Correlating the In Vitro Dissolution Behavior of Inhalation and Nasal Drug products with In Vivo Performance: Pitfalls and Potential Solutions using the Transwell® System

IPAC-RS/RDD 2016 Symposium:

Meeting the Quality Challenge for Orally Inhaled Drug Products

IPAC-RS

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- **FDA** (Mohammad Absar, Denise Conti, Renish Delvadia, Larry Lee, Murewa Oguntimein, Bavna Saluja)
  - U01FD004950 (Dissolution)
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- **Juergen Bulitta (UF)**
- **Sharvari Bhagwat, Mark Rohrschneider (Students),**
  - YeLaetitia Sandini, Martin Jetzer
  - Adriely Goes, Sara Broenner
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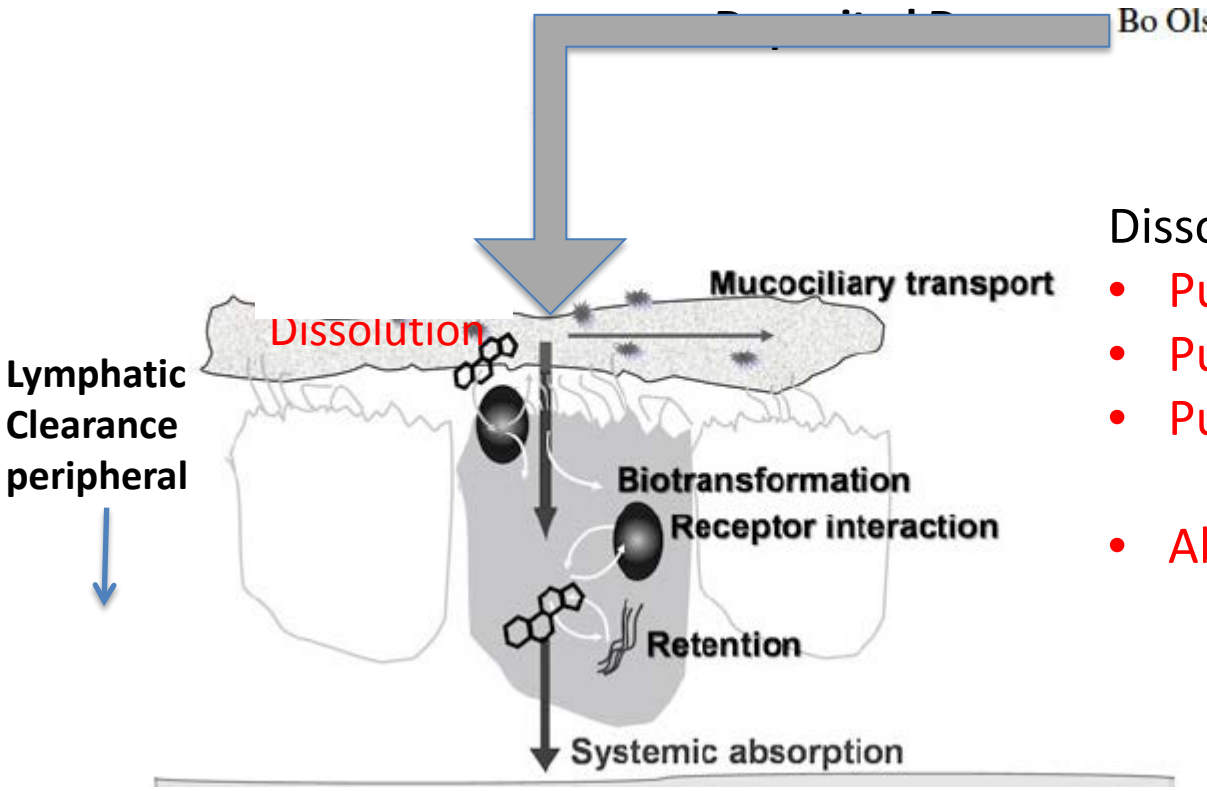
- **Dissolution, DPI, Nasal: Jag Shur, Rob Price (University of Bath)**
- **Dissolution, MDI: Dennis Sandell (S5 Consulting)**
- **MDI: Aliyah Sheth , Andrew Hamer (Cirrus)**

The Particle has Landed (Patton)

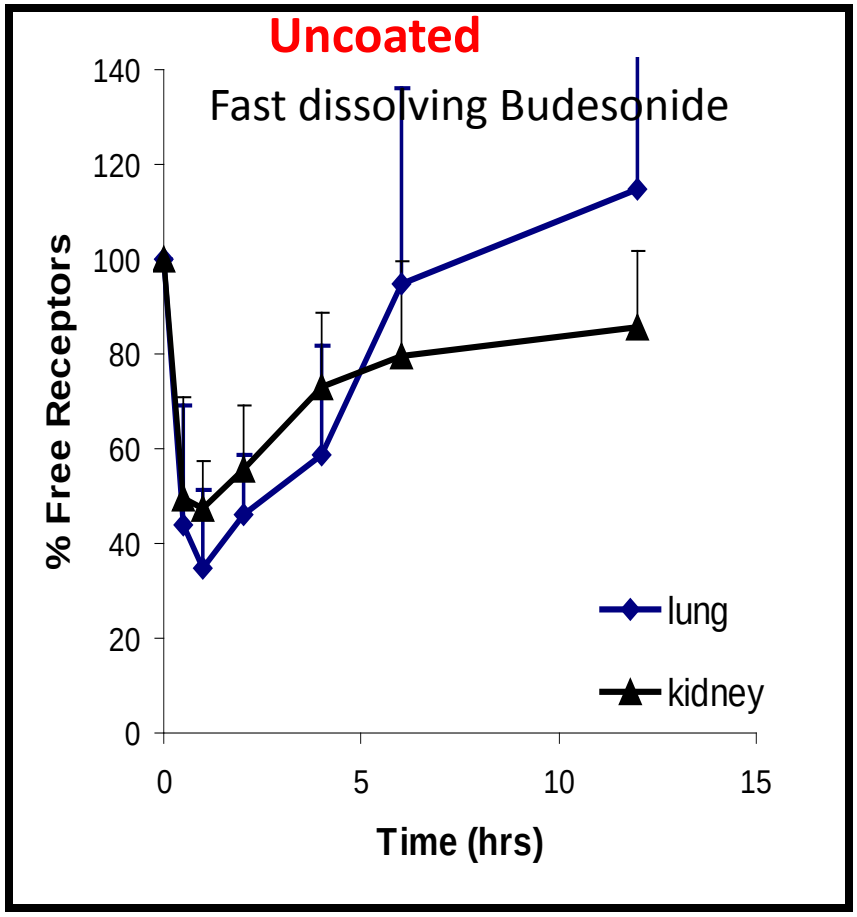


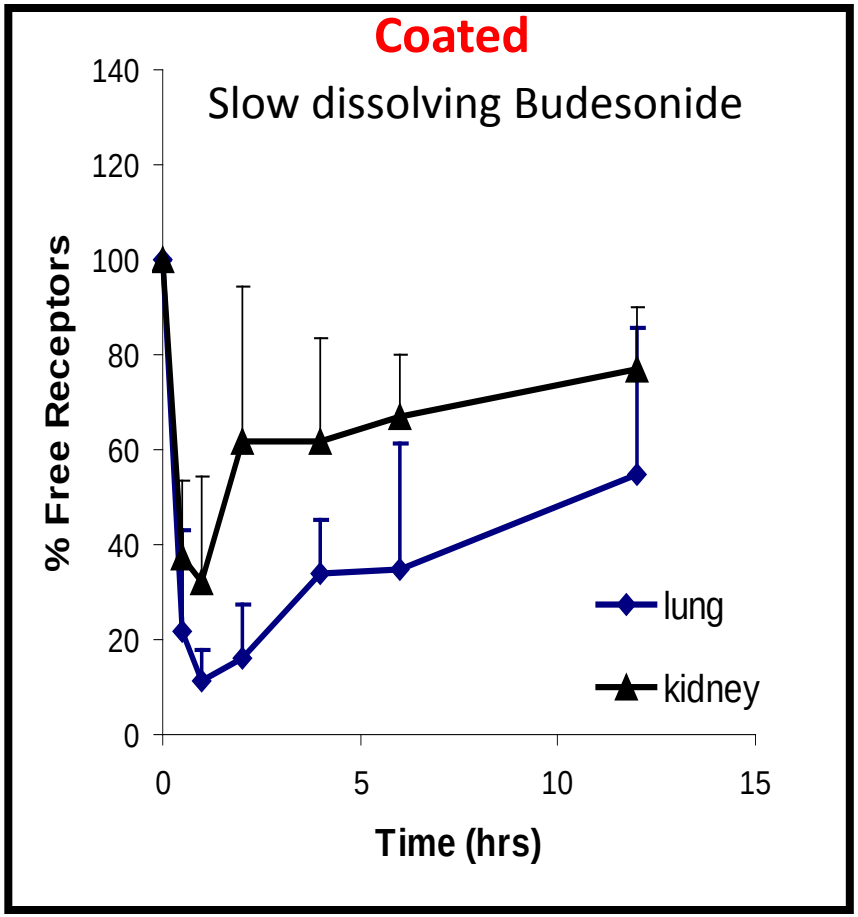
Dissolution rate affects:

- Pulmonary available dose
- Pulmonary residence time
- Pulmonary targeting

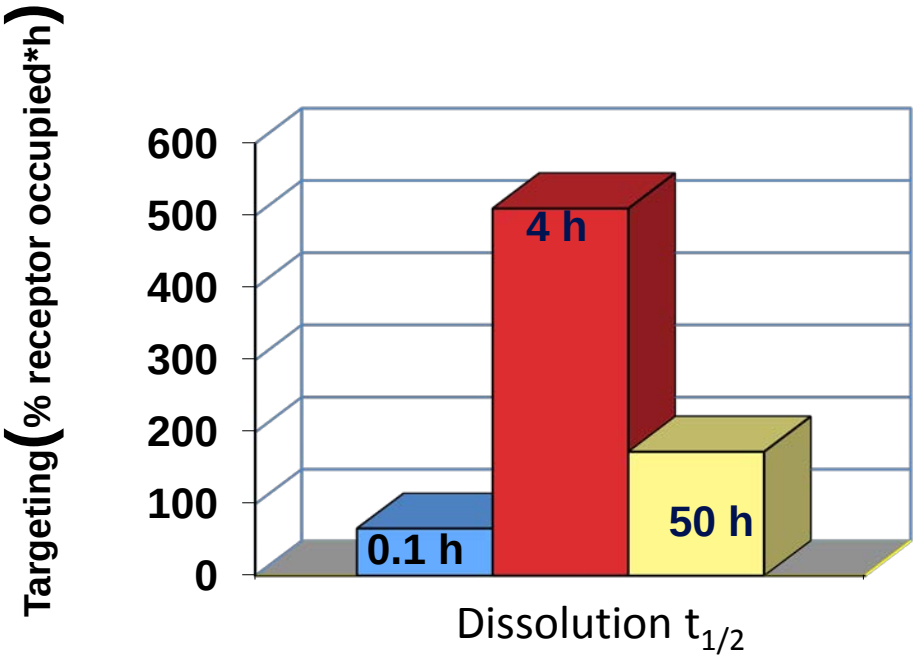
- Absorption rate

Coated (slow dissolving) Budesonide shows increased pulmonary Targeting in Rats



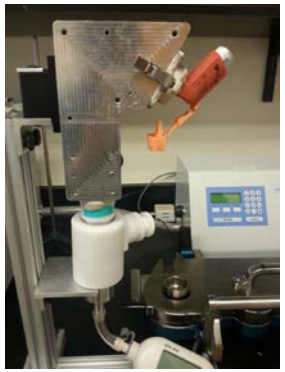


Dissolution Rate, Mucociliary Transport and Pulmonary Targeting

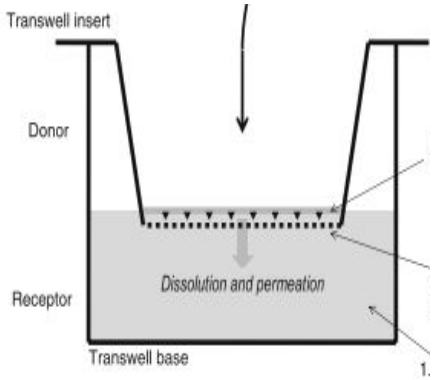


- **There is an Optimal Dissolution Rate**
  - **Difference in Dissolution Rate between T and R are relevant**
  - **No Tests are currently suggested in USP or FDA Guidances**
  - **FDA invested in Development**

What Method?



1. **Deposition:**
   - Dosage Unit Sampling Apparatus (DUSA (?))
   - NGI (Specific Stages or UB's UniDose Approach)
   - Anatomical Throat (inhalable fraction)
2. **Dissolution**:
   - USP Dissolution Systems
   - Franz Cell
   - Transwell® System

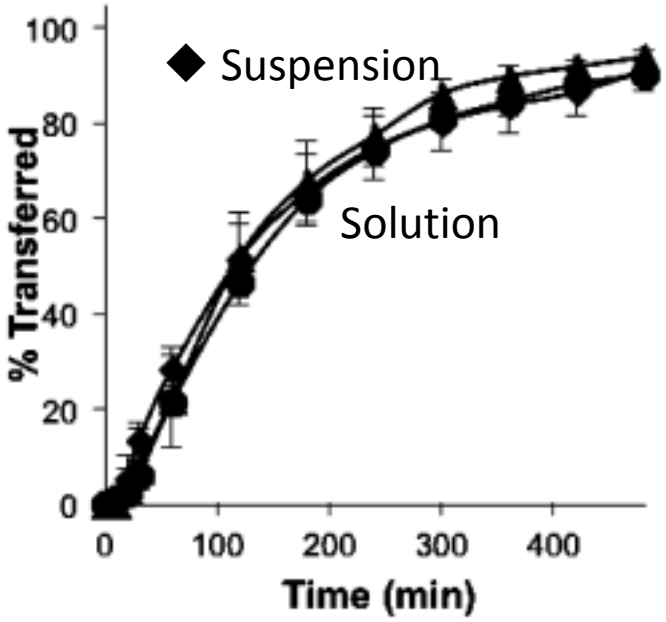


- Fast Diffusion across Membranes
- No "Dose" Effect
- The Right Solvent foe IVIVC

Pitfall 1: Diffusion across Membranes?

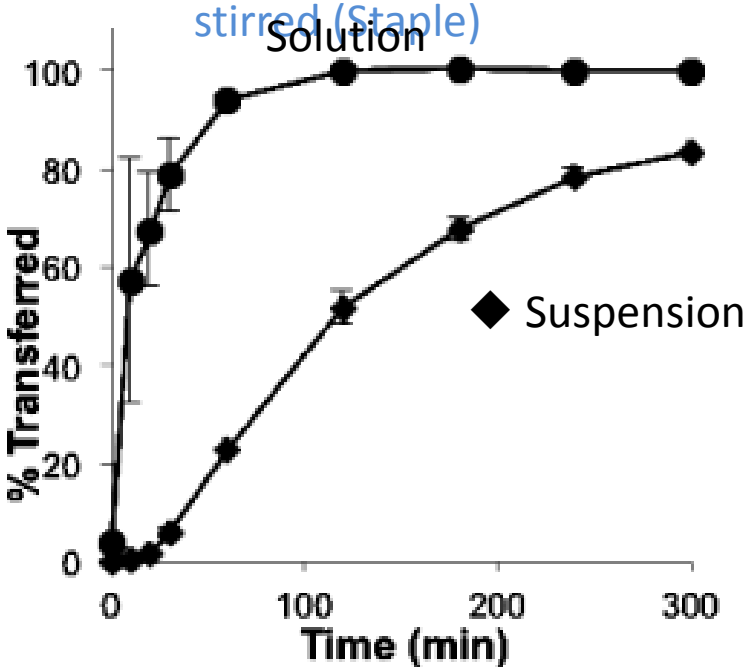
Ciclesonide Solution vs MDI

0.4 µm Transwell® Membrane



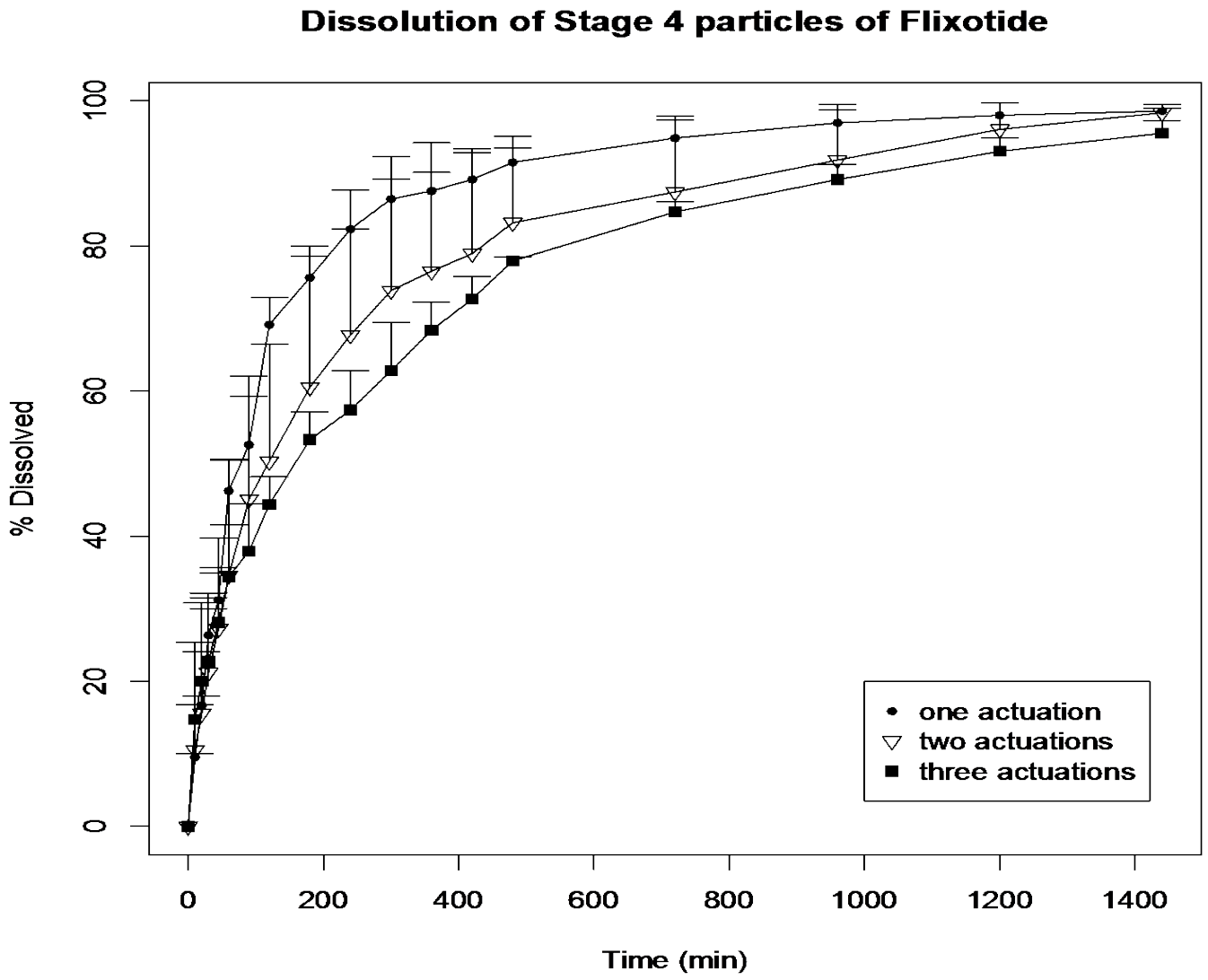
8 µm Transwell® Membrane

stirred (Staple)



Use 8 µm Membrane, Stirred

Pitfall 2: Dose Effect?



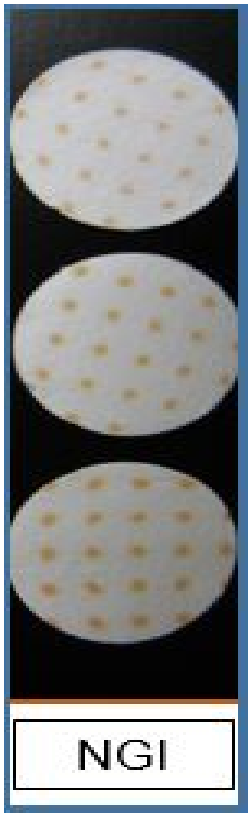
Dose Effect (1-3 Actuations)

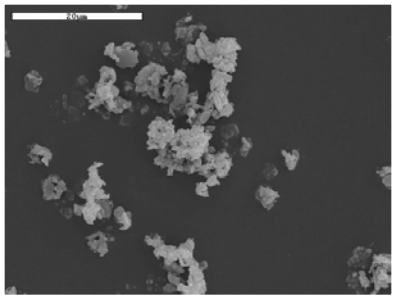
NGI

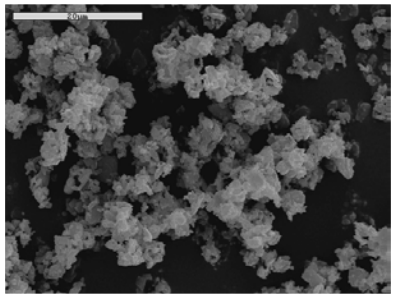
1x

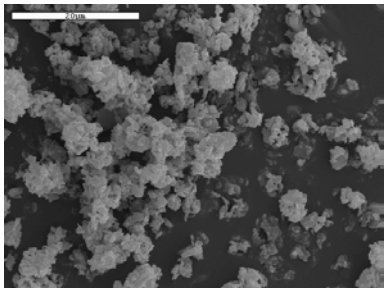
2x

3x

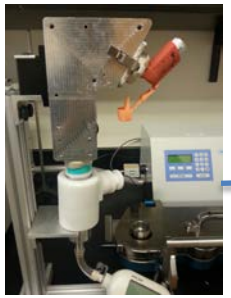


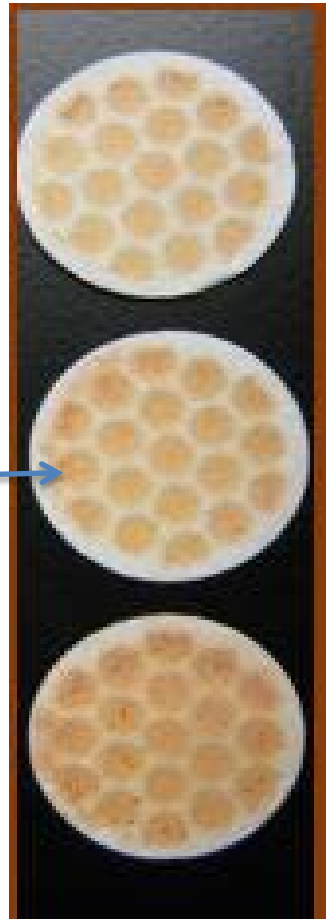




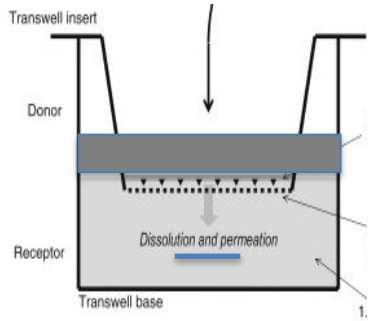


Anatomical Throat

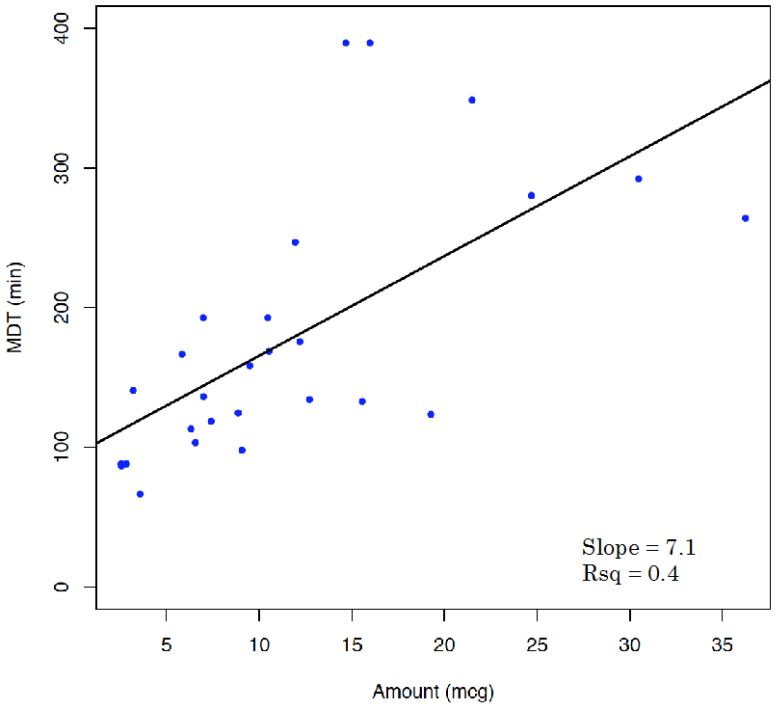




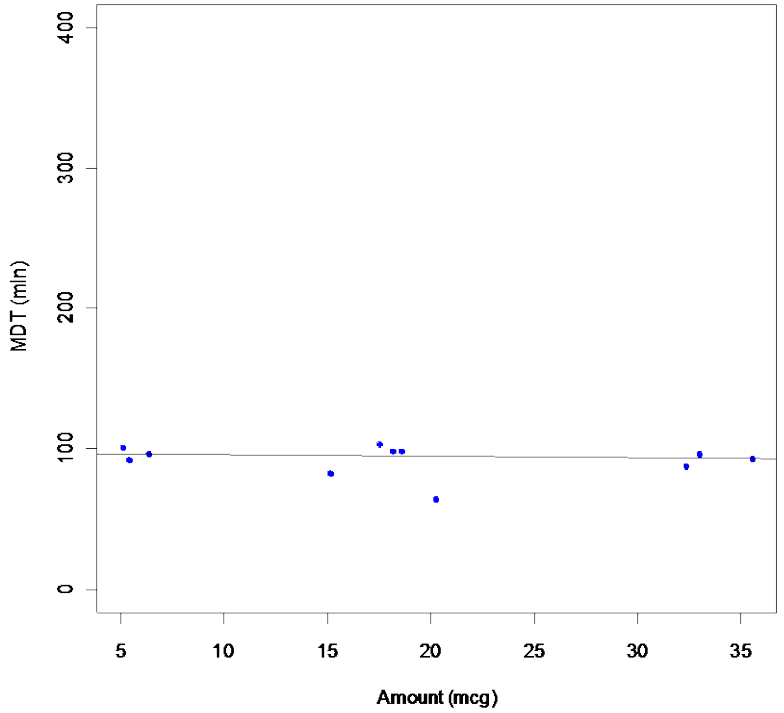
“Dose Effect”:
100 µl vs 500 µl in Donor Compartment



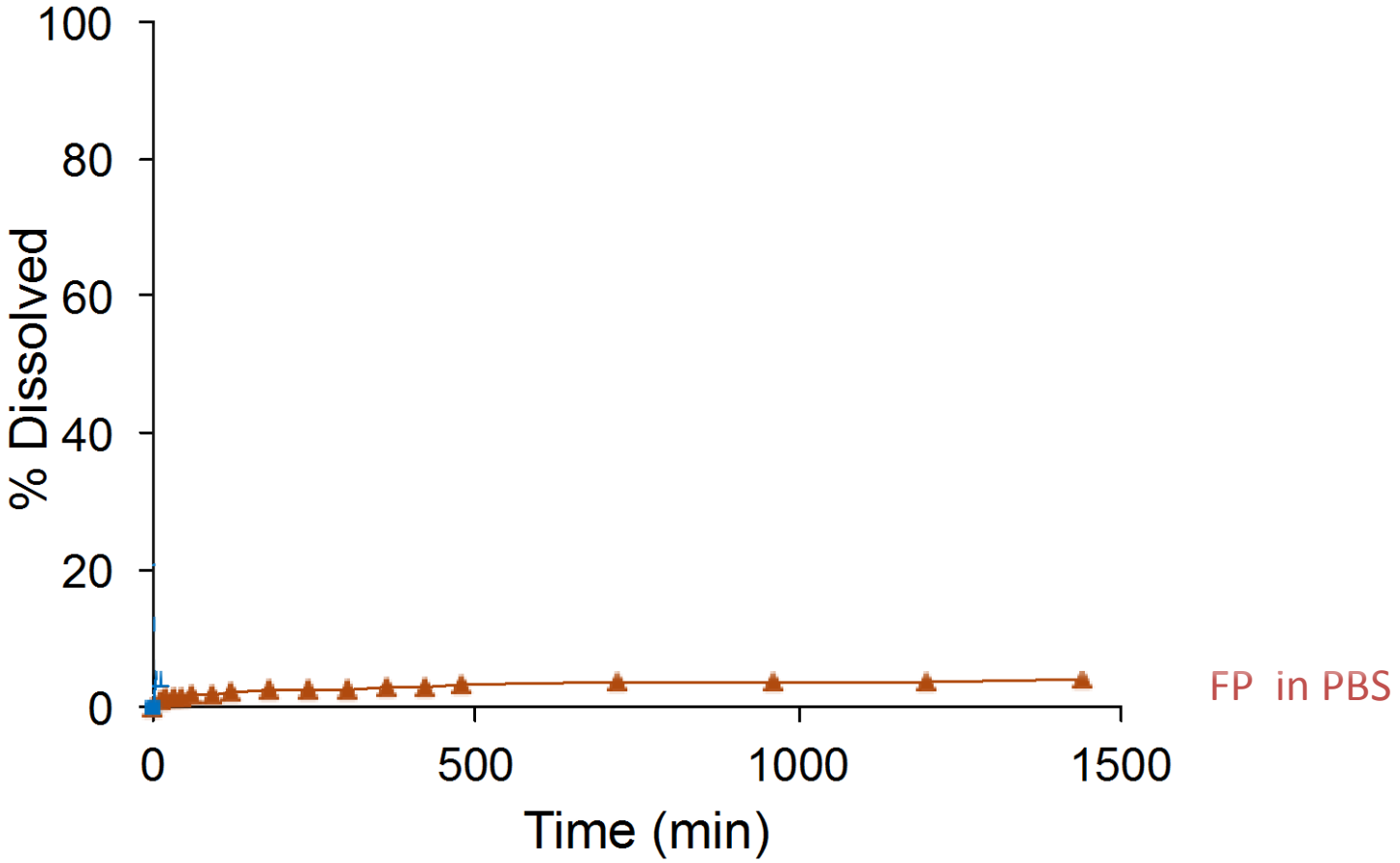
100 µl (0.5% SDS, unstirred)



500 µl (0.5% SDS, stirred)

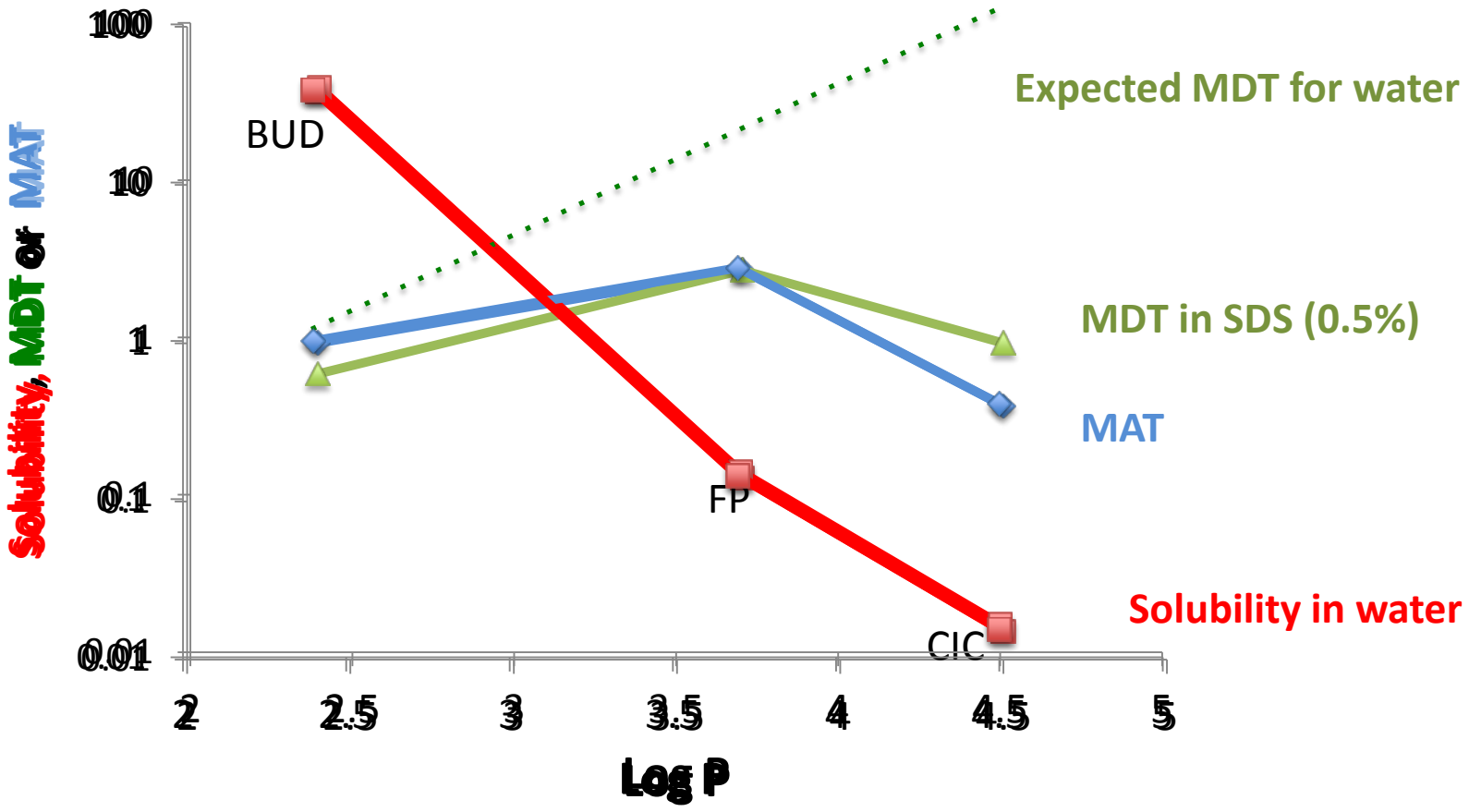


Pitfall 3: Solvent (1)?



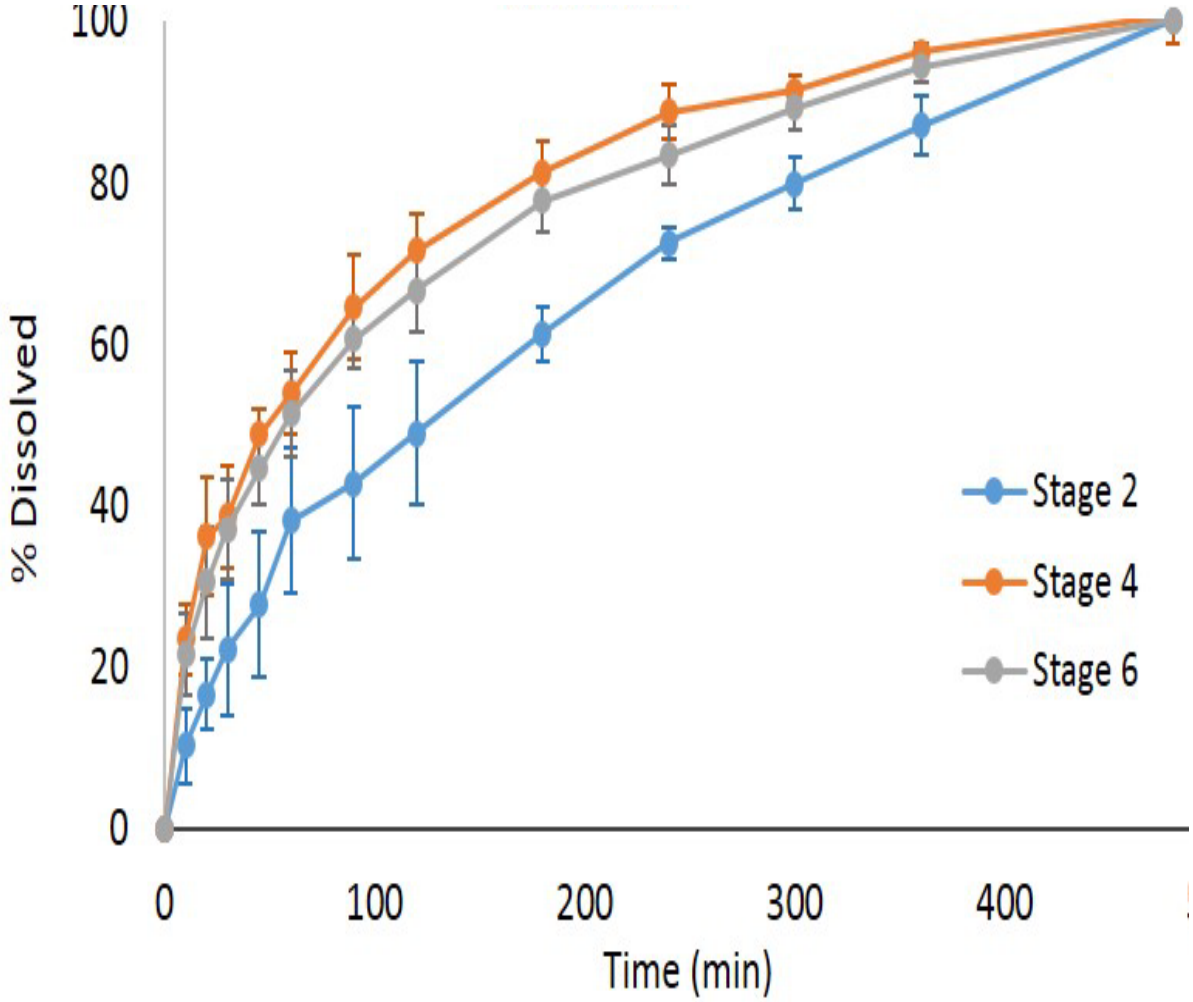
Solvent needs to contain surfactant.

Pitfall 3: What Solvent (2)?



Solvent needs to contain surfactant.

Pitfall 4:
Sensitivity to Particle Size (0.5% SDS)
(Flovent DPI)



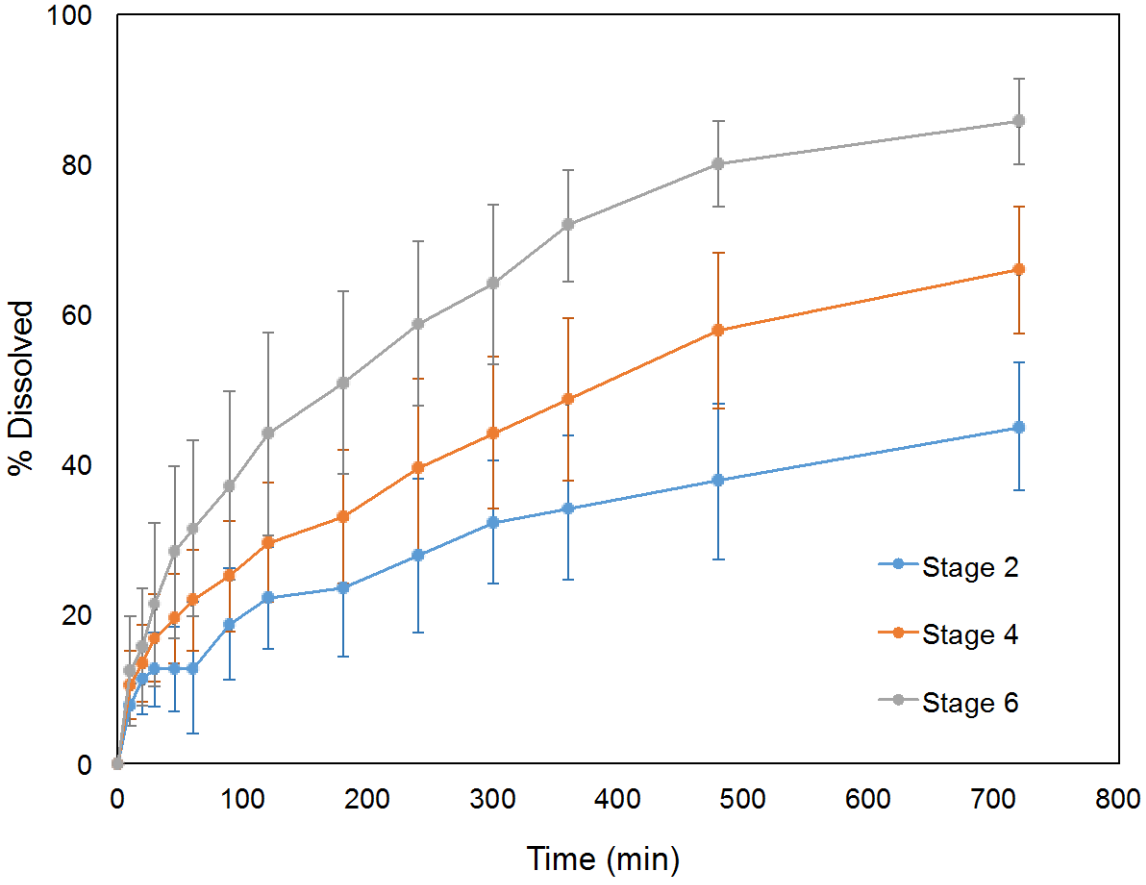
4.7 µm

2.1 µm

0.7 µm

Sensitivity to Particle Size with (0.5% Tween)

(Flovent DPI)



0.5% Tween might be a better medium for lipophilic corticosteroids

Do Data Agree with Dissolution Theory?

- Nernst-Brunner:

  Dissolution Rate determined by Diffusion Coefficient (**D)**, Surface area ($\mathbf{S_e}$), Thickness of Diffusion Layer (**h**) and Solubility (**Cs**).

$$\frac{dX_{sum}}{dt} = \sum_{i=1}^{n} \frac{DSe_i(t)}{h_i(t)} \left(Cs - \frac{Xd}{V} \right)$$

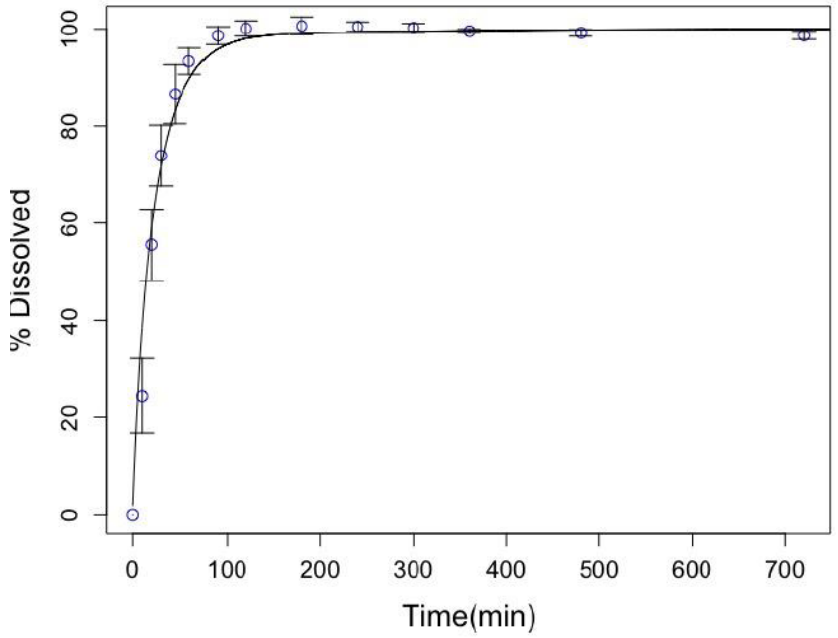
  - Determine Solubility in Solvent, Calculate Diffusion Coefficient
  - Consider Changing Surface Area and Diffusion Layer
  - Calculate Cumulative Dissolution Rates for all ISM stages

S. May, C-M Lehr

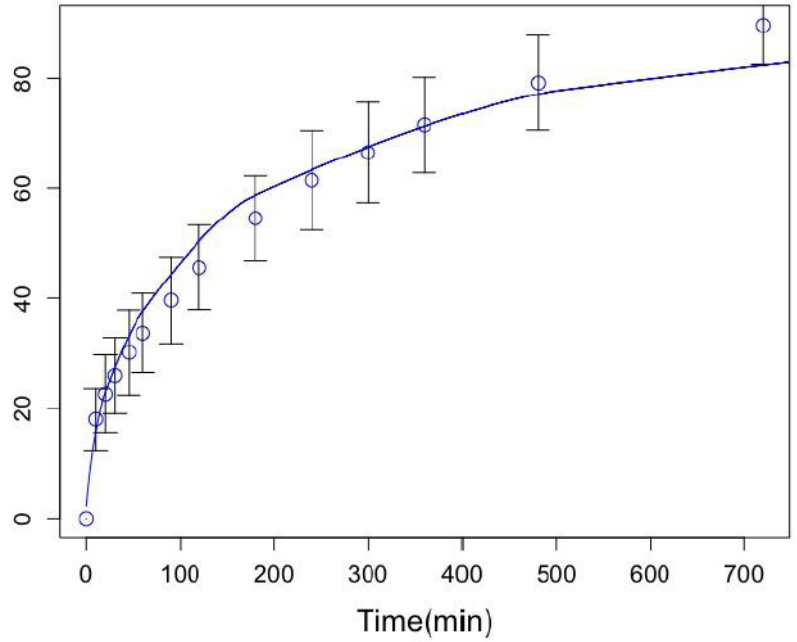
Agreement with Dissolution Theory:

Observed (Data Points) vs Predicted (Line) for BUD and FP

Budesonide (Turbohaler DPI)

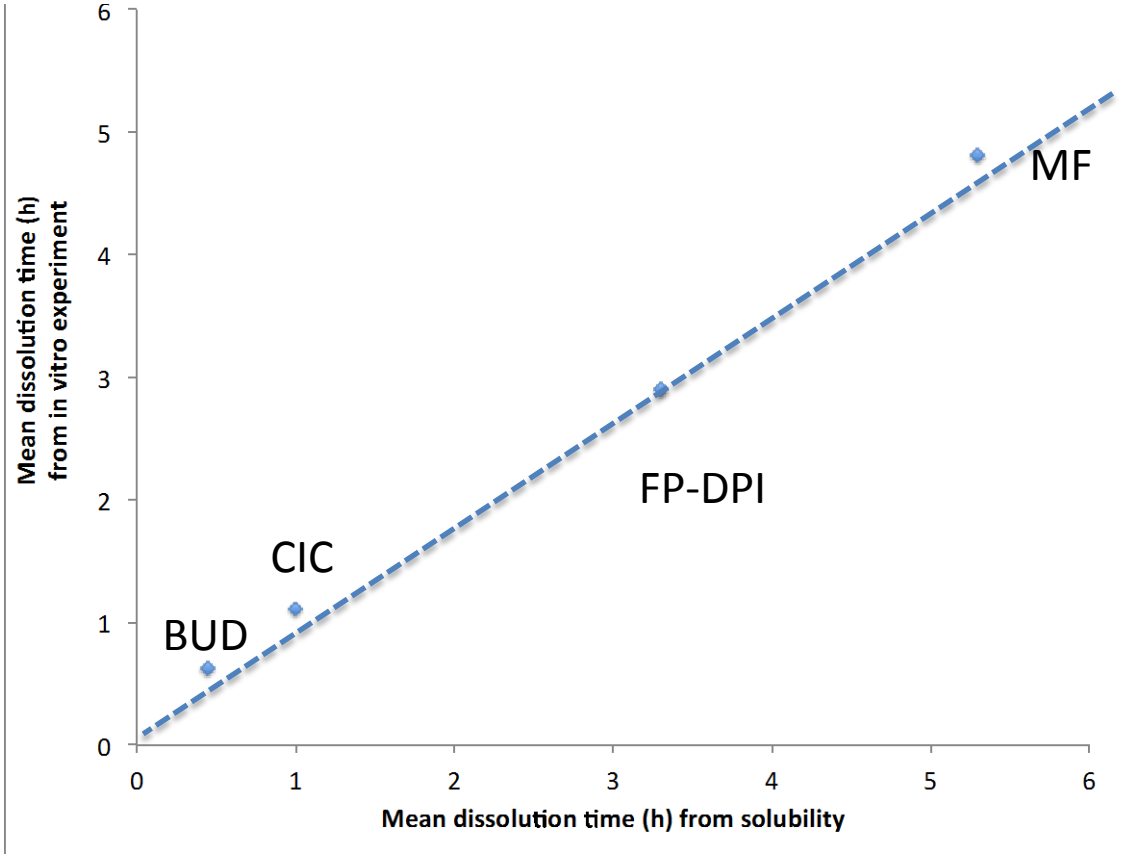


Fluticasone propionate (Flovent DPI)

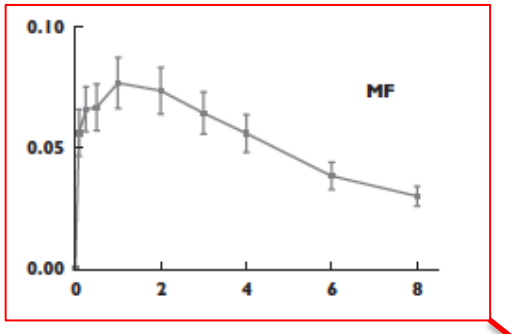


Experimental Data agree with Dissolution Theory

Correlation between Experimental and Solubility/NGI based MDTs

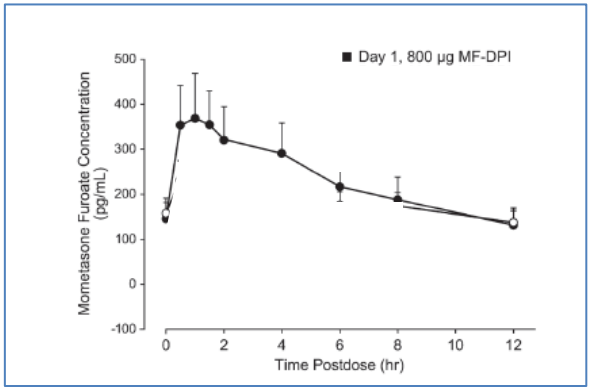


Estimation of *in vivo* solubility – MF

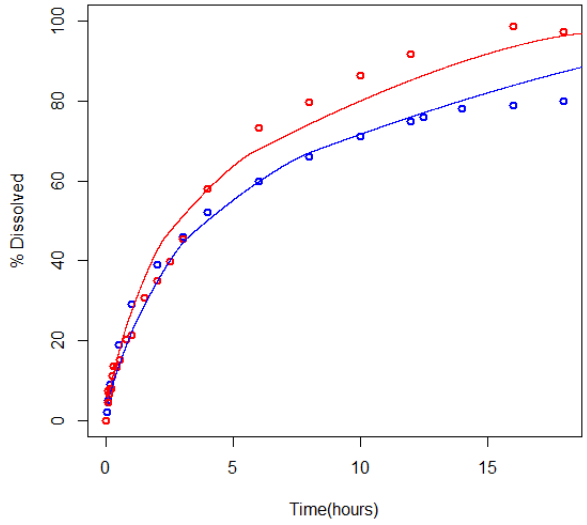


Study 1

Deconvolution



Study 2



Dissolution rate

$$\frac{dX_{sum}}{dt} = \sum_{i=1}^{n} \frac{DSe_i(t)}{h_i(t)} \left(Cs - \frac{Xd}{V}\right)$$

Solubility: 7.5 mcg/ml
12 mcg/ml

Study 1: Sahasranaman S. , Hochhaus G. 2004
Study 2: Derived from “Kosoglou, T., et al., Clin Pharmacol in Drug Development”

In vivo and *in vitro* Solubility

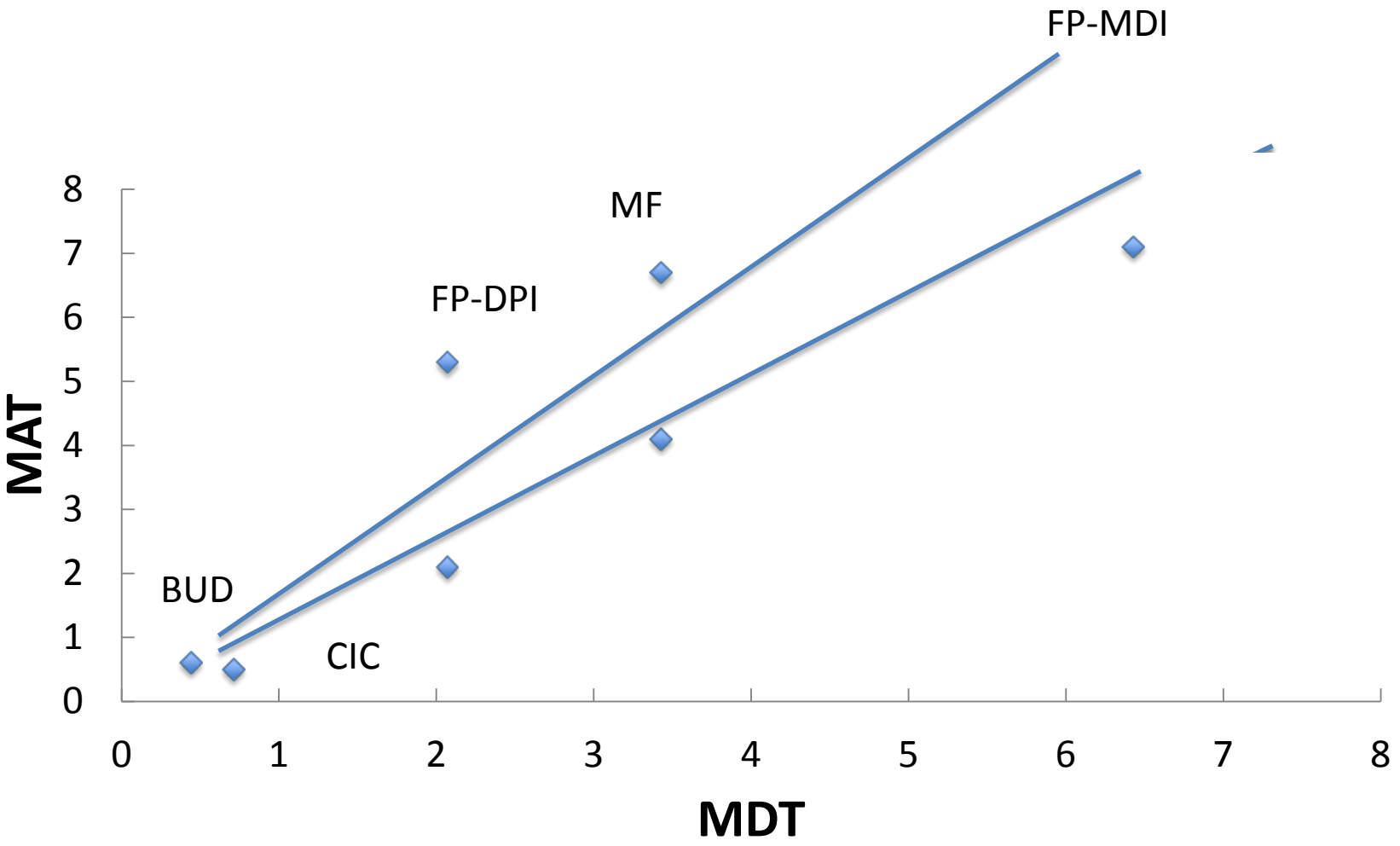
Drug	Solubility In vivo (µg/ml)	Solubility In vitro 0.5% Tween measured (µg/ml)	Solubility In vitro 0.7% Tween calculated (µg/ml)	Solubility In vitro 0.8% Tween calculated (µg/ml)
BUD	50[8]- 175[7]	125	170	191
MF	7.5[6]-12[3]	7.5	10	12
FP	6.5[9]- 9[1]	5.5	7	7.5

0.7 – 0.8 % Tween seems adequate

[1]Thorsson L et al., J Clin Pharmacol. 2001;52:529–38.
[3] Sahasranaman S. , Hochhaus G. 2004
[5]Derived from: Bethke, T. D.et al., J. Allergy Clin. Immunol. 2003, 111 (suppl), S217 abstract 593
[6]Derived from: Kosoglou, T., et al., Clin Pharmacol in Drug Development, 2014. **3**: p. 229-234 and iv data (Affrime et al.).
[7]Derendorf, Hochhaus (unpublished)
[8]Lahelma, S., et al., Br J Clin Pharmacol, 2005. **59**(2): p. 167-73

Correlation between MDT and MAT

(0.7% TWEEN)



Correlation between MDT and MAT seems to exist

Summary of Dissolution Method

System:

- Transwell® system with 8.0 micron polycarbonate membrane
- Stirred receptor compartment (staple)
- 0.5% - 0.8% Tween as dissolution medium
- Anatomical Throat model, NGI

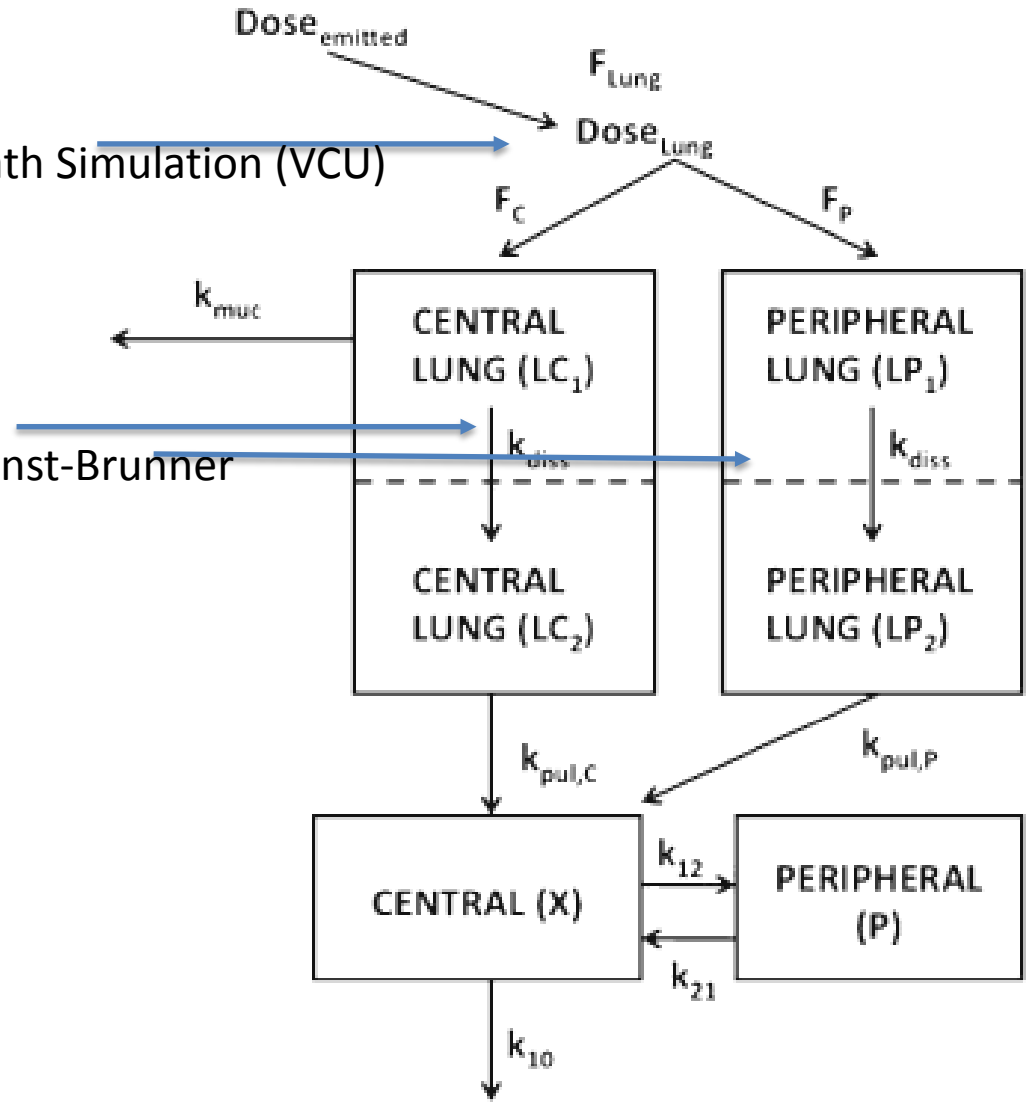
Performance

- Rank order of dissolution similar to in vivo
- Sensitive to particle size
- In agreement with dissolution theory
- IVIVC possible

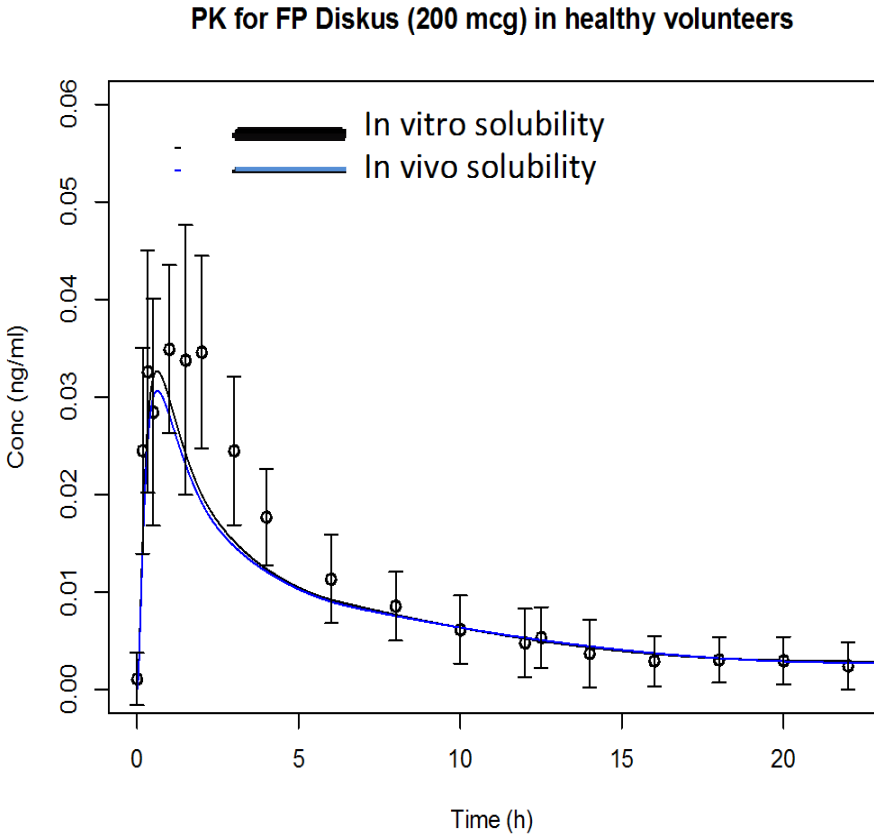
Can Dissolution + NGI Data Predict PK?

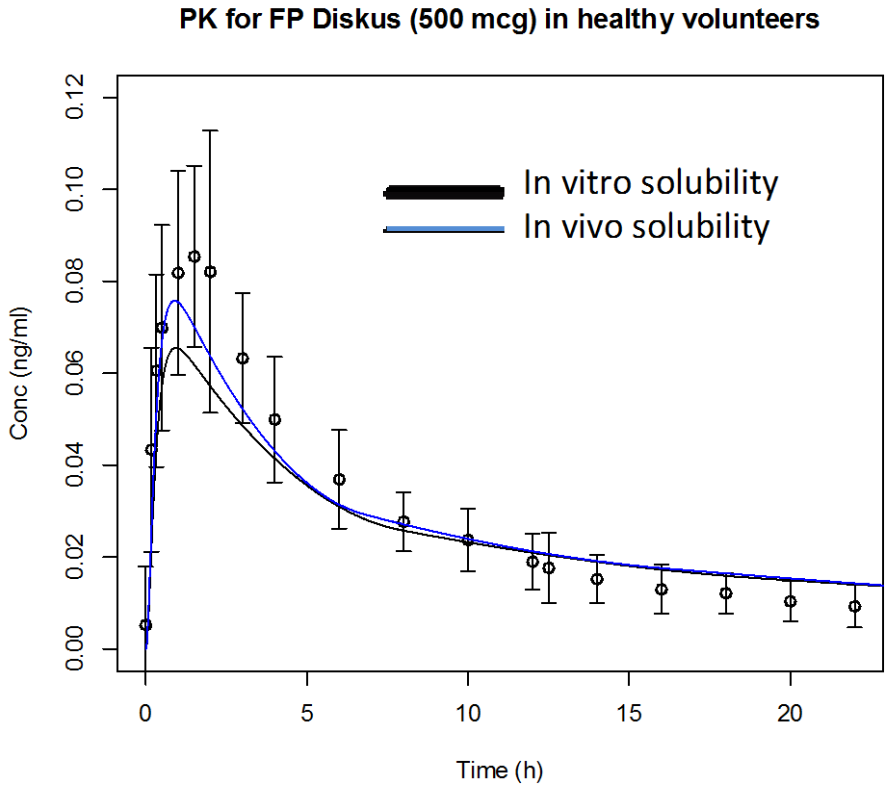
Dose deposited:
ISM, Anatomical throat, NGI, Breath Simulation (VCU)
c/p: Deposition Model (MPPD)

Dissolution rate:
Particle size distribution (NGI)
Solubility in 0.7%-0.8% Tween, Nernst-Brunner

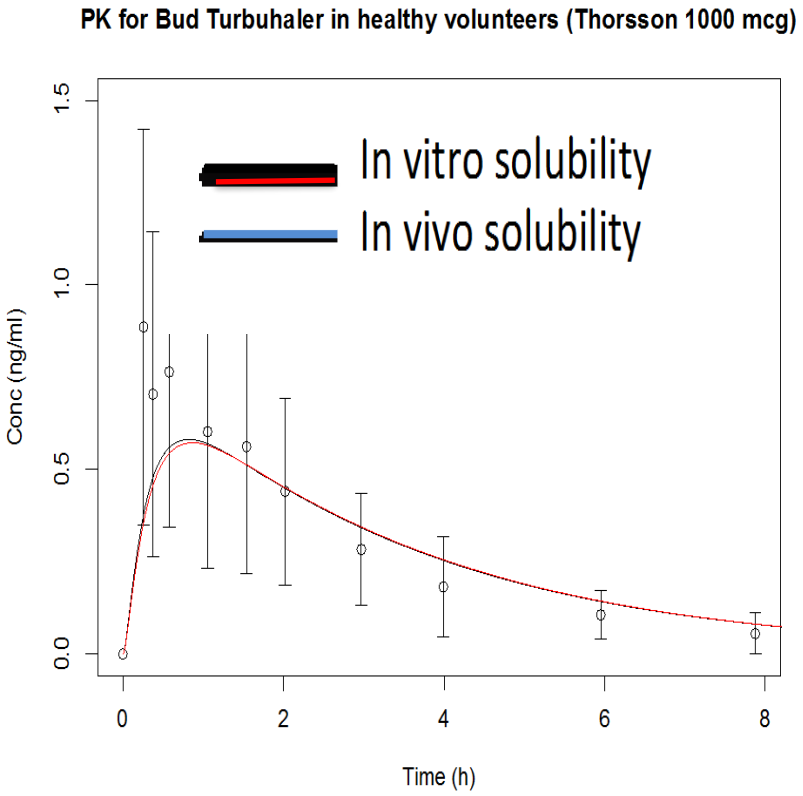


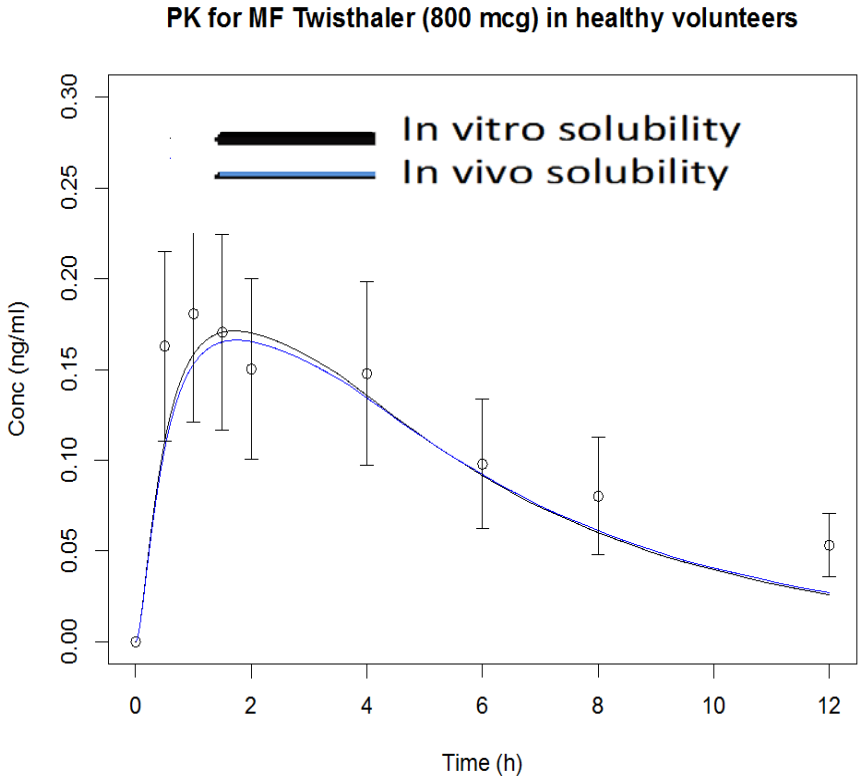
Simulated PK profiles for FP
(0.8 % TWEEN)





Simulated PK for BUD AND MF
(0.8 % TWEEN)



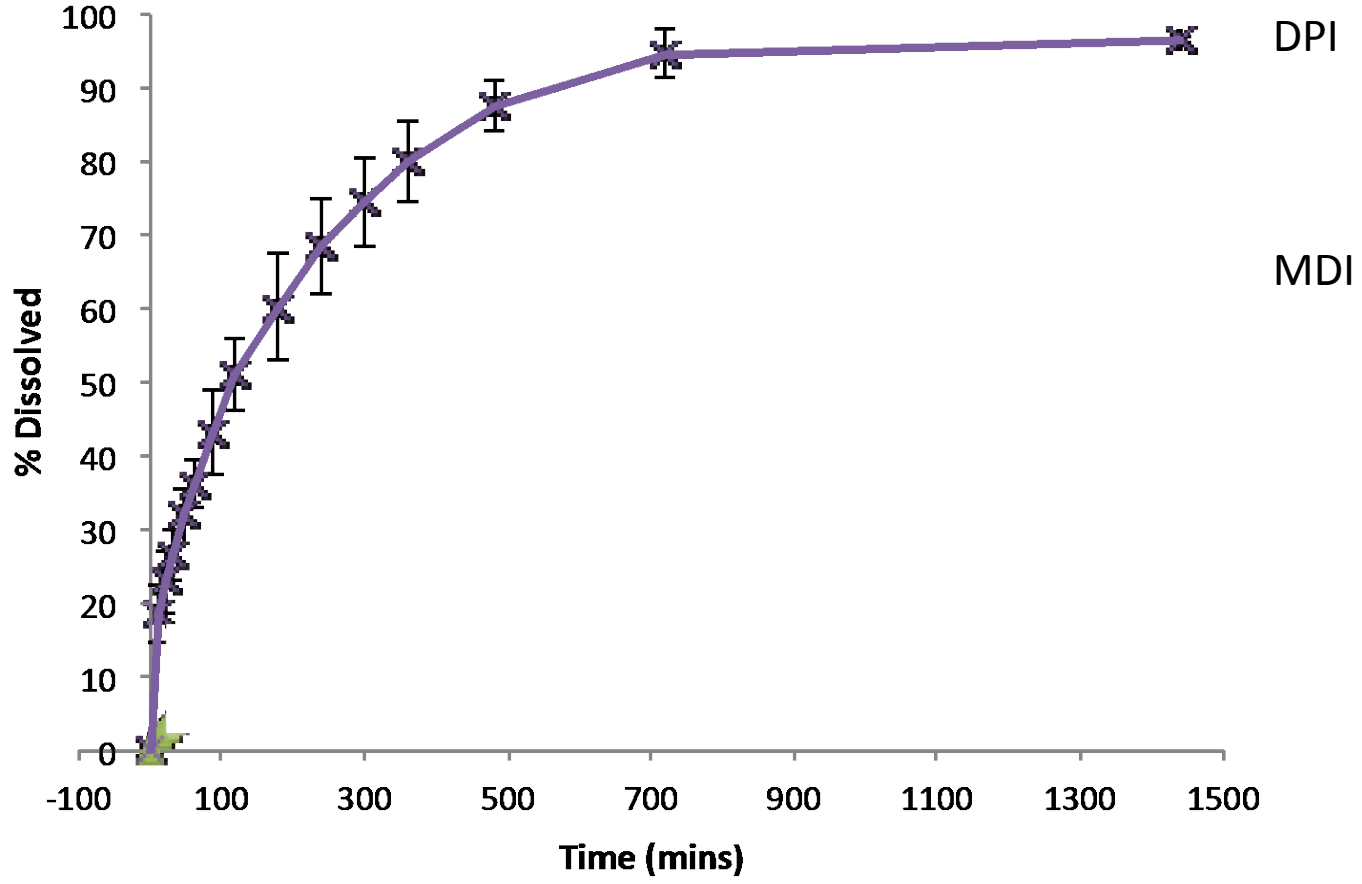


Summary: PK

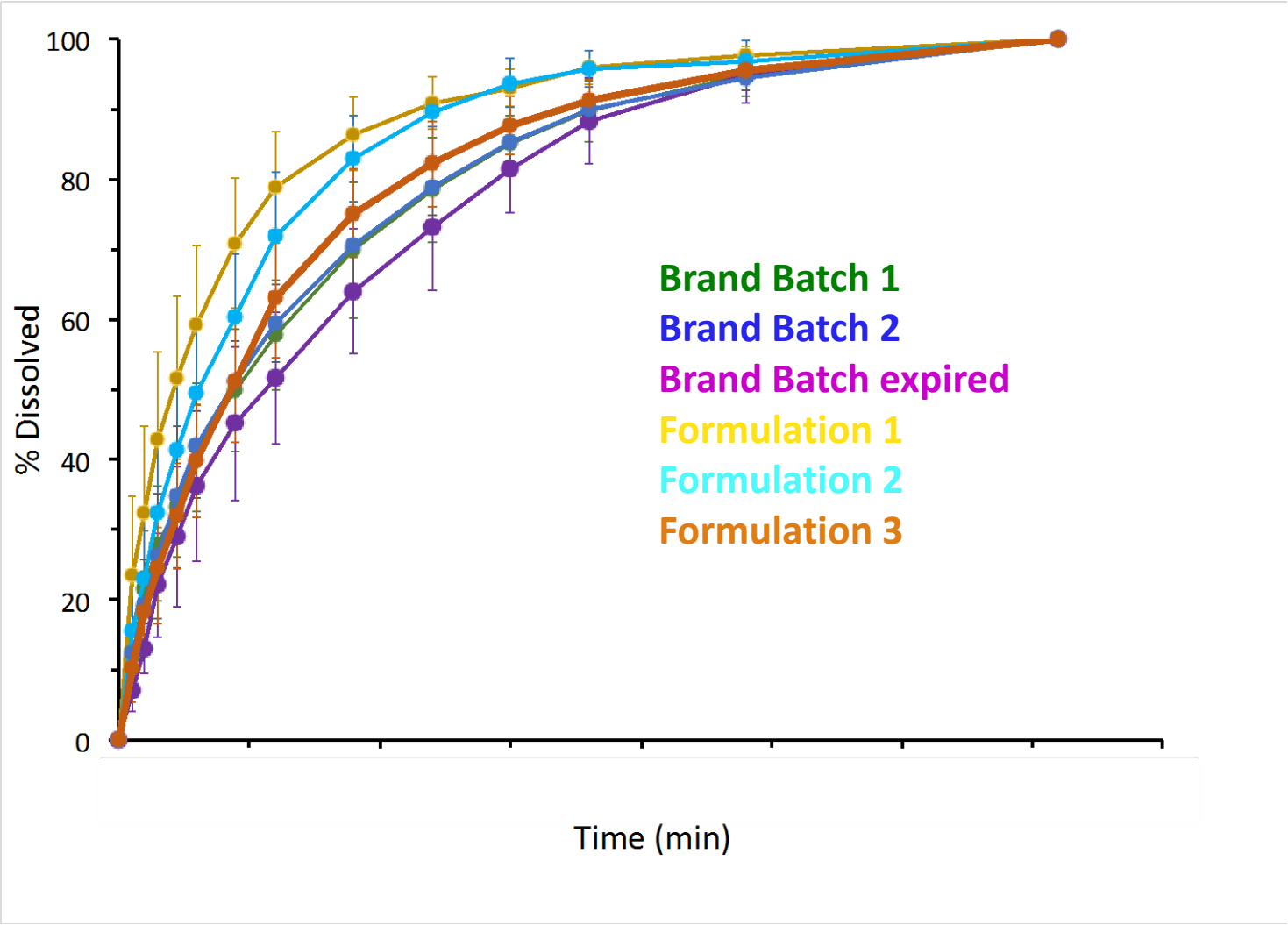
- In vitro data (dissolution, deposition) might be helpful to predict pulmonary fate and effect on PK

Case Studies

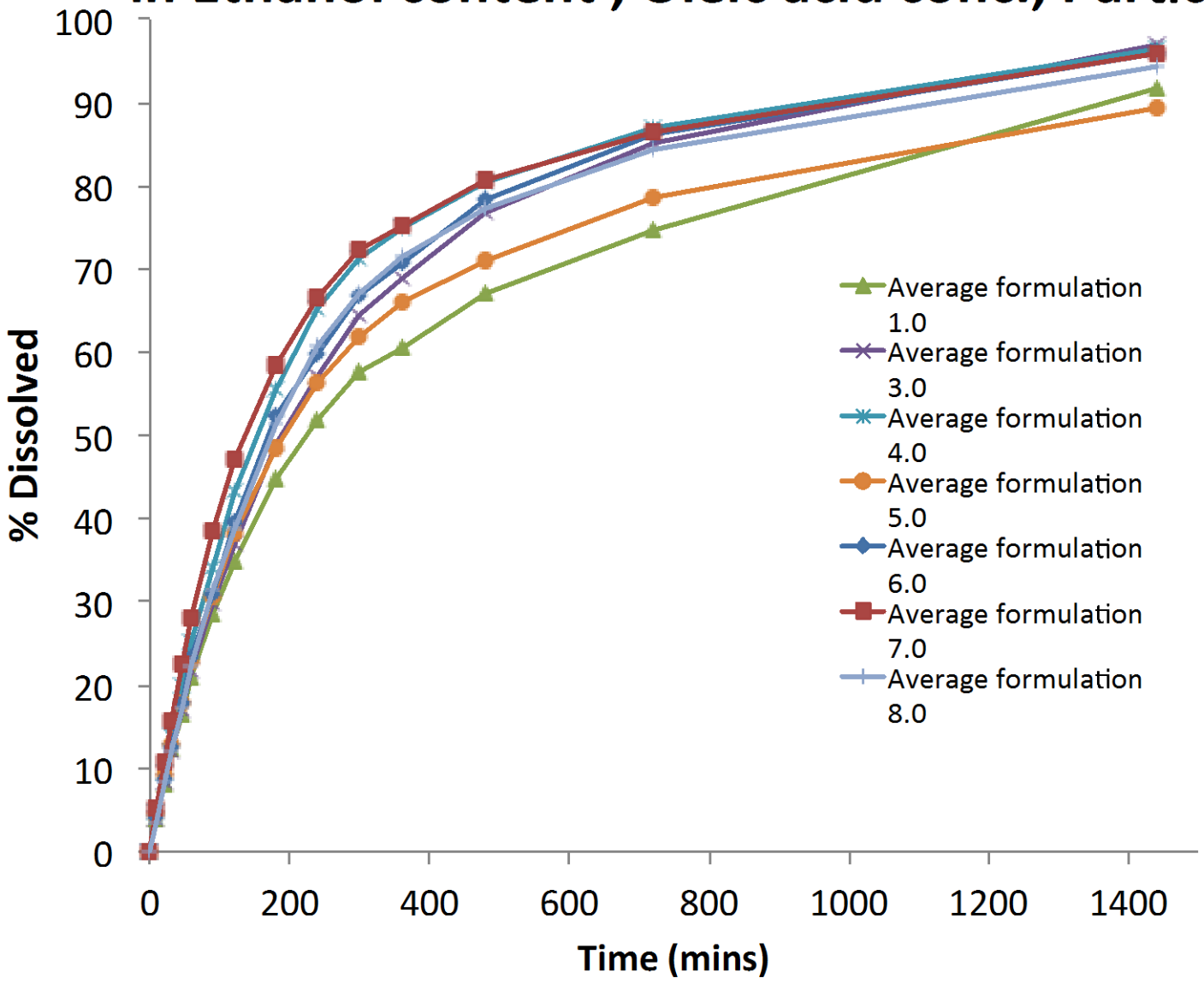
Case 1: Flovent HFA-MDI vs DPI (Diskus)



Case 2: Brand vs other Formulations



Case 3: Mometasone Furoate MDI Differing in Ethanol content , Oleic acid conc., Particle Size



Summary

- Dissolution Method seems to behave
- Method can provide additional information over established regulatory in vitro methods.
- Differentiation of formulations is possible.
- Data can be used to help predicting effects of formulation on PK.

Acknowledgement

- **FDA** (Bavna Saluja, Renish Delvadia, Absar Mohammad (Abir), Denise Conti)
  - Grant U01FD004950 (Dissolution)
  - Contract: 5U01FD004943-05 (MDI)
  - Contract: FDA-SOL-1120918 (Nasal Spray)

- **Sharvari Bhagwat, Mark Rohrschneider (UF)**
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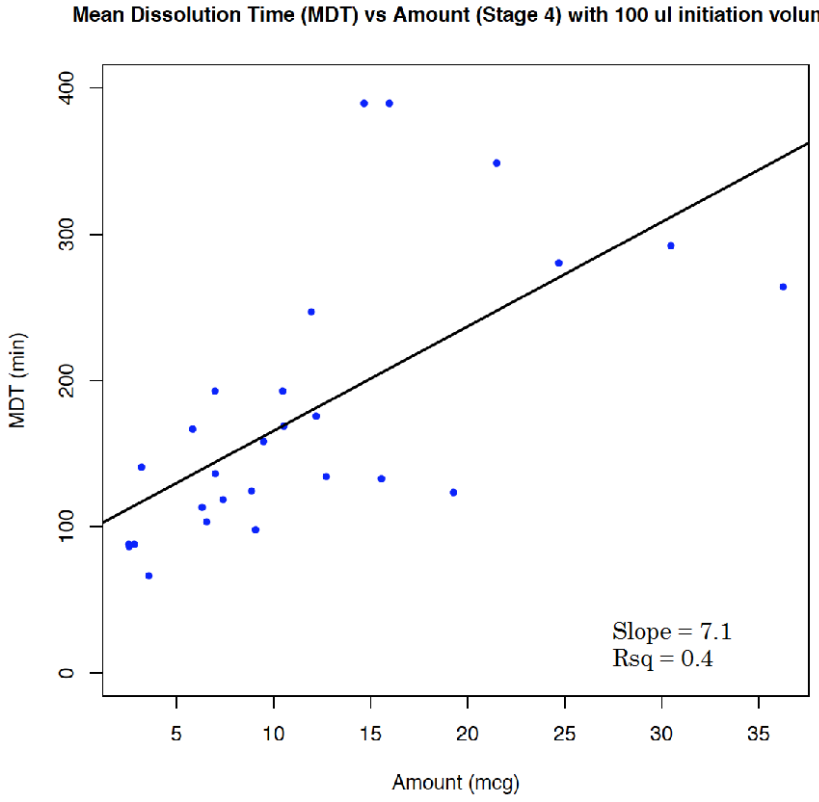
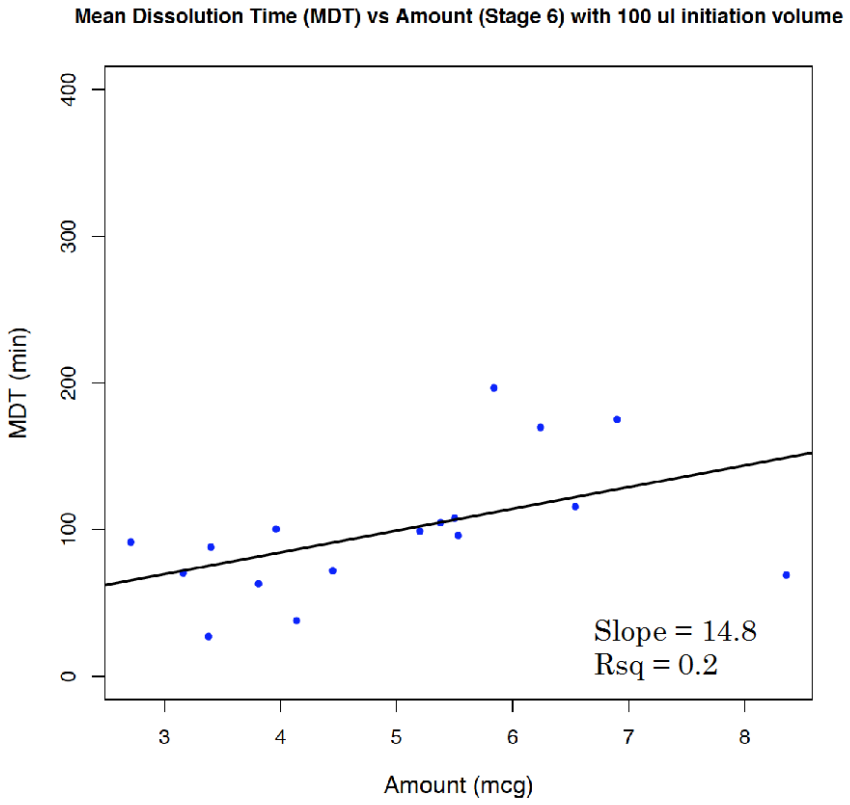
- **Mike Hindle, Worth Longest, Xiangyin Wei (VCU)**
- **Jag Shur, Rob Price (University of Bath)**
- **Dennis Sandell (S5 Consulting)**
- **Aliyah Sheth, Andrew Hamer (Cirrus)**

FP Dose effect – 100 µl in donor compartment



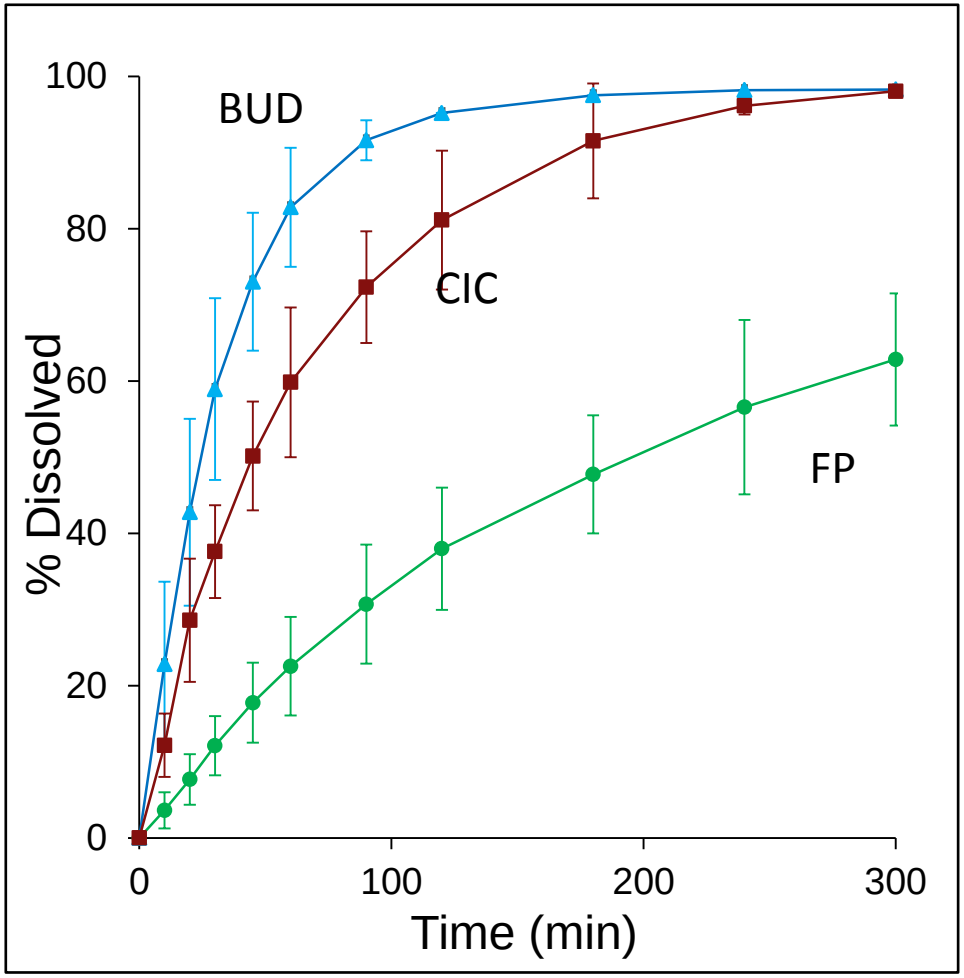


Solubility, Mean dissolution time (MDT) and Mean Absorption time (MAT)

Drug	Formulation	Solubility In vitro 0.5% Tween (µg/ml)	Solubility In vivo (µg/ml)	MDT calculated from *in vitro* solubility (h)	MDT calculated from *in vivo* solubility (h)	MDT (h) Measured *in-vitro* (h)	MAT (h) *in vivo* (h)
BUD	Turbuhaler	125	50[8]- 175[7]	0.45	0.3-1.1	0.62	0.6[4]
CIC	MDI	50		1.1		1	0.5[5]
MF	Twisthaler	7.5	7.5[6]-12[3]	5.3	3.7-5.3	4.8	4.1[3]-6.7[6]
FP	Flovent MDI Flovent DPI	n.d 5.5	n.d 6.5[9]- 9[1]	n.d 3.3	n.d 2.7-3.1	9 2.9	7.1[1] 2.1[2]-5.3[1]

[1]Thorsson L et al., J Clin Pharmacol. 2001;52:529–38.
[2]Allen A et al., Clin Pharmacokinet. 2013;52:37–42.
[3] Sahasranaman S. , Hochhaus G. 2004
[4]Thorsson,Let al. Eur. Respir. J. 1994, 7, 1839–1844.
[5]Derived from: Bethke, T. D.et al., J. Allergy Clin. Immunol. 2003, 111 (suppl), S217 abstract 593
[6]Derived from: Kosoglou, T., et al., Clin Pharmacol in Drug Development, 2014. **3**: p. 229-234 and iv data (Affrime et al.).
[7]Derendorf, Hochhaus (unpublished)
[8]Lahelma, S., et al., Br J Clin Pharmacol, 2005. **59**(2): p. 167-73
[9] H. Möllmann et al., J Clin Pharmacol. 41, 1329-1338 (2001)

Comparing dissolution profiles of different drugs in 0.5% SDS in water

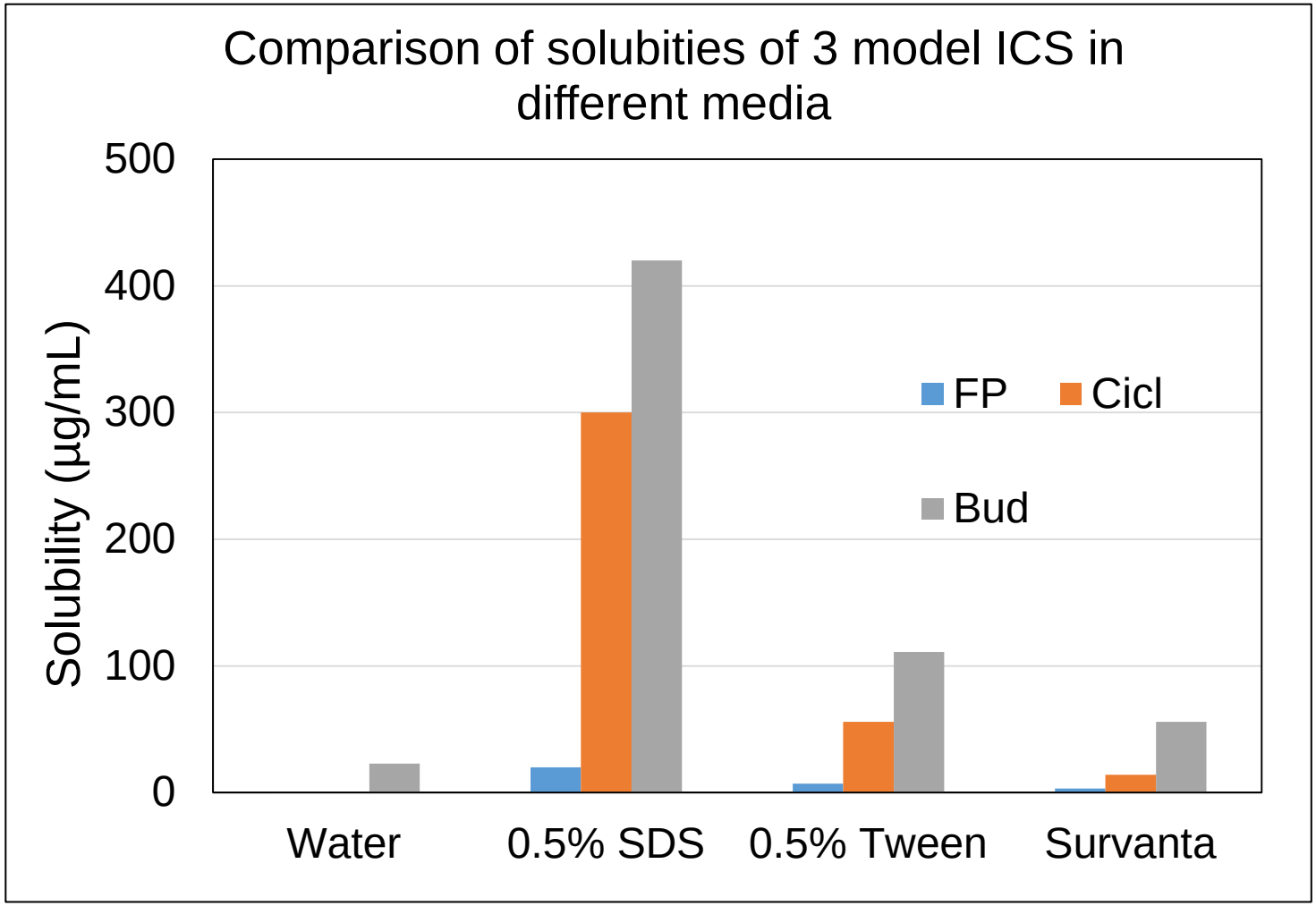


Rohrschneider et al. , Mol. Pharmaceutics, 2015

ICS	MAT (h)	MDT in experimental setup (h)
Ciclesonide	<1 (0.43)	1.2 ± 0.2
Fluticasone Propionate	5-7	5 ± 1.2
Budesonide	1 (0.3 – 1.8)	0.6 ± 0.1

0.5 % SDS seems suitable medium

Selecting a more discriminating medium



Necessary equation, applied to every stage of the cascade impactor experiments

Radius and Change in radius over time/stage (NGI)

$$d_{geo} = d_{aero}\sqrt{\frac{1}{\rho}} \qquad r = \frac{d_{geo}}{2} \qquad r_i(t) = \left(\frac{3X_i(t)}{4\pi\rho N_i}\right)^{1/3} = h_i$$

Number of particles/stage (NGI)

$$N = X_i(t=0)\left(\frac{4\pi r(t=0)^2\rho}{3}\right)_{D=}^{-1}$$

Diffusion coefficient

$$D = \frac{13.26 * 10^{-5}}{\eta_{water}^{1.4} * V_M^{0.589}}$$

Surface area/stage (NGI)

$$Se_i(t) = N4\pi r_i(t)^2$$

Dissolution rate NGI, solubility d

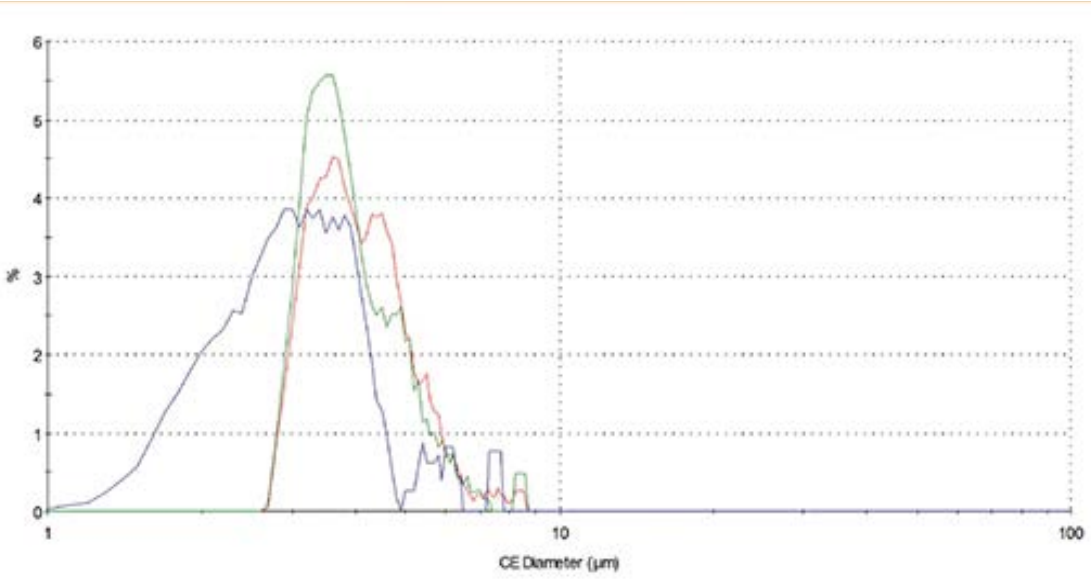
$$\frac{dX_{sum}}{dt} = \sum_{i=1}^{n} \frac{DSe_i(t)}{h_i(t)}\left(Cs - \frac{Xd}{V}\right)$$

X_{sum} - total amount of undissolved drug (gm)
D – diffusion coefficient (cm^2/min)
Se_i – surface area of particle associated with size i
h_i – diffusion layer thickness of the particle with size i (cm)
P= density
Cs – saturation solubility (gm/ml)
Xd – amount dissolved (gm)
V – volume (ml)
η –viscosity
V_M– Van der Waals volume

S. May et al., Pharm Res (2014) 31:3211–3224

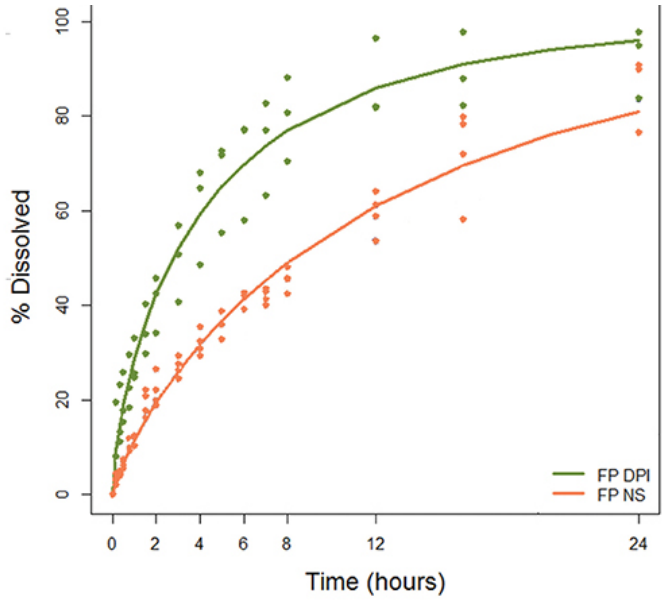
Fluticasone DPI vs Nasal Spray

Particle size: Imagining with Raman spectroscopy



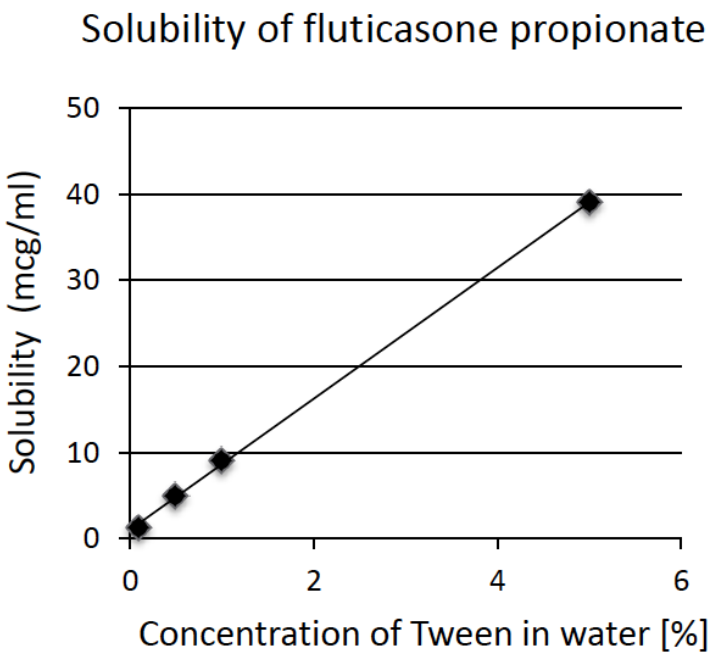
FP delivered using a DPI (blue curve) has a finer particle size compared to that observed using a NS (red and green curves).

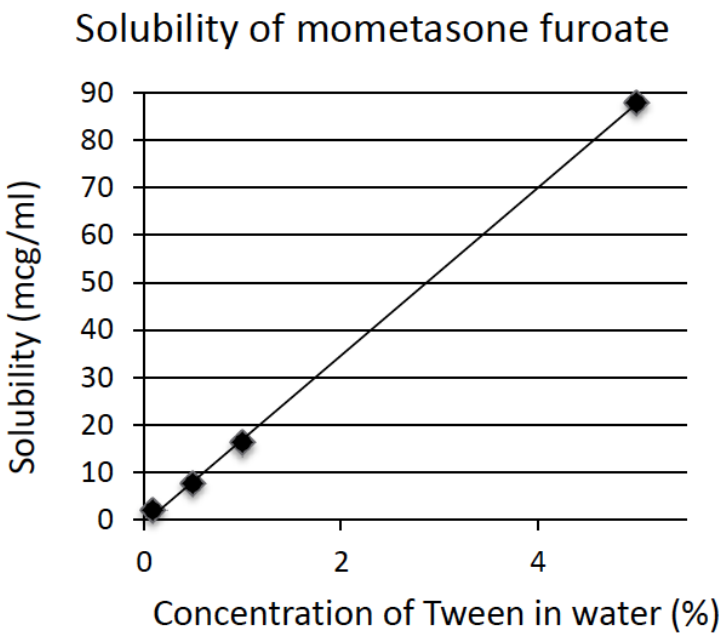
Dissolution Test



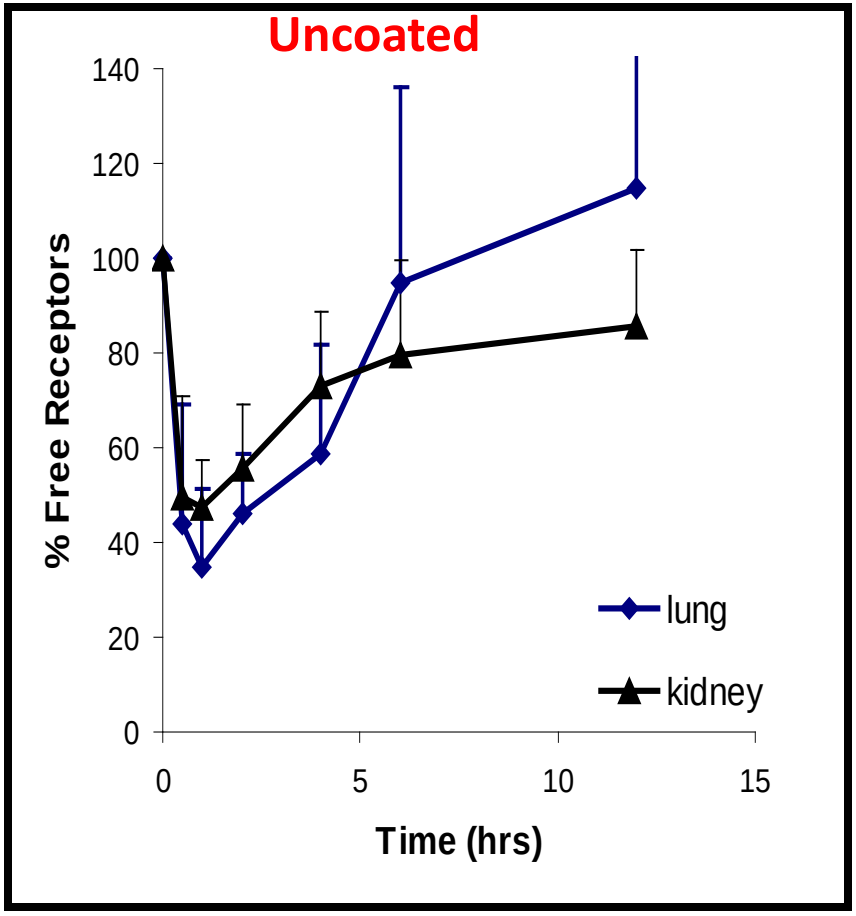
Dissolution profiles for Fluticasone Propionate delivered by DPI and Nasal Spray. The delivery device substantially impacts the dissolution rate of the drug.

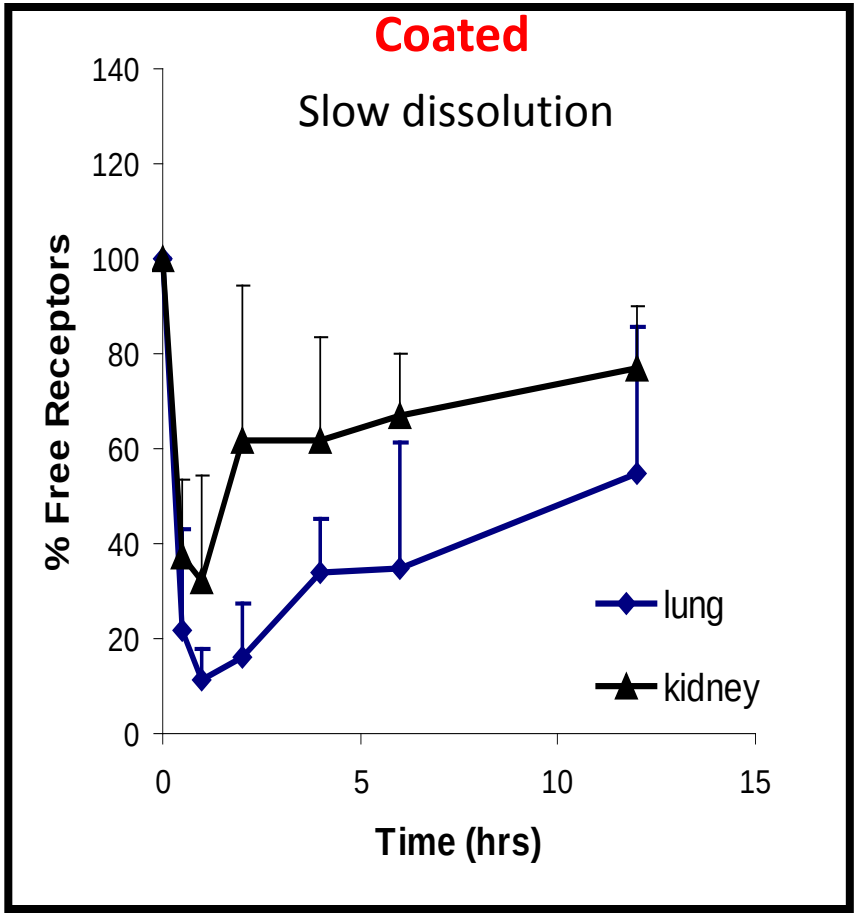
P. Kippax, D. Huck-Jones, J.D. Suman, G. Hochhaus, S. Bhagwat. Drug Development and Delivery, March 2016, 28-35


Solubility of fluticasone propionate
Solubility (mcg/ml)
50
40
30
20
10
0
0
2
4
6
Concentration of Tween in water [%]


Solubility of mometasone furoate
Solubility (mcg/ml)
90
80
70
60
50
40
30
20
10
0
0
2
4
Concentration of Tween in water (%)

Coated (slow dissolving) Material shows increased pulmonary Targeting in Rats





How can we Identify Solvent with *In Vivo* Characteristics?

- **Dissolution rate** *(in vivo*) is determined by
  - **Particle size** (distribution), known
  - **Solubility** (unknown for Lung Lining Fluid)
- For **slowly dissolving drugs** (dissolution is rate limiting step)**:**
  - **Absorption profiles = Dissolution profile**
- Determine Solubility necessary to match Absorption profiles
- Identify Medium providing the same Solubility.