Research opportunities to support further PSG development for orally inhaled products

Andrew Cooper

Development for In-Vivo Performance Lead,

Global Respiratory Scientific Affairs, R&D

Paradigm shift in BE requirements for OIPs

e.g. Draft PSG for fluticasone propionate and salmeterol xinafoate inhalation powder

Sep 2013

<u>In-vitro studies</u>
- Single actuation content
- Aerodynamic particle size distribution

<u>PK BE study</u>
- Two-way crossover in healthy subjects (FP and salmeterol)

<u>Clinical Endpoint Study</u>
- 4-week parallel group study using low strength product in asthma patients with FEV_1 endpoints

Nov 2024

Option 1

<u>In-vitro studies</u>
- Single actuation content
- Aerodynamic particle size distribution
- Realistic APSD
- Dissolution

<u>Comparative characterization study</u>
- Particle morphology of the emitted dose

<u>In-vivo BE studies with PK endpoints</u>
- Two-way crossover in healthy subjects (FP and salmeterol)
- Two-way crossover in healthy subjects with charcoal block (salmeterol)

Option 2 (as 2013)

<u>In-vitro studies</u>
- Single actuation content
- Aerodynamic particle size distribution

<u>PK BE study</u>
- Two-way crossover in healthy subjects

<u>Clinical Endpoint Study</u>
- 4-week parallel group study using low strength product in asthma patients with FEV_1 endpoints

"An optional computational modeling study may be used to support BE."

VIATRIS

Dissolution in USP-2 apparatus with dose collection by liquid impingement

Collect dose by liquid impingement in non-solubilising medium

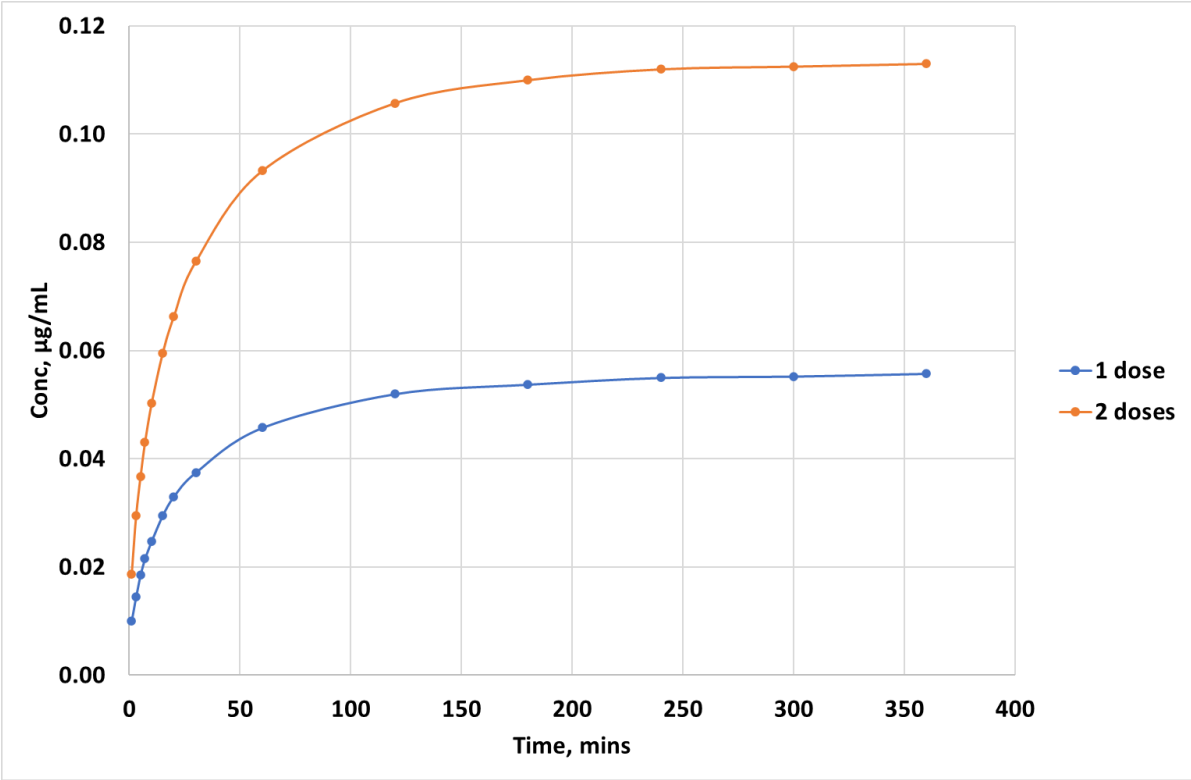
Quantitatively transfer cup contents to USP-2 vessel

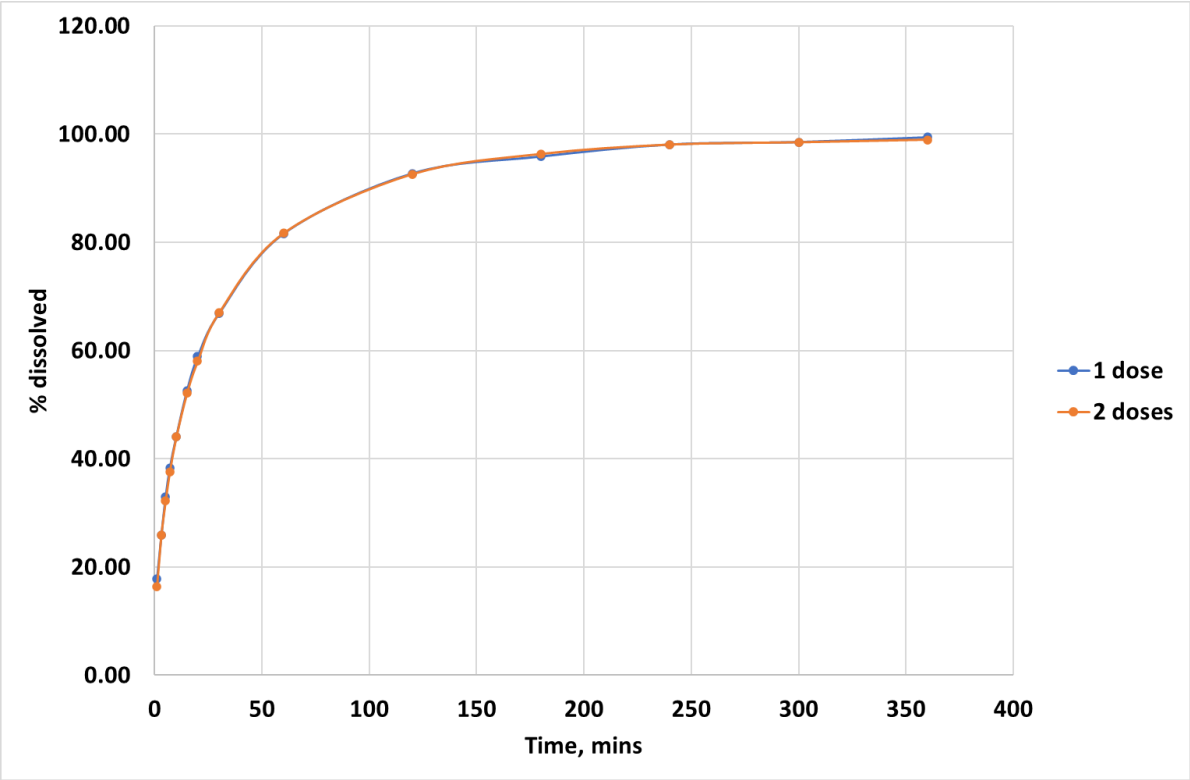
Add solubilizing medium to vessels and start dissolution

Take samples at required timepoints and filter for analysis

At final timepoint, add solubilizing solvent to an unfiltered sample to determine 100 % value.

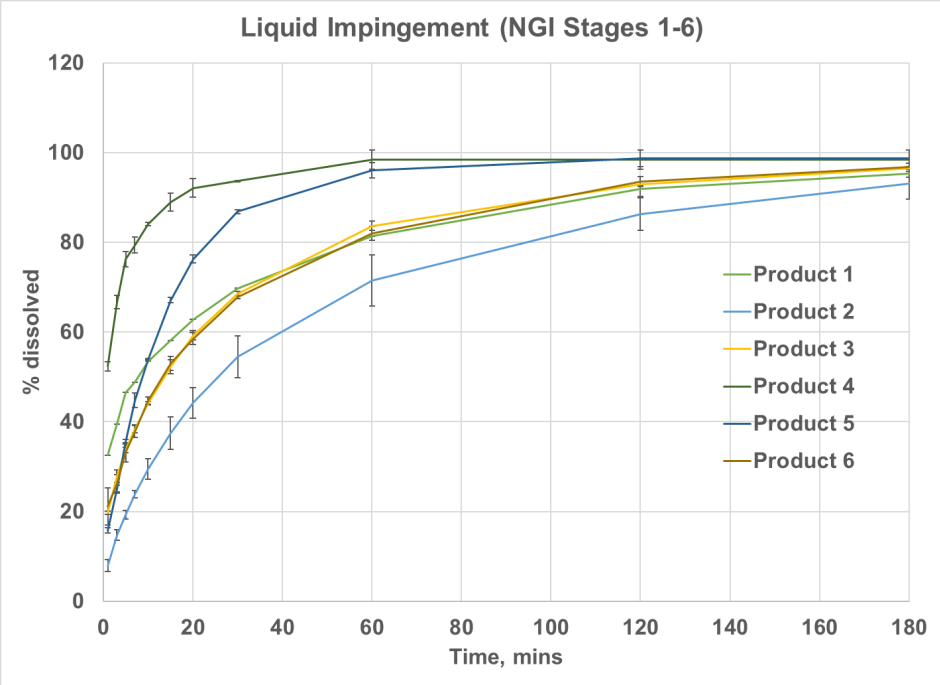
Dose collection by liquid impingement: effect of number of doses on dissolution

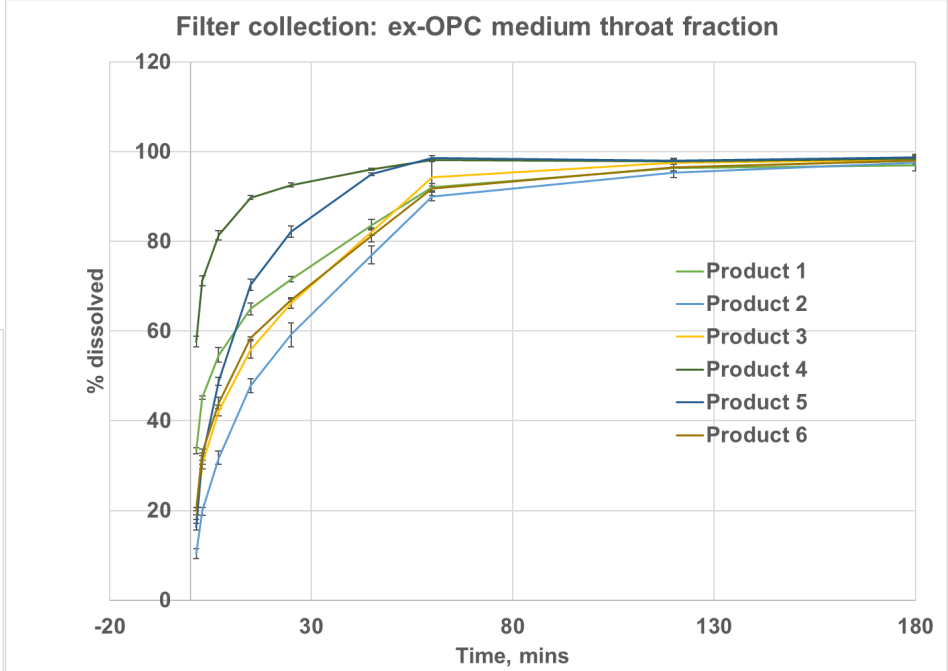


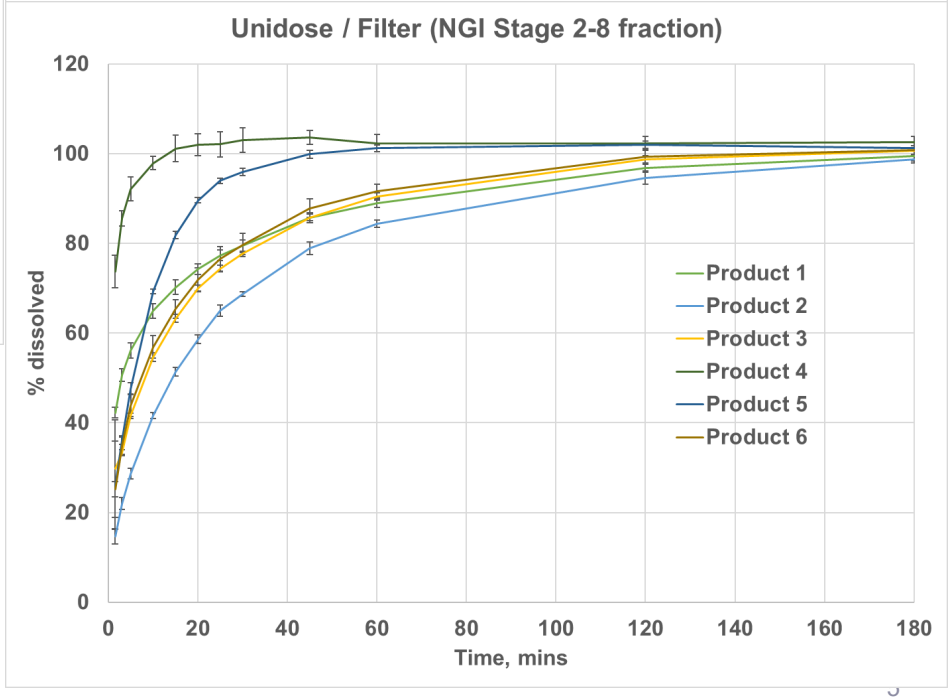


Comparison of dose collection methods

Using the same dissolution media and USP-2 apparatus, similar discrimination observed between 6 products variants using 3 different collection methods.







Filter collection: ex-OPC med throat carried out using an abbreviated ACI as described by May, S. *et al, Dissolution Techniques for In Vitro Testing of Dry Powders for Inhalation,* Pharm. Res. **29** 2157–2166 (2012)

Unidose™ apparatus described by Price, R. et al, *Development of an Aerosol Dose Collection Apparatus for In Vitro Dissolution Measurements of Orally Inhaled Drug Products, AAPS J.* **22:**47 (2020).

Mean ± Standard Deviation shown in all cases.

VIATRIS

Comparison of dissolution apparatus: USP-2 vs Transwell

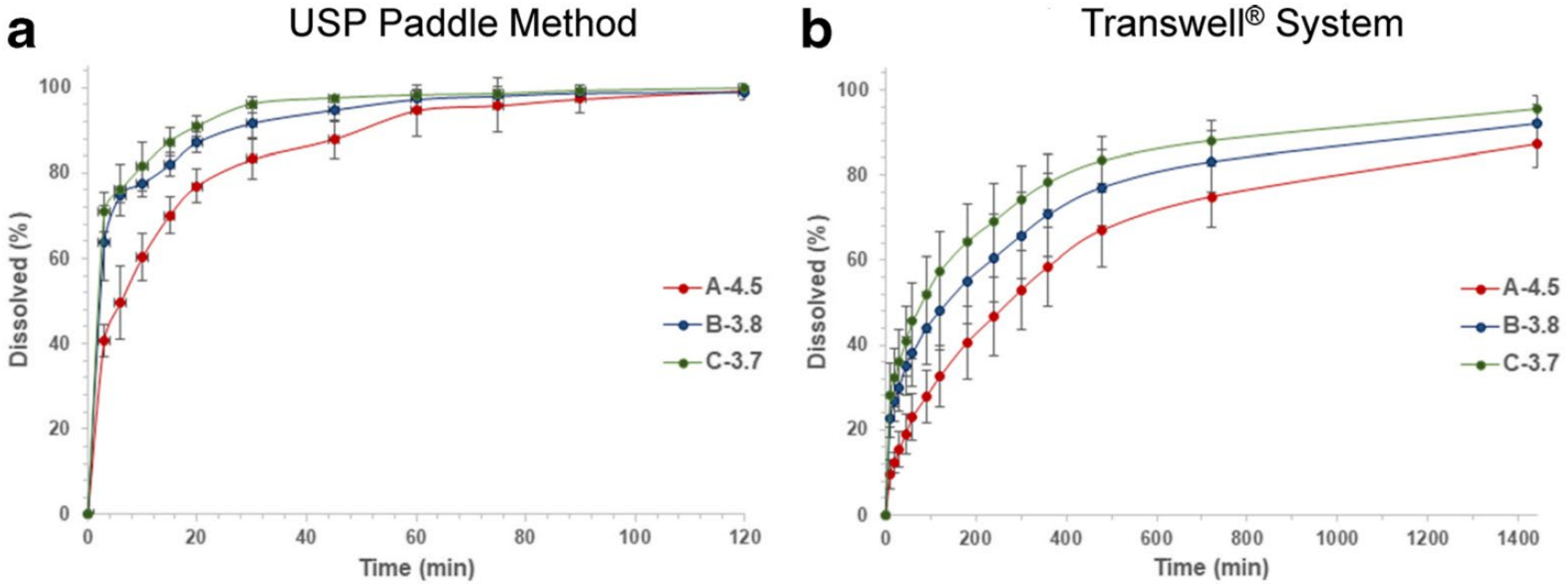


Figure 2. Dissolution of FP DPI formulations. Percent dissolved (mean ± standard deviation) of FP DPI formulations A-4.5, B-3.8, and C-3.7 using either the USP paddle apparatus (**a**) or the Transwell® system (**b**)

Hochhaus, G. *et al, Can Pharmacokinetic Studies Assess the Pulmonary Fate of Dry Powder Inhaler Formulations of Fluticasone Propionate?, AAPS. J.* **23**:48 (2021)

Dissolution: conclusions

- Standardization of currently non-standard apparatus may lead to improved consistency of approach, e.g. filter dose collection set-ups with proven ability to avoid mass loading effects.
- Maintaining diversity of available approaches is also important
  - Different methods may be optimized to show similar discrimination, but different approaches may be required for different applications depending on drug solubility, dose and formulation characteristics.

Predicted sensitivity of systemic pharmacokinetic BE parameters to differences in factors affecting local bioavailability

Class	iBCS Class I e.g. Terbutaline Sulfate, Vilanterol Trifenatate	iBCS Class II e.g. Budesonide, Mometasone Furoate, Fluticasone Propionate, Fluticasone Furoate	iBCS Class III, e.g. Salbutamol Sulfate, Salmeterol Xinafoate, Tiotropium Bromide, Ipatropium Bromide	iBCS Class IV
Lung Dose	AUC, Cmax	AUC, Cmax	AUC, Cmax	AUC, Cmax
Regional Deposition (C/P ratio)	Cmax	AUC, Cmax	Cmax	AUC
Dissolution Rate	N/A	Cmax, tmax	N/A	

NB: Assumes negligible oral bioavailability of swallowed fraction, or oral absorption blocked using charcoal.

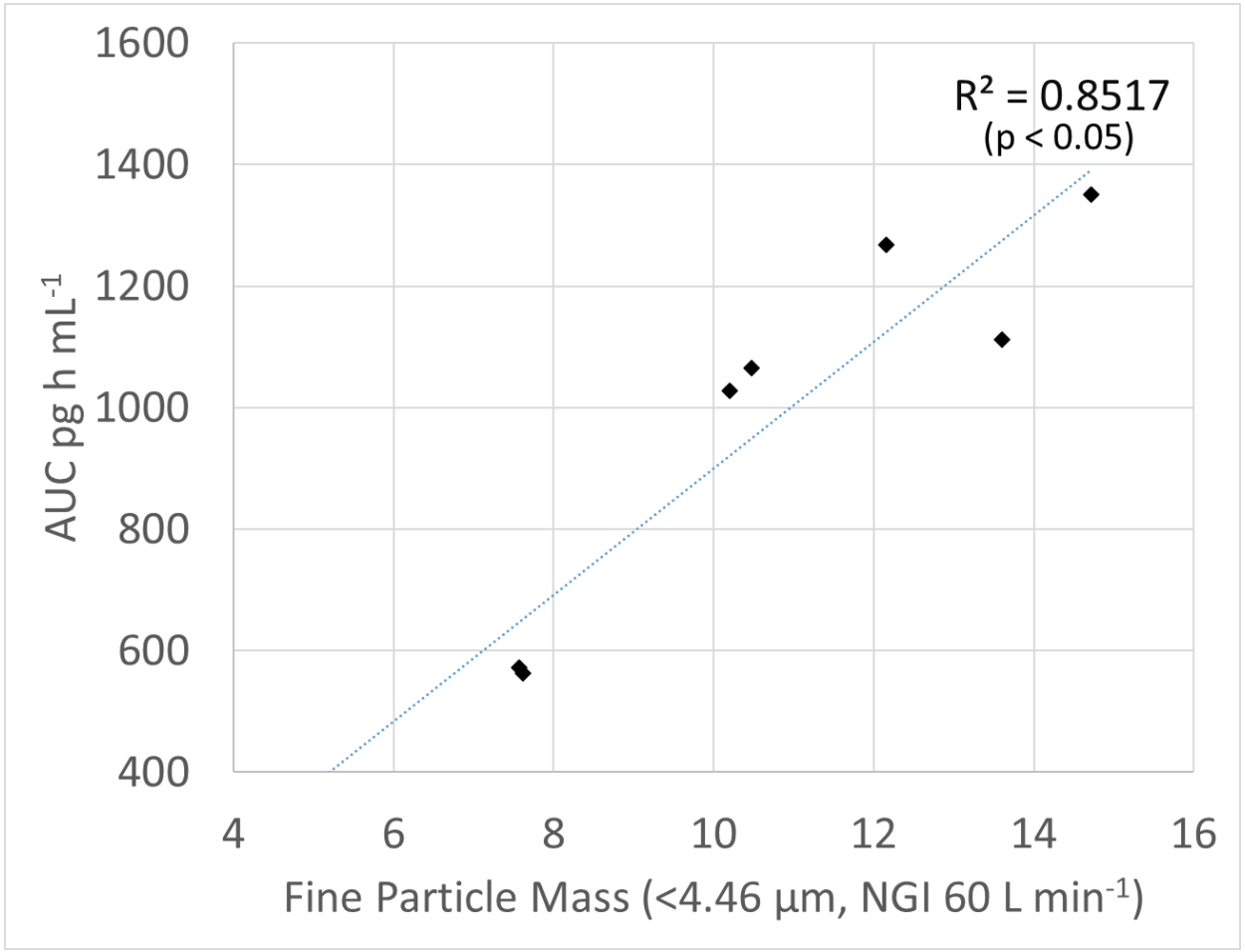
Derived from Forbes *et al, iBCS: 4. Application of the Inhalation Biopharmaceutics Classification System to the Development of Orally Inhaled Drug Products*, *Mol. Pharmaceutics* **22** 1740−1751 (2025)

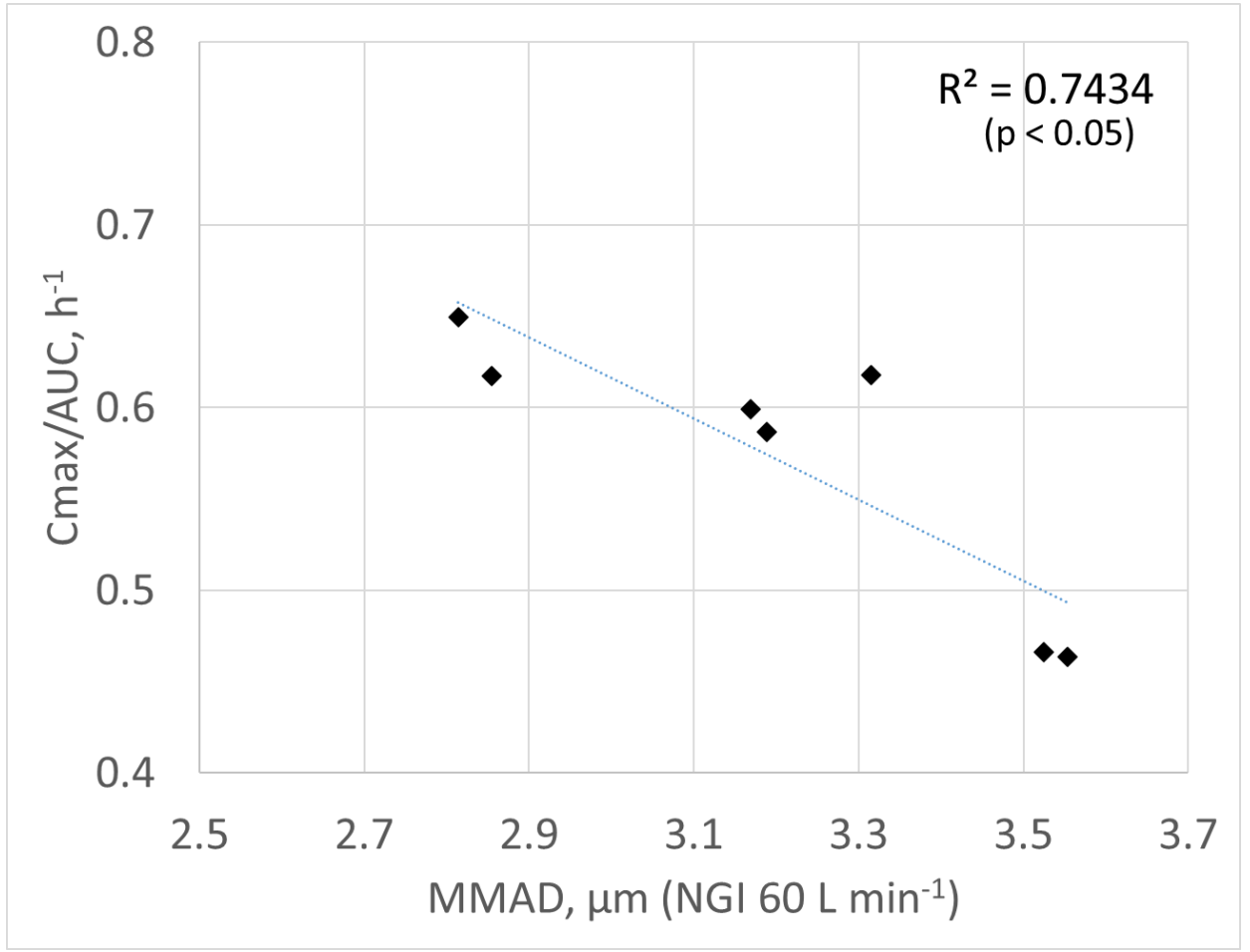
VIATRIS

Sensitivity of PK to regional deposition: fluticasone propionate DPI (iBCS Class II)

- Hochhaus, G. *et al, Can Pharmacokinetic Studies Assess the Pulmonary Fate of Dry Powder Inhaler Formulations of Fluticasone Propionate?, AAPS. J.* **23**:48 (2021).
- Drescher, S. *et al, Central and peripheral lung deposition of fluticasone propionate dry powder inhaler formulations in humans characterized by population pharmacokinetics, Pharm Res*. **40** 1177–1191 (2023). doi:10.1007/s11095-023-03472-6.
- Study involved PK comparison of three FP formulations with differing APSD, with the intent to investigate sensitivity of PK to differences in regional deposition.
- Interpretation of regional deposition effects was somewhat confounded by differences in lung dose and dissolution rate.
- Pop-PK analysis supported hypothesis that PK was sensitive to differences in both regional deposition and and dissolution rate between formulations.

Sensitivity of PK to regional deposition: salmeterol DPI (iBCS Class III)





Conclusions: Leveraging charcoal block PK to assess regional deposition

- The limited body of existing data is consistent with the predicted sensitivity of PK to regional deposition
- Use of charcoal block for APIs with significant oral absorption ensures that the PK is fully reflective of the lung-deposited fraction.
- There is scope for well-designed studies to further explore this, and to increase understanding of the significance of PK vs in-vitro results within the weight of evidence supporting local bioequivalence

Conclusions

- “Option 1” BE paradigm provides new opportunities for science-based approval of generic inhaled products without the need for costly clinical endpoint studies
- Several new and technically complex in-vitro tests are involved which are previously unprecedented in OIP quality assessment
- Research into improved standardization of novel in-vitro test equipment may improve consistency of approach, but the flexibility to use different approaches for different products must be maintained.
- The inclusion of charcoal block studies provides an increased opportunity to use PK to support local equivalence of regional deposition. Further research may be required to underpin this.