Development of an Optimized Dissolution Test System for OINDPs

FDA Workshop Jan 9, 2018:

New Insights for Product Development and Bioequivalence Assessments of Generic Orally Inhaled and Nasal Drug Products (OINDPs)

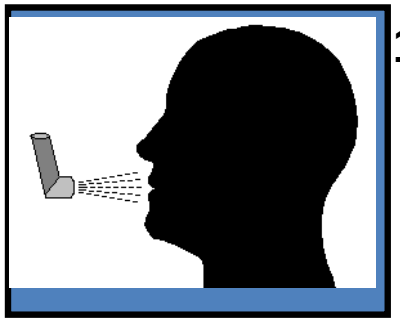
UF UNIVERSITY of FLORIDA

Hochhaus@ufl.edu

Acknowledgements

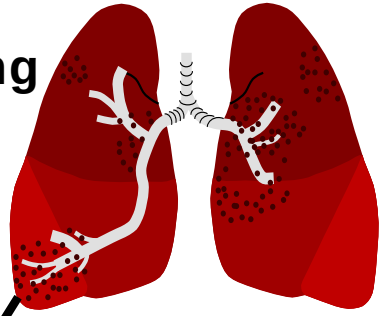
- **FDA** (Mohammad Absar, Denise Conti, Renish Delvadia, Larry Lee, Murewa Oguntimein, Bavna Saluja)
  - U01FD004950 (Dissolution)
  - 5U01FD004943-05 (MDI)
  - FDA-SOL-1120918 (Nasal Spray)
  - HHSF223401610099C (DPI)
- **Juergen Bulitta (UF)**
- **Sharvari Bhagwat, Mark Rohrschneider, Uta Schilling (former Students), Abhinav Kuramaddali**
  - YeLaetitia Sandini, Martin Jetzer
  - Adriely Goes, Sara Broenner
  - Anna Krome, Raju Rajan, Deborah Spiess
  - Hannah Kranich, Martin Mueller
  - Brianna Glenn, Aksha Patel, Annabelle Bouanane
- **DPI, Nasal: Mike Hindle, Xiangyin Wei (VCU)**
- **Dissolution, DPI, Nasal: Jag Shur, Rob Price (University of Bath)**
- **Dissolution, MDI: Dennis Sandell (S5 Consulting)**
- **MDI: Aliyah Sheth , Andrew Hamer (Recipharm), Madeline Hallinger (Recipharm)**

The Fate of Inhaled Drugs



Mouth and Pharynx

10 - 60 % Lung Deposition



Lung

Pulmonary Effects

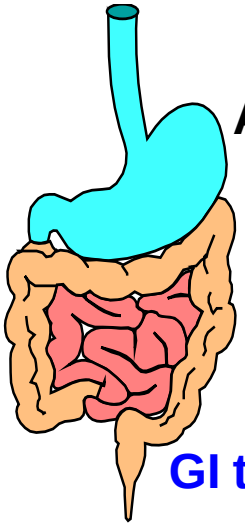
Complete Absorption from the Lung

Systemic Circulation

Selectivity

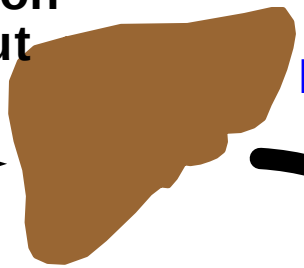
Orally absorbed Fraction

40 - 90 % swallowed
(reduced by spacer or mouth rinsing)



GI tract

Absorption from Gut



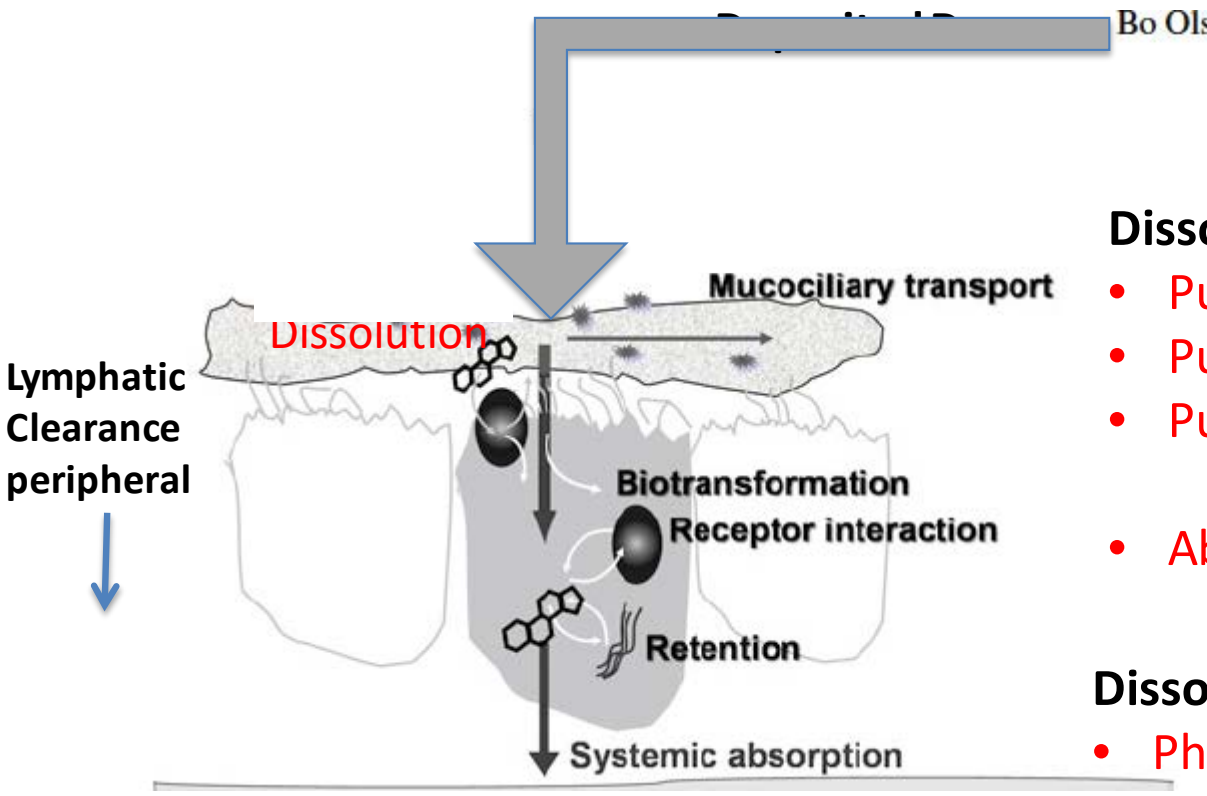
Liver

First-pass Inactivation

Systemic Side Effects

Clearance

Biopharmaceutical Aspects



Dissolution rate affects:

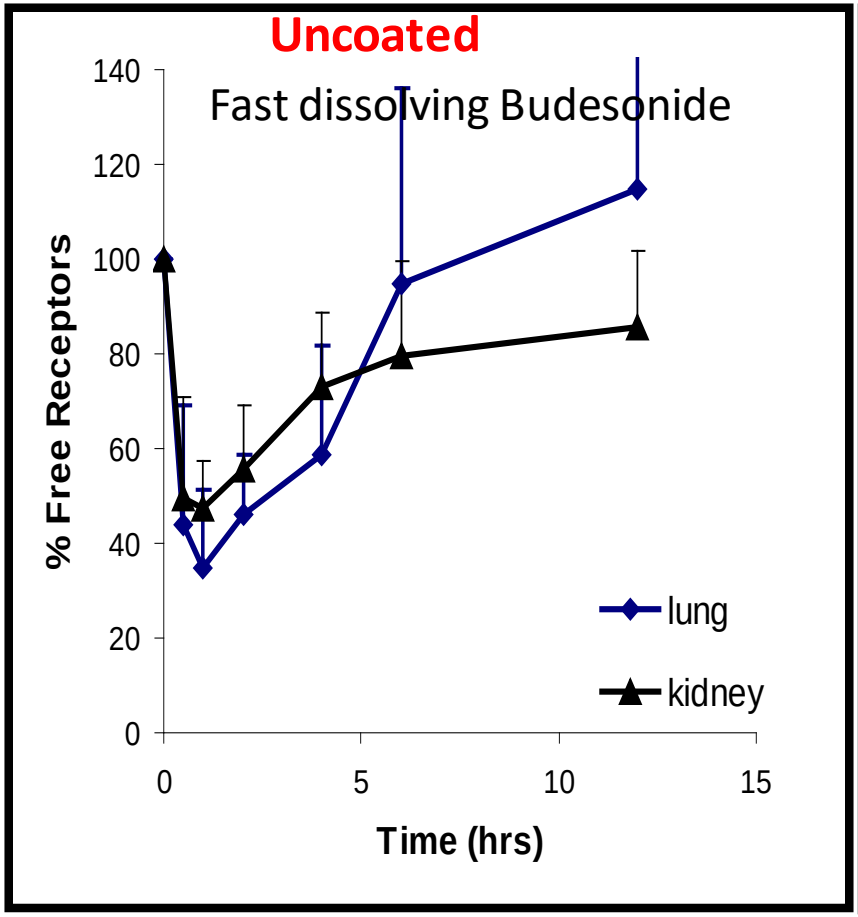
- Pulmonary available dose
- Pulmonary residence time
- Pulmonary targeting

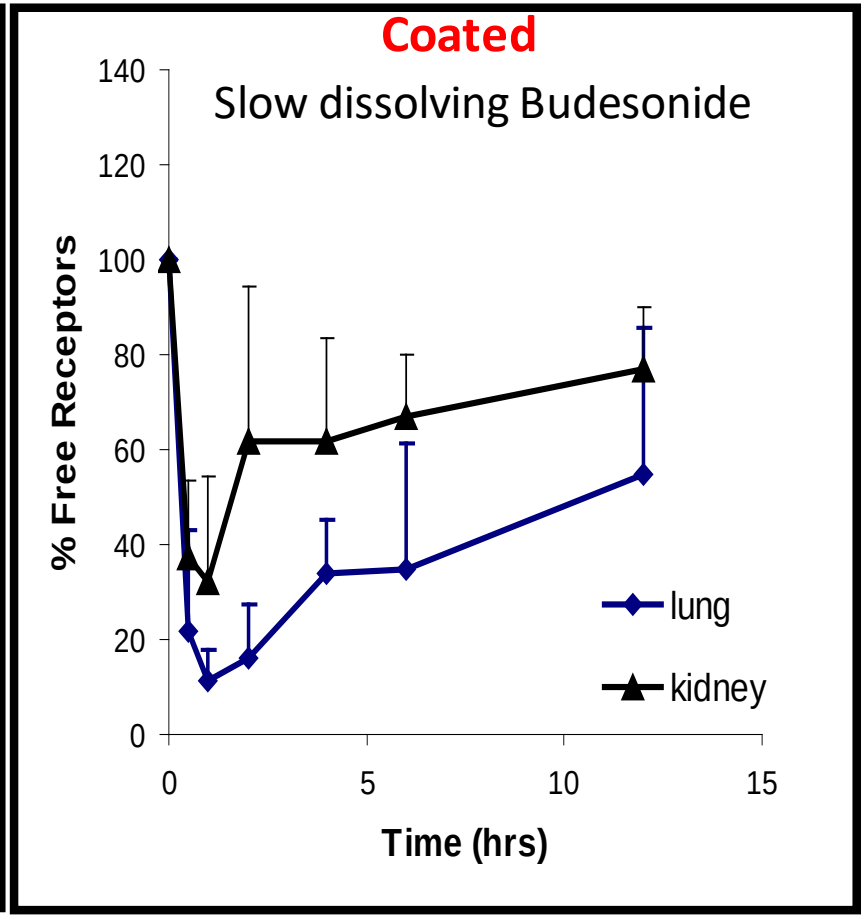
- Absorption rate

Dissolution rate is affected by:

- Physicochemical properties
- Formulation (size, crystal structure, adjuvants)
- Sink conditions (c/p)

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





Bioequivalence and in vitro Assays

- Same dose (pulmonary available dose, impactor)
- Same regional deposition (impactor + *in silico* methods)
- Same pulmonary residence time

  Dissolution/Permeability

  - Interaction with membranes
  - Lysosome trapping,
  - Ester formation
  - **Dissolution rate**

  } Not formulation dependent

- Conclusion: Dissolution rate is relevant for defined **lipohilic drug** for which **dissolution is the rate limiting step.**

What Drugs should be Tested?

Class	Drug	Cascade impactor FPD+ C/p	Dissolution Rate
(I) High solubility High Permeability	Albuterol	X	-
(II) Low solubility High Permeability	Budesonide Mometasone propionate Fluticasone furoate Fluticasone propionate	X X X X	X X X X
(III) High solubility Low Permeability	Tiotropium Oladaterol Salmeterol Formoterol	X X X X	- - - -
(IV) Low solubility Low Permeability	???	x	x

Structure of Talk

- Method Development and Validation
  - Sample preparation
  - Dissolution method
    - Making Dissolution the Rate Limiting Step
    - Overcoming/Evaluating the Dose Effect
    - The right solvent
- Case Studies
- In vitro/in vivo Correlations

Method Design

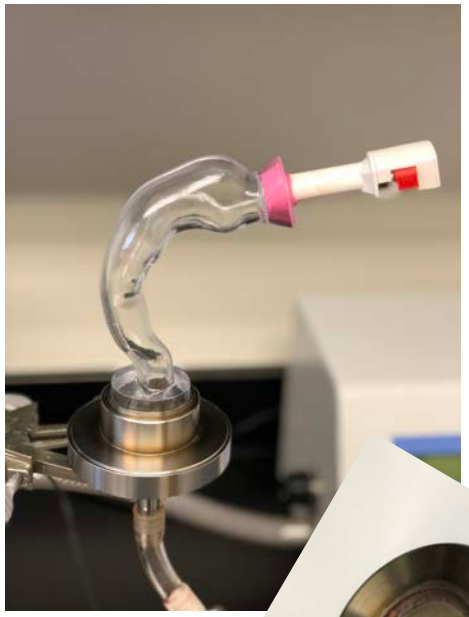
- **Sample Preparation**

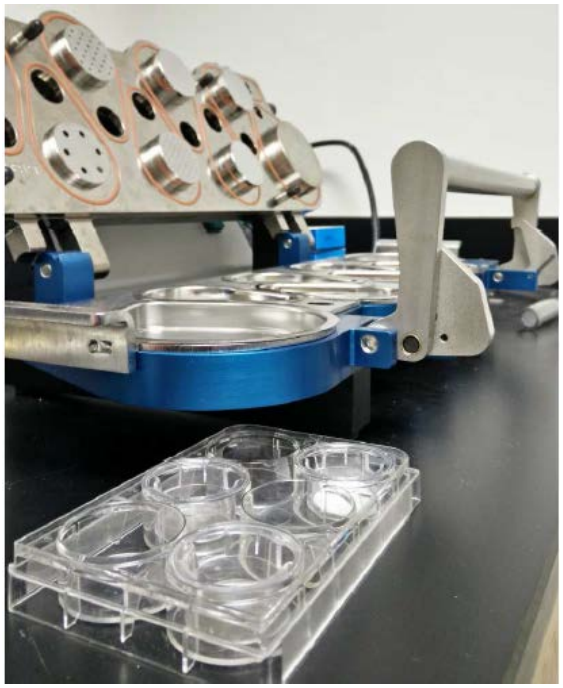
  Inhalation
  - DUSA >>> full range of particles
  - Cascade Impactor >>> defined stage(s)
  - **Anatomical Throat** >>> ex-throat dose

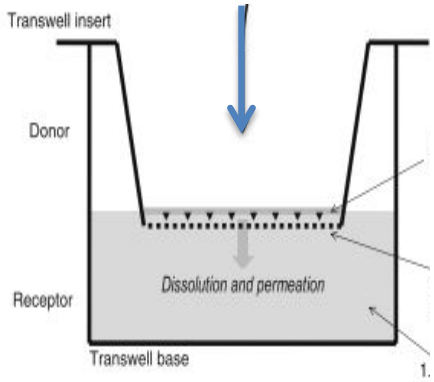
  Nasal
  - No preparation necessary
    - Open nasal spray vial, remove aliquot, pipet into receptor compartment of a Transwell or onto filter paper (USP method)

- **Dissolution Test Systems**
  - Systems Including diffusion across membrane (biomimetic)
    - **Transwell system**/Franz cell
    - Dissolvit® system (Gerde et al., ASSAY and Drug Develop. Technol., 2017)
  - Systems without controlled membrane diffusion step
    - USP II and IV

Applying the Dose (Inhalation)



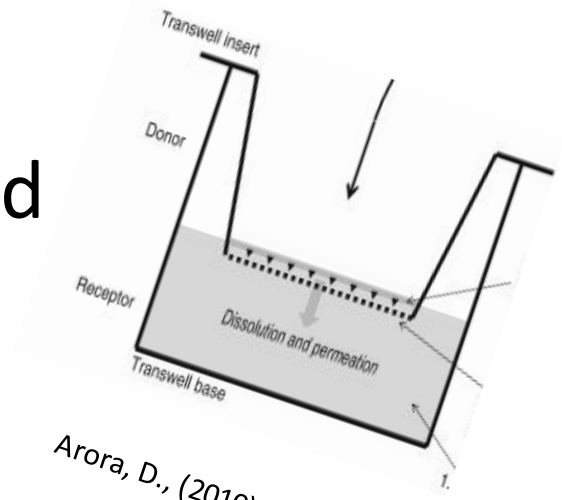




DEVELOPMENT OF TRANSWELL SYSTEM

Transwell® system is a two step process: dissolution + diffusion across membrane

- Dissolution has to be rate limiting step
- Relevant solvent
- In vitro/in vivo correlation should exist

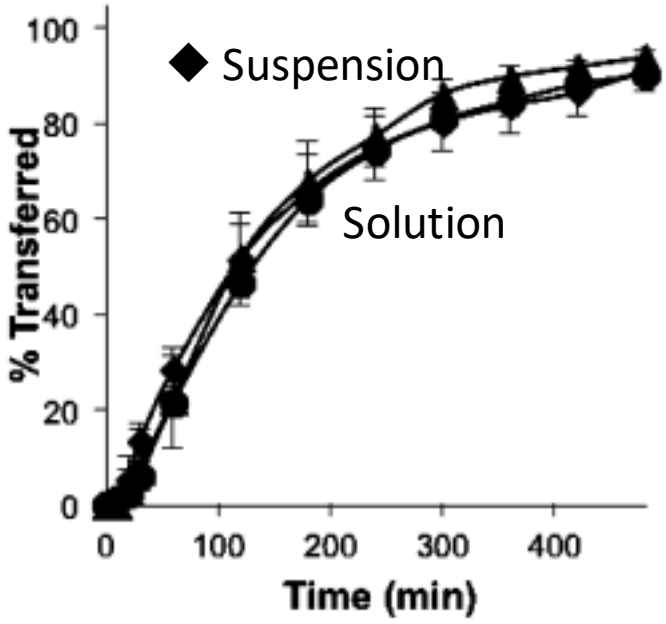


Arora, D., (2010)

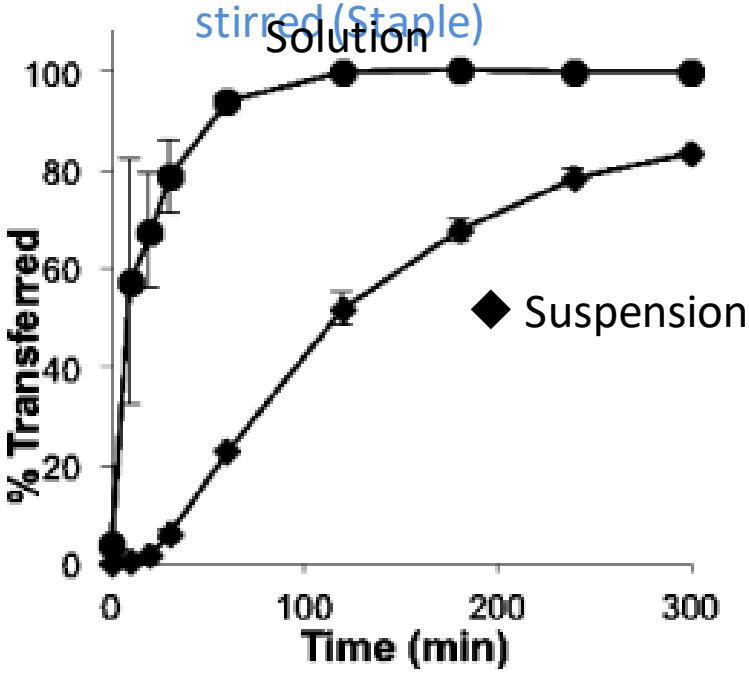
Pitfall 1: Diffusion across Membranes?

Ciclesonide Solution vs MDI

0.4 µm Transwell® Membrane

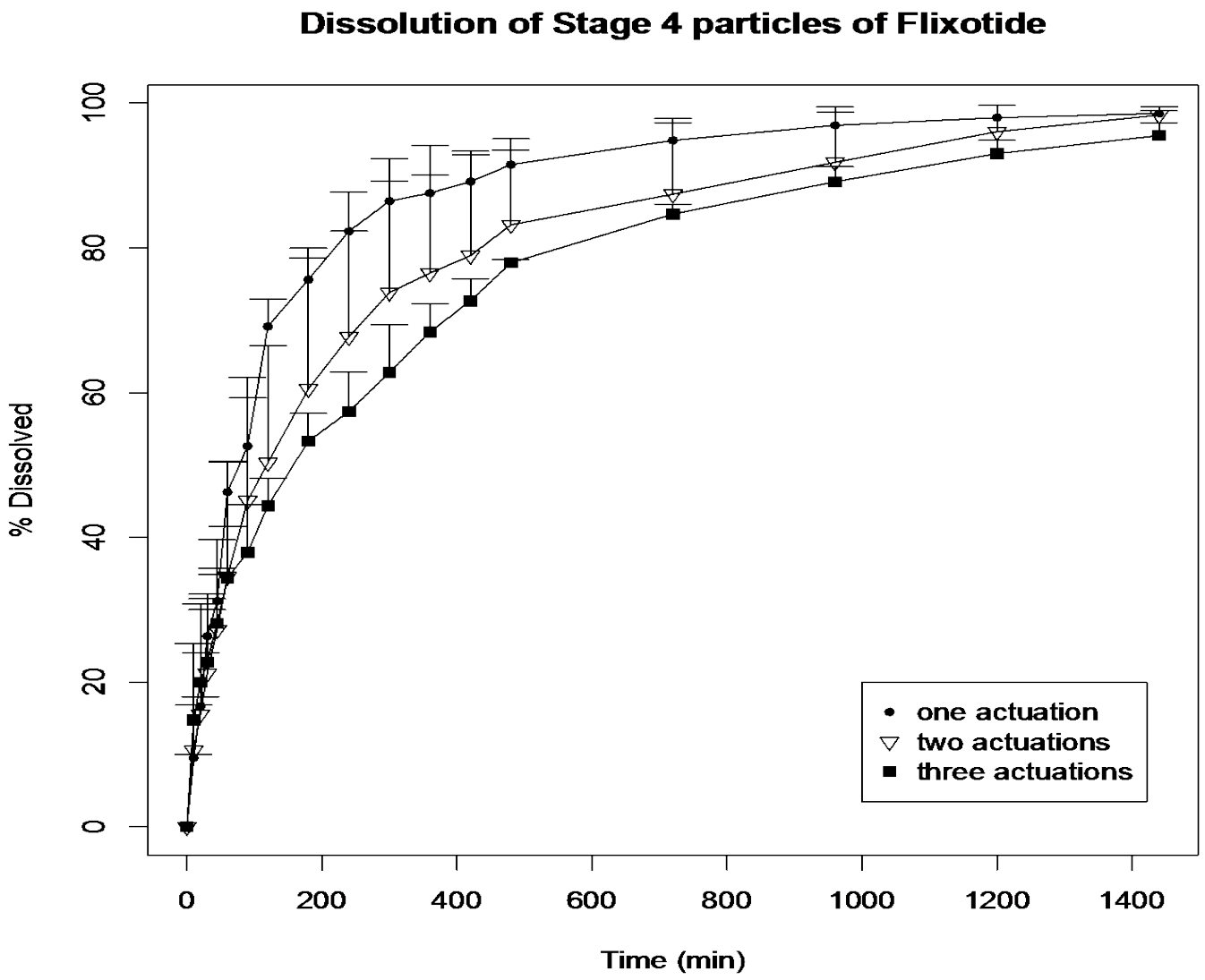


8 µm Transwell® Membrane, stirred (Staple)

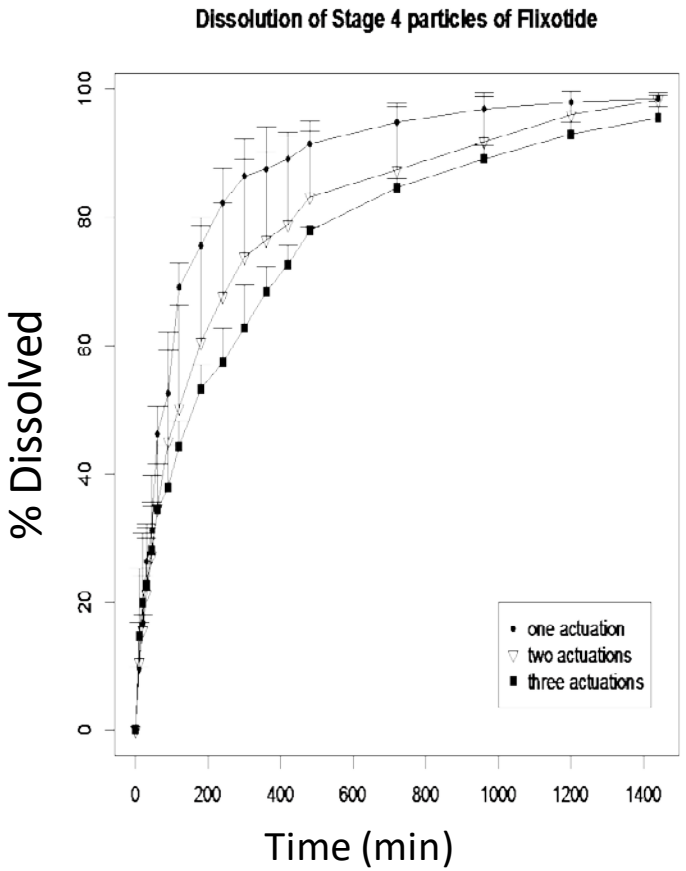


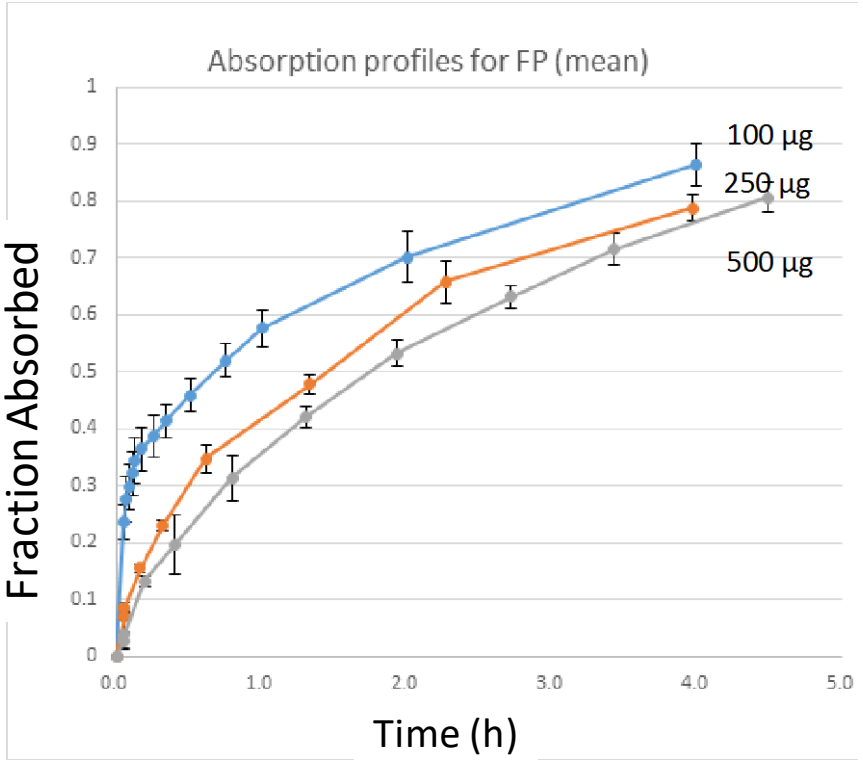
Use 8 µm Membrane, Stirred

Pitfall 2: Dose Effect?



Dose Effect: in vitro/in vivo





- **Dose effect occurs in vivo (Sandoz Citizen Petition)**

However:

- **For dissolution test to be used for quality control and within ANDA work, it should be eliminated.**

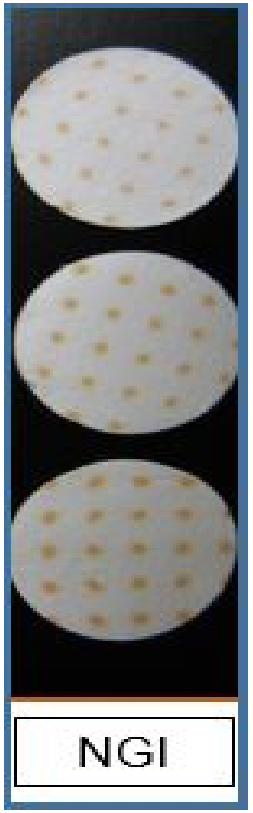
Dose Effect (1-3 Actuations)

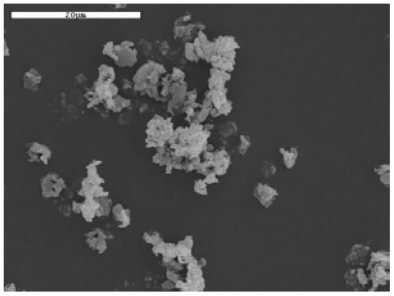
NGI

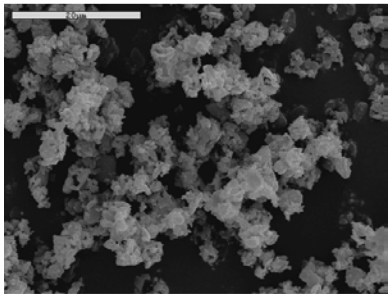
1x

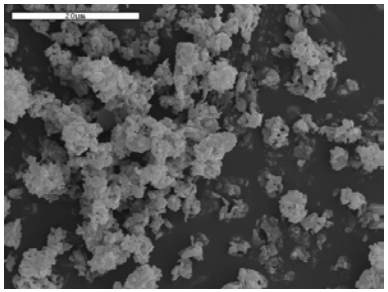
2x

3x

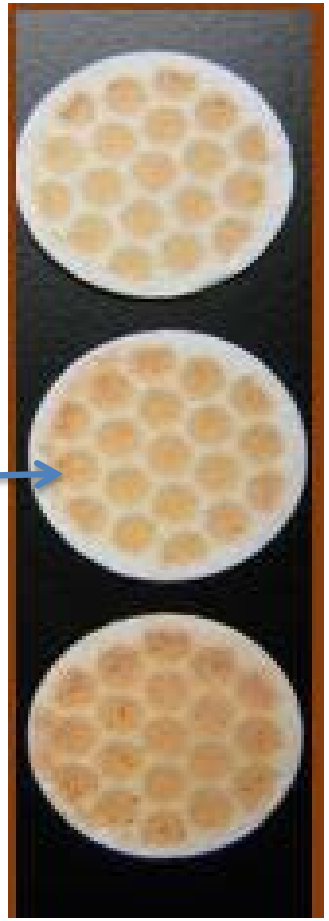




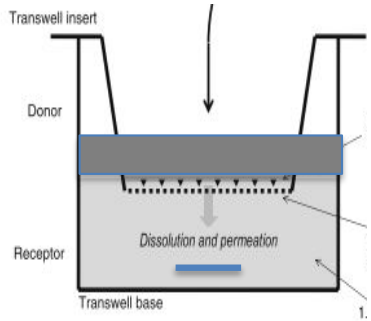




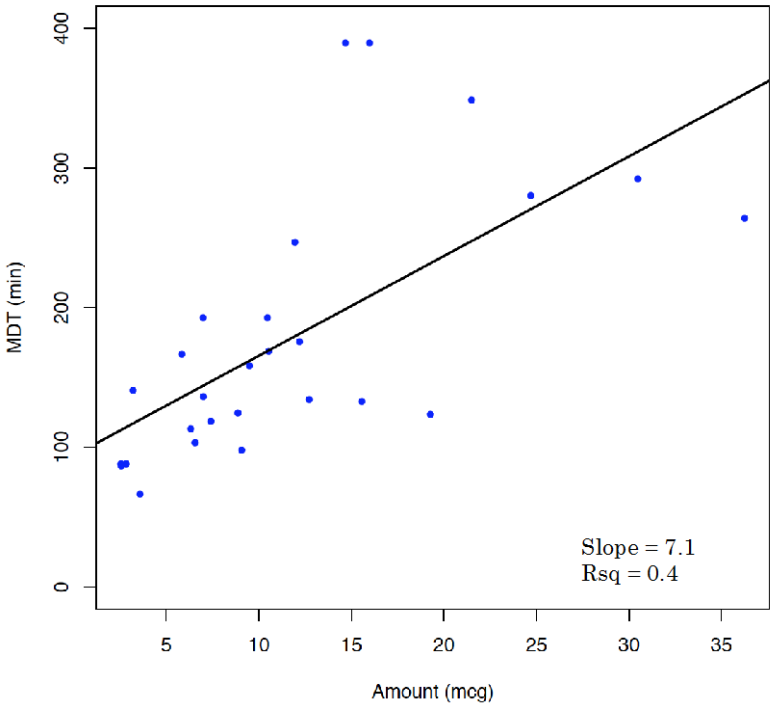
Anatomical Throat



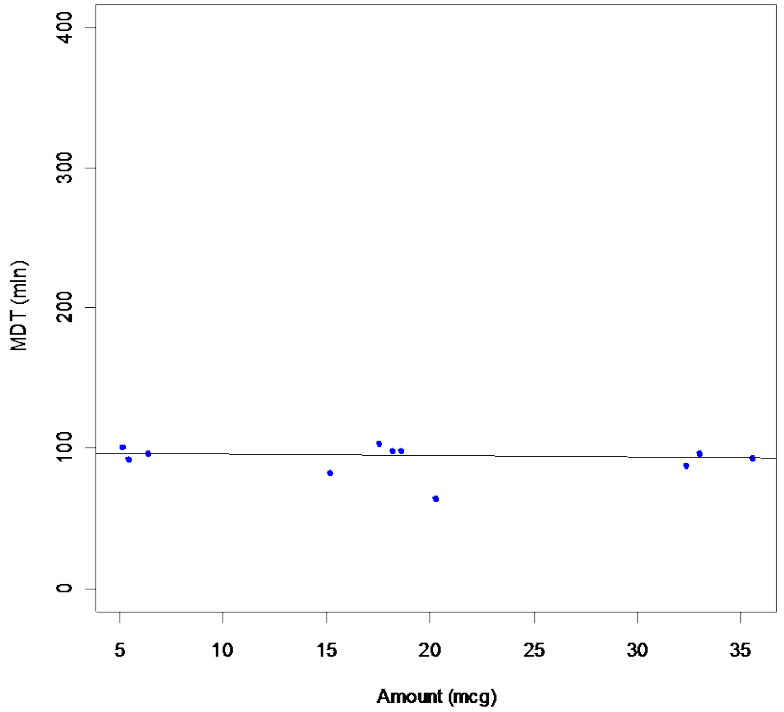
“Dose Effect”:
100 µl vs 500 µl in Donor Compartment



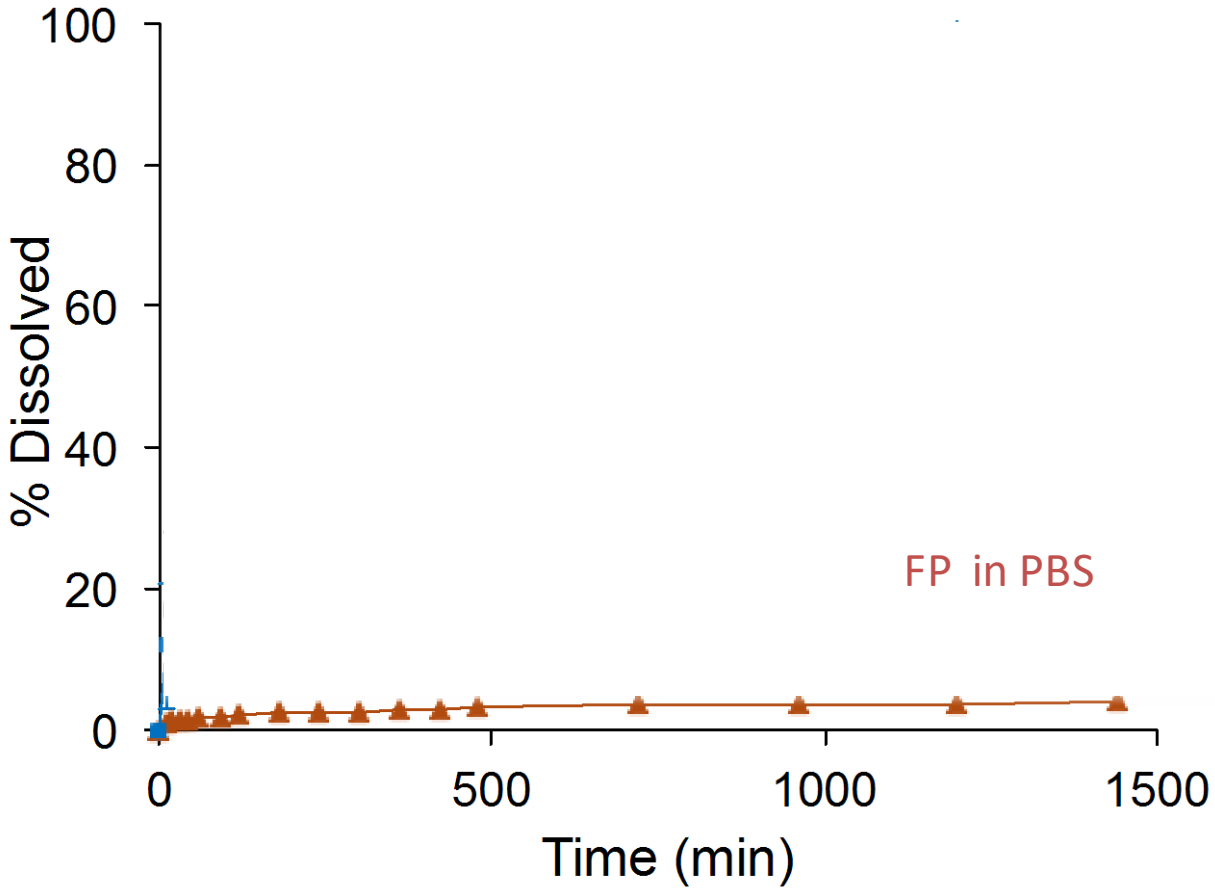
100 µl (0.5% SDS, unstirred)



500 µl (0.5% SDS, stirred)

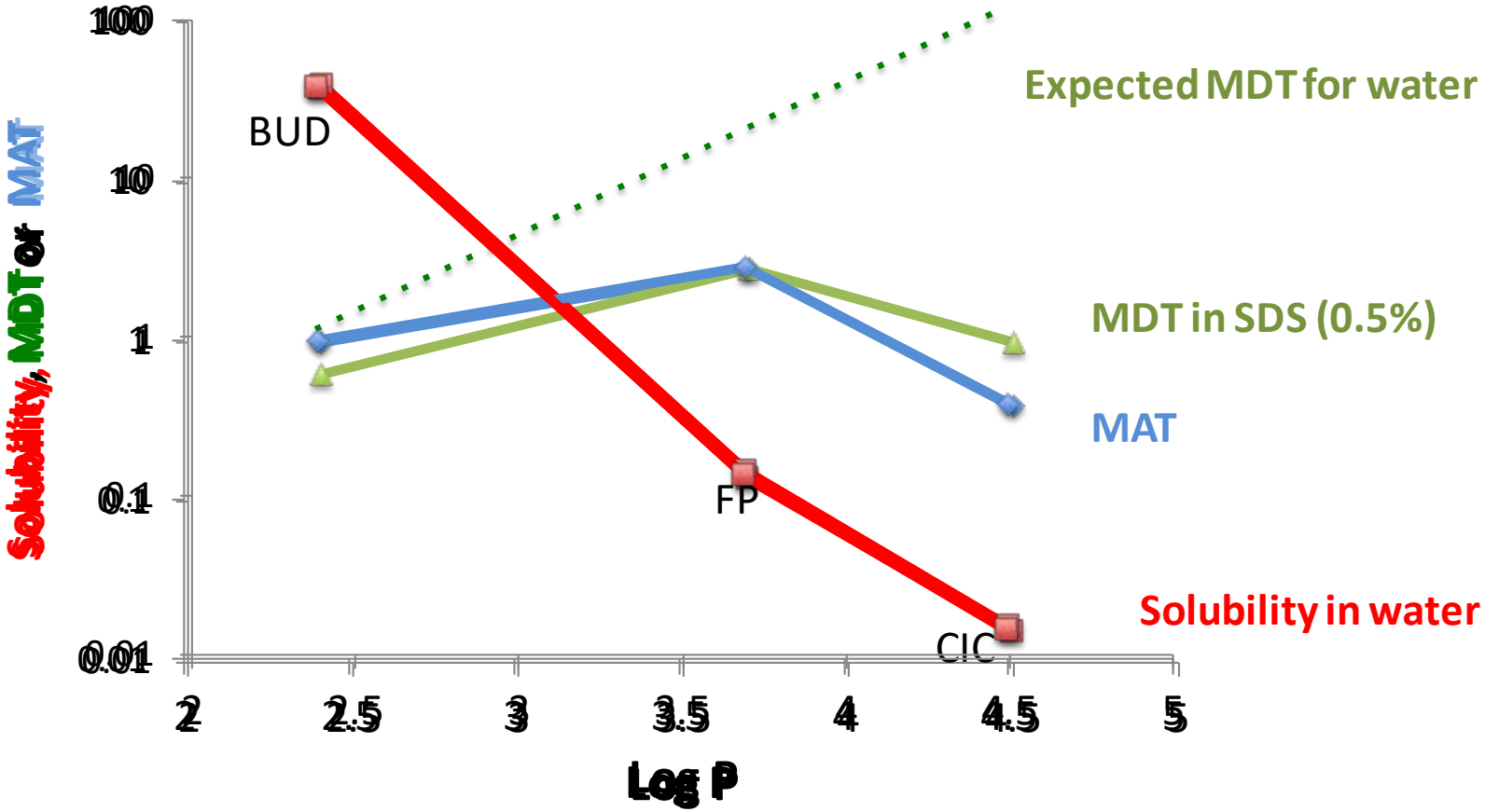


Pitfall 3: Solvent (1)?



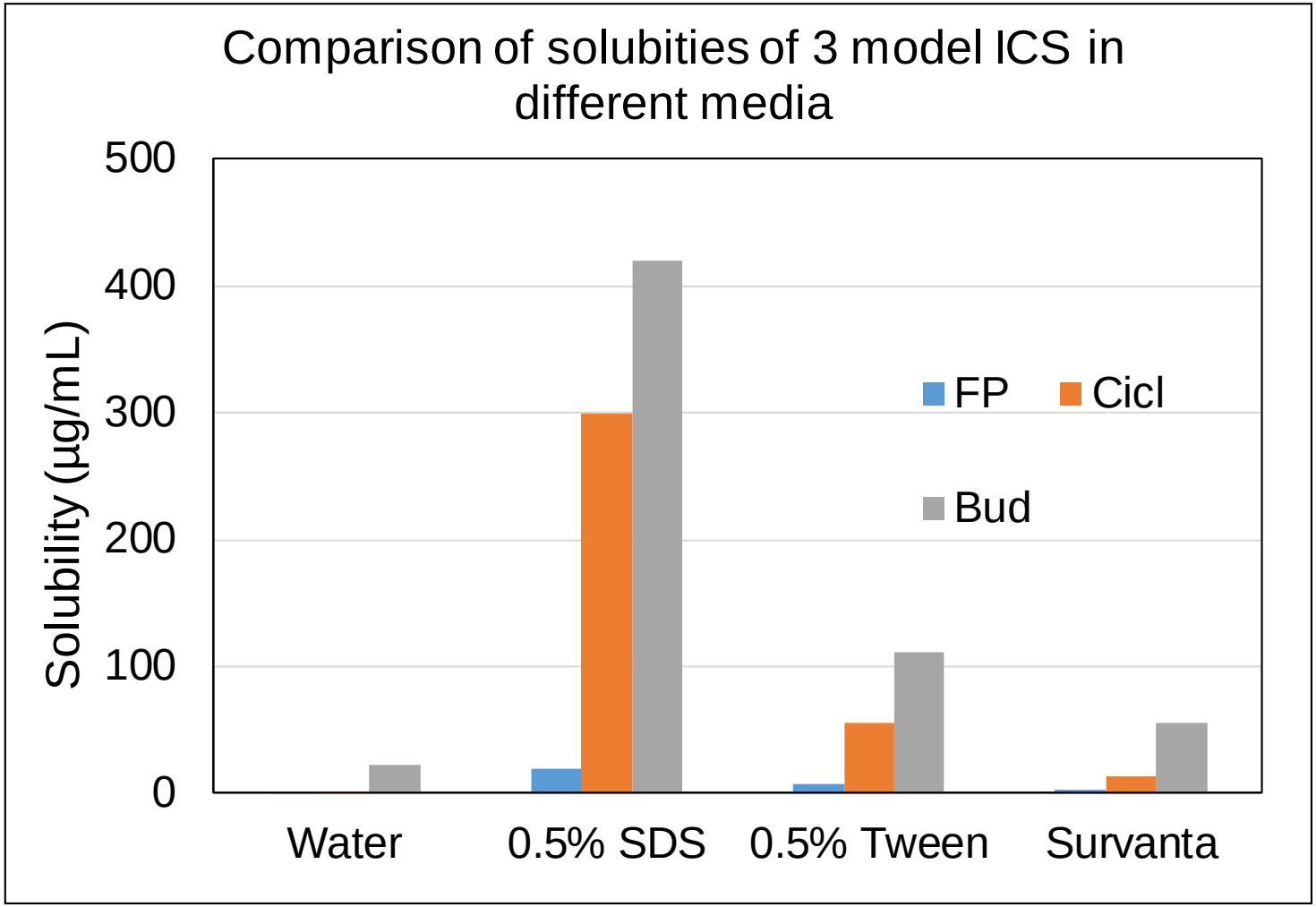
Solvent needs to contain surfactant.

Pitfall 3: What Solvent (2)?

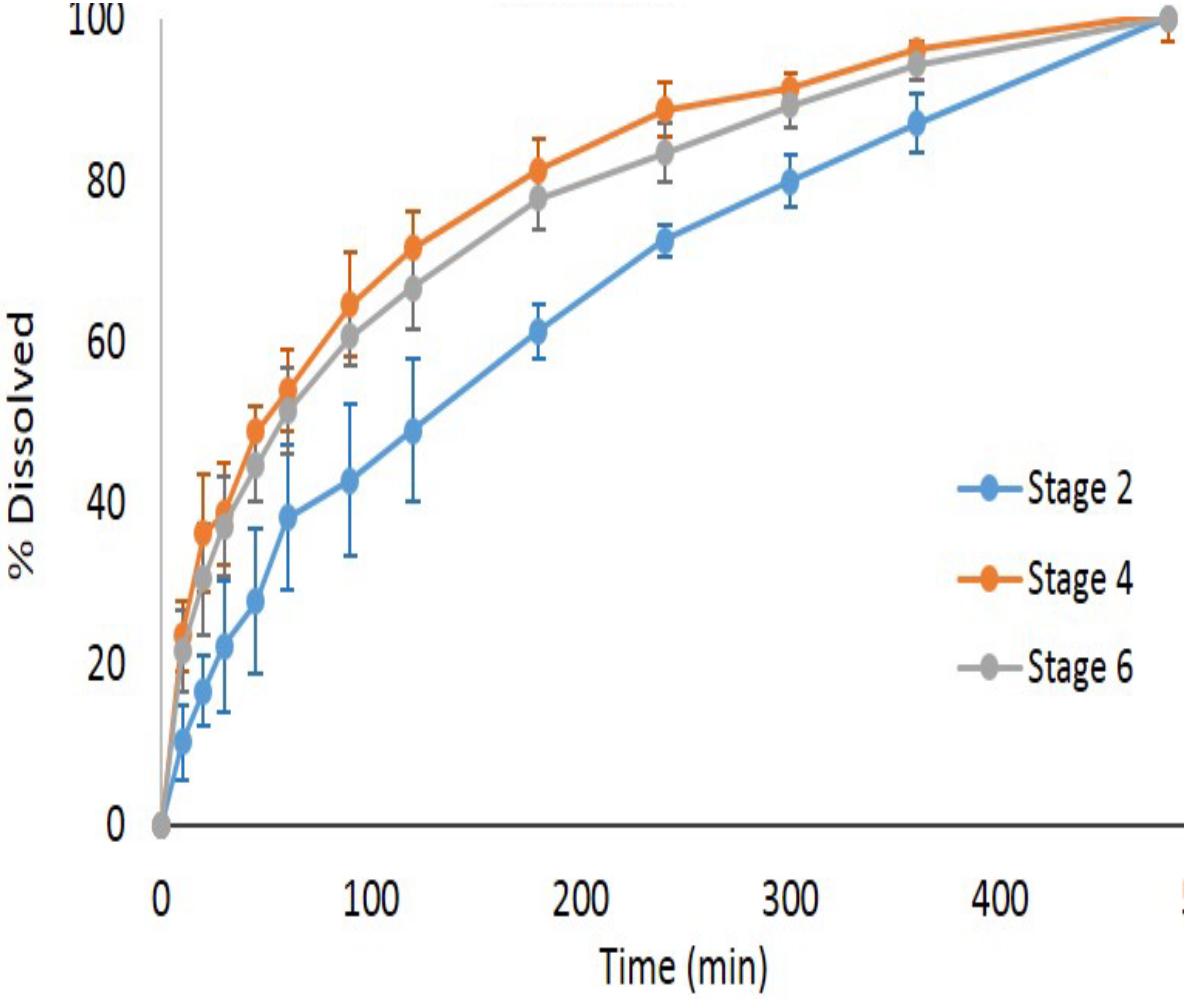


Solvent needs to contain surfactant.

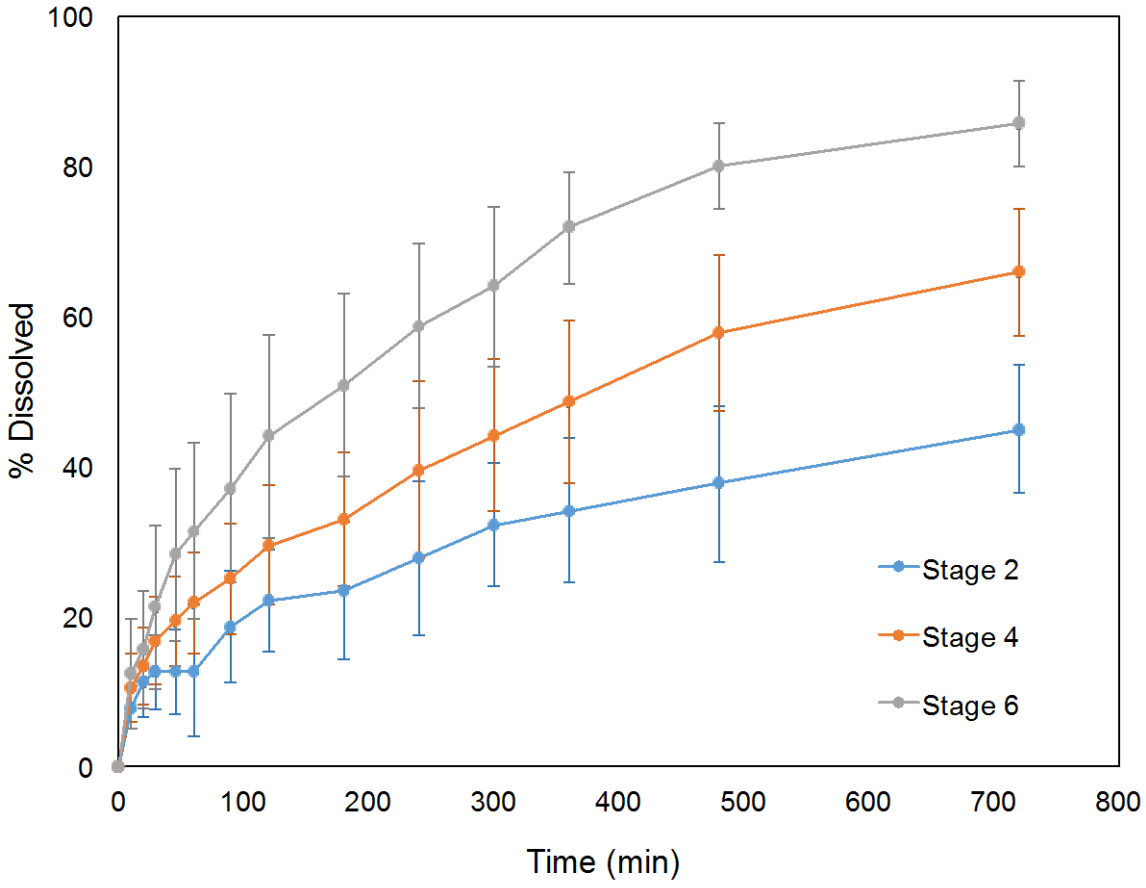
What Solvent? (3)



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



Sensitivity to Particle Size with (0.5% Tween) (Flovent DPI)



0.5% Tween might be a better medium for lipophilic corticosteroids

Summary of Dissolution Method

System:

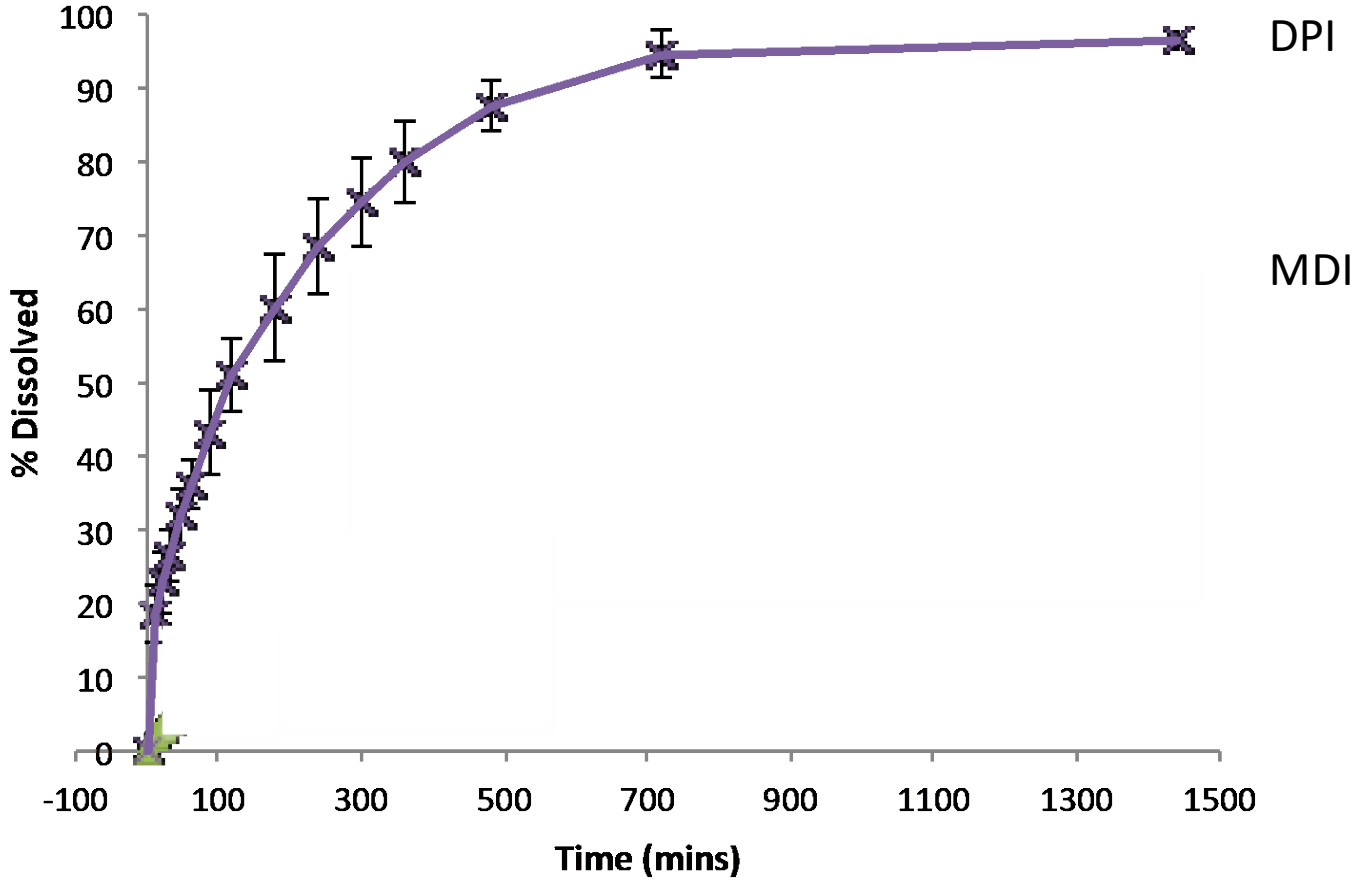
- Transwell® system with 8.0 micron polycarbonate membrane
- Stirred receptor compartment (staple)
- 0.5% - 0.8% Tween as dissolution medium
- Anatomical Throat model, NGI

Performance

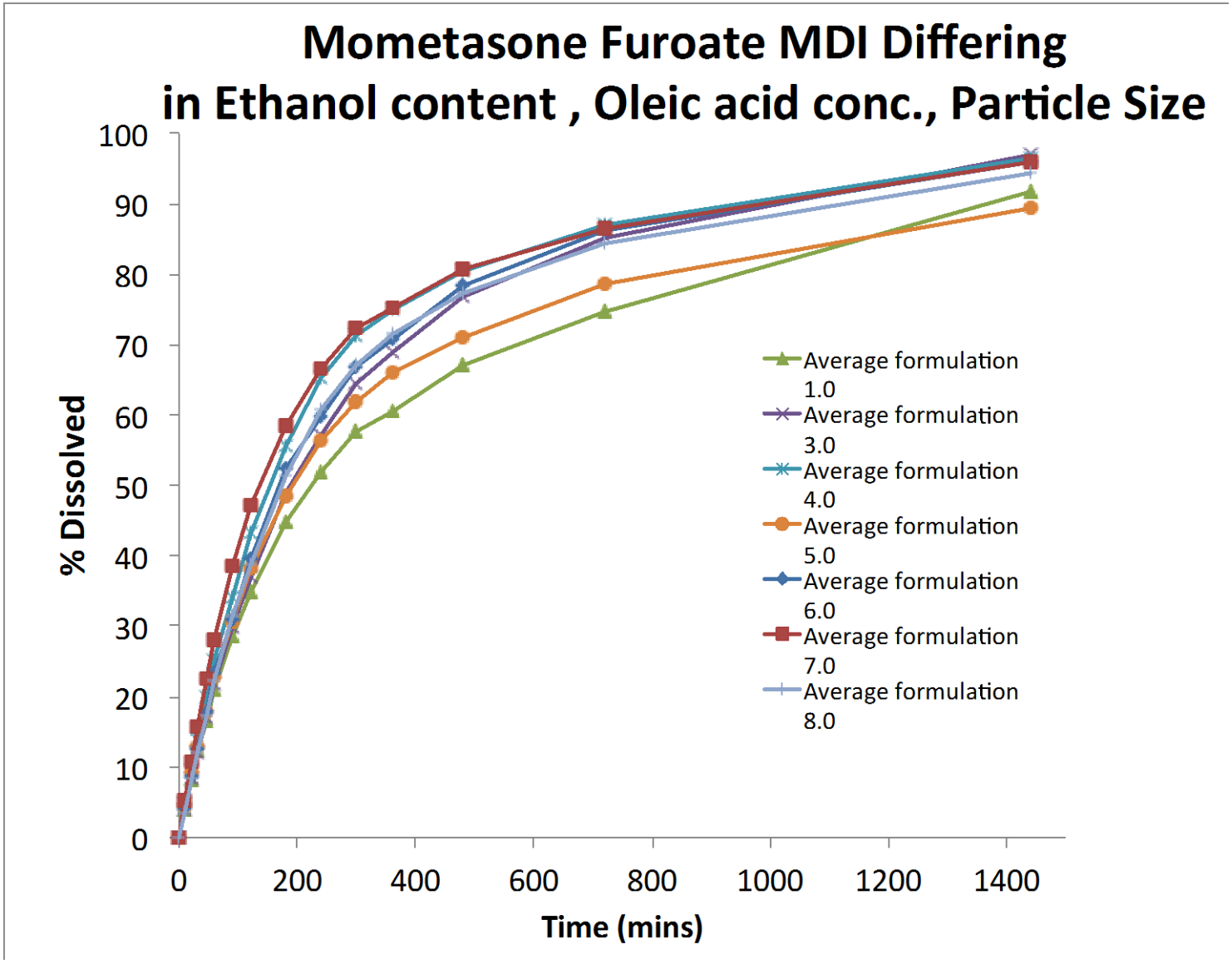
- Rank order of dissolution similar to in vivo
- Sensitive to particle size
- IVIVC possible

Case Studies

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

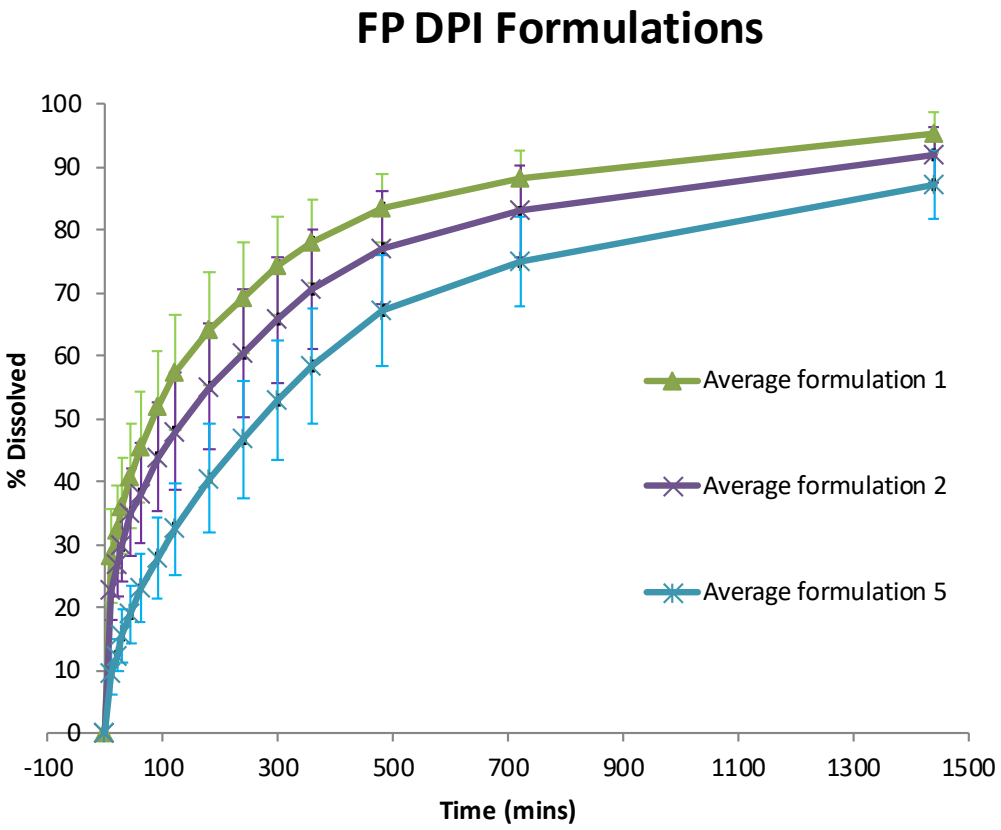


Case 2: (MDI)


Mometasone Furoate MDI Differing in Ethanol content , Oleic acid conc., Particle Size
% Dissolved
Time (mins)
0
10
20
30
40
50
60
70
80
90
100
0
200
400
600
800
1000
1200
1400
Average formulation 1.0
Average formulation 3.0
Average formulation 4.0
Average formulation 5.0
Average formulation 6.0
Average formulation 7.0
Average formulation 8.0

Case 3 (DPI)

- Fluticasone propionate (formulated UoB)
  - Same API, same API particle size,
  - different lactose fines

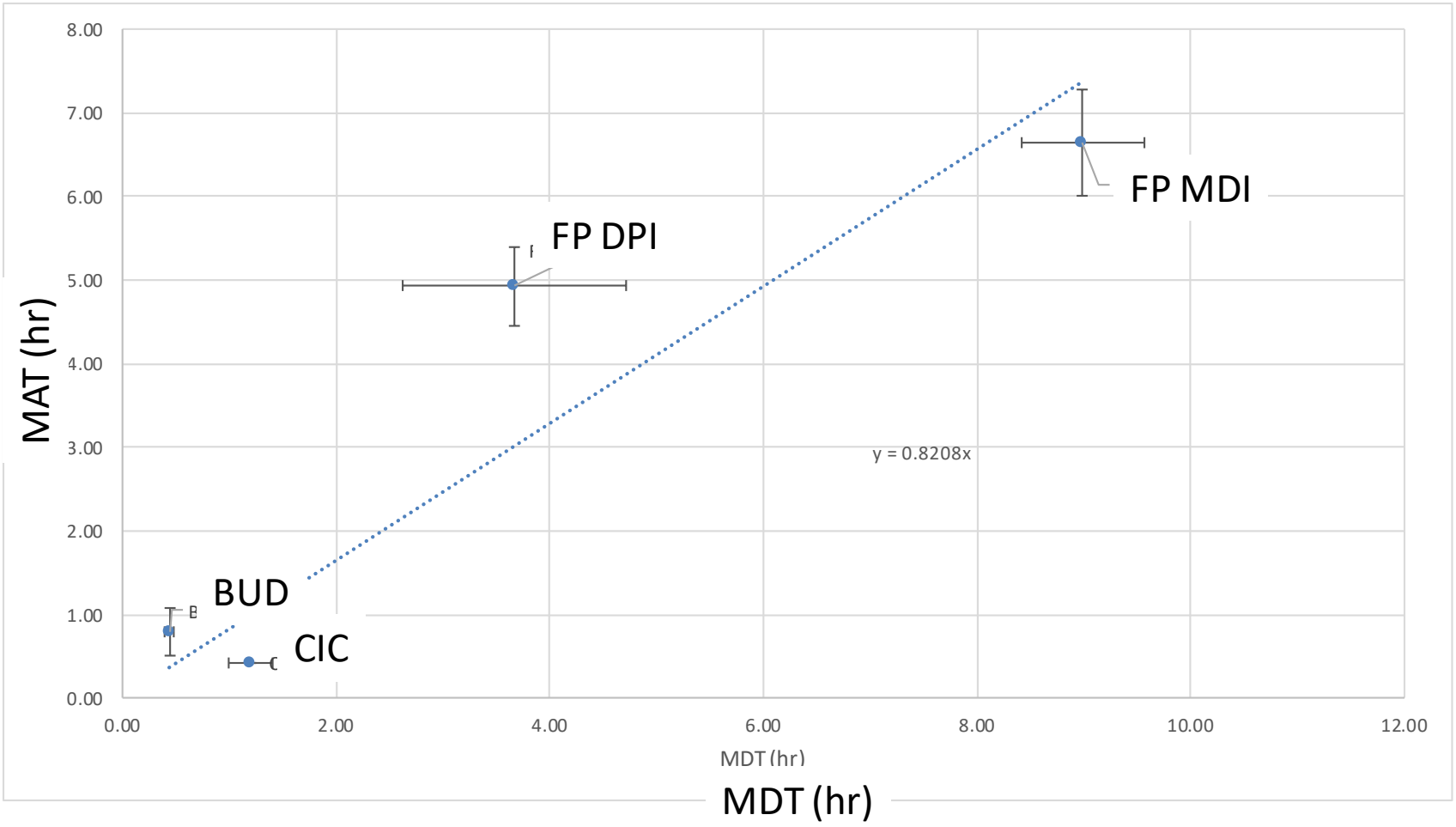


Conclusions of Case Studies

- Dissolution methods are discriminatory
- Can provide critical information for regulatory decision making

- Question: what method should be used?

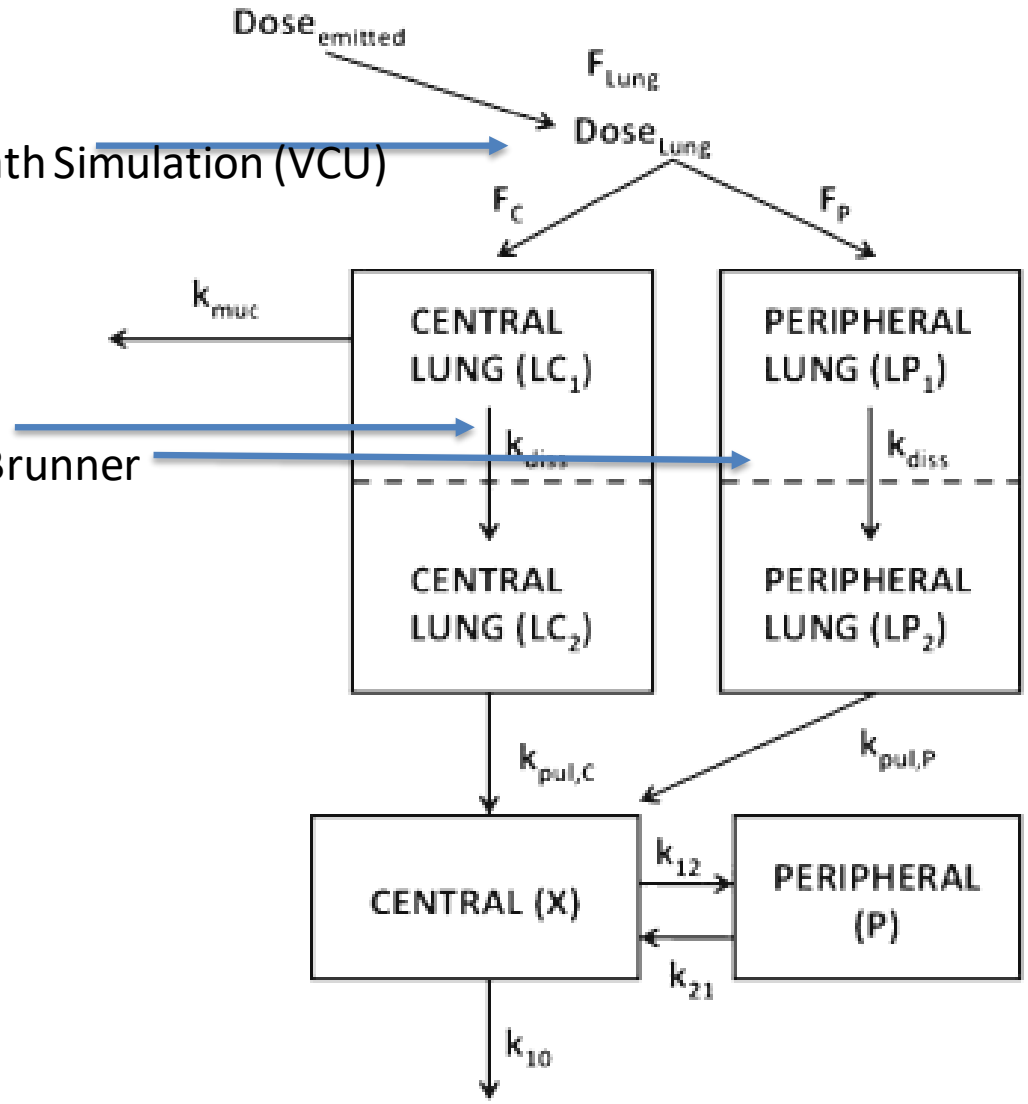
Correlation between Mean Dissolution and PK based Mean Absorption Times



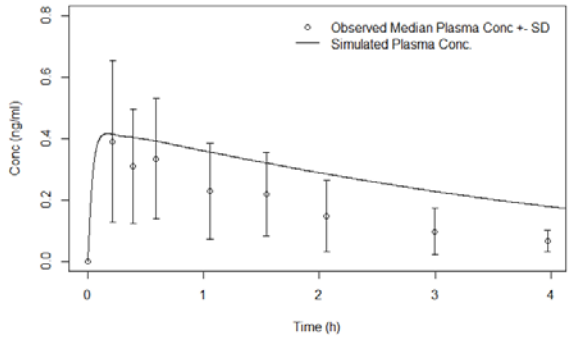
Can Dissolution + NGI Data Predict PK?

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

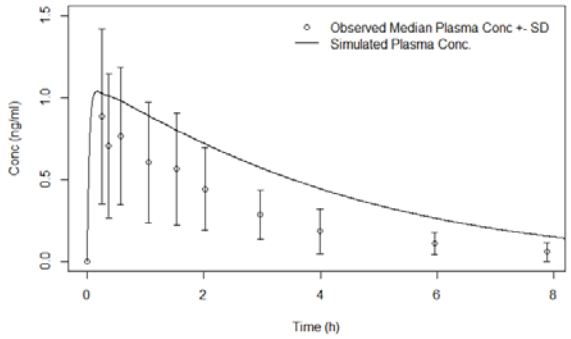
Dissolution rate:
Particle size distribution (NGI)
Solubility in test medium, Nernst-Brunner



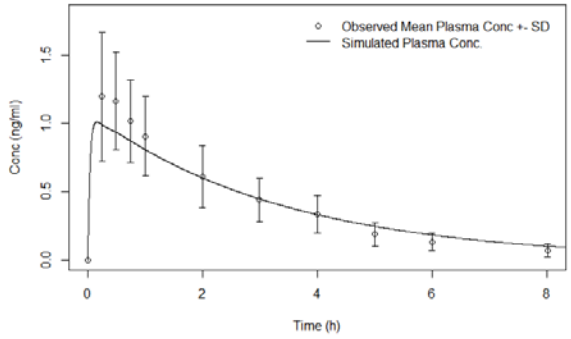
A : 400 µg budesonide



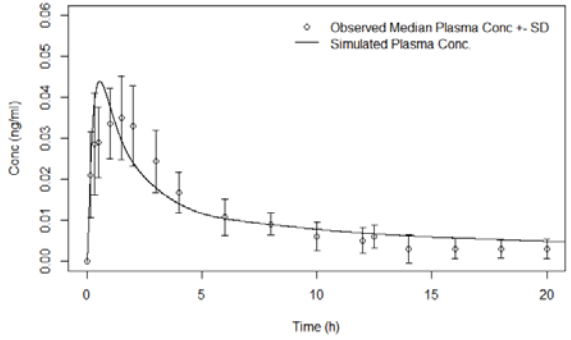
B: 1000 µg budesonide



C: 1000 µg budesonide with charcoal block



D: 200 µg fluticasone propionate



Summary

- Dissolution method seems to behave
- Method can provide additional information over established regulatory in vitro methods.
- Differentiation of formulations is possible (T vs R) .
- Able to help predicting effects of formulation on PK (Bhagwat et al., Pharm. Res. 2017)

Questions for FDA to Answer

- What products should be tested?
- What method should be used?
  - What sample preparation?
  - What dissolution method?
    - Monitoring of dissolution alone?
      - UPS methods