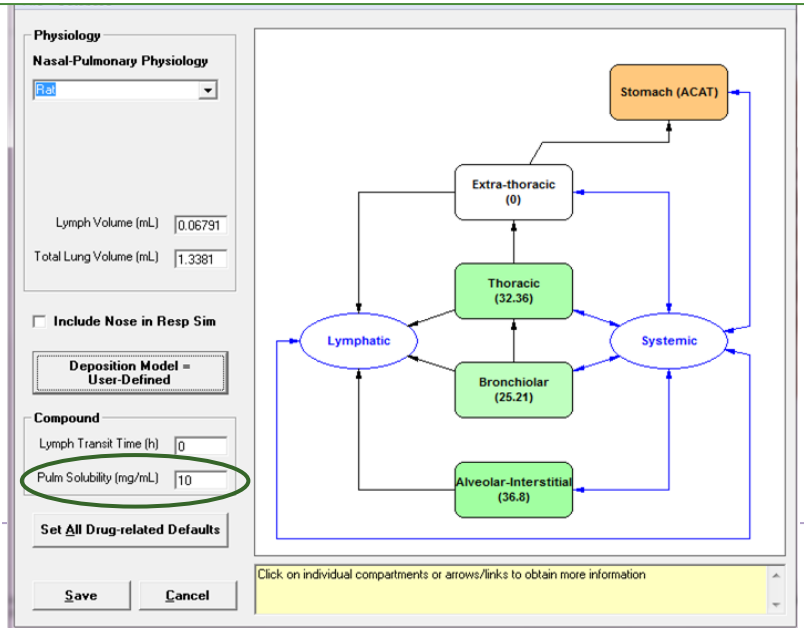
Yang et al, doi: 10.1002/jps.21380

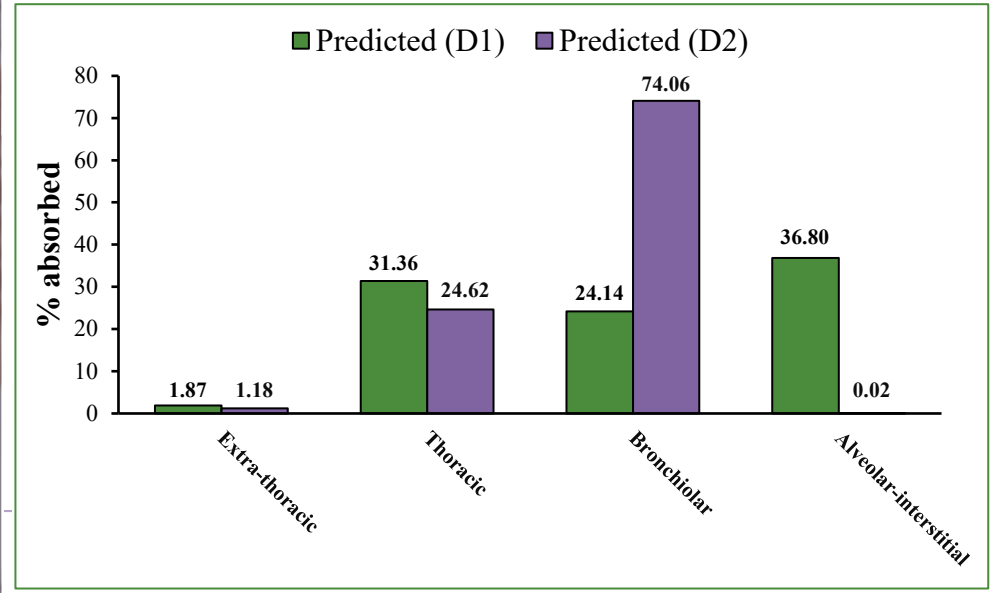
2. BUD-NC


Predicted, Cs(pulm) 0.05 mg/ml (D1)
Predicted, Cs(pulm) 0.05 mg/ml (D2)
Observed
Predicted, Cs(pulm) 10 mg/ml (D1)
Predicted, Cs(pulm) 10 mg/ml (D2)
Plasma concentration (ng/ml)
1000
100
10
1
0
2
4
6
8
10
Time (h)


Pharmacokinetic data
Two-fold error
Predicted
Observed
D1
R² = 0.9917

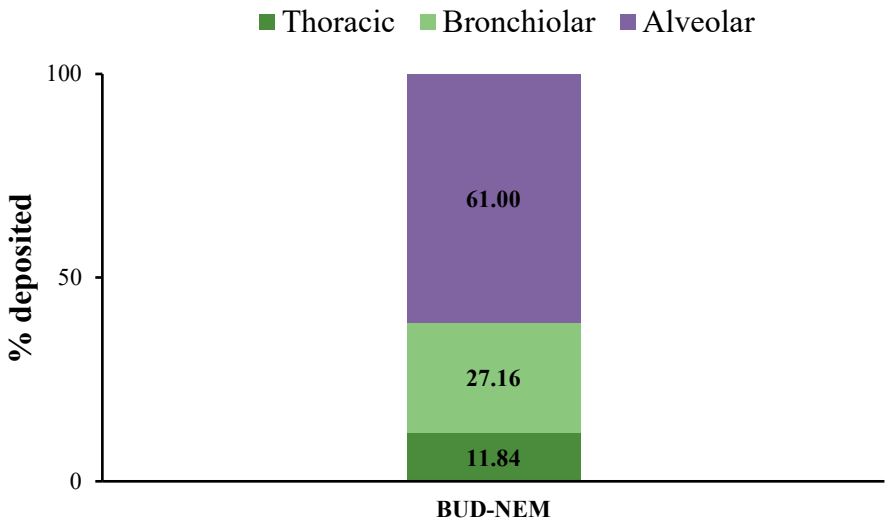

Pharmacokinetic data
Two-fold error
Predicted
Observed
D2
R² = 0.9997


Physiology
Nasal-Pulmonary Physiology
Rat
Lymph Volume (mL) 0.06791
Total Lung Volume (mL) 1.3381
Include Nose in Resp Sim
Deposition Model = User-Defined
Compound
Lymph Transit Time (h) 0
Pulm Solubility (mg/mL) 10
Set All Drug-related Defaults
Save
Cancel
Stomach (ACAT)
Extra-thoracic (0)
Thoracic (32.36)
Lymphatic
Systemic
Bronchiolar (25.21)
Alveolar-Interstitial (36.8)
Click on individual compartments or arrows/links to obtain more information

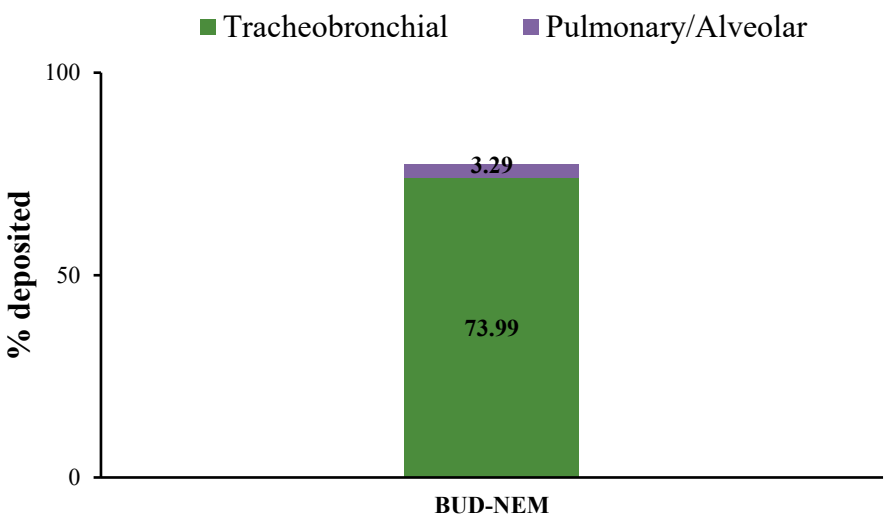

Predicted (D1)
Predicted (D2)
% absorbed
80
70
60
50
40
30
20
10
0
1.87
1.18
31.36
24.62
24.14
74.06
36.80
0.02
Extra-thoracic
Thoracic
Bronchiolar
Alveolar-interstitial

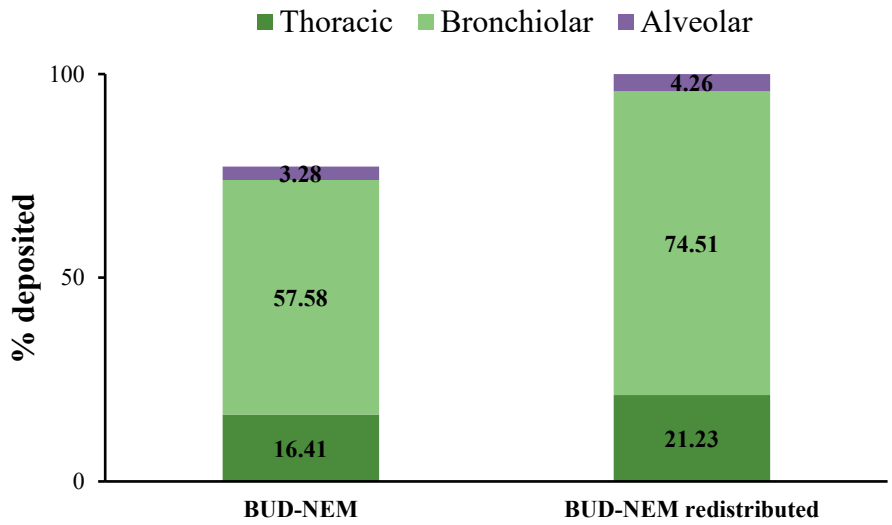
3. BUD-NEM

- D1 (*in vivo*) deposition

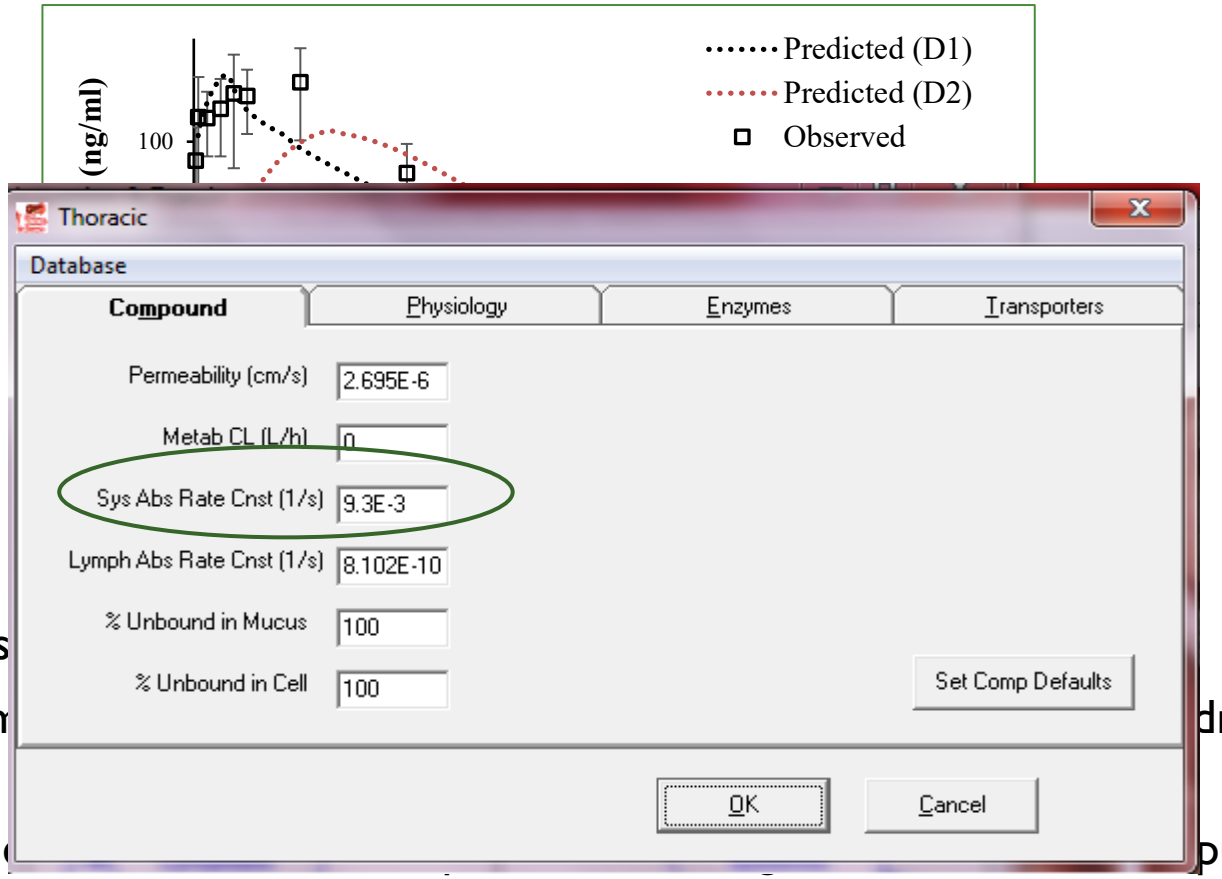


- D2 (*in silico*) deposition





3. BUD-NEM



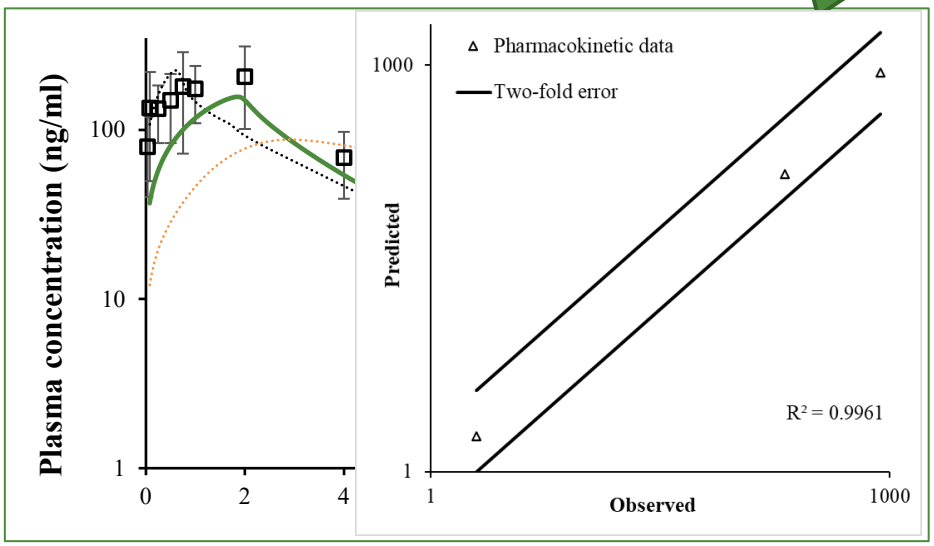
- The *in vivo* res
- Pronounced m drug retention in the lungs
- PCAT™ mod put

Optimizing apsorption rate constant from pulmonary compartments (k_a)

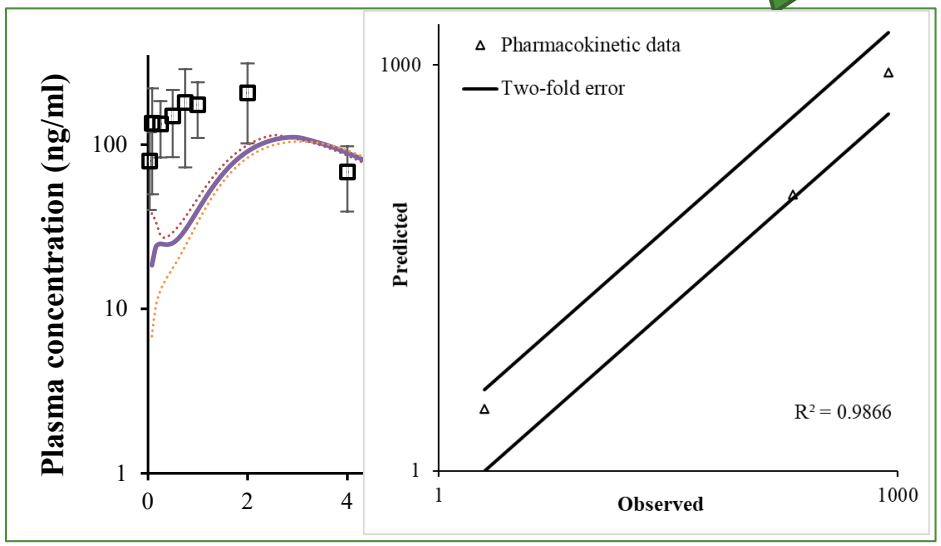
Shi et al, doi:10.1016/j.ajps.2020.12.001

3. BUD-NEM

D1



D2



Parameter	Observed	Predicted k_a=9.30×10^{-3} 1/s		Predicted k_a=2.93×10^{-3} 1/s		Predicted k_a=9.30×10^{-4} 1/s	
		D1	D2	D1	D2	D1	D2
C_{max} (ng/ml)	206.43	223.49	113.98	157.29	110.68	87.82	104.56
t_{max} (h)	2.00	0.64	2.56	1.84	2.88	2.88	3.04
$AUC_{0\rightarrow\infty}$ (ng h/ml)	864.60	883.40	881.54	883.27	881.31	883.07	881.00

Shi et al, doi:10.1016/j.ajps.2020.12.001

Case study 3

- *In silico* predicted pulmonary drug deposition - a suitable alternative to predict drug absorption following inhalation of relatively simple formulations (e.g., BUD-PT)
- *In silico* modeling enabled to elucidate the differences in drug regional absorption distribution in the lungs, even when these differences were not reflected in the Cp-t profiles (e.g., BUD-NC)
- Prediction of drug absorption pattern following administration of inhaled formulations with pronounced mucoadhesive properties - still challenging
- The applied approach, based on the optimization of k_a, can be used for rough predictions of pulmonary drug absorption
- Such an approach - not applicable in the early phases of formulation development

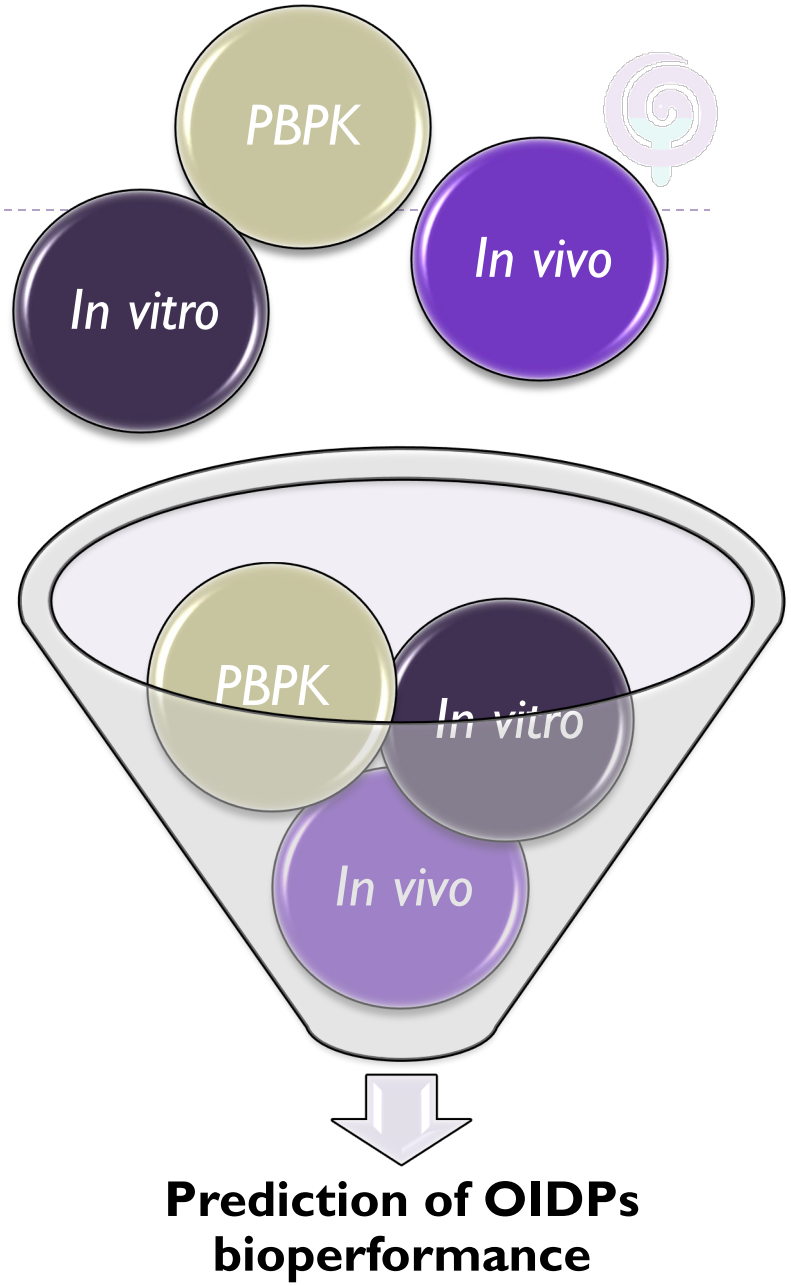
Overview

- Rational models
- Mechanistic interpretation of the complex phenomena that happen *in vivo*
- Enable virtual "case studies"
- Time and cost effective
- Contribute to formulation of patient-tailored medicines
- Facilitate regulatory decision making

- Lack of information/Limited access to relevant biopharmaceutical data
- Incomplete knowledge of human (lung) physiology and relevant physiological mechanisms
- Lack of biorelevant data (method) on particle deposition
- Lack of *in vivo* data for model verification
- Complex and data intensive tools

Future directions

- Improvement in knowledge on human lung physiology and drug-related physiological mechanisms
- Development of appropriate (biorelevant?) *in vitro* assays
- Further refinement of physiologically-based *in silico* models
- Wider acceptance in pharmaceutical development
- Regulatory support & acceptance



gsandra@pharmacy.bg.ac.rs
jelisavetai@pharmacy.bg.ac.rs
amarelezovic@gmail.com