Dissolution Methodologies

ISAM, Boise

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Properties important for Lung Delivery Performance

- Pulmonary deposited dose
- Regional deposition (central to peripheral)

- Pulmonary residence time

Factors important for long Residence Time

Dissolution/Interaction with Lung tissue

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

Not formulation dependent

Dissolution rate is relevant for defined **lipophilic drugs** for which **dissolution is affecting absorption rate**

Fluticasone propionate, mometasone furoate/propionate, budesonide, …..)

Methods

1: Sample Preparation

- DUSA (full range of particles),
- Sedimentation approach: Dry powder Chamber (Vitrocell)
- Cascade Impactor (defined stage(s))
- **Fine Particle Dose**
  - Modified Cascade impactors (Price)
  - Abbreviated systems (May, Sakagami)
- **Anatomical Throat** (ex-throat dose)

FPD and ex-throat approach is the most relevant

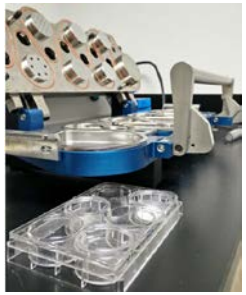
2: Dissolution Test

- Systems without controlled membrane diffusion
  - USP II and IV, V

- Systems Including diffusion step(biomimetic)
  - Transwell system/Franz cell (
  - Dissolve it® system (Gerde et al., ASSAY and Drug Develop. Technol., 2017)

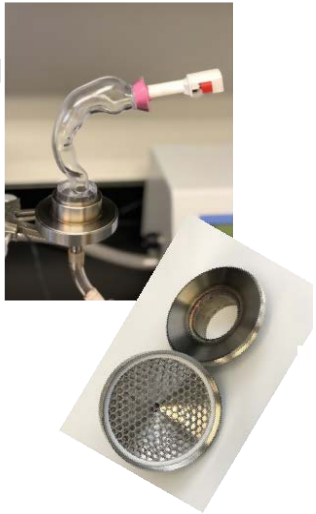
Method Overview

NGI

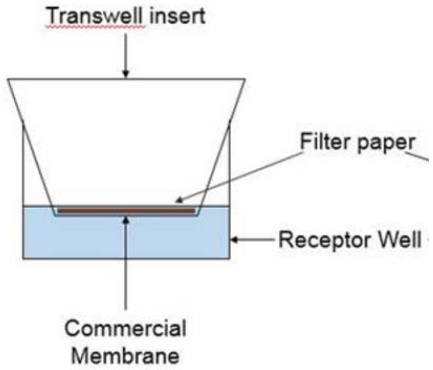


USP

Anatomical Throat (VCU)



Transwell®
Volume limited



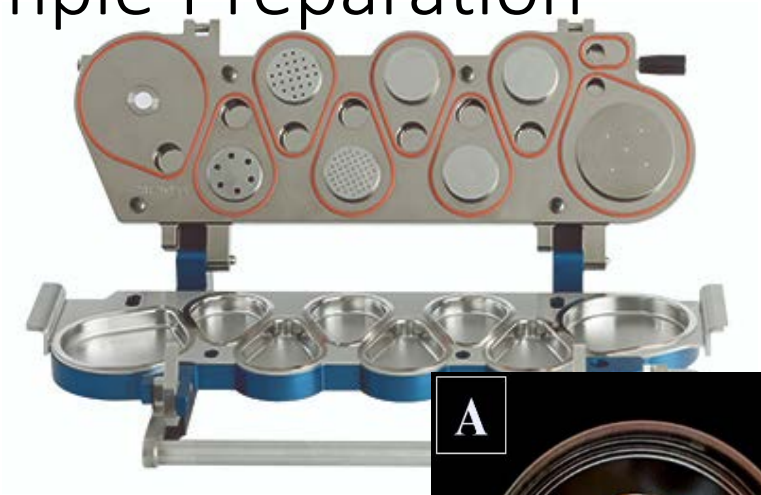
Two step process

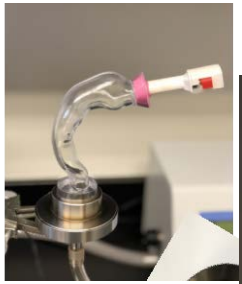
Solvent strength?
Volumes?

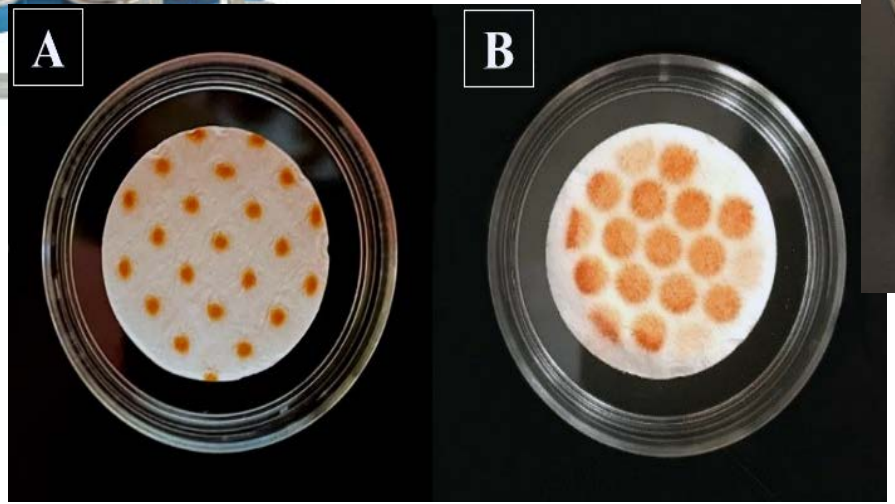
- Donor,
- Receptor
- Sampling?

Challenge: Dose Effect

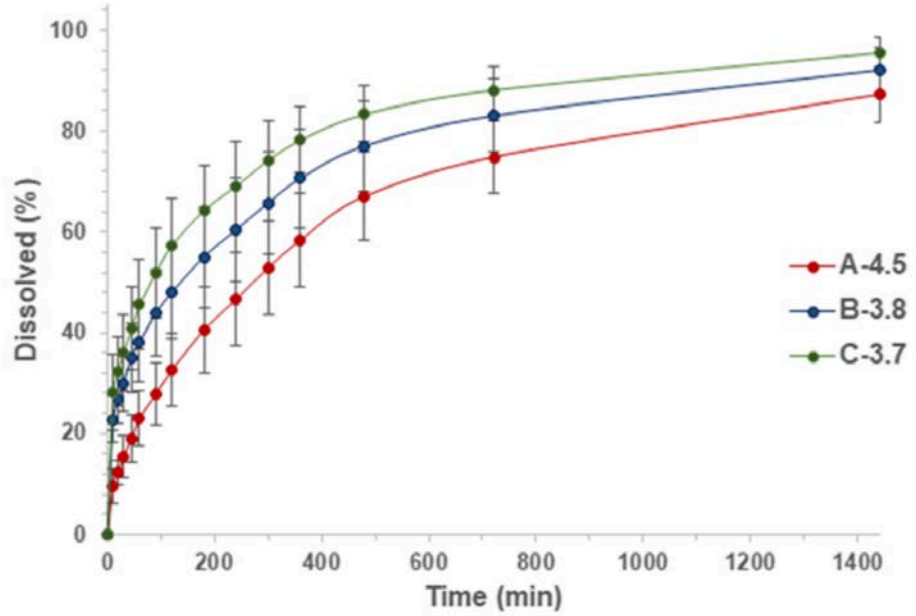
Sample Preparation







Result: FP-DPI formulation



0.5% Tween ®
Donor volume: 0.58 ml
Receptor volume: 1.5 ml
Sampling volume: 0.5 ml

Optimum Conditions?

Simulations for further Optimizing System

- Cascade impactor data for particle size distribution
- Nernst-Brunner equation for dissolution

$$\frac{dX(i)}{dt} = \frac{-D * SA_i t}{r_i t} * (Cs - \frac{X_d}{V_d})$$

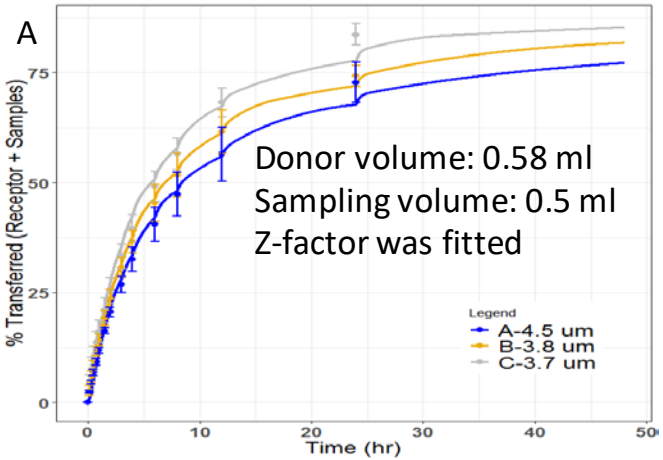
- Fick's law for dissolution

$$\frac{dXd}{dt} = -P * SM * \left(\frac{X_d}{V_d} - \frac{Y}{Vr}\right)$$

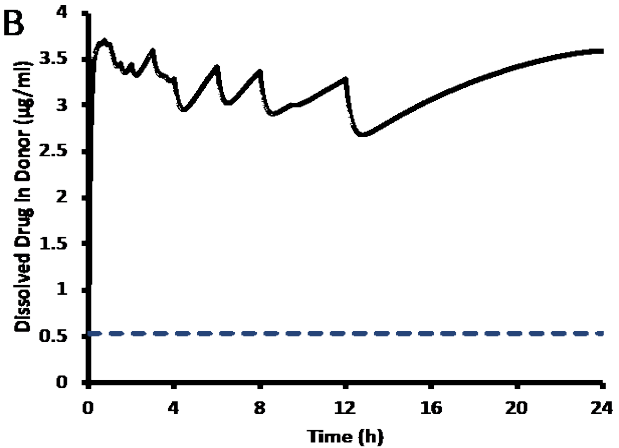
- Considering donor, receptor, sampling volume

Applying Simulations to three experimental DPI Formulations

Dissolution profile



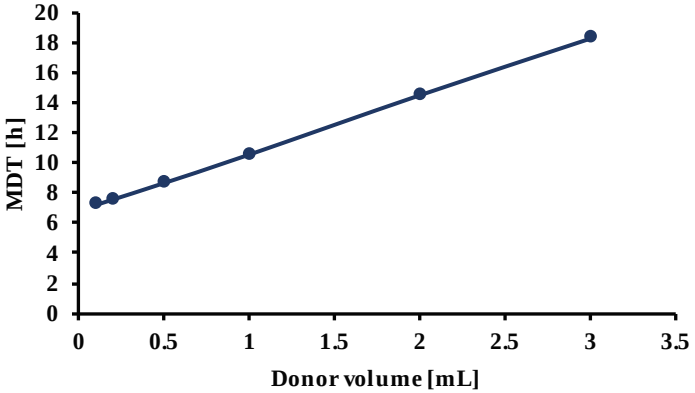
Drug Concentration in Donor for formulation B-3.8 µm



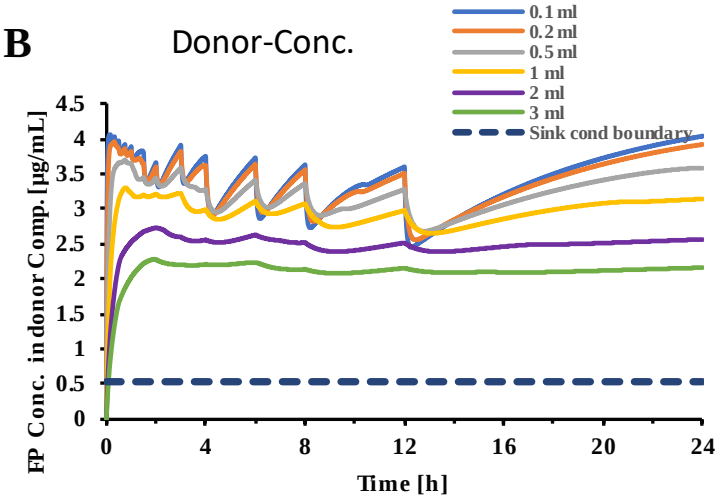
Rel. Diameter: 1 : 1.2 : 1.5
Rel. MMAD: 1 : 1.0 : 1.2

Simulations: Donor Volume

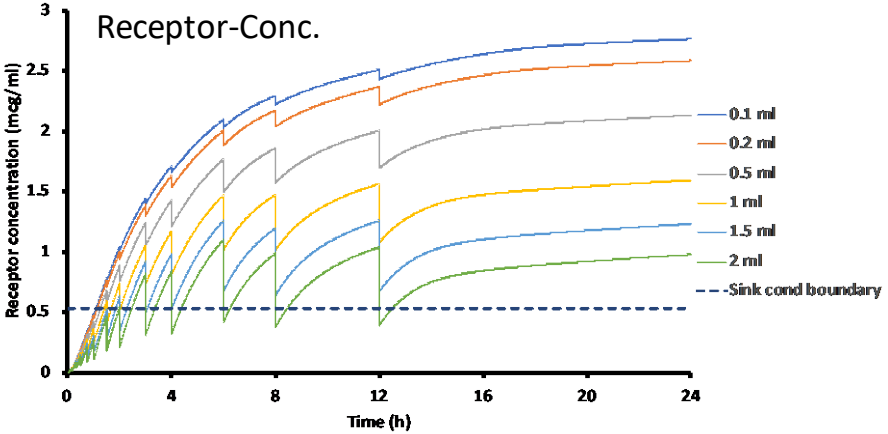
A



B

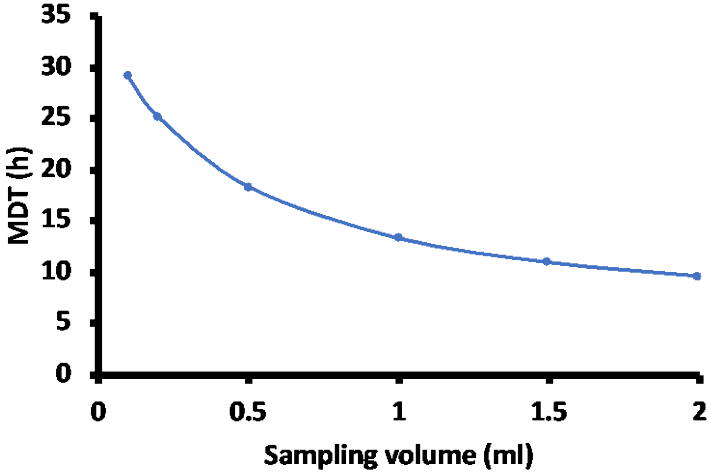


C

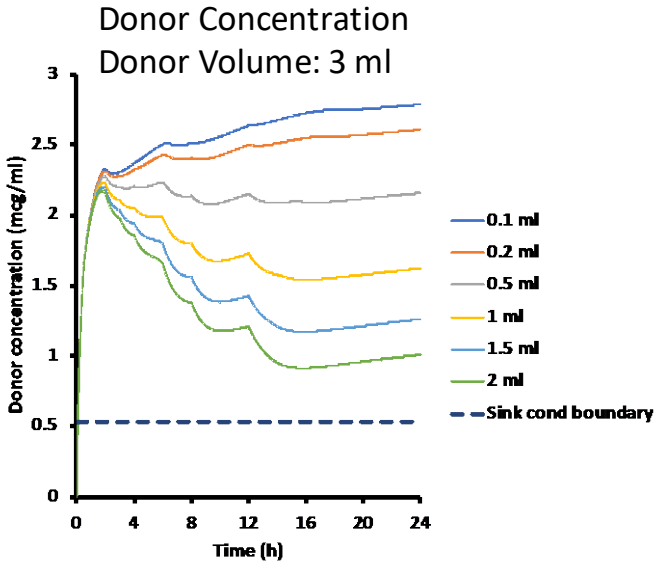


Donor volume increase: slight decrease in donor conc.
Increase in MDT because of reduced conc. Gradient

Simulations: Sampling Volume



Donor-Conc.

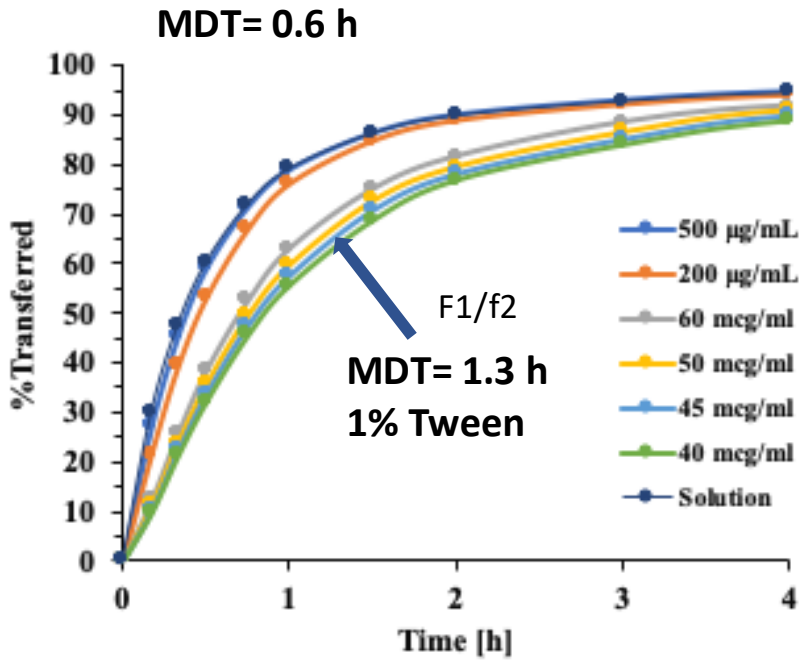


Sampling volume: **Decrease in MDT**, because of more pronounced concentration gradient
Further **decrease in donor concentrations.**

Increase in donor volume (**3 ml vs 0.58 ml**) and sampling volume (**2 ml vs 0.5 ml**) provide **close to sink conditions**.

Dissolution Medium? –

1: Compare: API (**FP**) in solution vs particles (4 µm):



For FP:
1% SDS
5% Tween

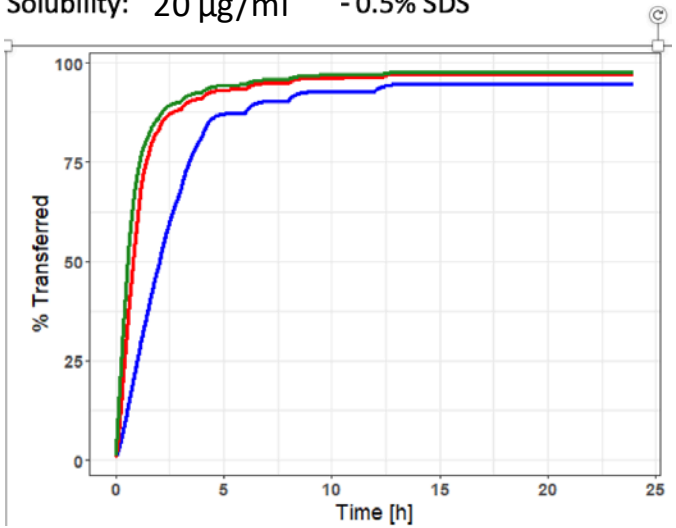
For Budesonide:
PBS, no surfactant

Dissolution Medium: Size Resolution

2. NGI stages: 2 (8 µm), 4 (1.66 µm), 6 (0.55 µm)

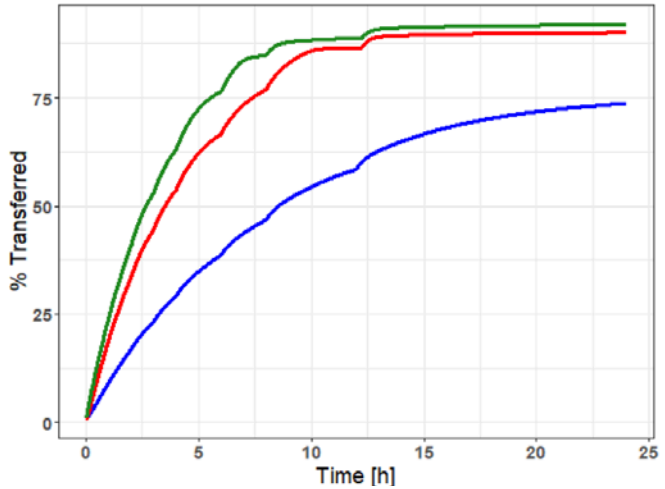
Stage 2, 4, and 6 (NGI)

Solubility: 20 µg/ml - 0.5% SDS



Stage 2, 4, and 6 (NGI)

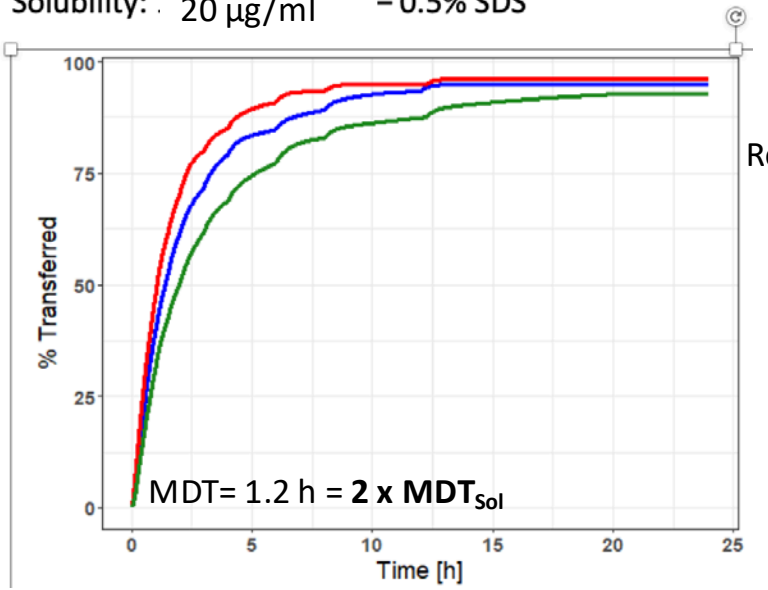
Solubility: 5 µg/ml · 0.5% Tween



MDT= 5 h ≈ 10 x MDT_{sol} **Sol: 5 µg/ml**

Simulations: Size resolution

Solubility: 20 µg/ml – 0.5% SDS



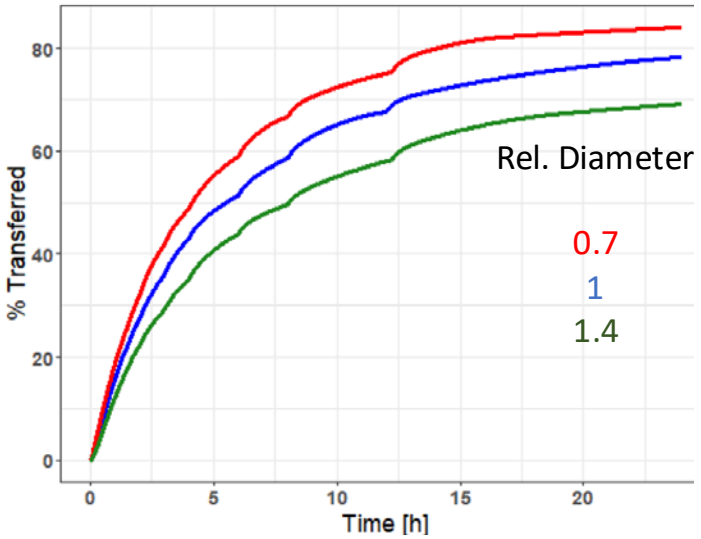
Rel. Diameter

0.7

1

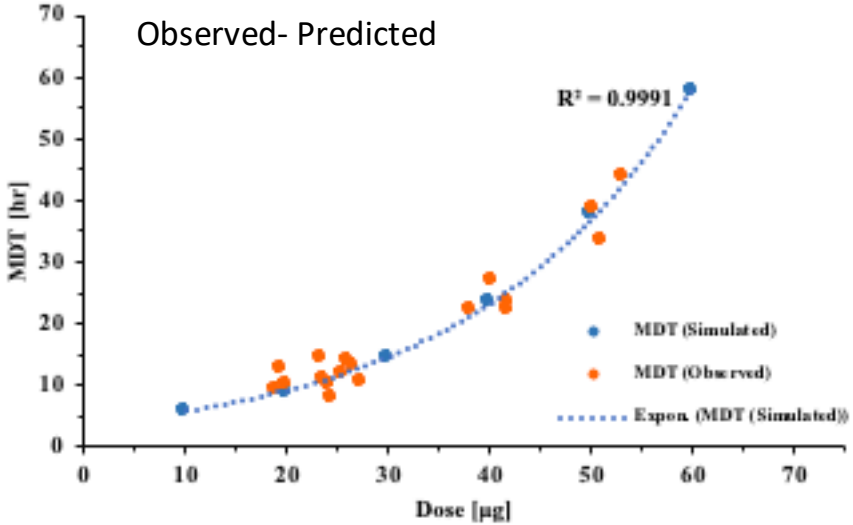
1.4

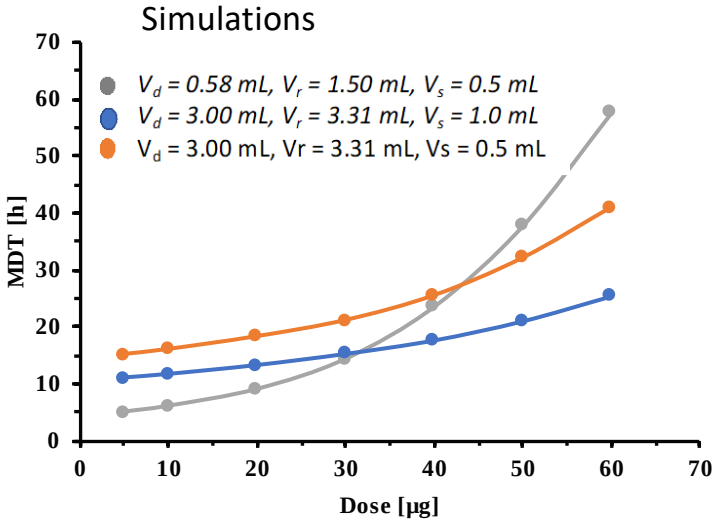
Solubility: 5 µg/ml 0.5% Tween



MDT= 7h = **10 x MDT$_{Sol}$; Solubility : 5 µg/ml**

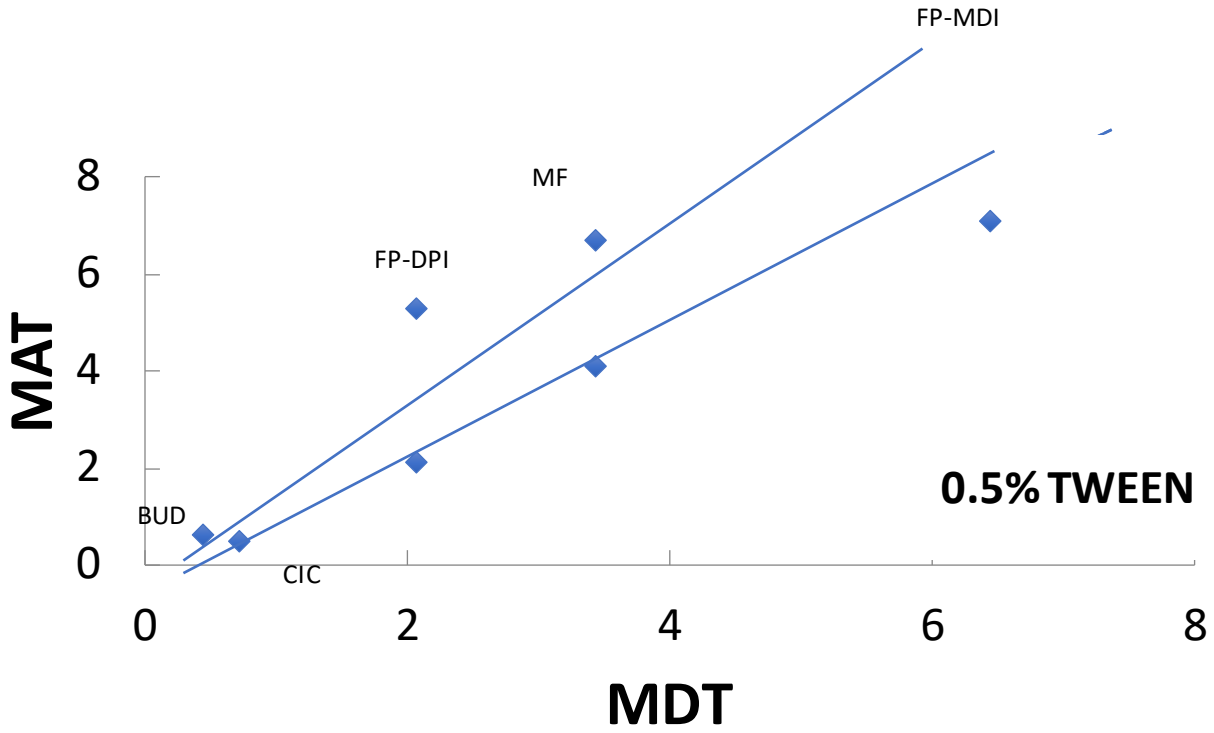
“Dose Effect” for experimental FP-DPI





Dose effect can be reduced: Donor: 3 ml
Sampling: 1-2 ml

Correlation between MDT and MAT

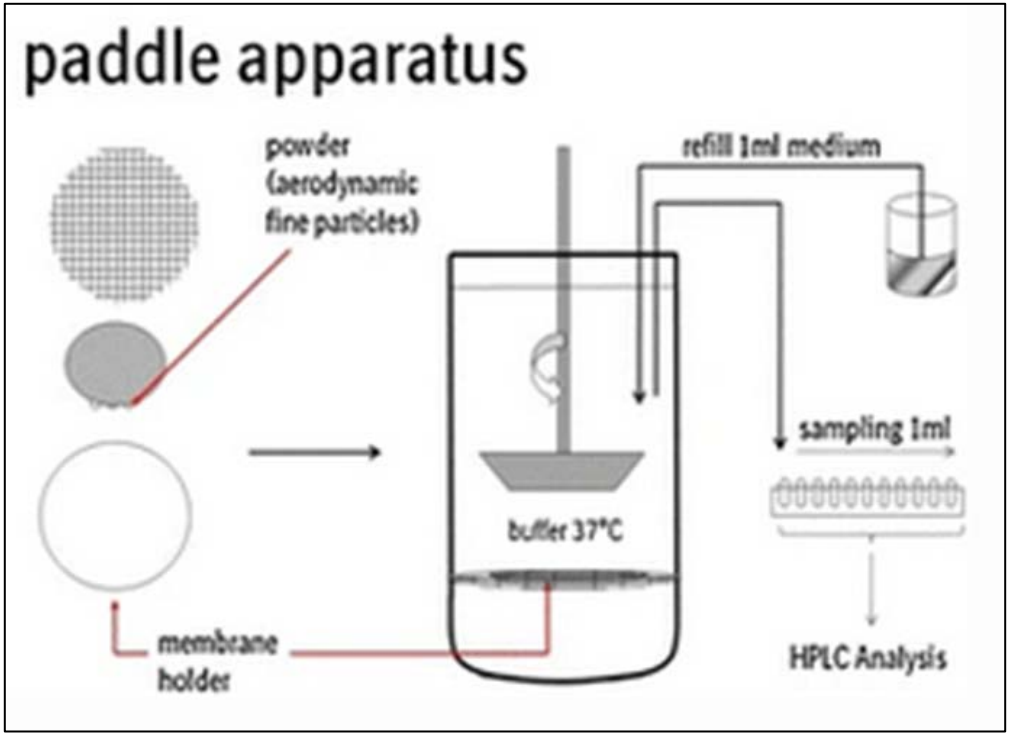


Correlation between MDT and MAT seems to exist

Summary: Transwell®

- More complex system
- Select solvent that provides MDT that is 2-**10** times longer than MTR of a solution (solubility of about 5 µg/ml)
- Use of a larger donor (3 ml) and sample volumes (2 ml) will provide close to sink conditions (FP)
- Under these conditions, “dose effect” is almost gone.

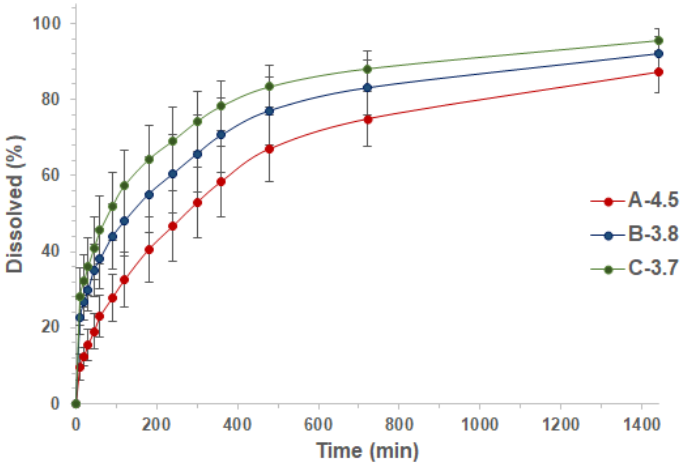
USP-Paddle over disc



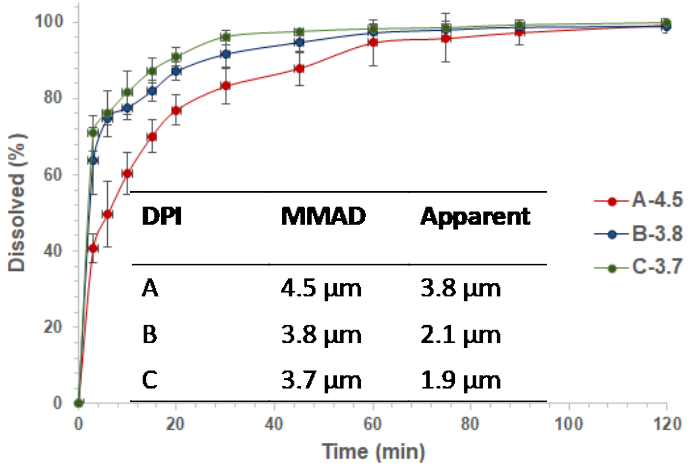
600 mL
0.5% Tween 80
80 RPM
37°C
2.5 cm

USP- Paddle over Disc vs Transwell®: 3 DPI formulations that only differ in lactose fines.

A: Transwell® System (0.5% Tween)



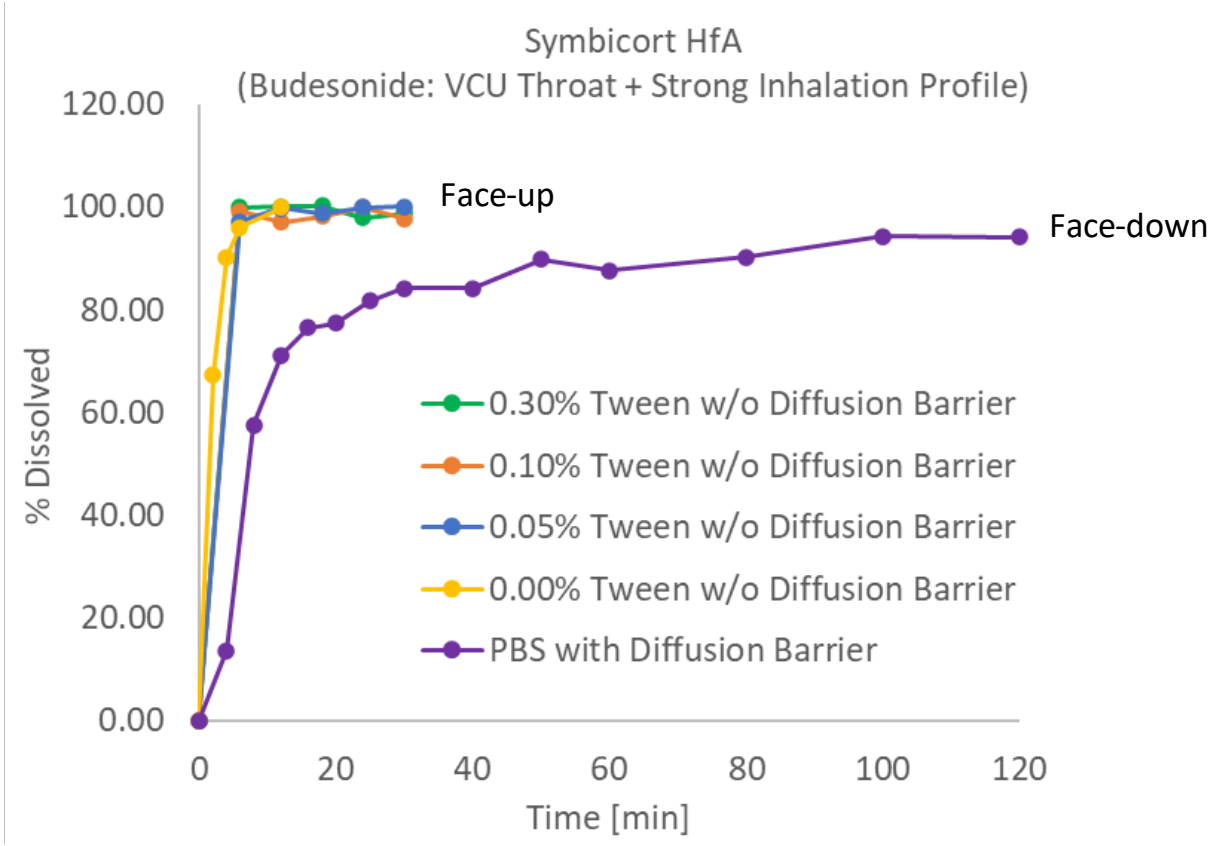
B: USP V Paddle Method (0.5% Tween), 600 ml



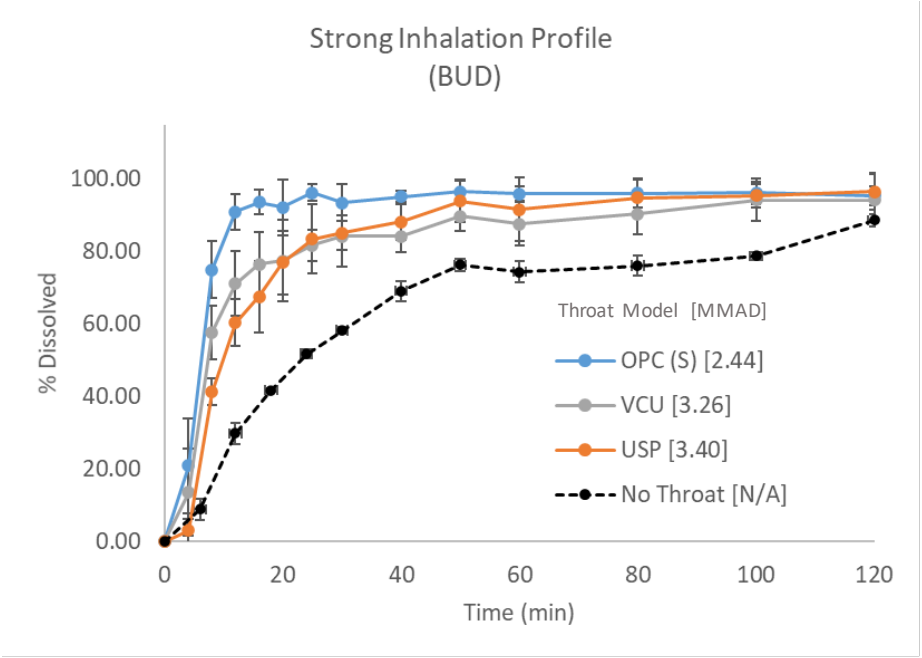
DPI	MMAD	Apparent
A	4.5 µm	3.8 µm
B	3.8 µm	2.1 µm
C	3.7 µm	1.9 µm

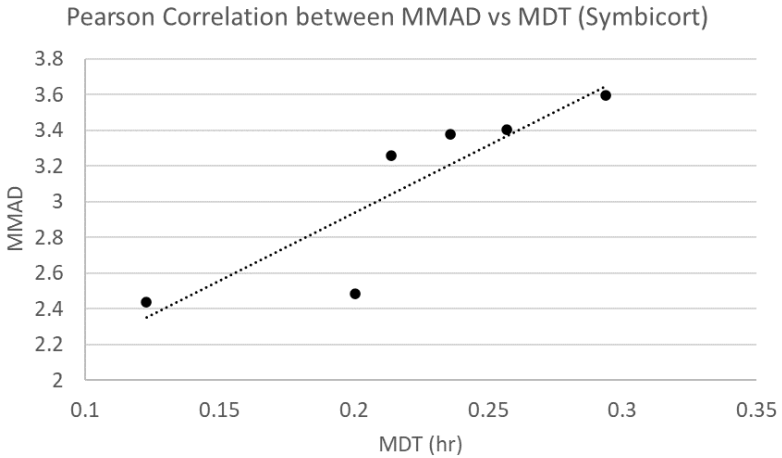
Hochhaus et al. The AAPS Journal (2021) http://doi.org/10.1208/s12248-021-00569-x

USP and Dissolution Media: Budesonide



Once optimized: high resolution power





Conclusion

- After proper optimization: USP and Transwell® system are robust and provide high resolution
- USP is less time consuming.
- Transwell® closer to in-vivo situation
- Good in vitro-in vivo correlation
- In vitro dissolution provides important information for PBPK.

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