Dissolution Methods for Orally Inhaled Drug Products

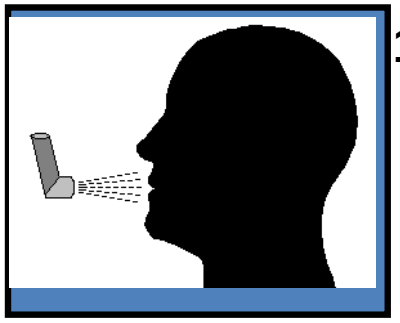
USP Workshop Dec 12, 2019:

Advancements in in-vitro Performance Testing of Drug Products, Bethesda MD

UF UNIVERSITY of FLORIDA

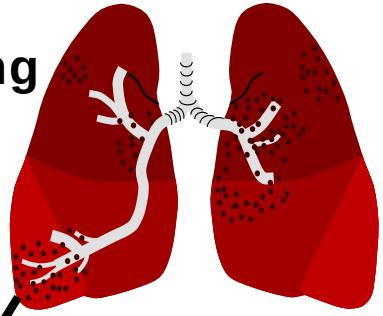
Hochhaus@ufl.edu

The Fate of Inhaled Drugs



Mouth and Pharynx

10 - 60 % Lung Deposition



Lung

Pulmonary Effects

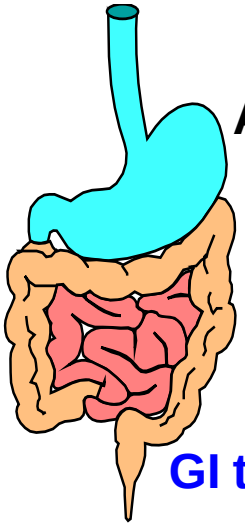
Complete Absorption from the Lung

Systemic Circulation

Selectivity

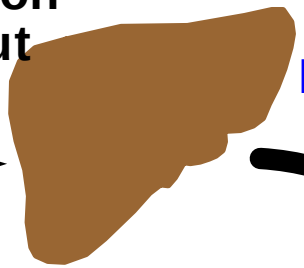
Orally absorbed Fraction

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



GI tract

Absorption from Gut



Liver

First-pass Inactivation

Systemic Side Effects

Clearance

Bioequivalence and in vitro Assays

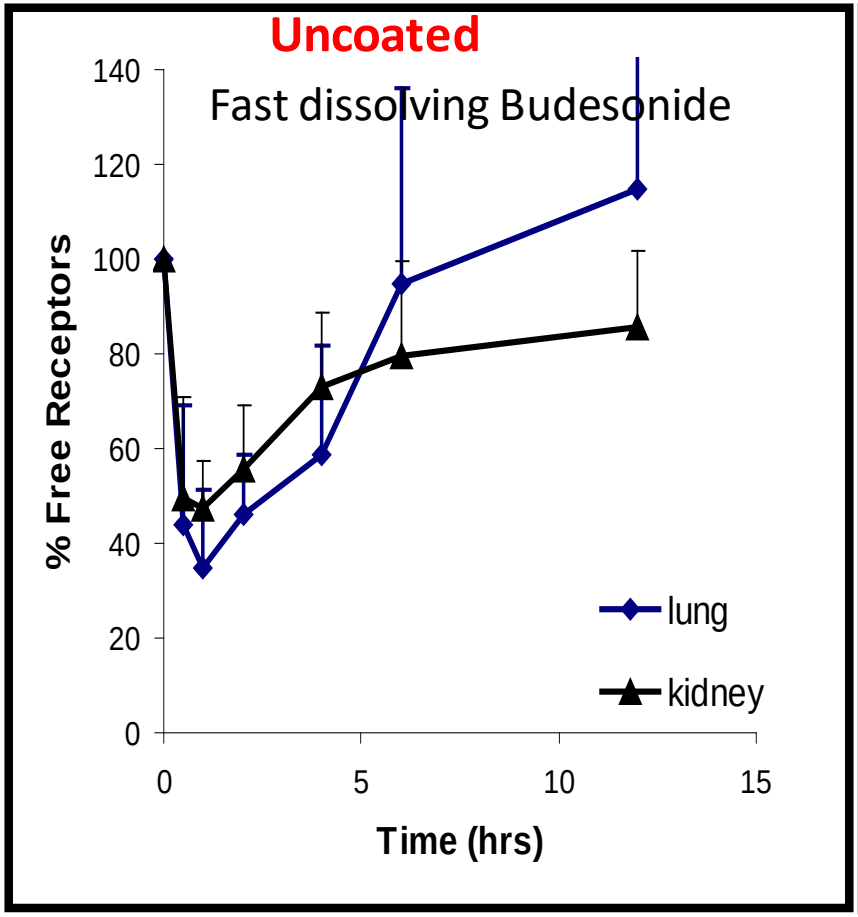
- Same pulmonary dose (anatomical throt, impactor)
- Same regional deposition (impactor + *in silico* methods)
- Same pulmonary residence time

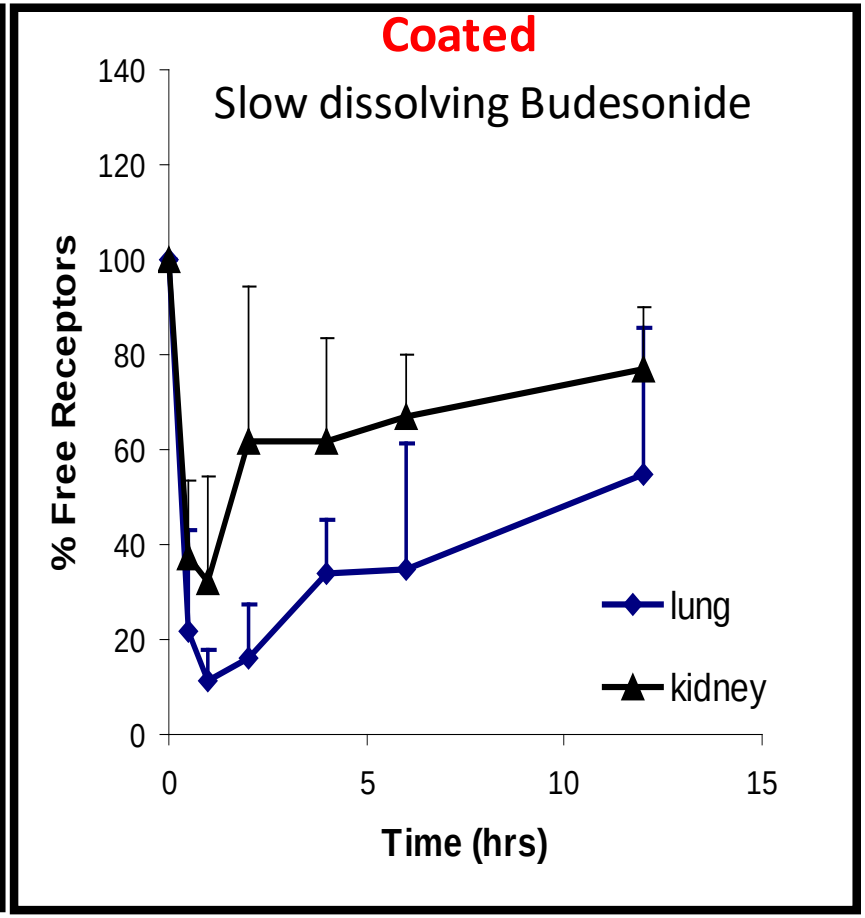
  Dissolution/Permeability

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

Not formulation dependent

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





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), modified NGI

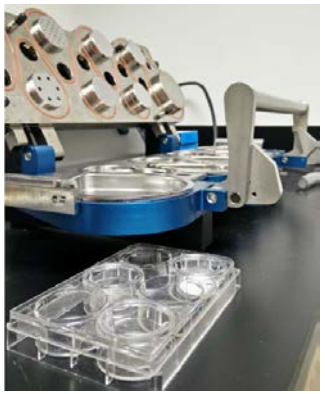
  - **Anatomical Throat** >>> ex-throat dose

  Nasal
  - No preparation necessary (pipet 20 *10 µl onto filter paper)

- **Dissolution Test Systems**
  - Systems Including diffusion across membrane (biomimetic)
    - **Transwell system**/Franz cell
    - Dissolve it® system (Gerde et al., Assay and Drug Develop. Technol., 2017)

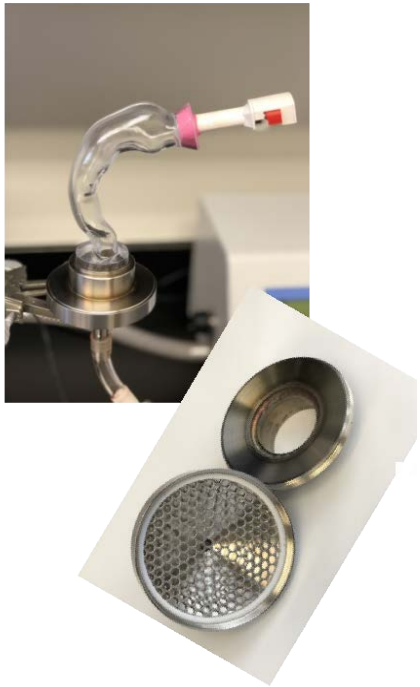
  - Systems without controlled membrane diffusion step
    - **USP II and IV**

Systems Evaluated

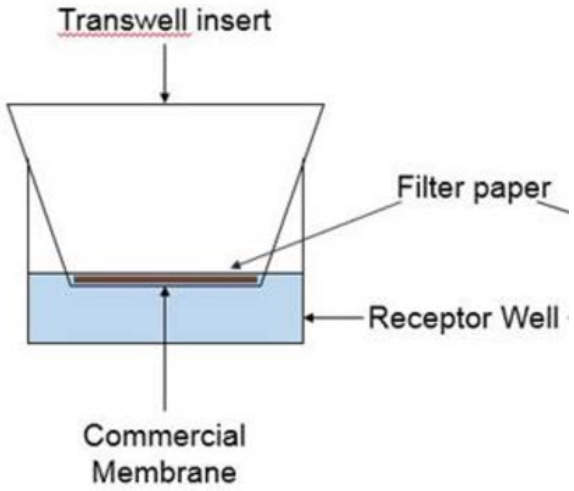


USP (watch glass)

?



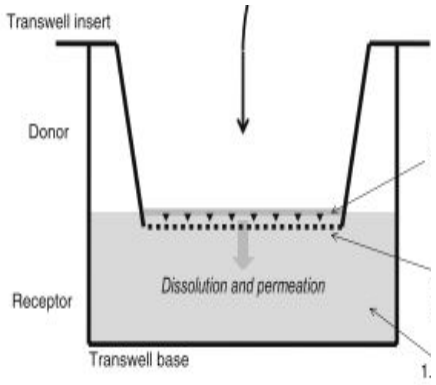
Transwell



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

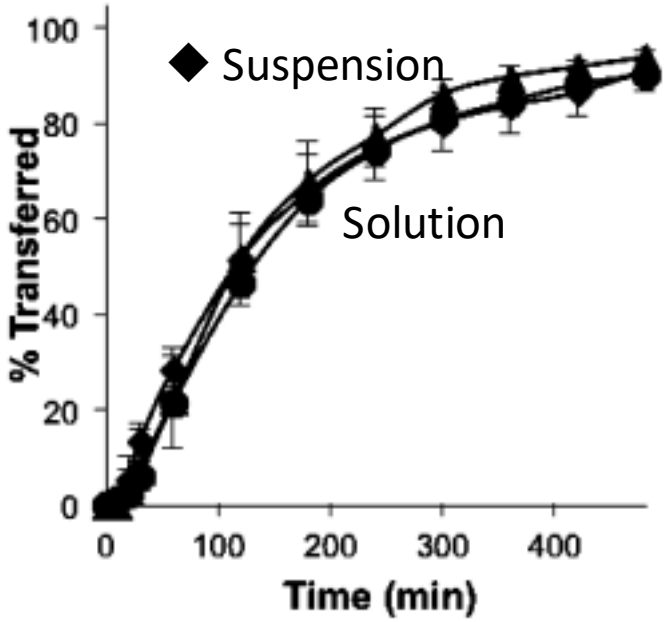


Arora, D., (2010)

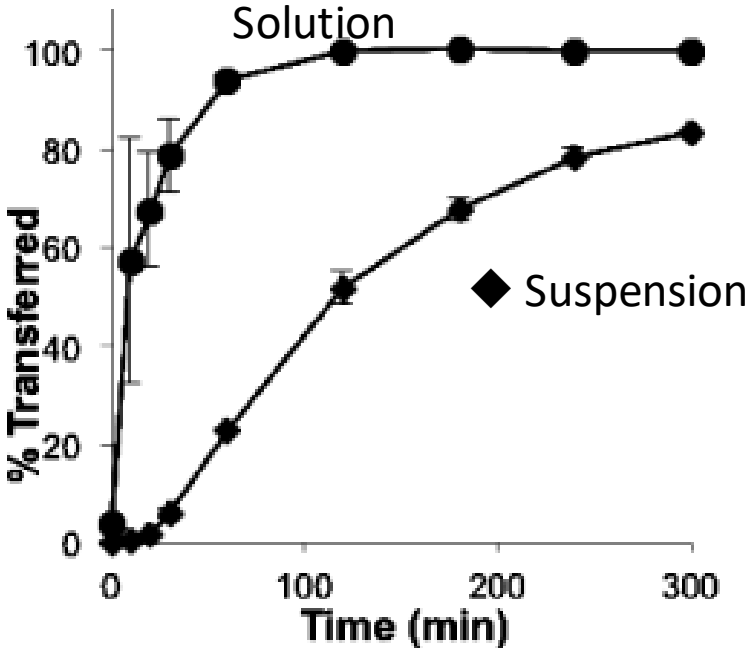
Diffusion across Membranes?

Ciclesonide Solution vs suspension based MDI

0.4 µm Transwell® Membrane

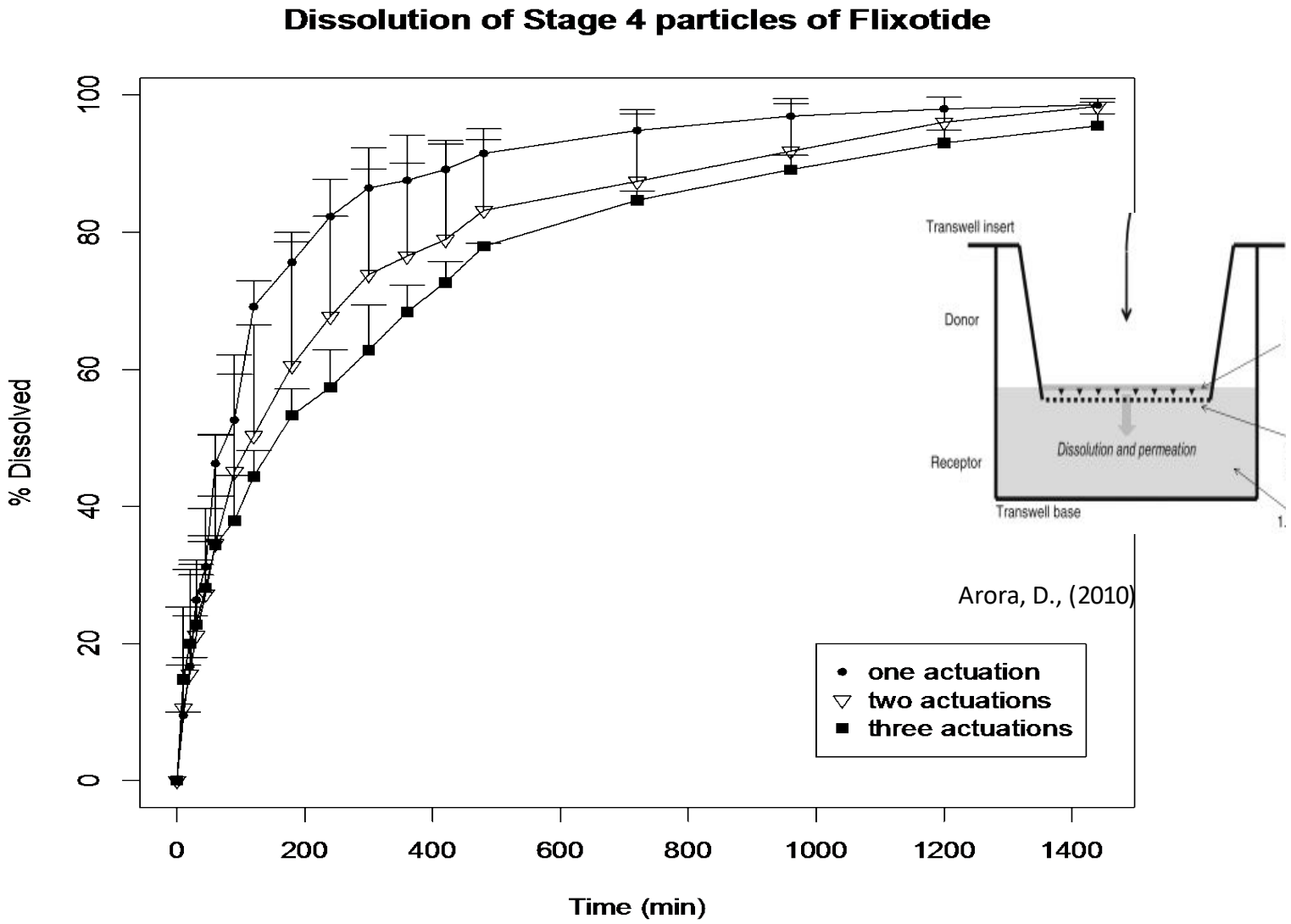


- **0.4 µm Transwell® Membrane**
- **stirred (Staple)**



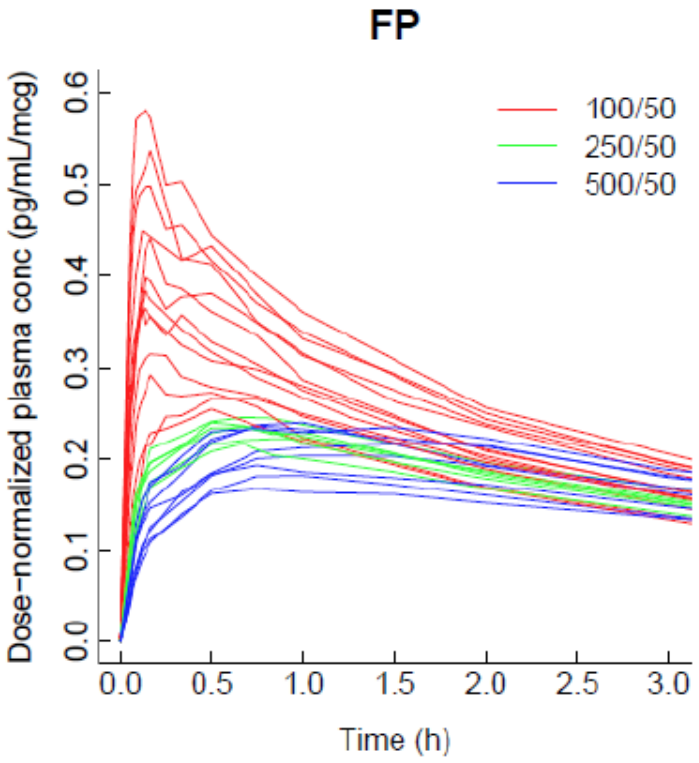
Use stirred system

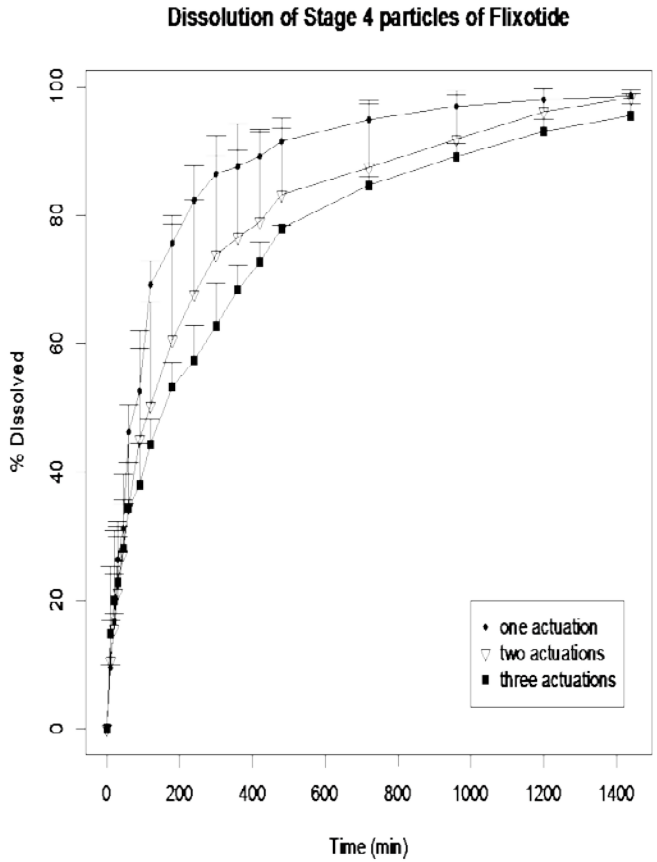
Dose Effect?



Arora, D., (2010)

Dose effect: in vitro/in vivo





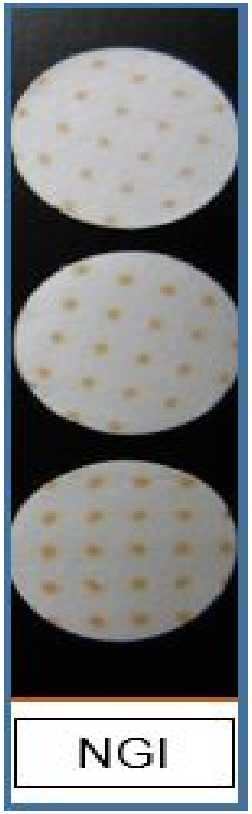
- **Dose effect might occur in vivo (Sandoz Citizen Petition)**

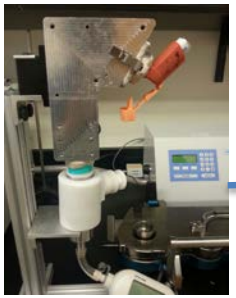
However:

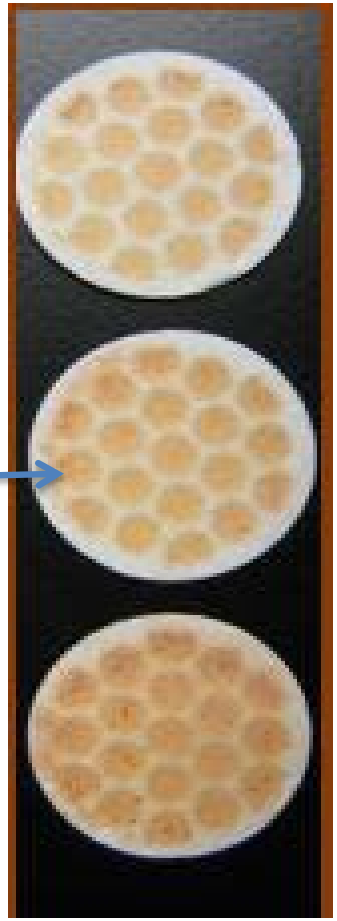
- **For dissolution test to be used for quality control and within ANDA work, dose effect should be eliminated.**

Dose Effect

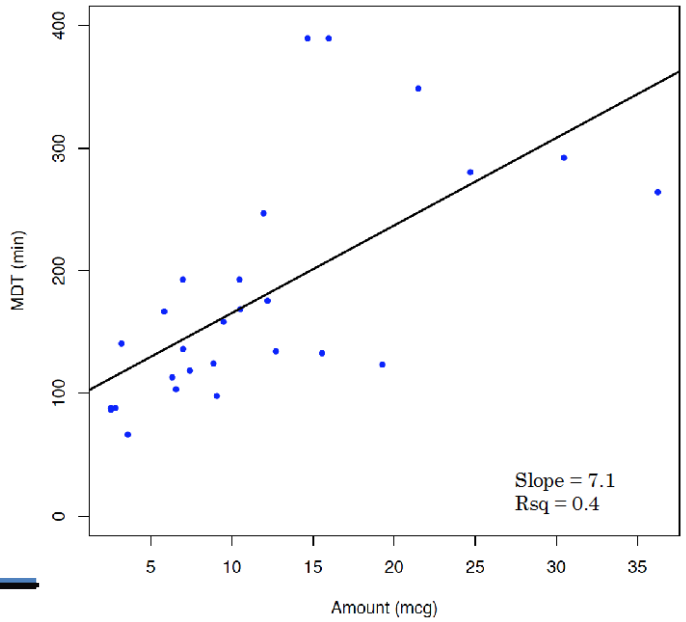
Anatomical Throat





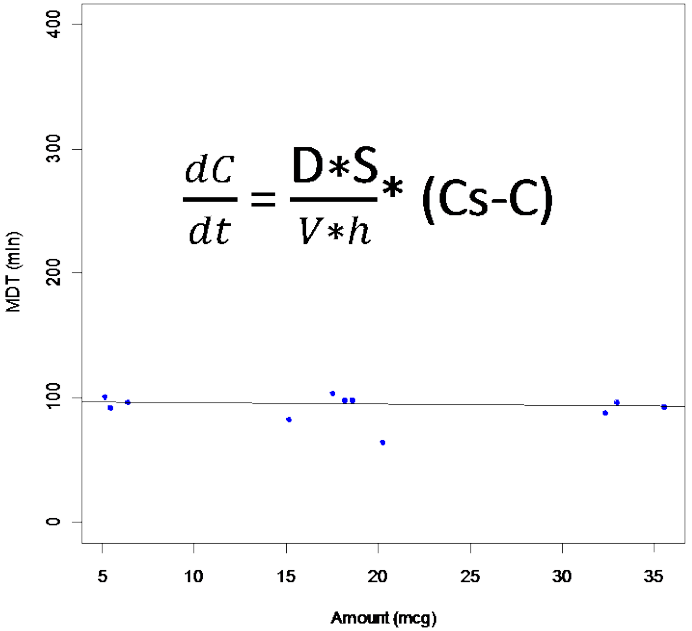


100 µl (0.5% SDS, **unstirred**)

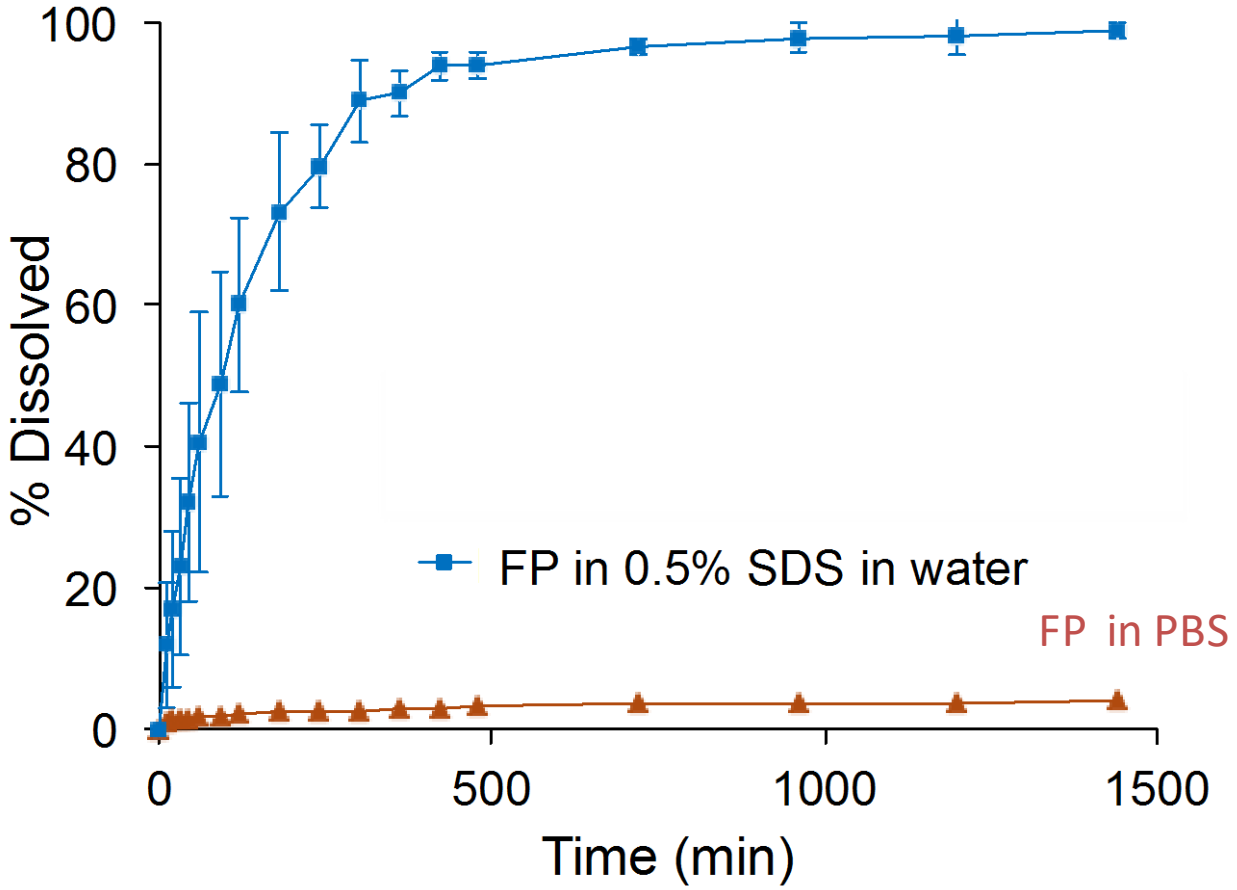


500 µl (0.5% SDS, **stirred**)

$$\frac{dC}{dt} = \frac{D*S}{V*h}* (Cs-C)$$

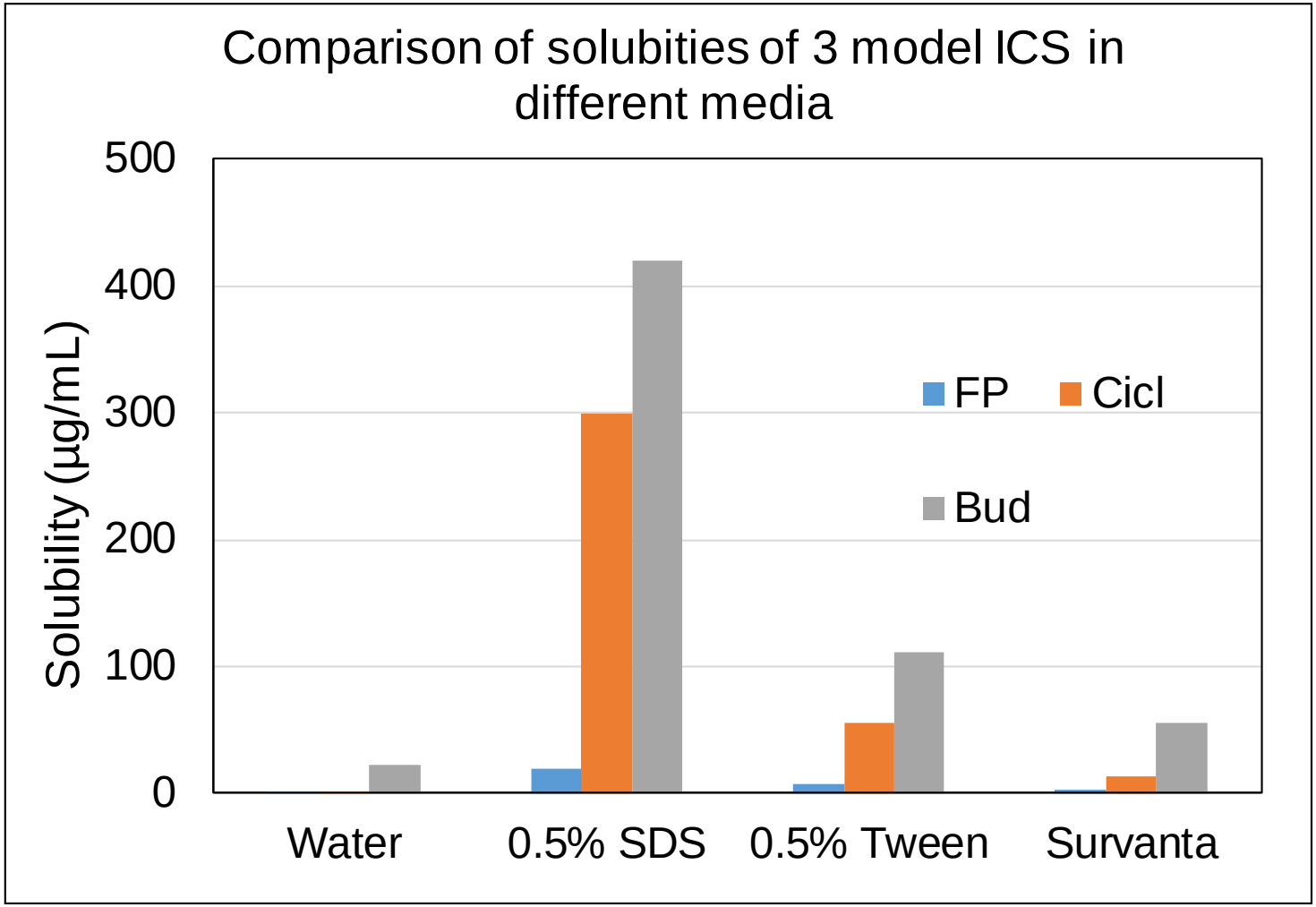


Solvent (1)?



Solvent needs to contain surfactant.

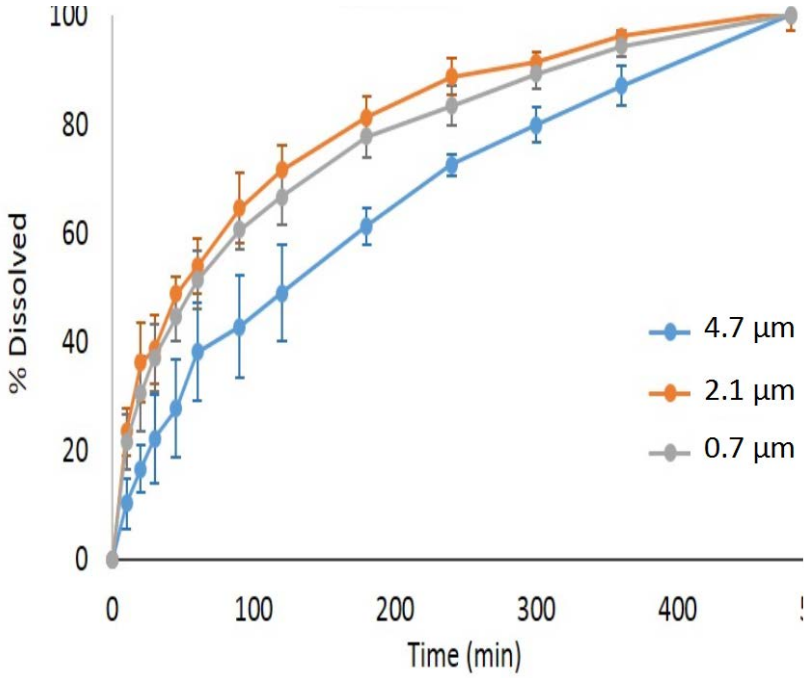
What Solvent? (2)



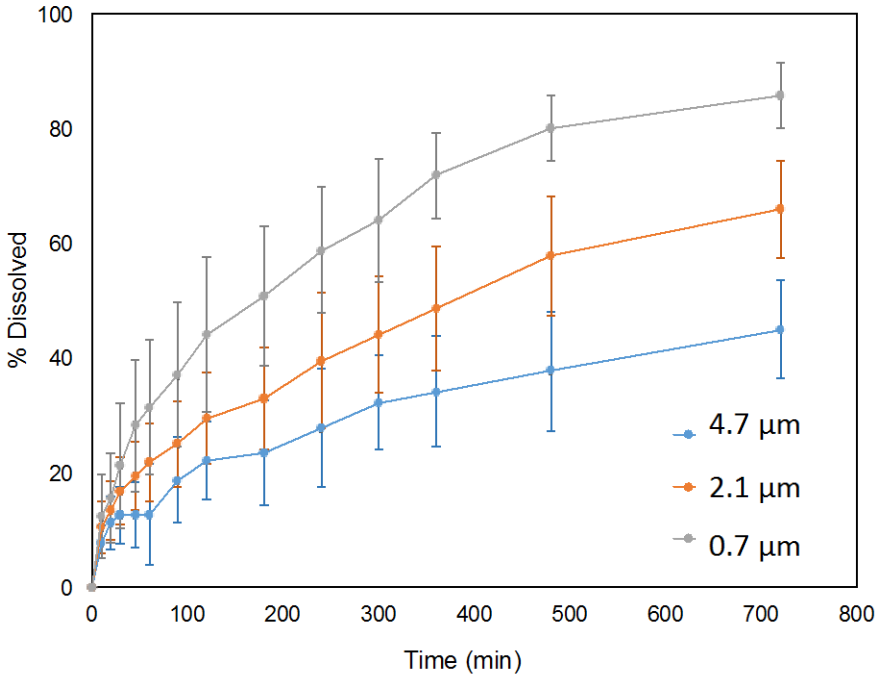
What Solvent? (3)

Detecting Differences in Particle Size

Flovent DPI: 0.5% SDS



Flovent DPI: 0.5% Tween



0.5% Tween might be a better medium for lipophilic corticosteroids

Summary of Dissolution Method: Transwell

System:

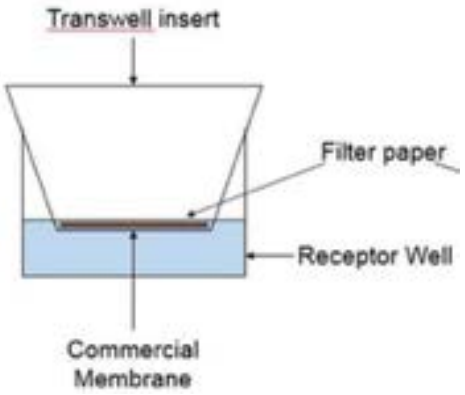
- Dose presentation: **Anatomical Throat model**, NGI
- Transwell® system with 0.4 µm polycarbonate membrane
- Stirred receptor compartment (staple)
- 0.5% - 0.8% Tween as dissolution medium

Performance

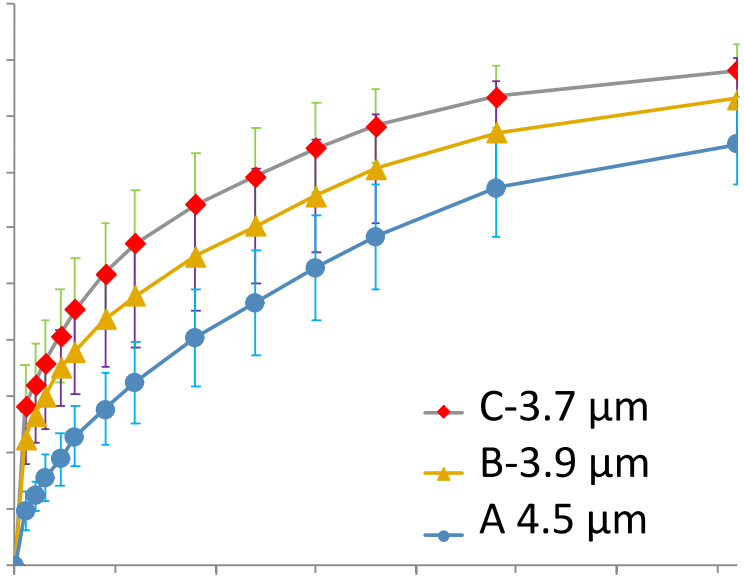
- Dose effect is controllable within ranges
- Sensitive to particle size

Examples

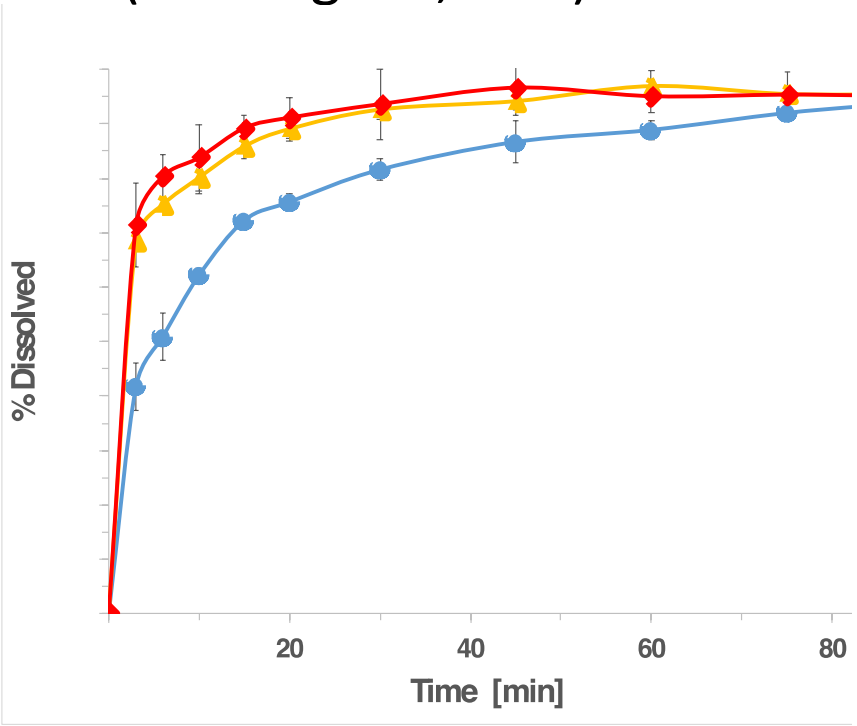
Fluticasone propionate (formulated UoB)
Same API, same API particle size, different lactose fines



Transwell® (non-sink)

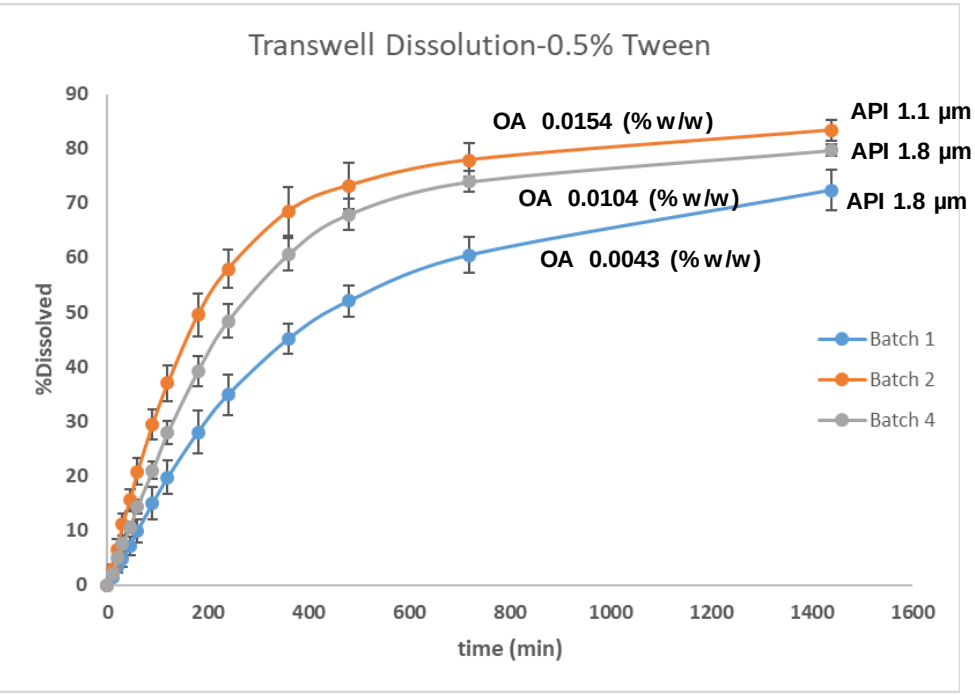


USP (watch glass, sink)

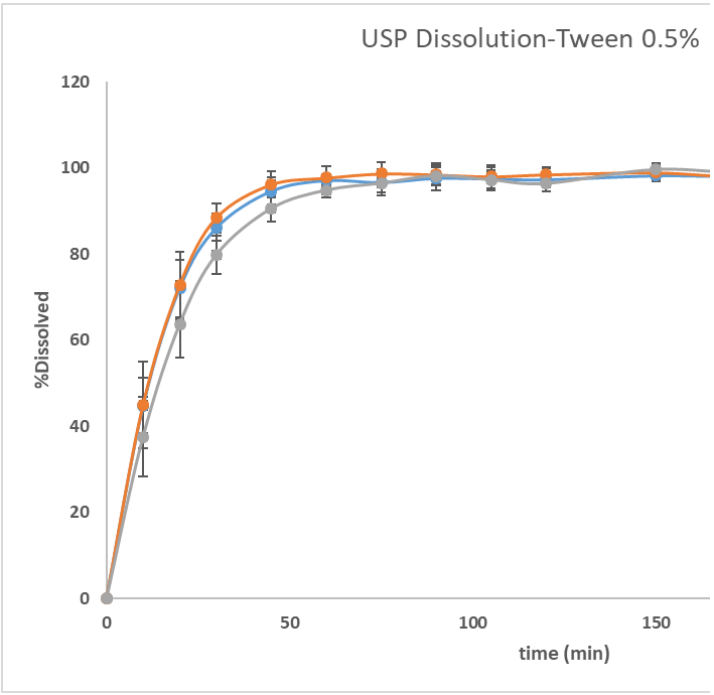


MDI: Mometasone furoate size - Oleic Acid

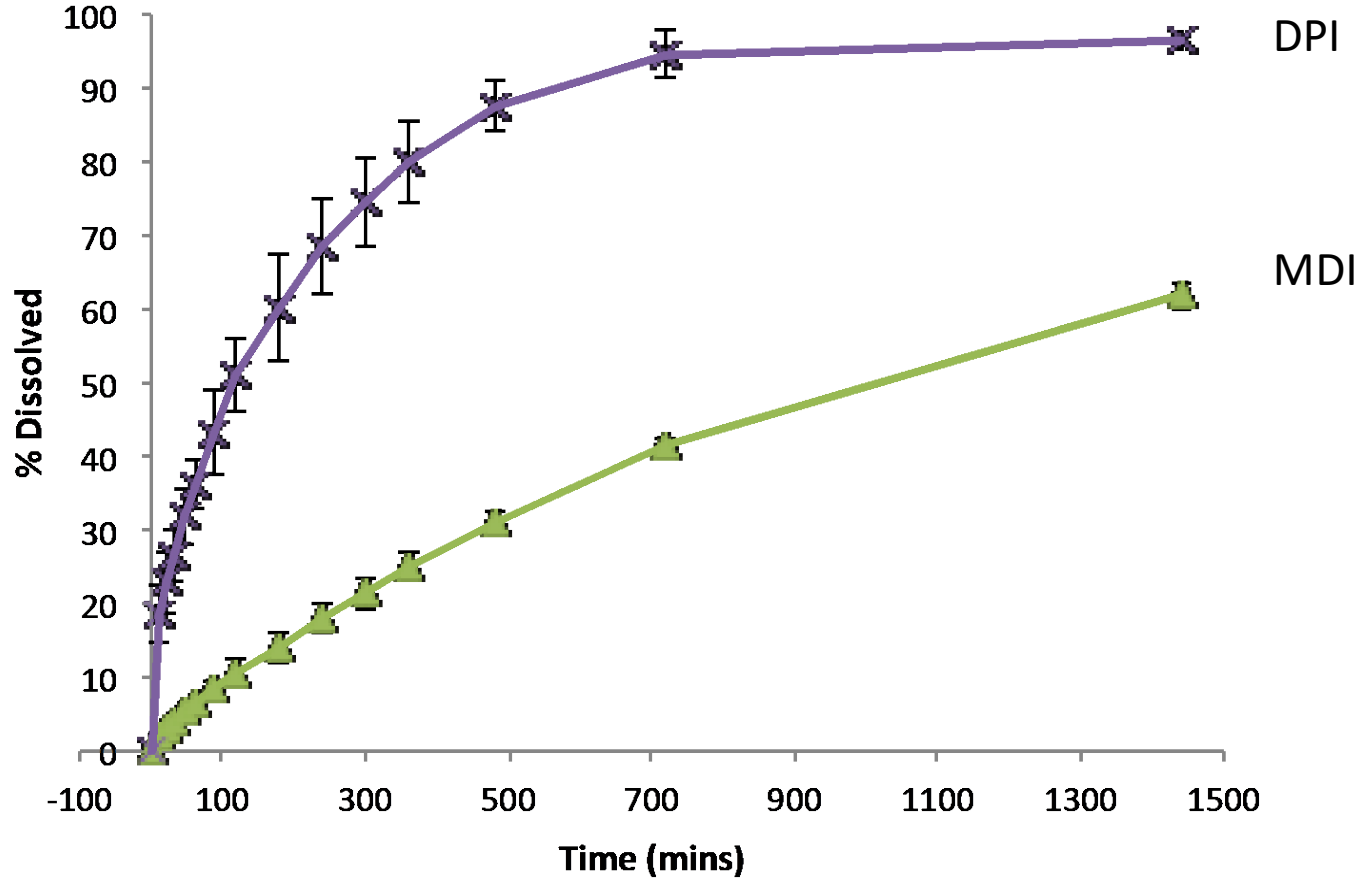
Transwell® (non-sink)



USP (watch glass, sink)

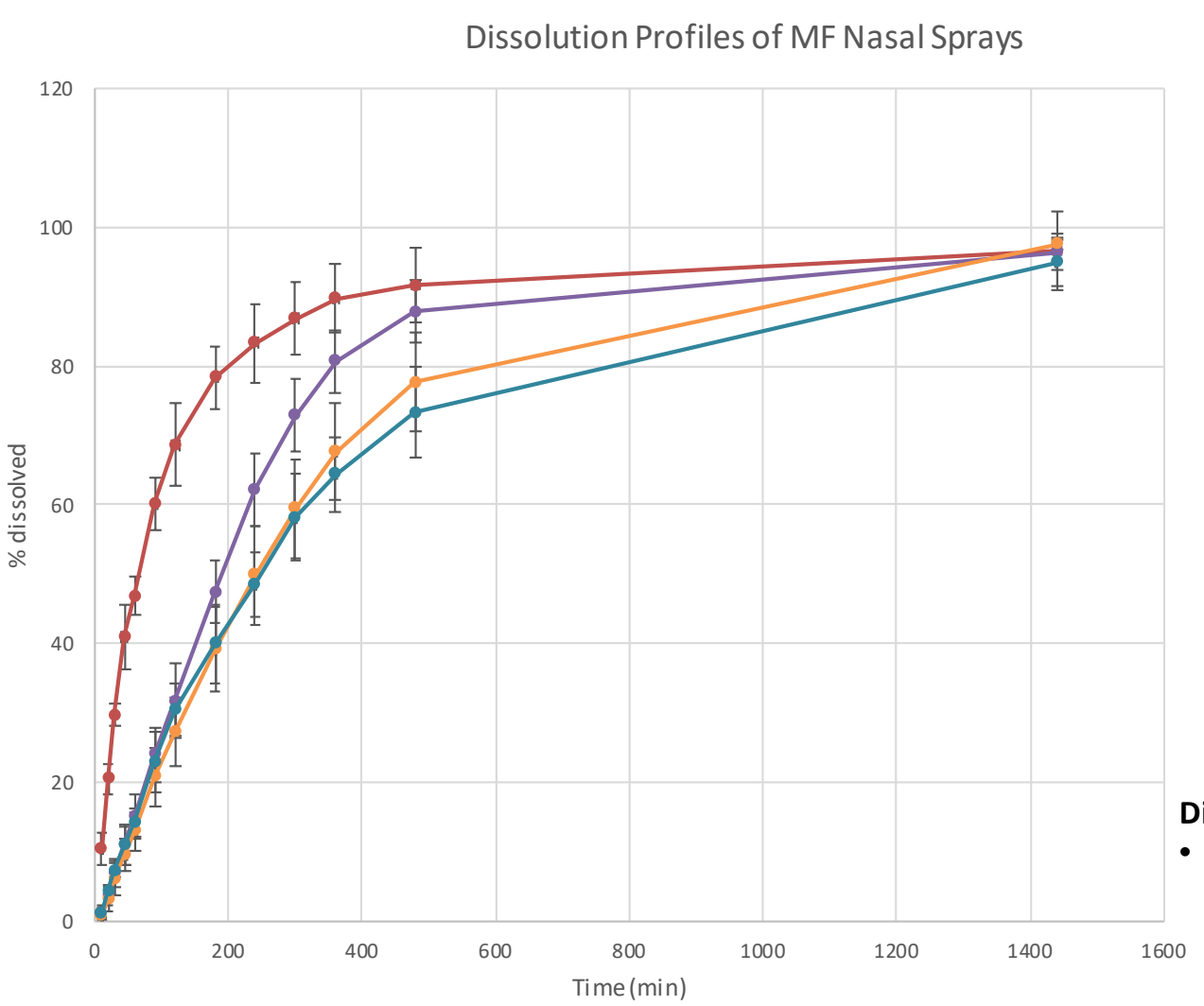


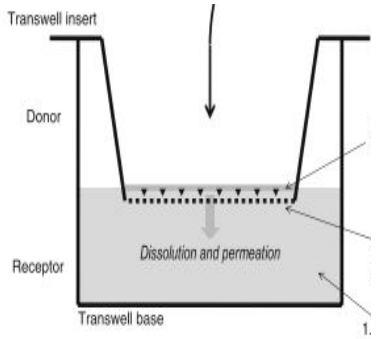
Flovent HFA-MDI vs DPI (Diskus)



Nasal Sprays:

Dissolution profiles of 2 custom-made and 2 commercially available Mometasone Furoate nasal sprays Transwell



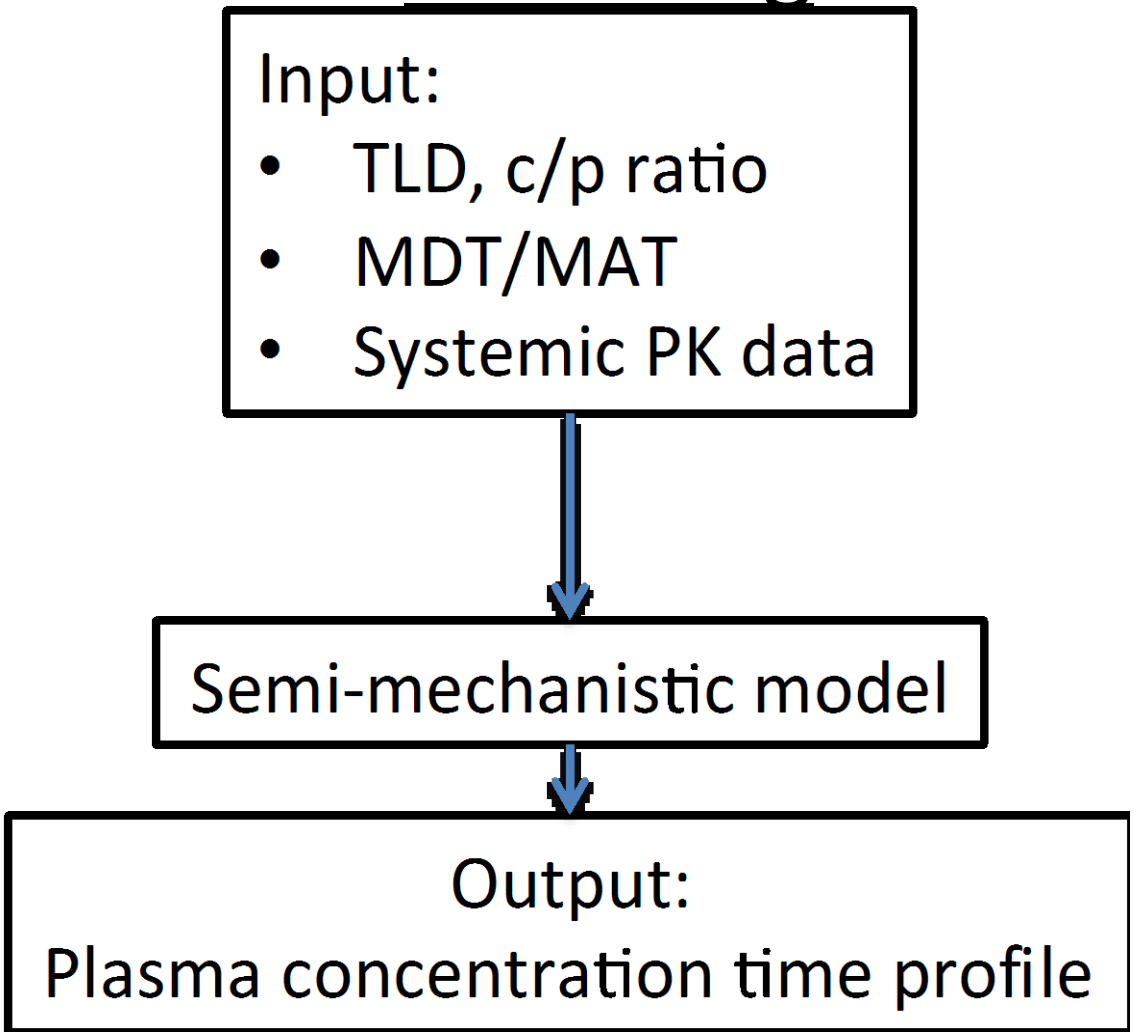


Arora, D., (2010)

Dissolution setup:

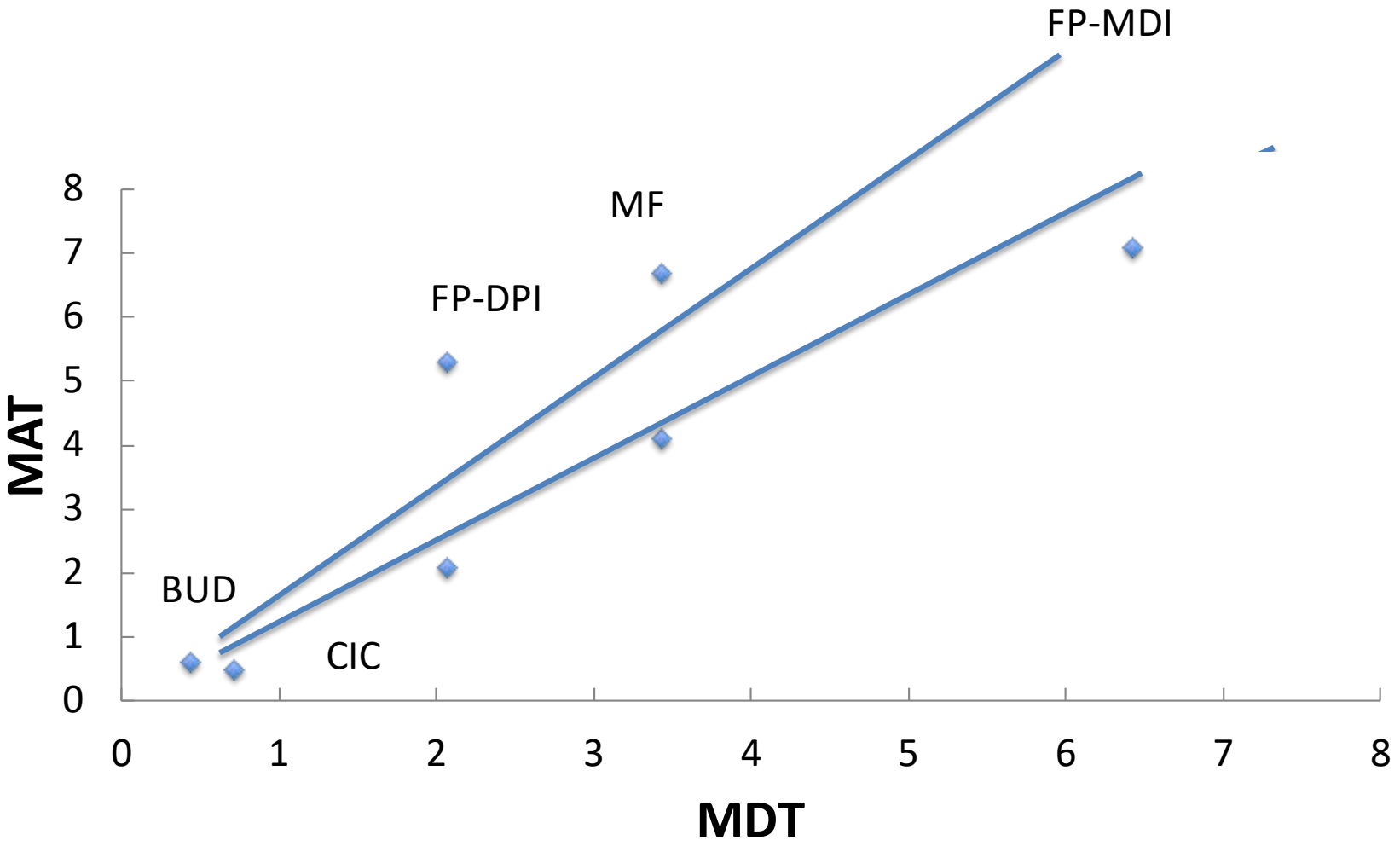
- Transwell® system (Corning, Inc.) on a 6-well plate with 24 mm inserts and 0.4 µm polycarbonate membrane pore size

Use of Dissolution data in PBPK Modeling



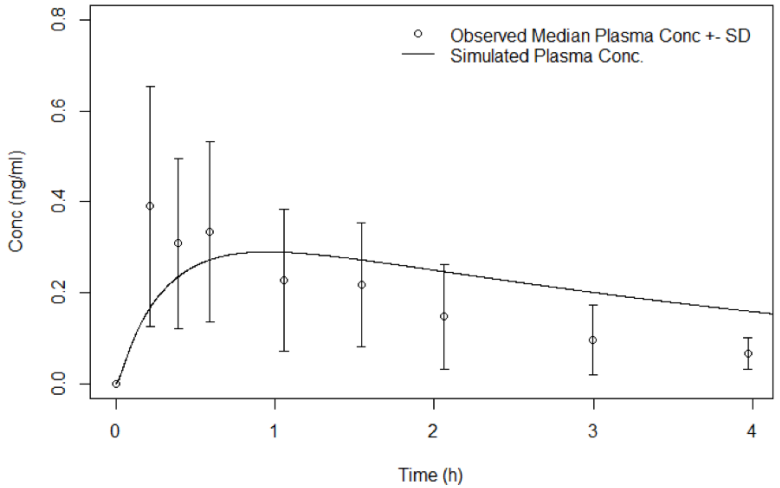
Correlation between MDT and MAT

(0.7% TWEEN)

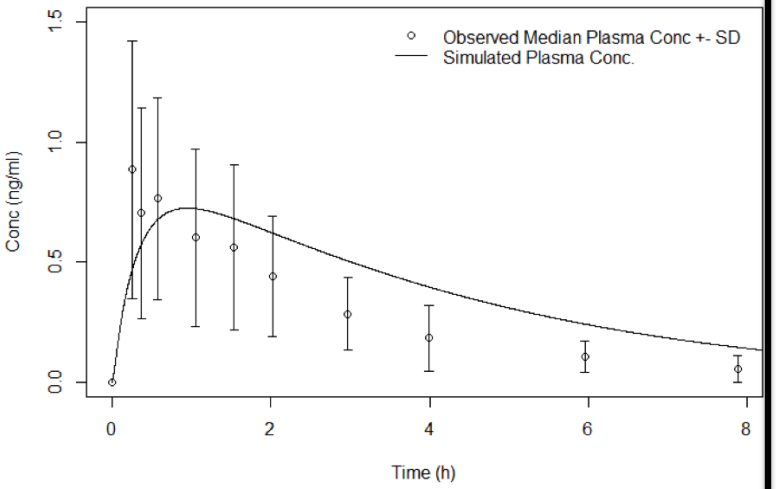


Correlation between MDT and MAT seems to exist

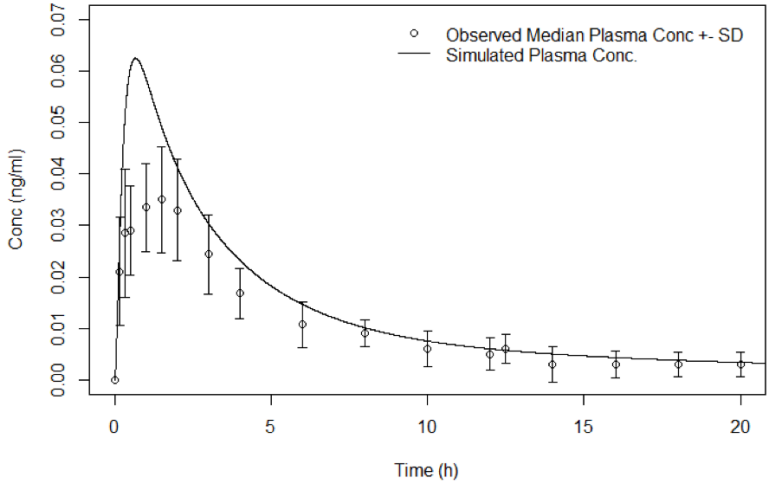
A: 400 µg budesonide



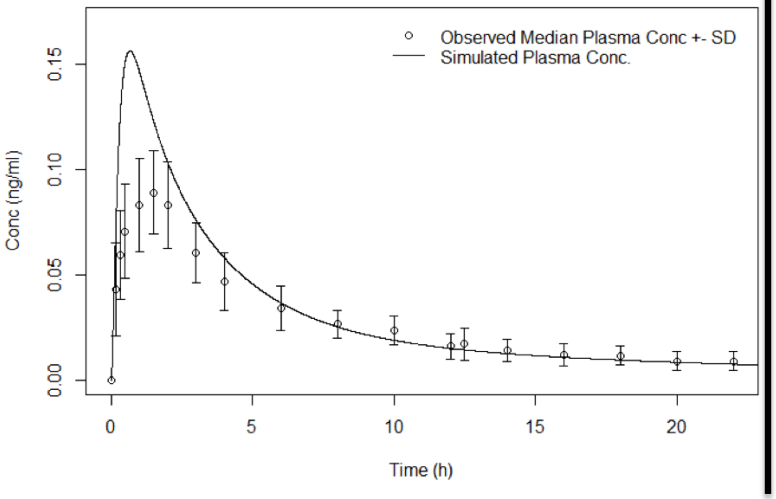
B: 1000 µg budesonide



C: 200 µg fluticasone propionate



D: 500 µg fluticasone propionate



Conclusions

- Dissolution method
  - Seems to be discriminatory
  - can provide critical information for regulatory decision making
  - First steps for ivivc correlations look promising.

  - Question: what method should be used?
    - What sample preparation?
    - What dissolution method?

Acknowledgement

- **FDA** (Bavna Saluja, Renish Delvadia, Absar Mohammad (Abir), Denise Conti)
  - HHSF223201110117A,
  - HHSF223201610099C,
  - HHSF223201300479A
  - 1U01FD004950

- **Elham Amini, Simon Berger, Steffi Drescher,**
- **Uta Schilling, Sharvari Bhagwat, Mark Rohrschneider (UF)**

- **Juergen Bulitta (UF)**
- **Mike Hindle, Worth Longest, Xiangyin Wei (VCU)**
- **Jag Shur, Rob Price (University of Bath)**
- **Dennis Sandell (S5 Consulting)**