

The Development of Predictive Dissolution Methods for Orally Inhaled Drug Products

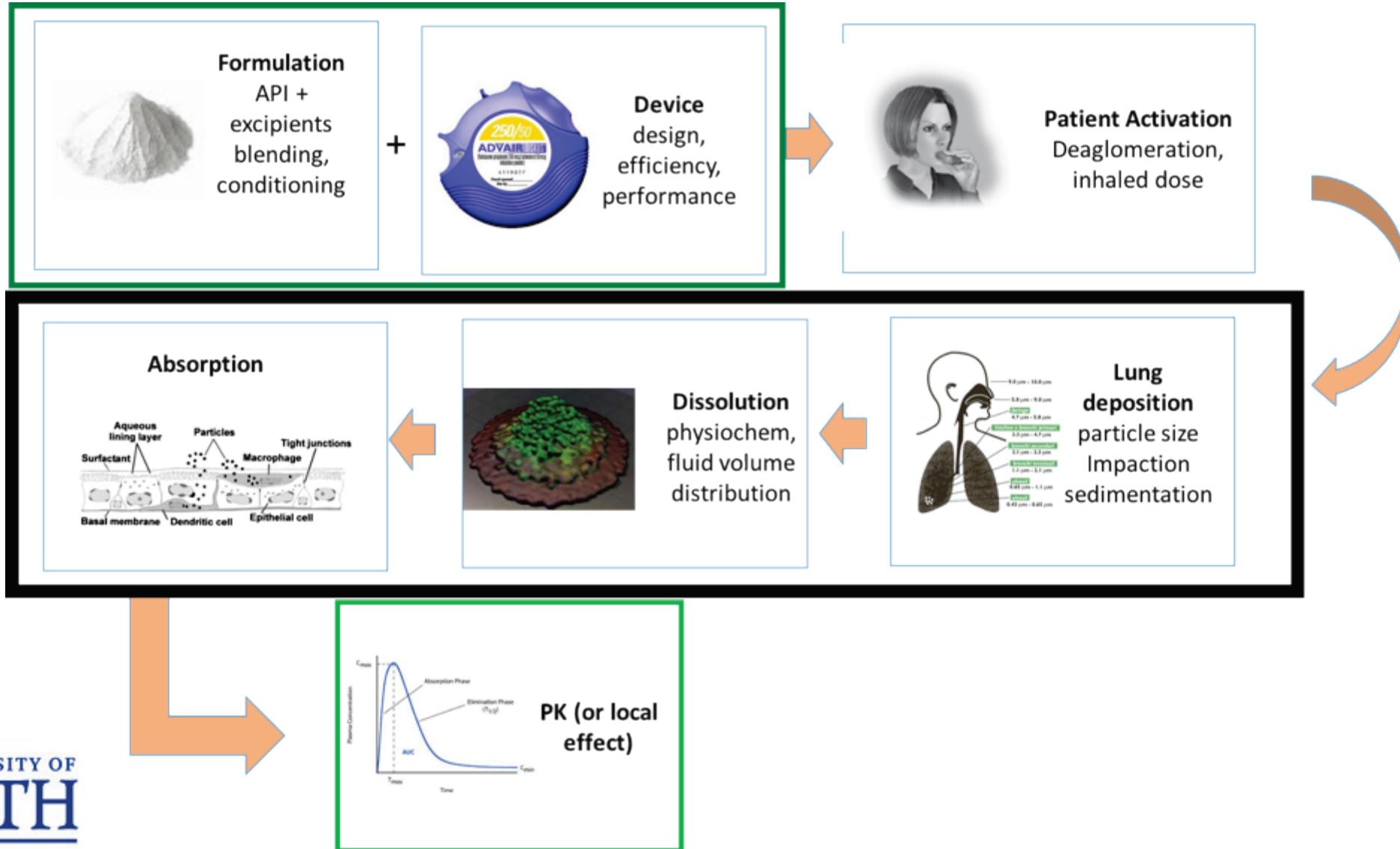
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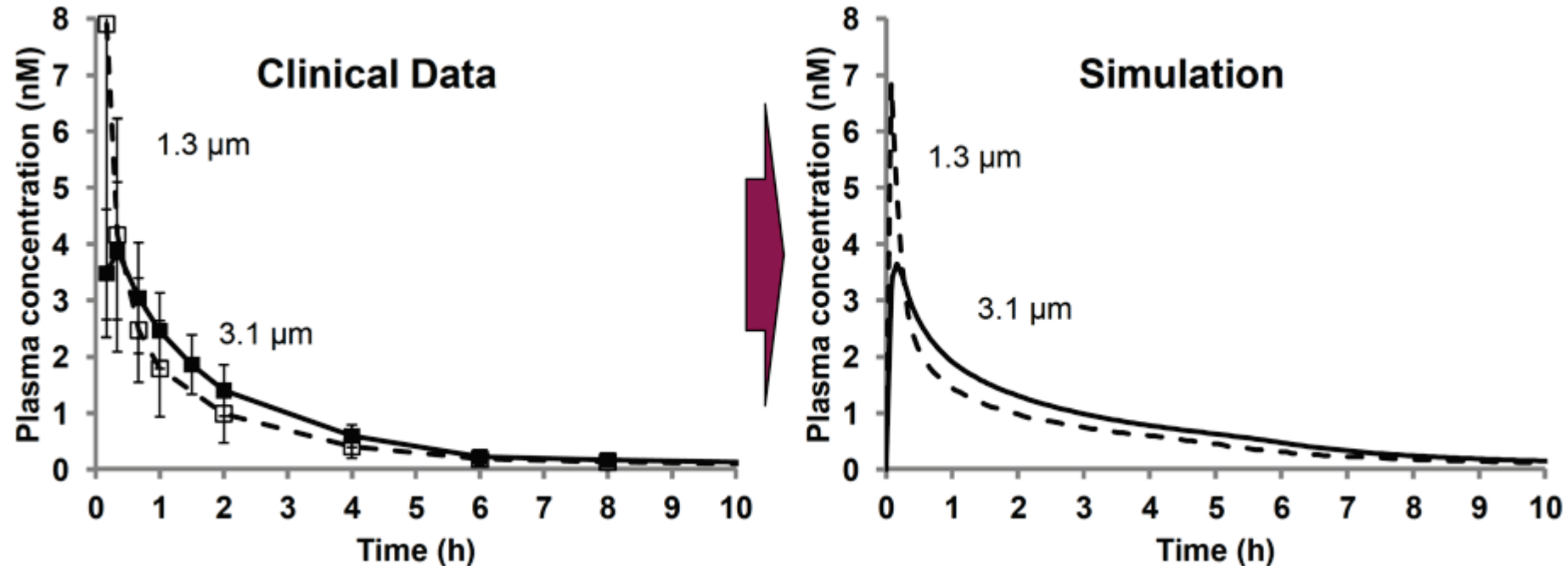
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Factors controlling bioequivalence



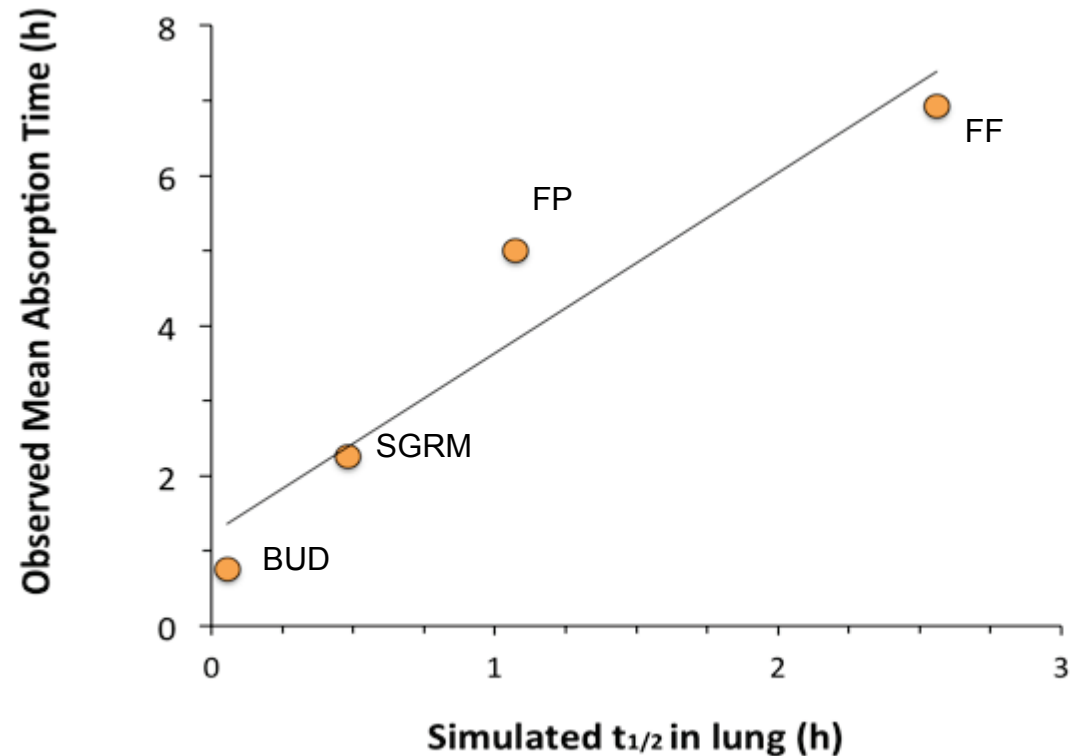
Particle Size - Simulated effect of dissolution on PK

A mechanistic physiologically based pulmonary compartmental absorption and transit model (PCAT- Gastroplus) was successfully used to simulate plasma profiles of an API with MMAD's of 3.1 and 1.3 μm .



Attempts to confirm using *in vitro* dissolution techniques all failed!

Simulations suggested dissolution rate is the main driver for drug retention in the lung



Simulations of dissolution rate ($t_{1/2}$) was based on solubility, particle size distribution and deposition patterns.

What is the relevance of dissolution?

The PK profile of locally acting OIDs depends on:

- Deposition
- **Particle dissolution**
- **Drug solubility and permeability**
- Particle clearance

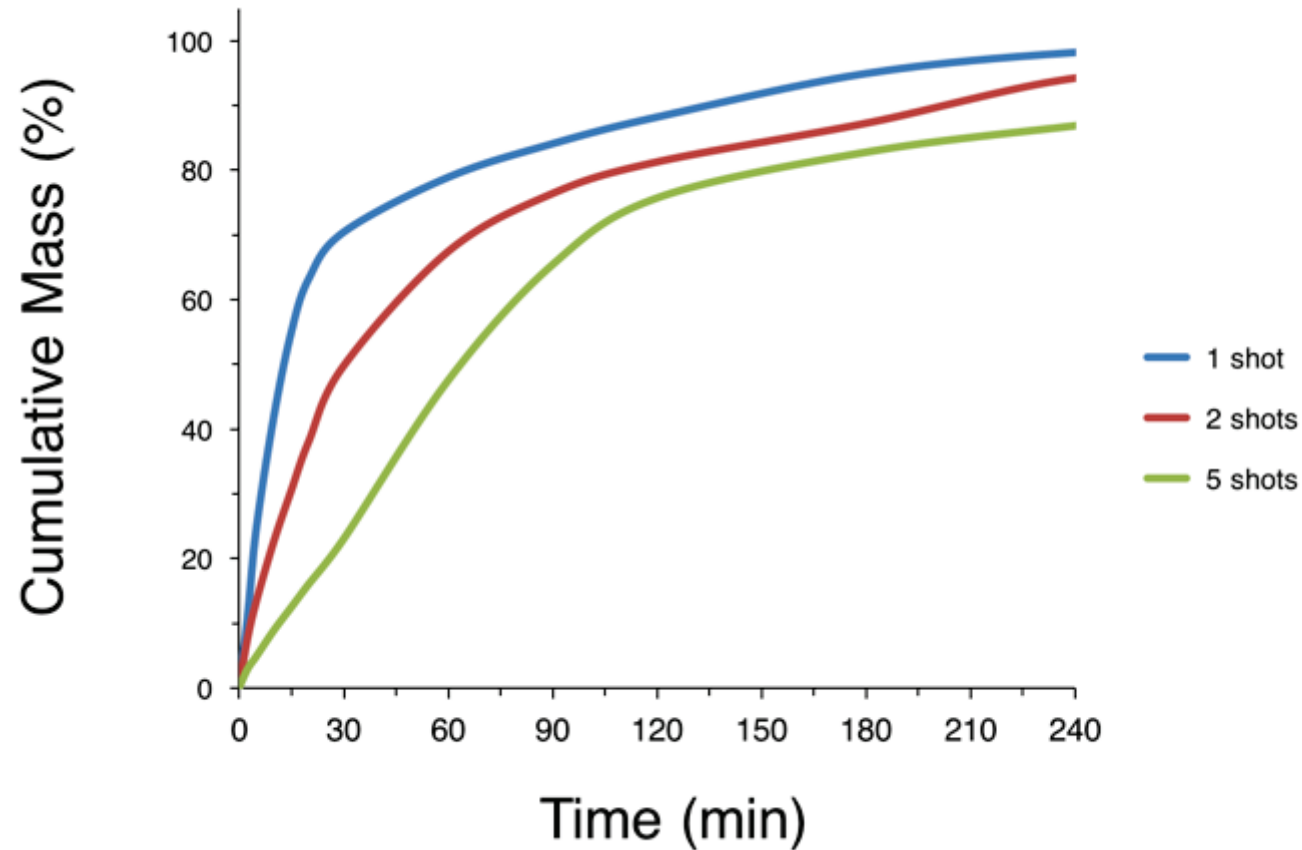
Relevance of Dissolution

- Low solubility drugs with slower dissolution show PK sensitivity to regional deposition
- Demonstrating PK and Dissolution equivalence may help to lessen the reliance on PD/clinical

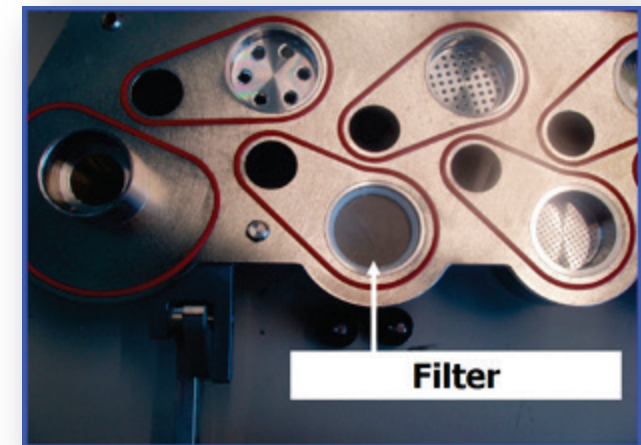
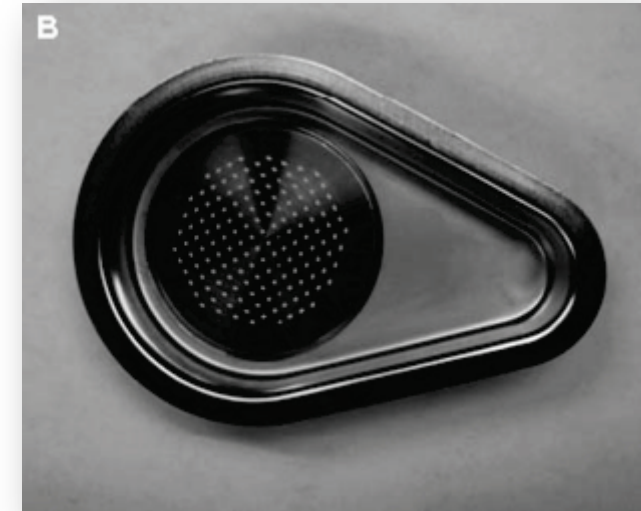
Problem

- Current dissolution models lack **discriminatory capability, ruggedness and stability**.
- Difficult to investigate the dissolution of the aerosol dose.

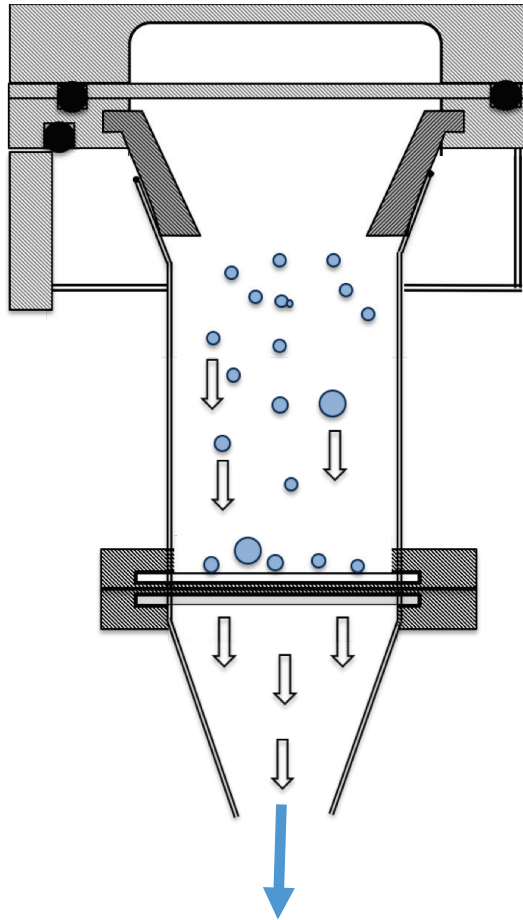
Current methodologies appear to be severely limited by mode of aerosol collection



GSK Flovent Diskus (100 μ g)



Dissolution independent of collected dose



Vacuum Controller

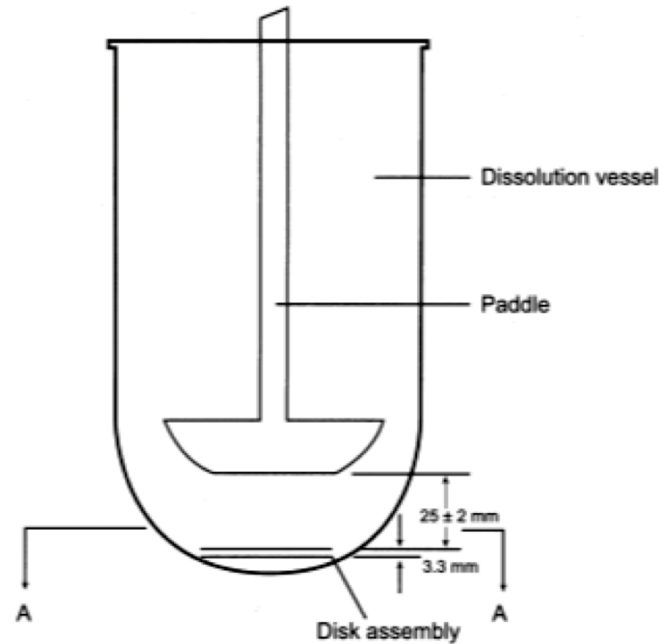
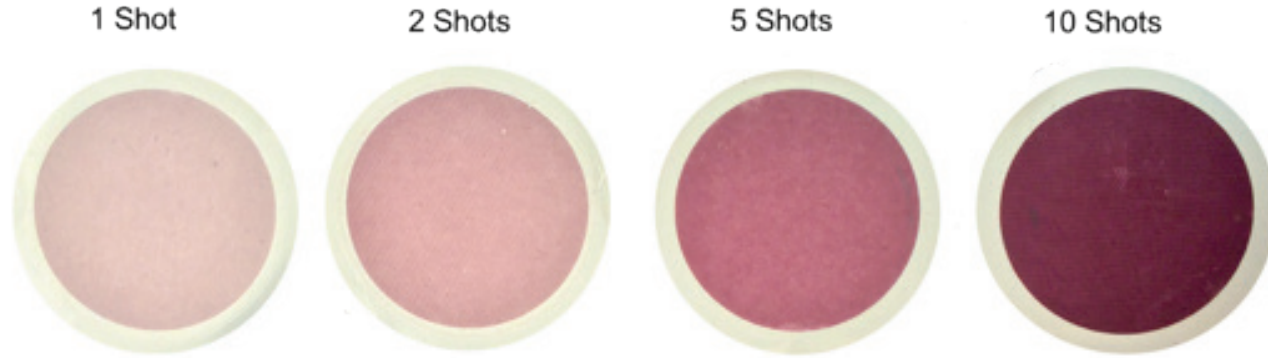


Figure 2.9.4-2. – Paddle and disk

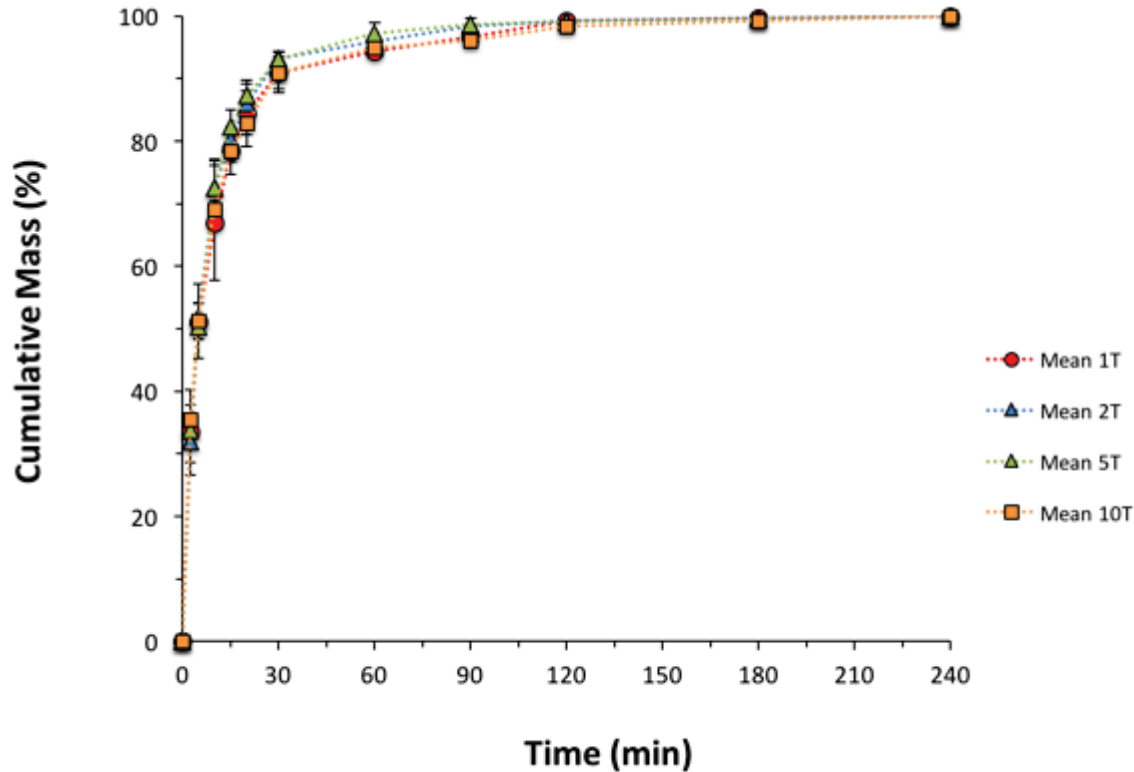
Case Study 1:

Investigation of the aerosol dose collection and dissolution using UniDose of DPI and MDI drug Products

Experimental Design

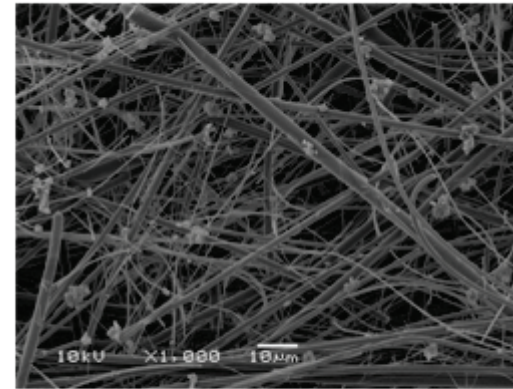
- Flovent[®] Diskus[®] 100 µg and Flovent[®] HFA 110 µg were tested in this study.
- Flovent Diskus was aerosolised into the UniDose system at 60 L/min and Flovent HFA was aerosolised into the UniDose system at 30 L/min.
- The UniDose collection system has been developed to uniformly deposit the whole impactor stage mass (i.e. below stage 2 of an NGI) onto a glass microfibre filter membrane.
- The filter is placed into disk cassette and POD (Paddle Over Disk) studies can be undertaken using 300ml PBS+SDS in a USP Apparatus II at 37C.

Dissolution profiles following different drug loading of FP from DPI

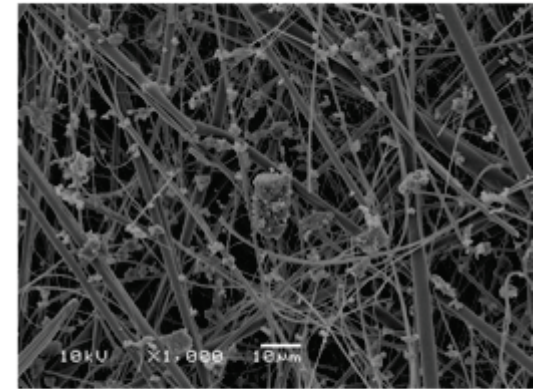


GSK Flovent Diskus (100 μ g)

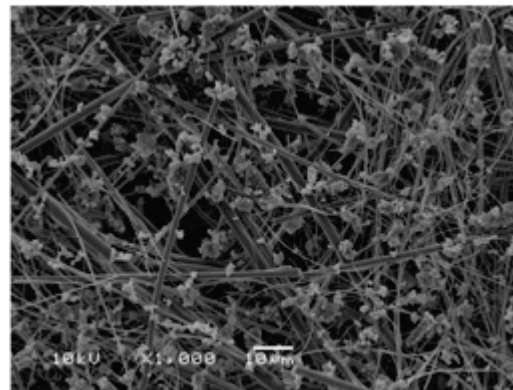
1 shot



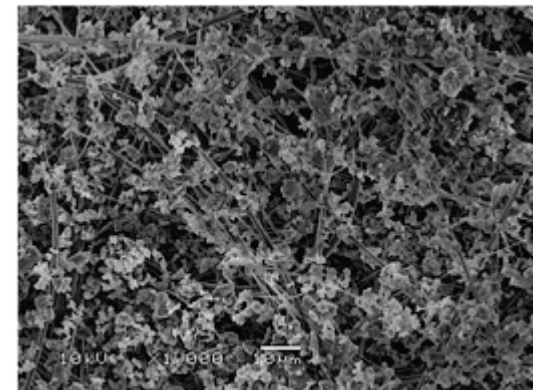
2 shots



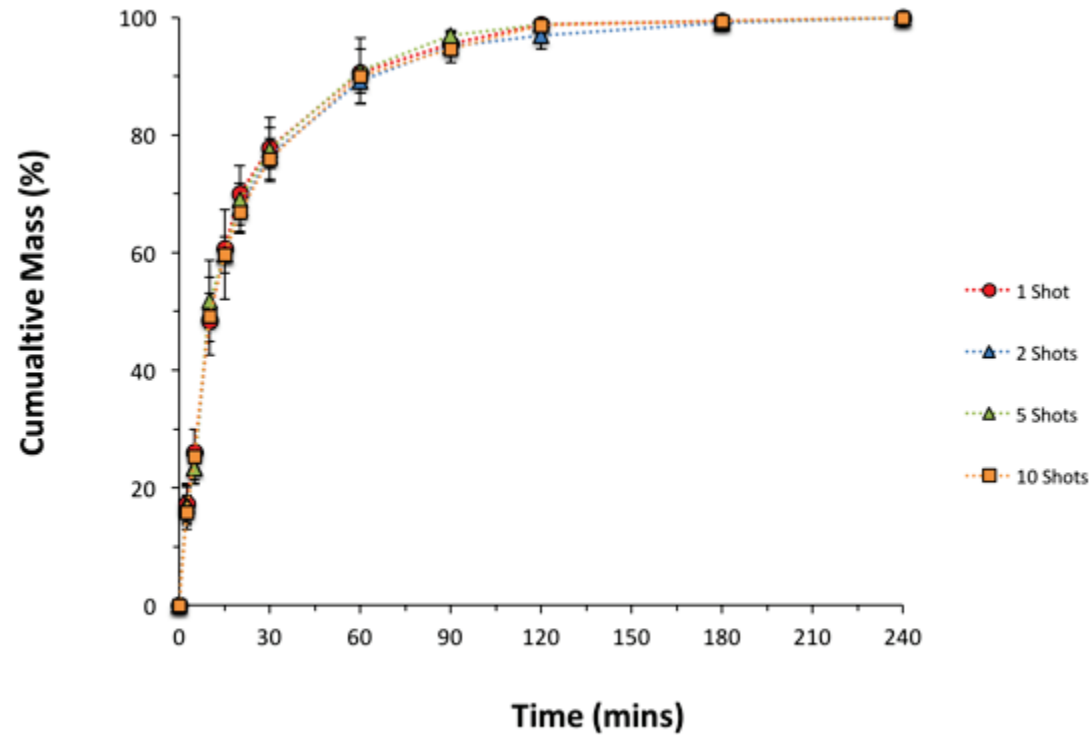
5 shots



10 shots

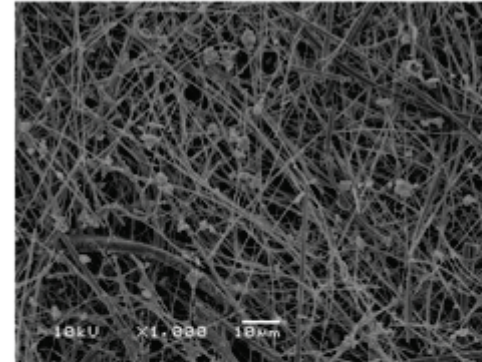


Dissolution profiles following different drug loading of FP from pMDI

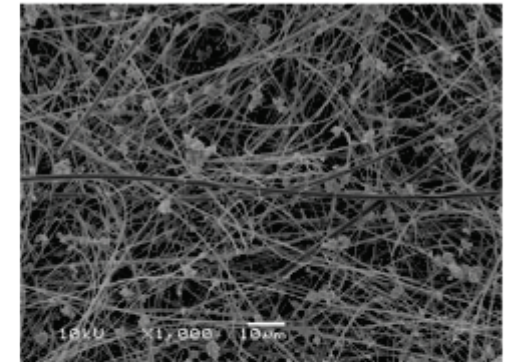


GSK Flovent HFA (110 µg)

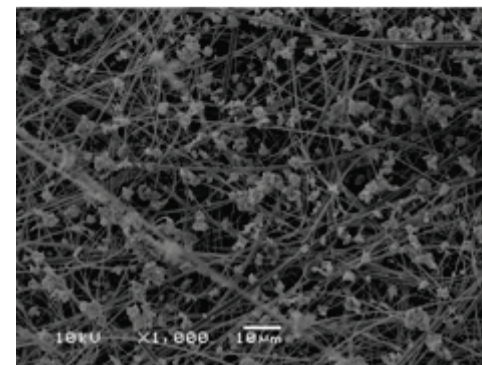
1 shot



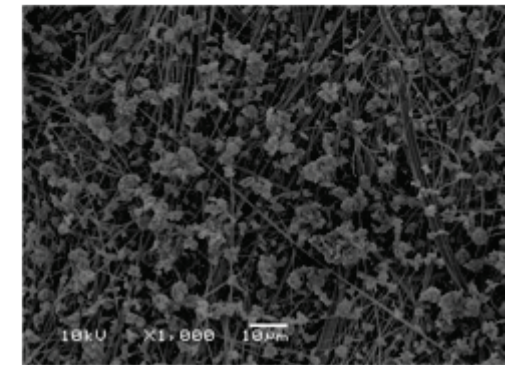
2 shots



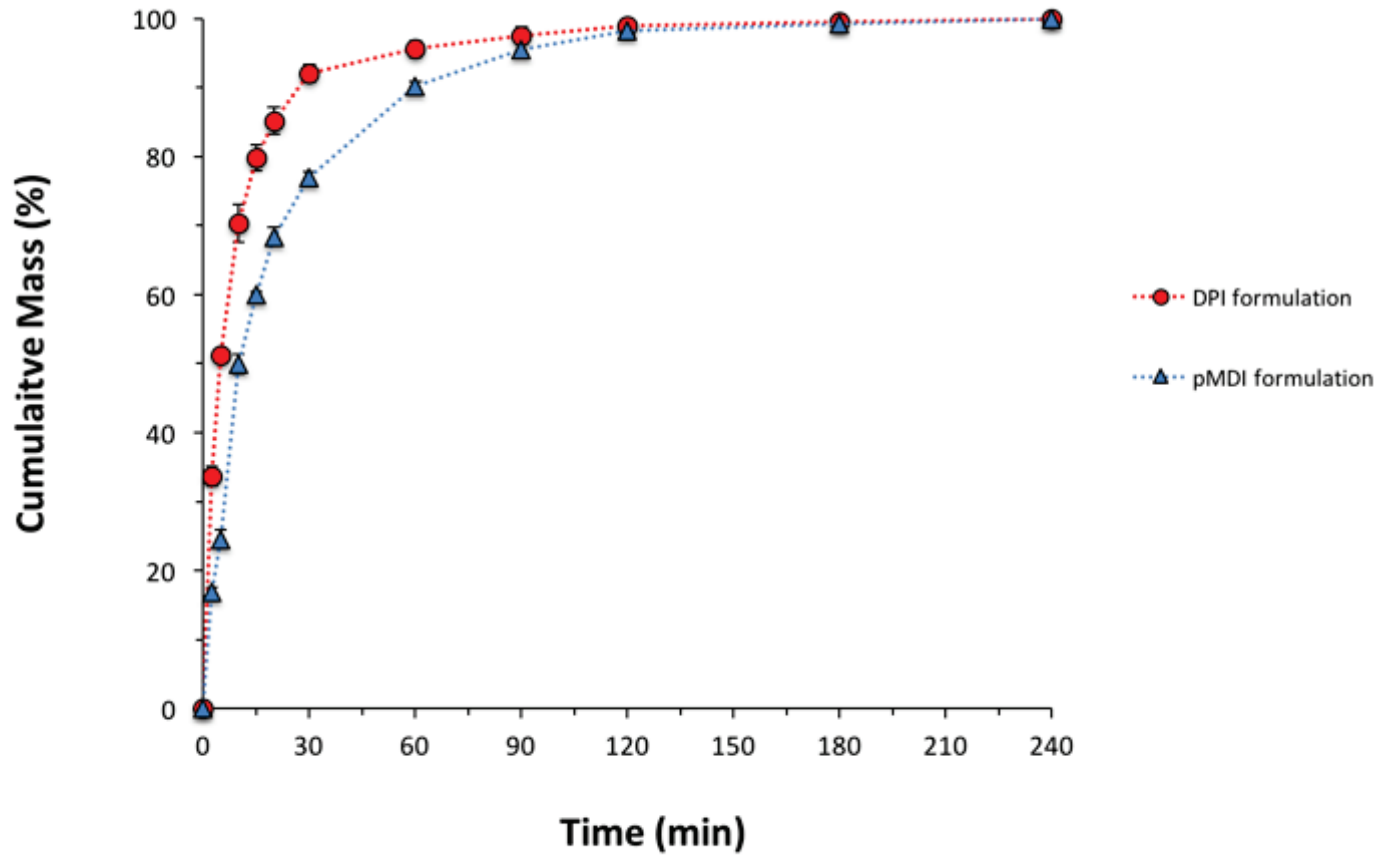
5 shots



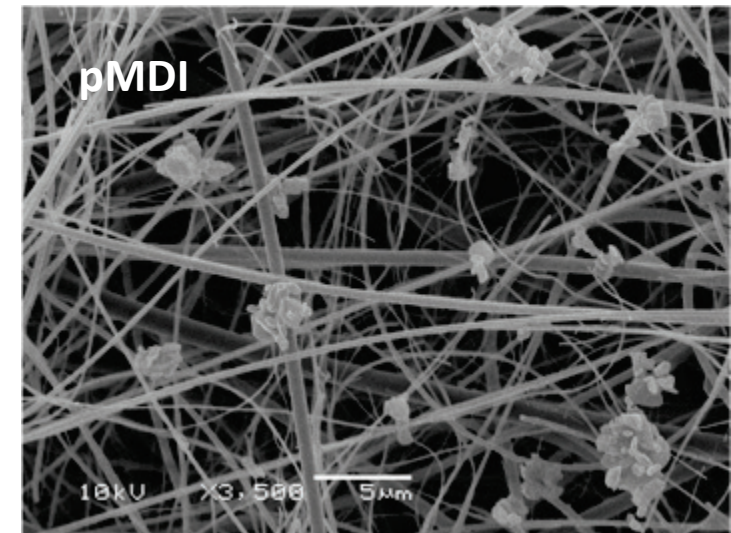
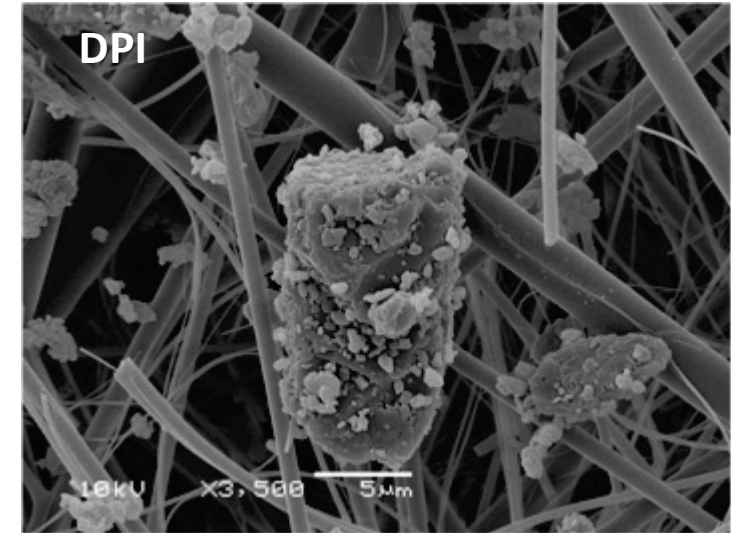
10 shots



Differentiation of Dissolution Release Profiles of FP in pMDI and DPI – Flovent DPI Vs. Flovent HFA



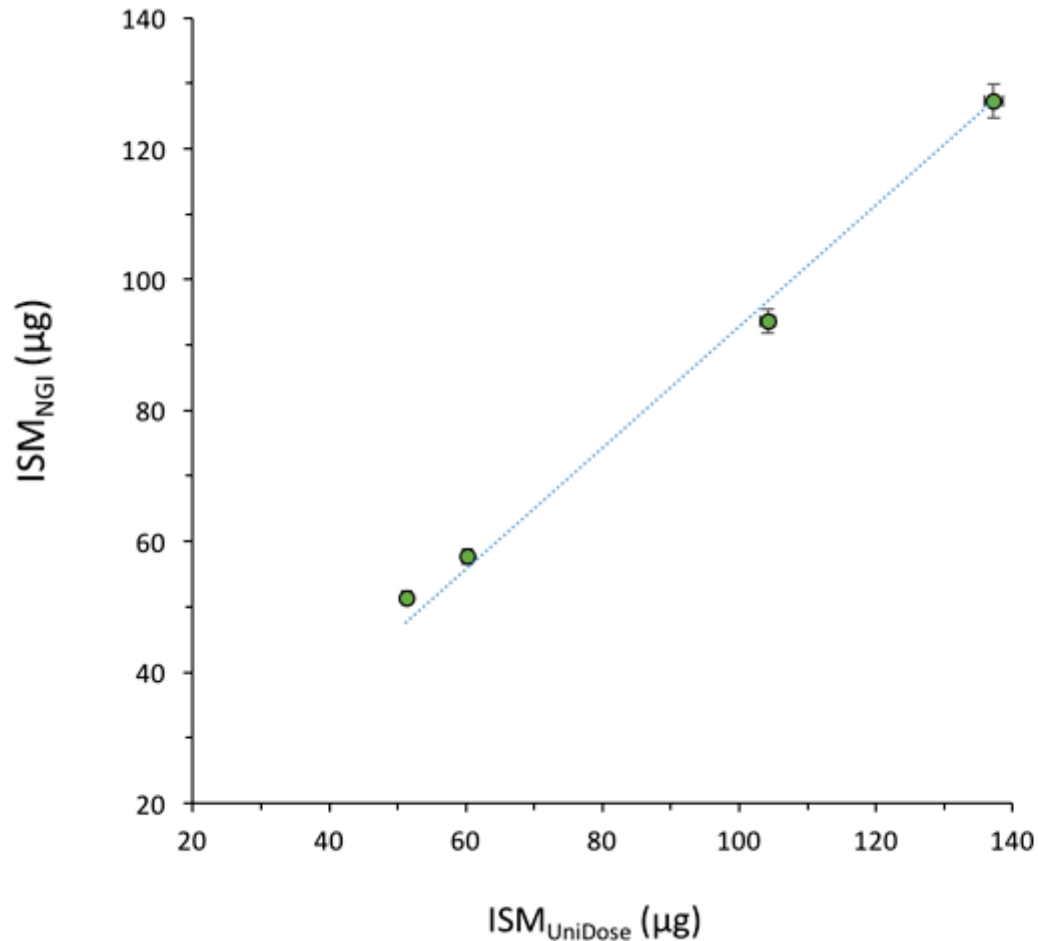
Enhanced wettability of FP in lactose matrix?



Case Study 2:

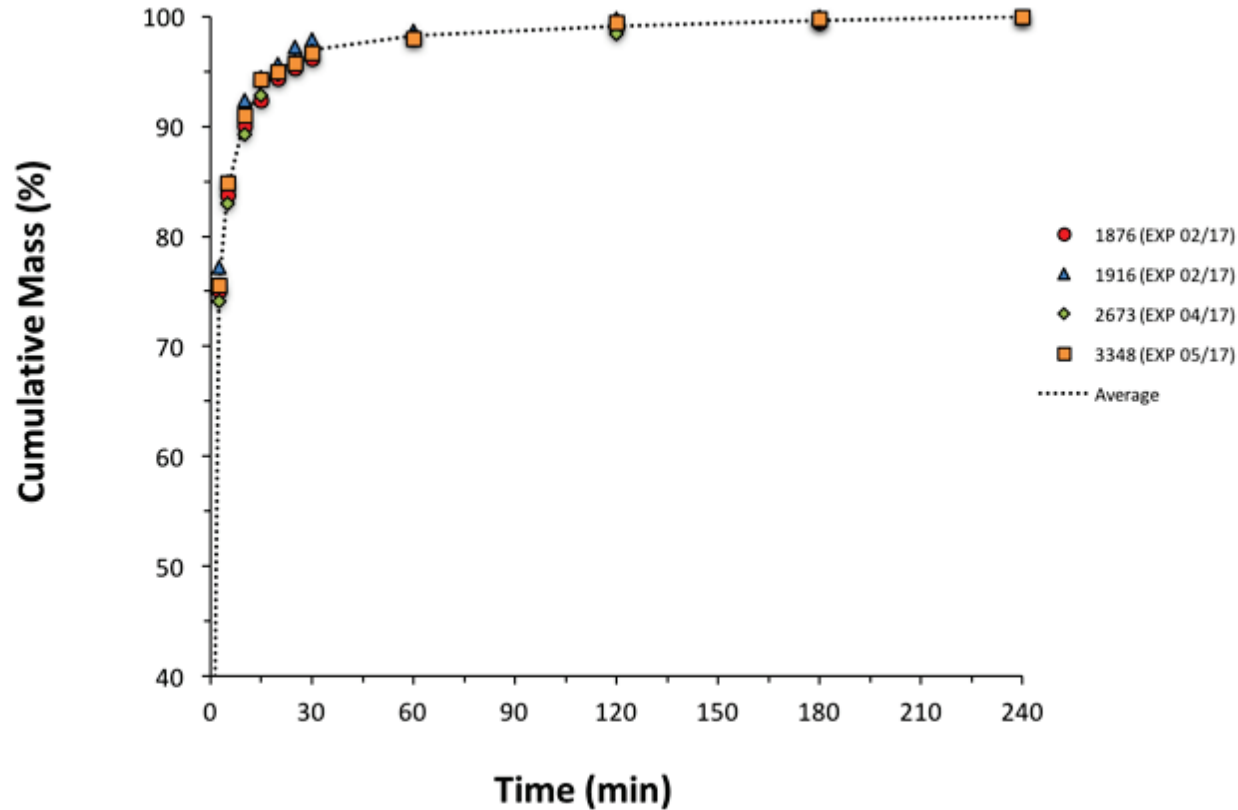
Investigation of the reproducibility of the ISM Dose collected by the UniDose

Relationship Between the ISM from NGI & UniDose



- Four different lots of Advair[®] (100/50) were investigated.
- Good agreement between the ISM measured from NGI and UniDose for different shots fired of Advair 100/50.
- Similar relationship for SX.
- Ensured that dissolution of the entire ISM from the finished product will be measured.

Dissolution of the FP component of Advair (100/50)



- Dissolution of the ISM of the FP component of Advair (100/50) was performed using UniDose.
- Four different lots of Advair 100/50 was aerosolised into the UniDose system at 60 L/min.
- The UniDose collection system has been developed to uniformly deposit the whole impactor stage mass (i.e. below stage 2 of an NGI) onto a glass microfibre filter membrane.
- The filter is placed into disk cassette and POD (Paddle Over Disk) studies can be undertaken using 300ml PBS+SDS in a USP Apparatus II at 37C.
- Data indicated excellent repeatability and accuracy.



GSK Original Claim:

“When salmeterol and fluticasone propionate were administered in combination by the inhaled route, the pharmacokinetics of each component were similar to those observed when the drugs were administered separately.”

PK results on the comparison of Seretide[®] 100/50 and Flixotide[®] 100

Population pharmacokinetic analysis (RM2005/00368/00)

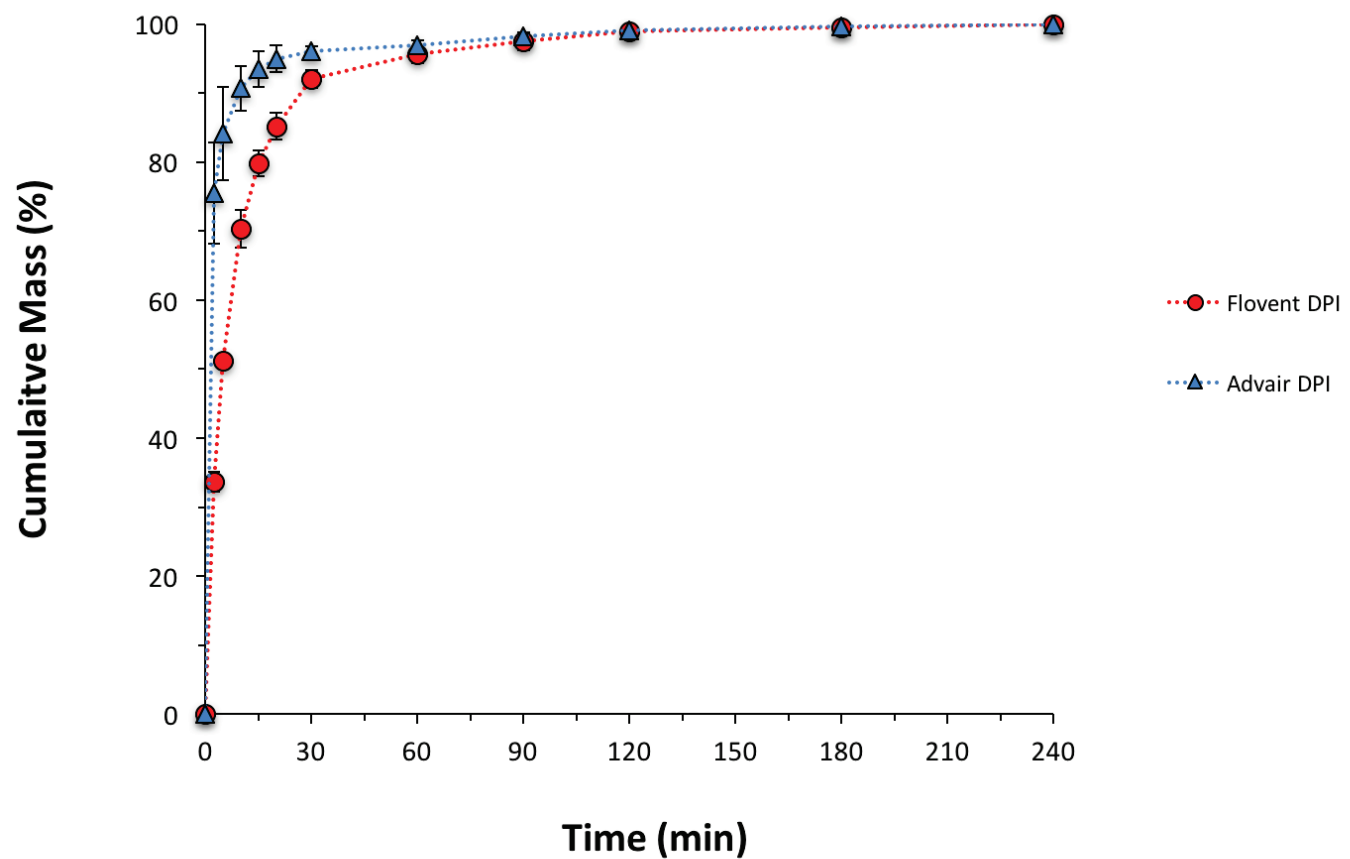
Ratio of Seretide/Flixotide (Healthy Adults)

C_{max} **1.39** (90% CI: 1.29, 1.51)

AUC_{last} **0.78** (90% CI: 0.56, 1.08)

C_{max} was found to be significantly higher after administration of the combination based product. Both AUC and **C_{max}** would fail bioequivalence PK test

Dissolution profile of FP in Flovent (100 µg) and Advair (100/50)



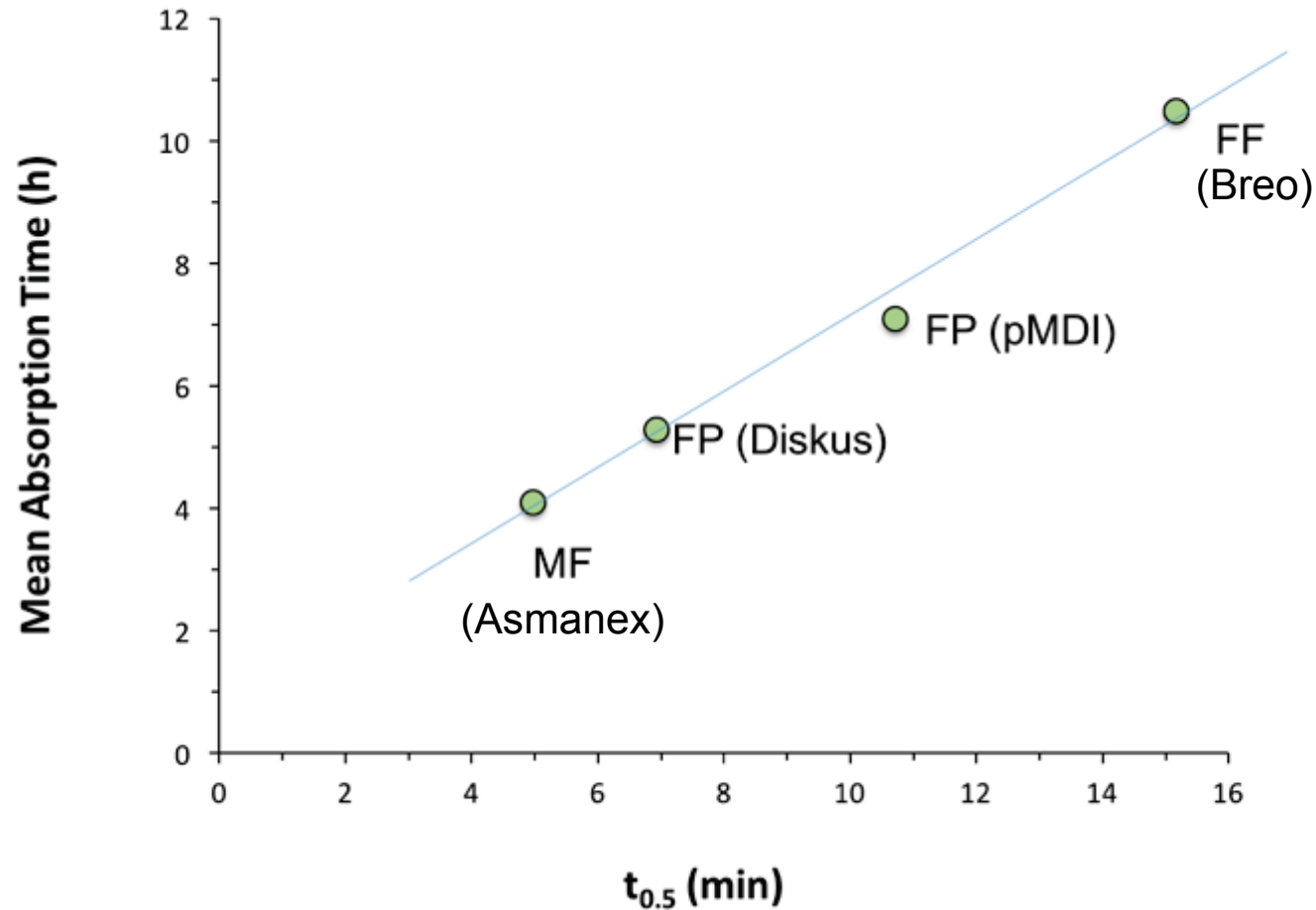
Product	$t_{0.5}$ (min)
Flovent	6.92
Advair	4.74



Summary

- Development of an aerosol collection system (UniDose), that deposits the whole impactor stage mass (ISM) uniformly over a high surface area filter for dissolution studies.
- No significant difference in dissolution rates with dose loading for DPI and pMDI with increasing number (1-10) of actuations ($P > 0.05$).
- UniDose has significantly increased the discriminatory capability, ruggedness and stability of aerosol dissolution testing.
- Possible to investigate the impact of raw material critical material attributes and formulation processing on dissolution.
- Utility to support IVIVC requires more work and input of clinical data.

Relationship between in vivo MAT and in vitro dissolution half-life for low soluble APIs





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