Dissolution and Beyond:
The use of advanced structural characterization tool for demonstrating pharmaceutical equivalence of orally inhaled drug products

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Major factors controlling the fate of an inhaled dose

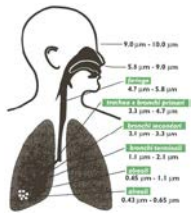
Formulation
API + excipients blending, conditioning

+

Device
design, efficiency, performance

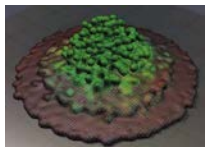
+

Patient Activation
Flow rate, Deagglomeration, Inhaled dose,



Lung deposition
Particle size Impaction, sedimentation , diffusion

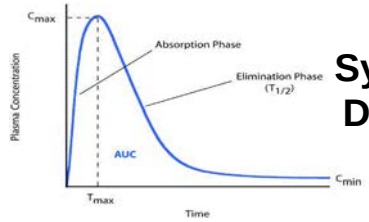
+



Dissolution & Permeability
Physiochem, fluid volume, retention time

GI Tract

Site of Action
(Local Effect)



Systemic Delivery

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The state of play of IVIVC tools for OIDPs

- Systemic exposure of inhaled compounds with low aqueous solubility and high permeability can vary significantly with both formulation and device factors.
- There appears to be a lack of a direct relationship between *in vitro* dosing parameters and PK profiles of these APIs.
- There is growing evidence that the extent and rate of pulmonary sorption is controlled by deposition pattern as well as pulmonary dissolution rate.
- To date, *in vitro* dissolution methodologies for characterizing aerosol products have generally failed.

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Quality by Design (QbD) of OINDPs

*"To determine how material properties and processing conditions determine the **structure of formulations** and influence product functionality"*

- **Predictively understand** the relationship between structure and functionality.
- Utilize this understanding to:
    - Guide product design with desired and consistent functionality
    - Specify properties of raw materials
    - Measure and limit material variability
    - Optimize and control processing
    - Achieve pharmaceutical equivalence

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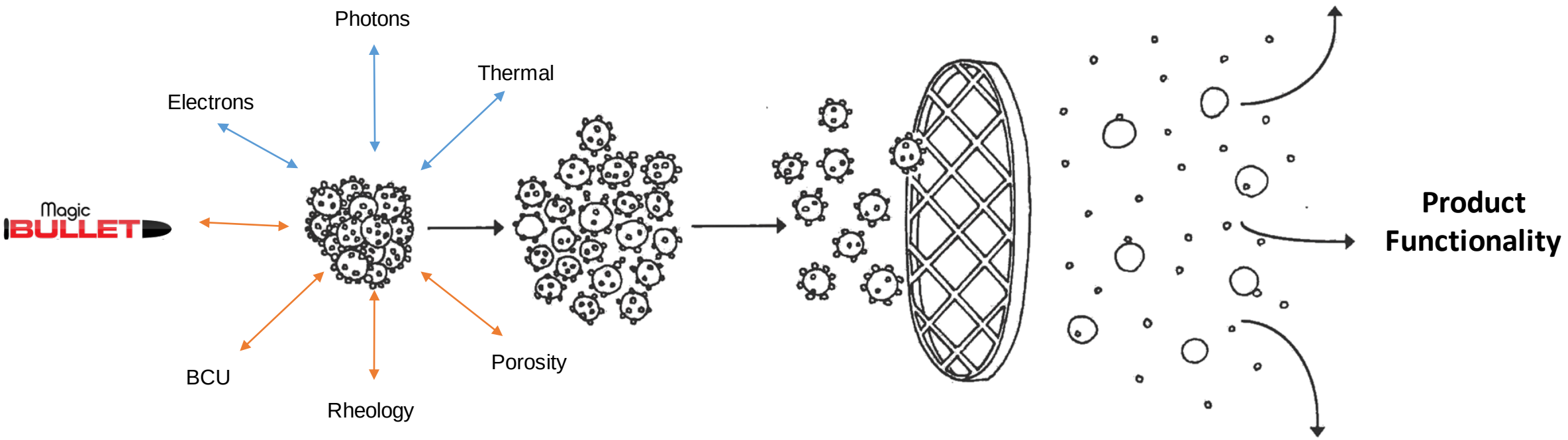
Can we determine a link between structure and functionality?



Characterization of formulation microstructure

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Role of Interactive Mixing in DPIs

- Interactive mixing facilitates deaggregation of drug powder agglomerates in a non-equilibrated state.
- Deaggregated particles are dispersed over the carrier surface as a function of the relative magnitudes of cohesive and adhesive interactions of the drug.
- Successful dispersion will lead to increased homogeneity of the mixture.
- Greater dispersion will increase the dissolution of sparingly soluble drugs because of the increase surface area exposure to the dissolution media.
- An increase in the rate and extent of dissolution has been shown to directly relate to the degree of dispersion in interactive mixtures within solid oral dosage forms.

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What are the key requirements in developing a dissolution test for OIDPs

- The collection of a representative aerosolised dose (e.g. ex cast TLD, Impactor stage mass (ISM) for dissolution.
- A QC tool for evaluating material properties, processing effects on API dissolution
- Ultimately, an IVIVC technique
- For a QC testing tool, dissolution models need to focus on **discriminatory capability, ruggedness and stability**.
- Critical to develop a dissolution method which can be validated and have the ability to assess drug product quality attributes.

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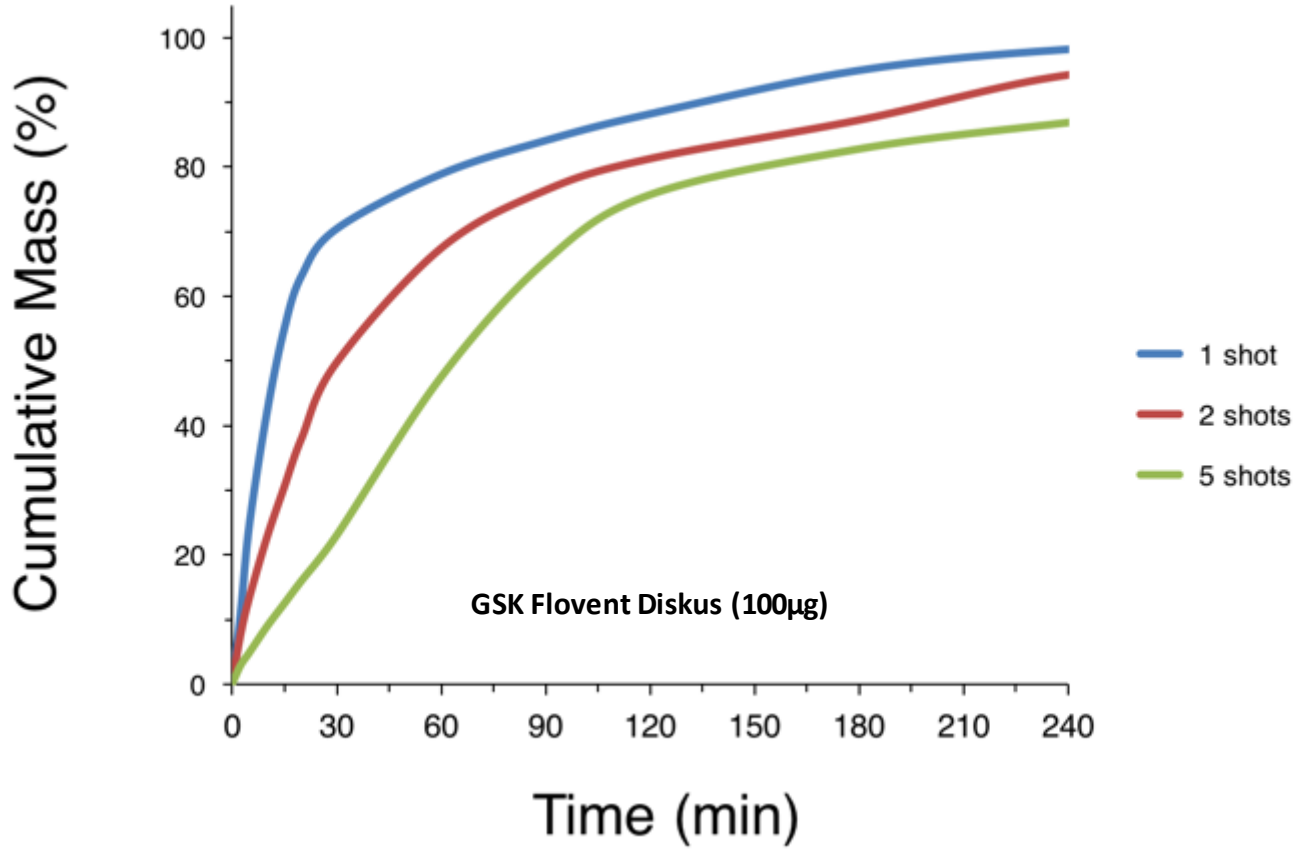
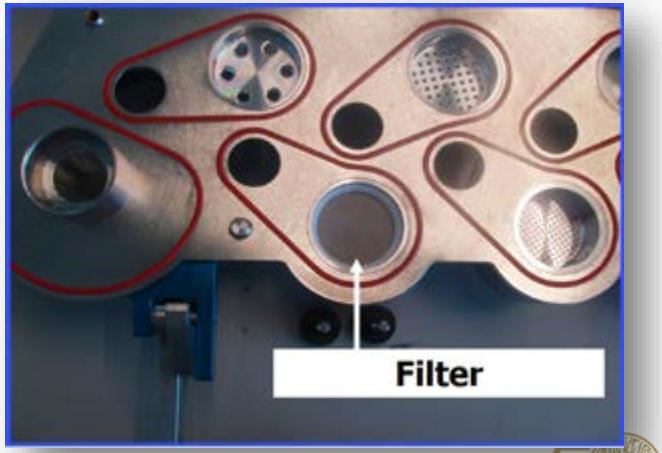
Current in vitro methodologies appear to be be severely limited by mode of aerosol collection





Current dissolution models lack **discriminatory capability, ruggedness and stability**.

It has been difficult to investigate the dissolution of a representative lung dose.

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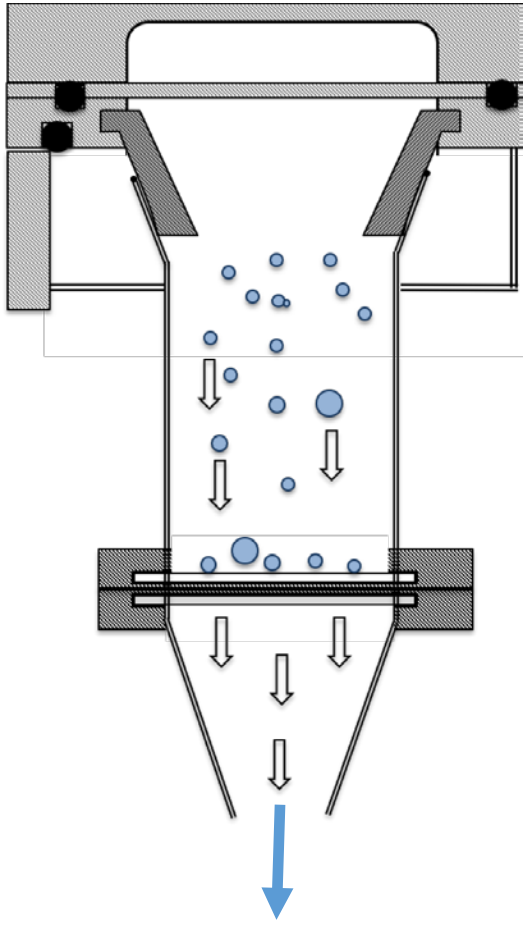
Aerosol Collection System – The uniform dosing of a representative aerosol dose



Vacuum Controller

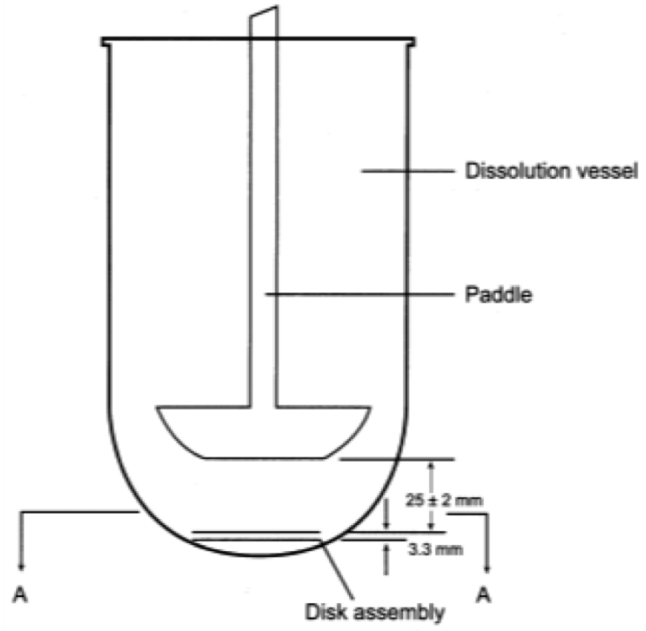


Figure 2.9.4.-2. – *Paddle and disk*

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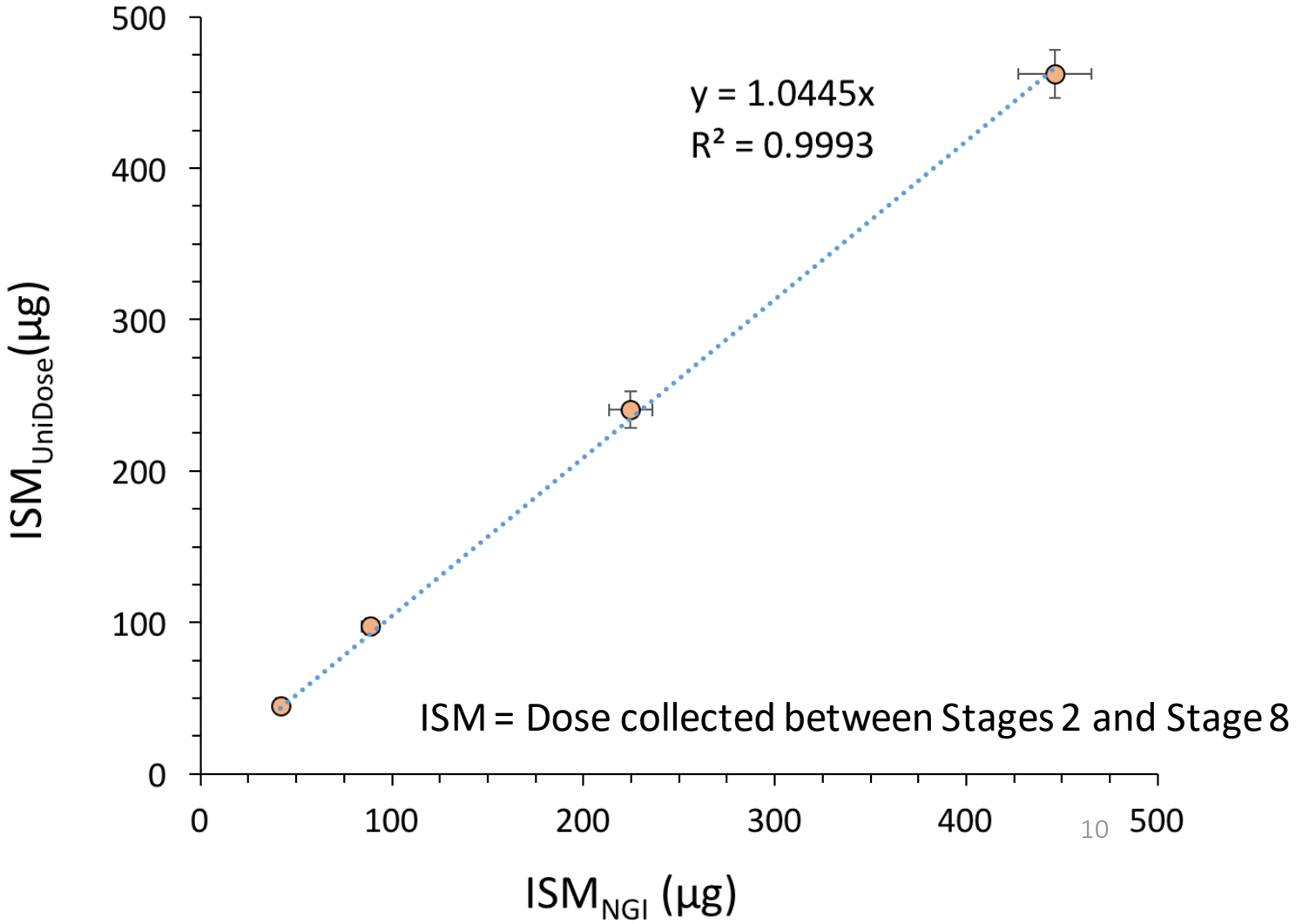
Validation of the ISM dose between Unidose and NGI



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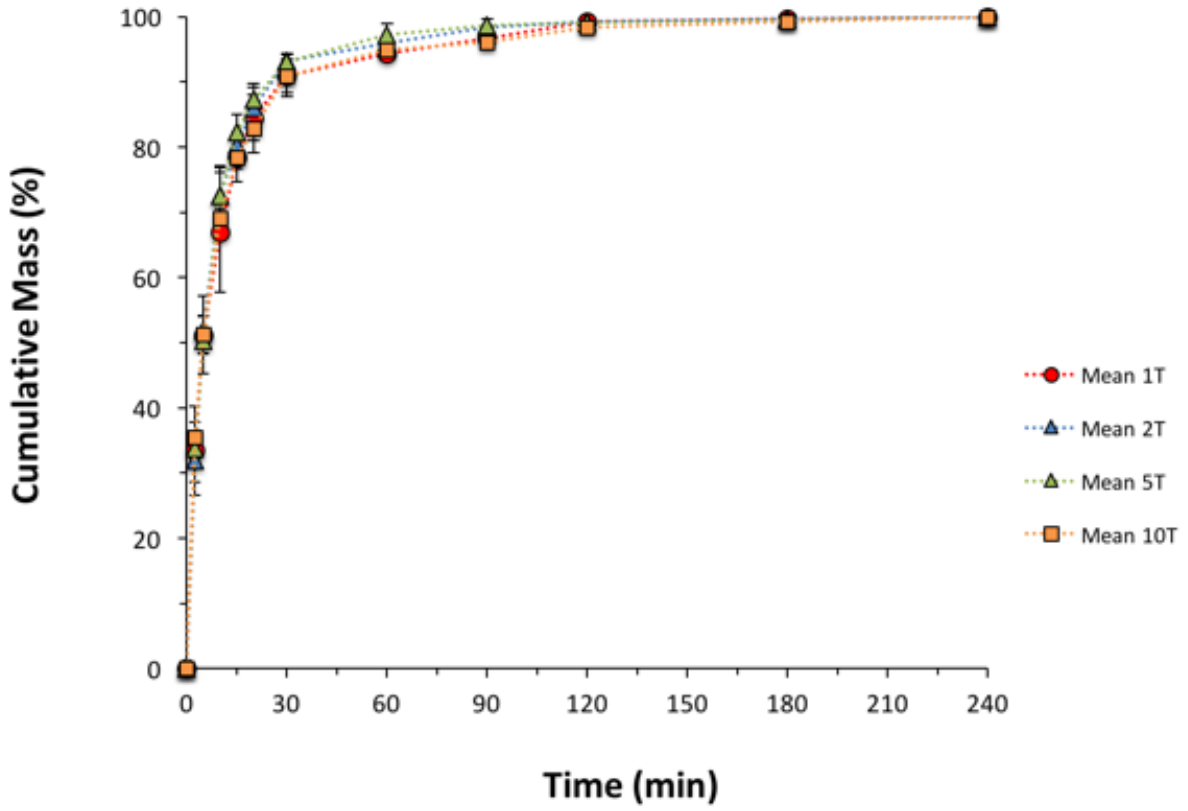
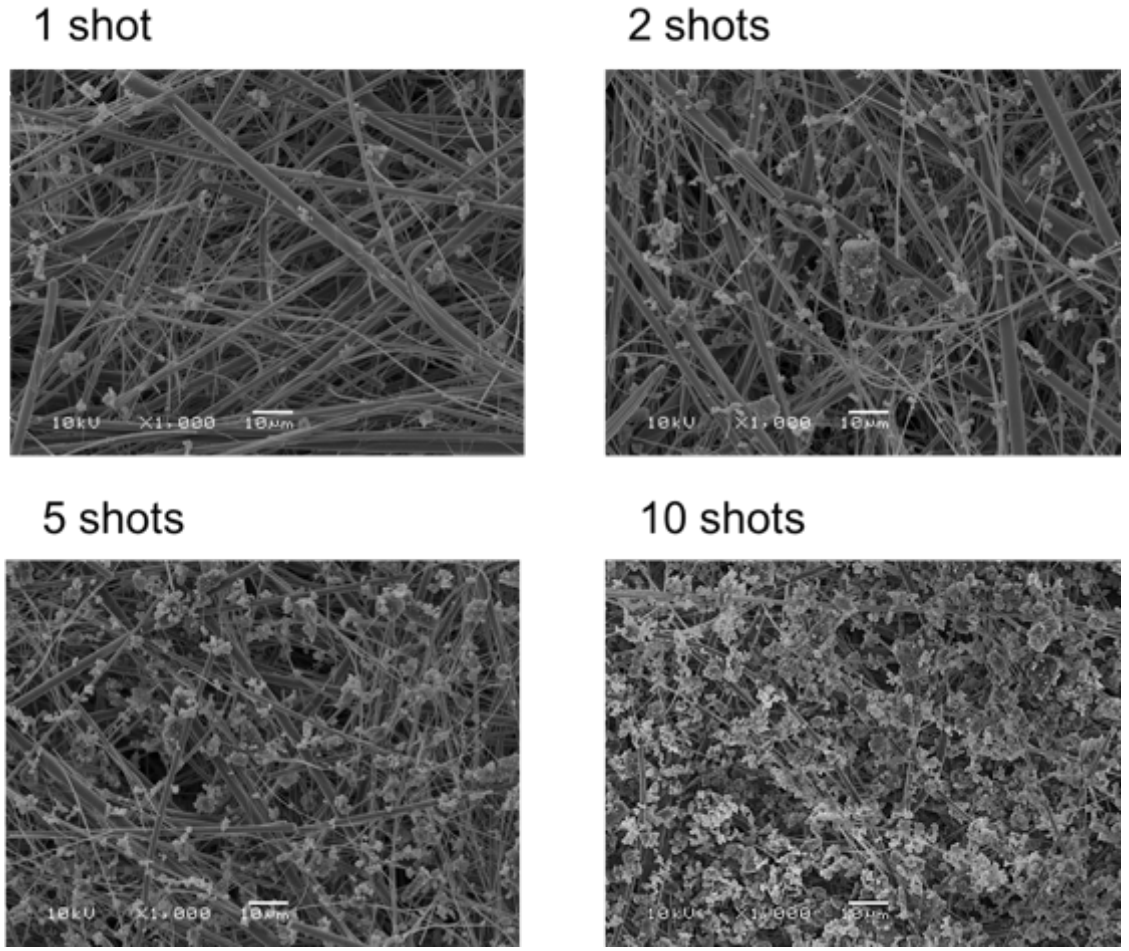
Dissolution profiles following different drug loading of FP from DPI



GSK Flovent Diskus (100µg)



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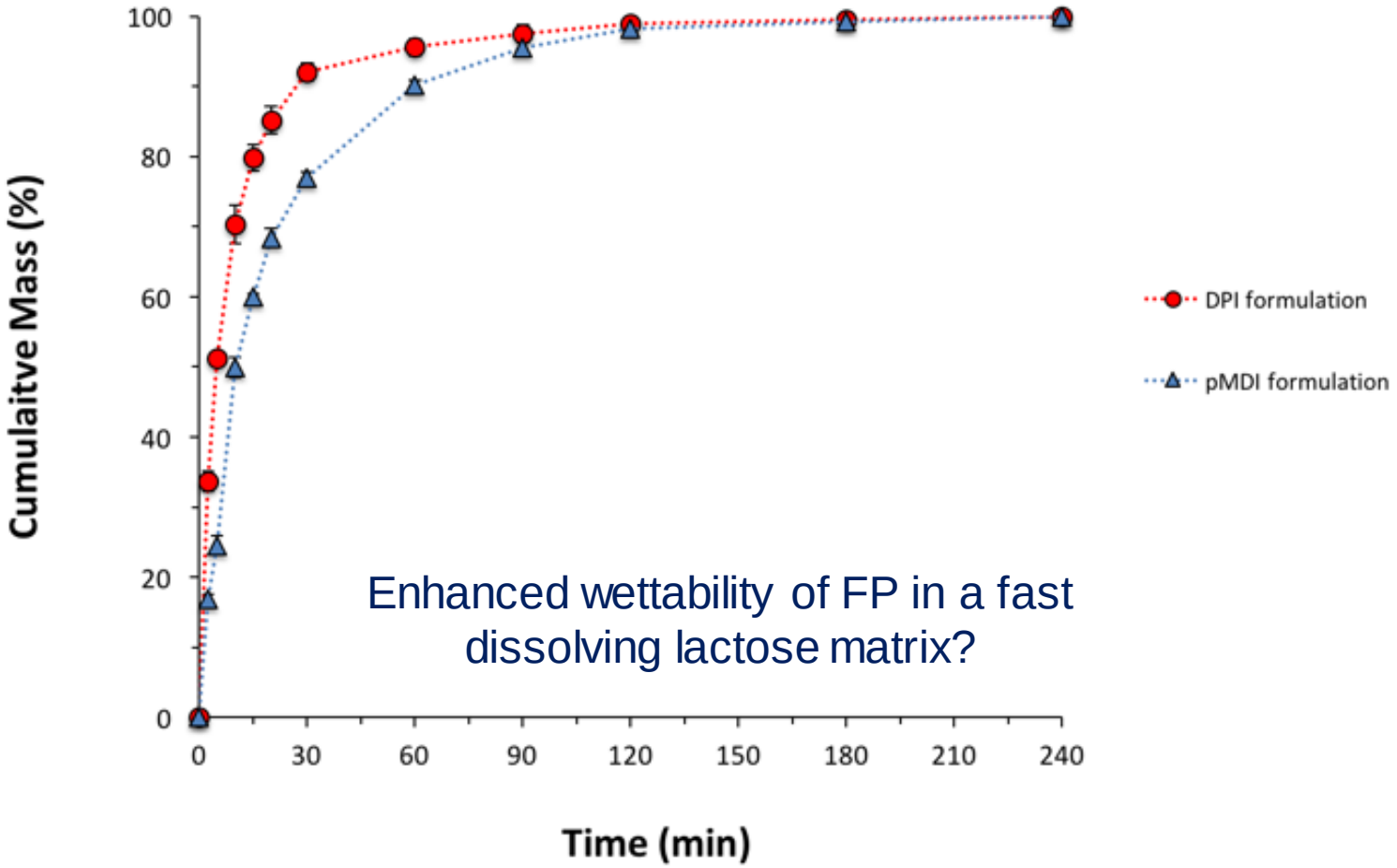
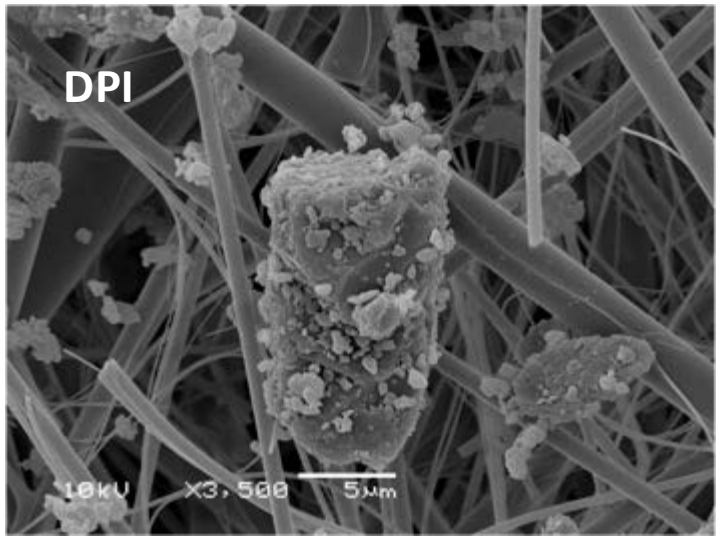
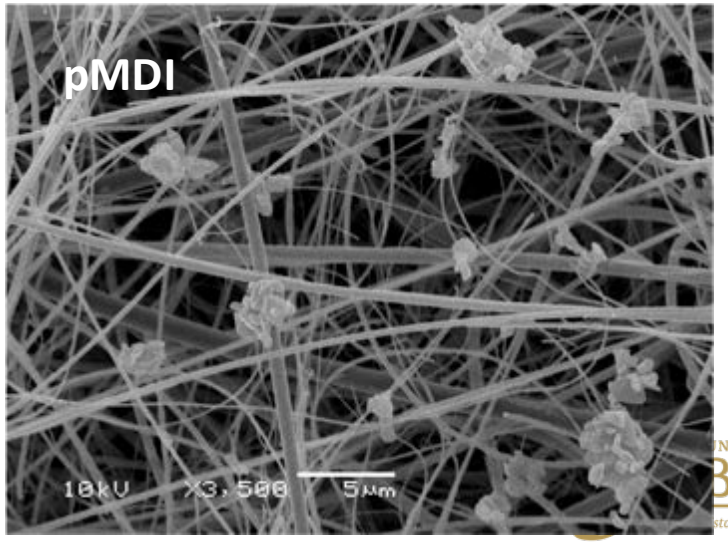
Differentiation of Dissolution Release Profiles of FP in pMDI and DPI – Flixotide DPI Vs. Flixotide HFA



Enhanced wettability of FP in a fast dissolving lactose matrix?





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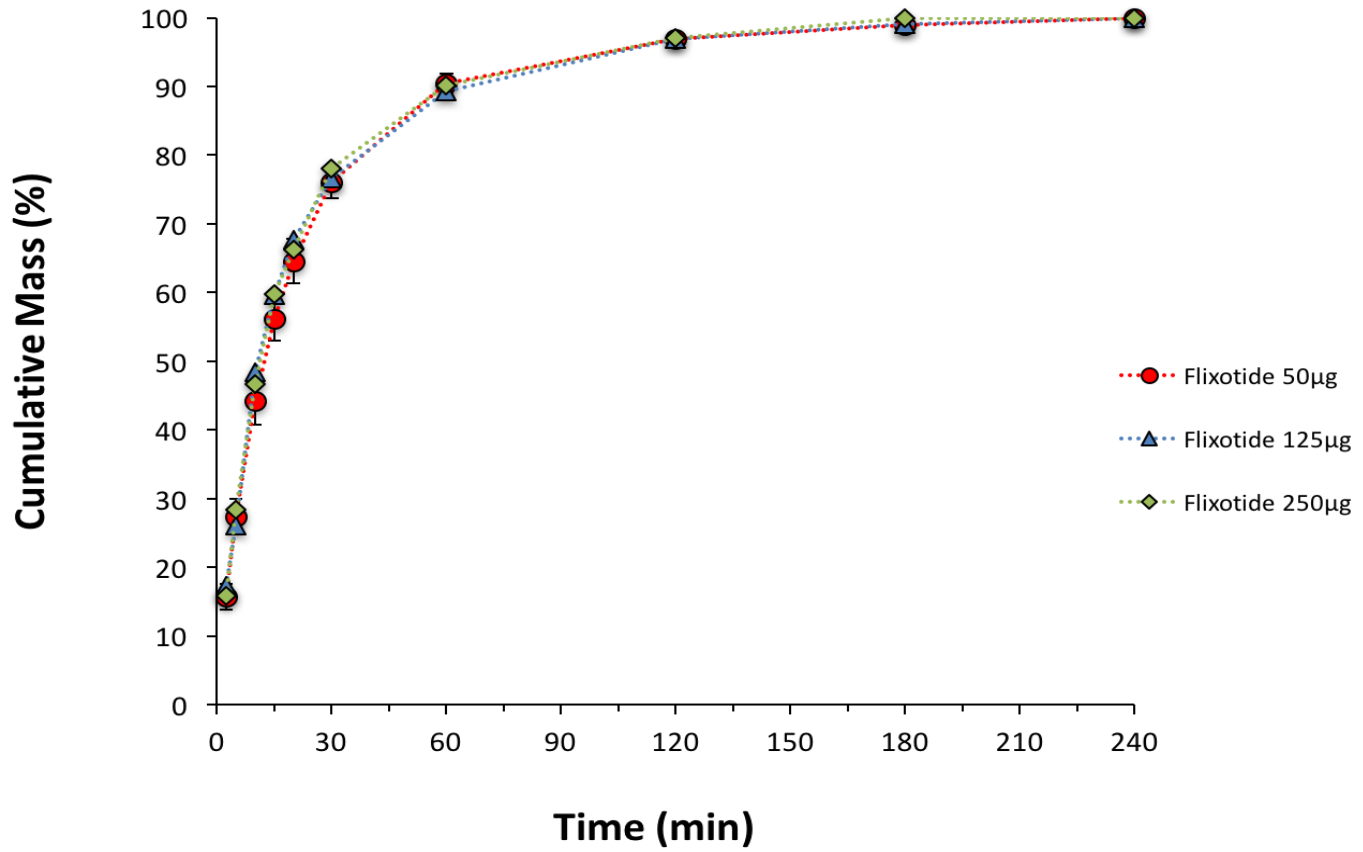
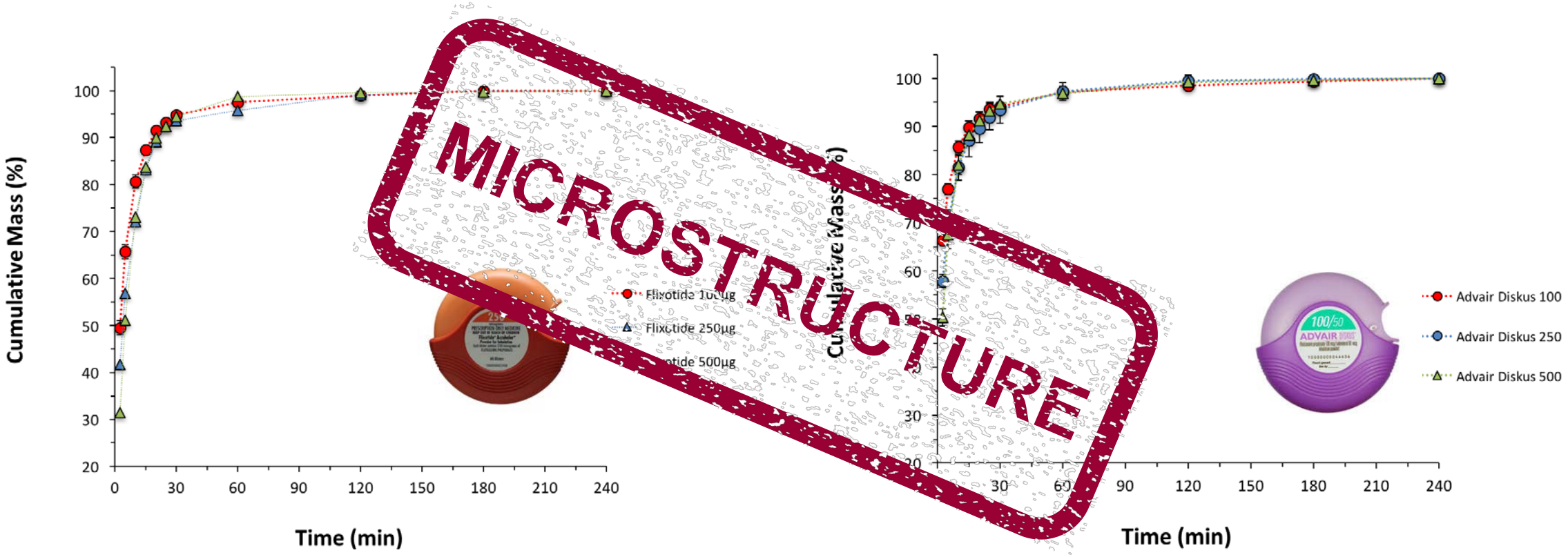
Dissolution profiles of different product strengths FP from Flixoide Evohaler (MDI)



Dissolution rate independent of loaded dose and MDI product strength

FP dissolution profiles of different product strengths from Flixotide and Advair Diskus (DPI)



Dissolution rate dependent on the DPI product strength and influenced by the presence of SX – Is there a link to formulation structure ?

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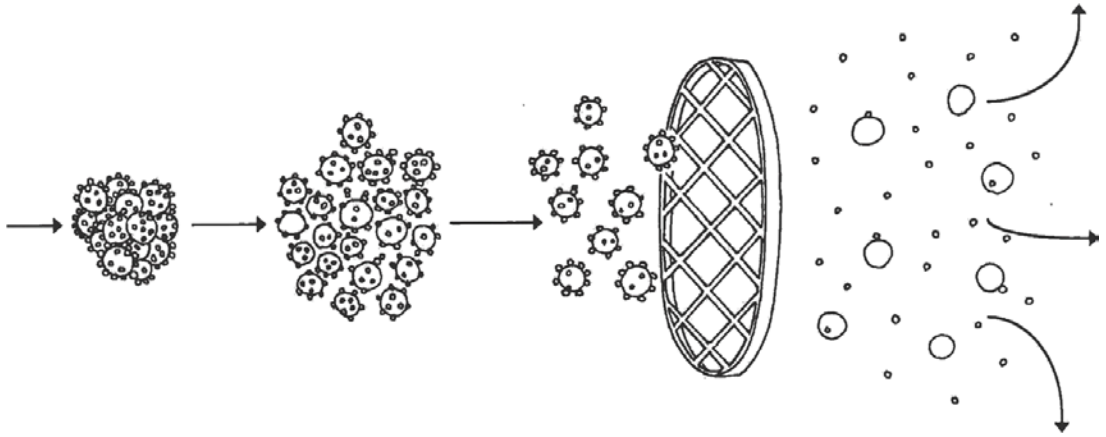
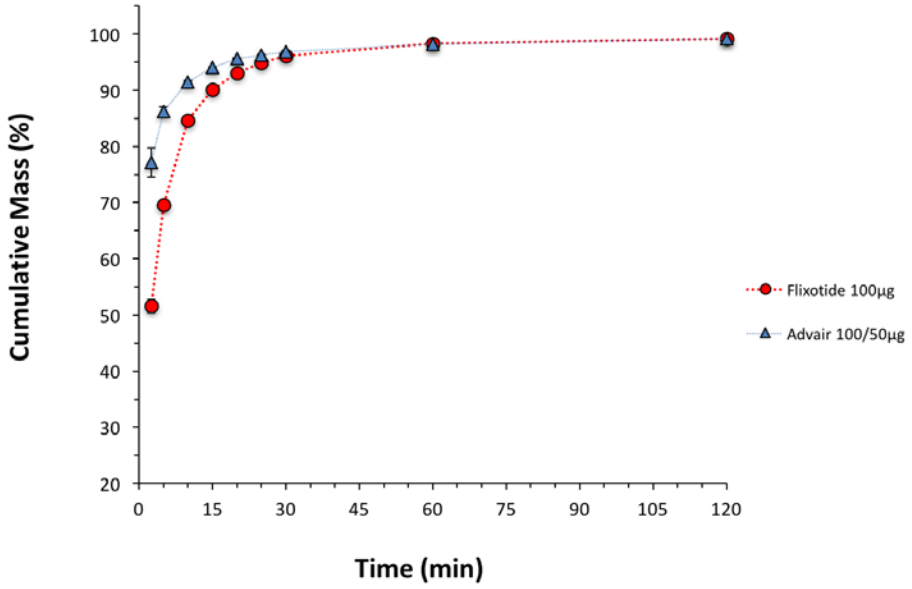
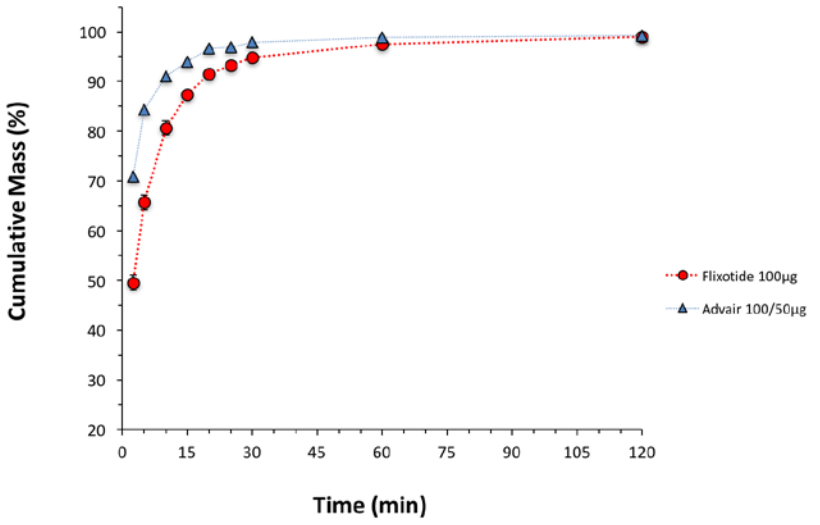
Is there a link between structure and functionality?



Formulated powder

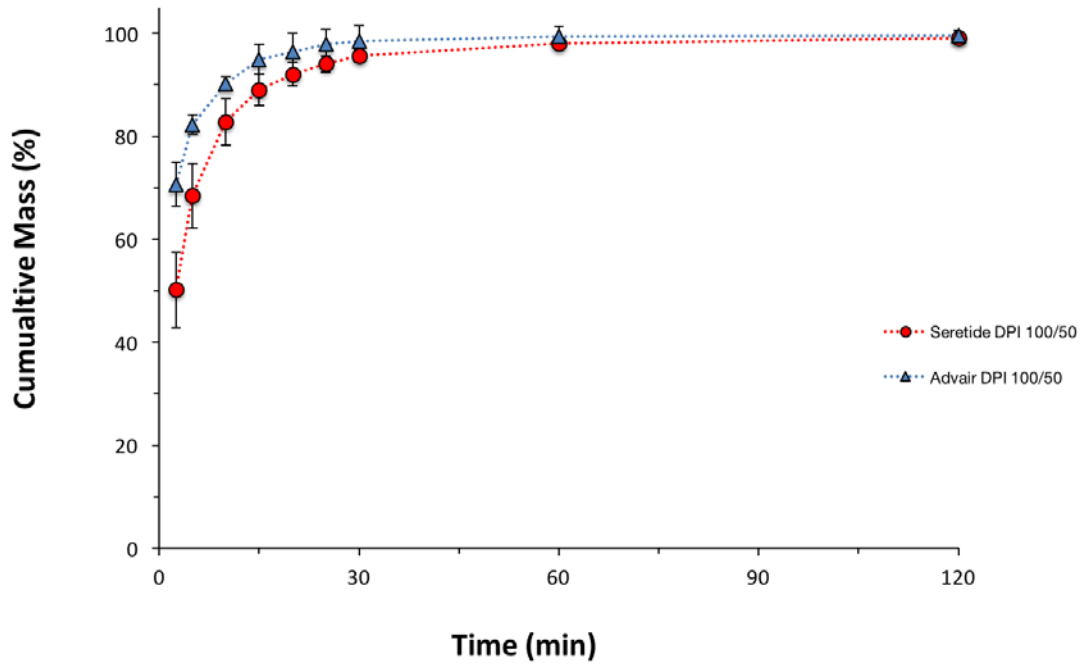


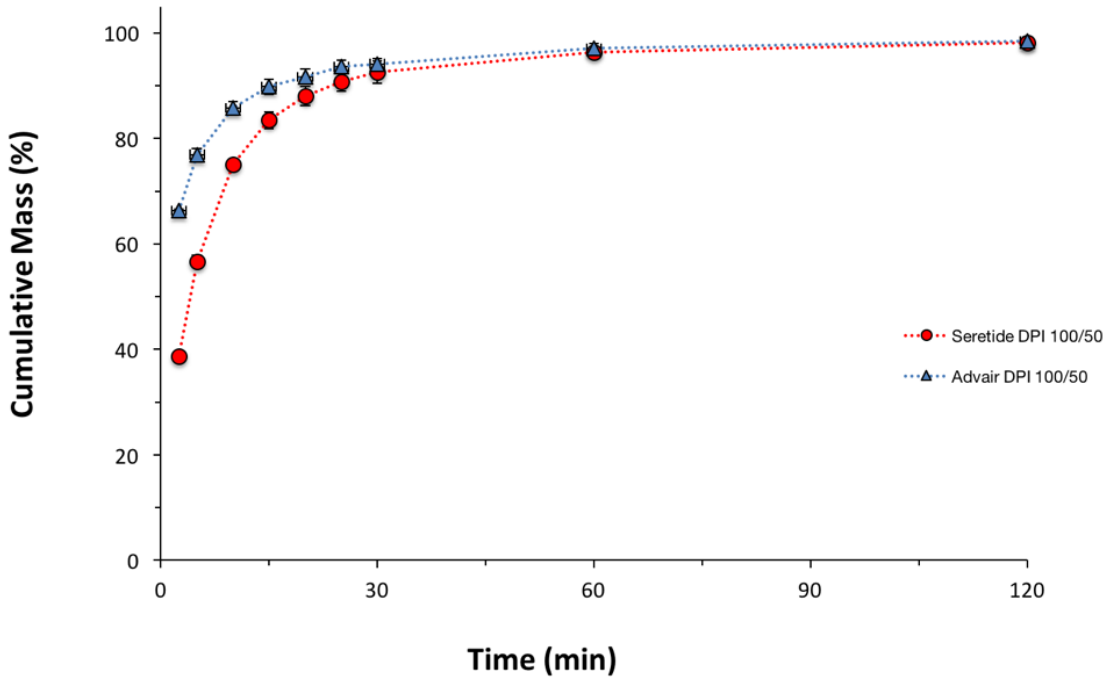
Aerosolised Dose



Formulated powder

Aerosolized Dose





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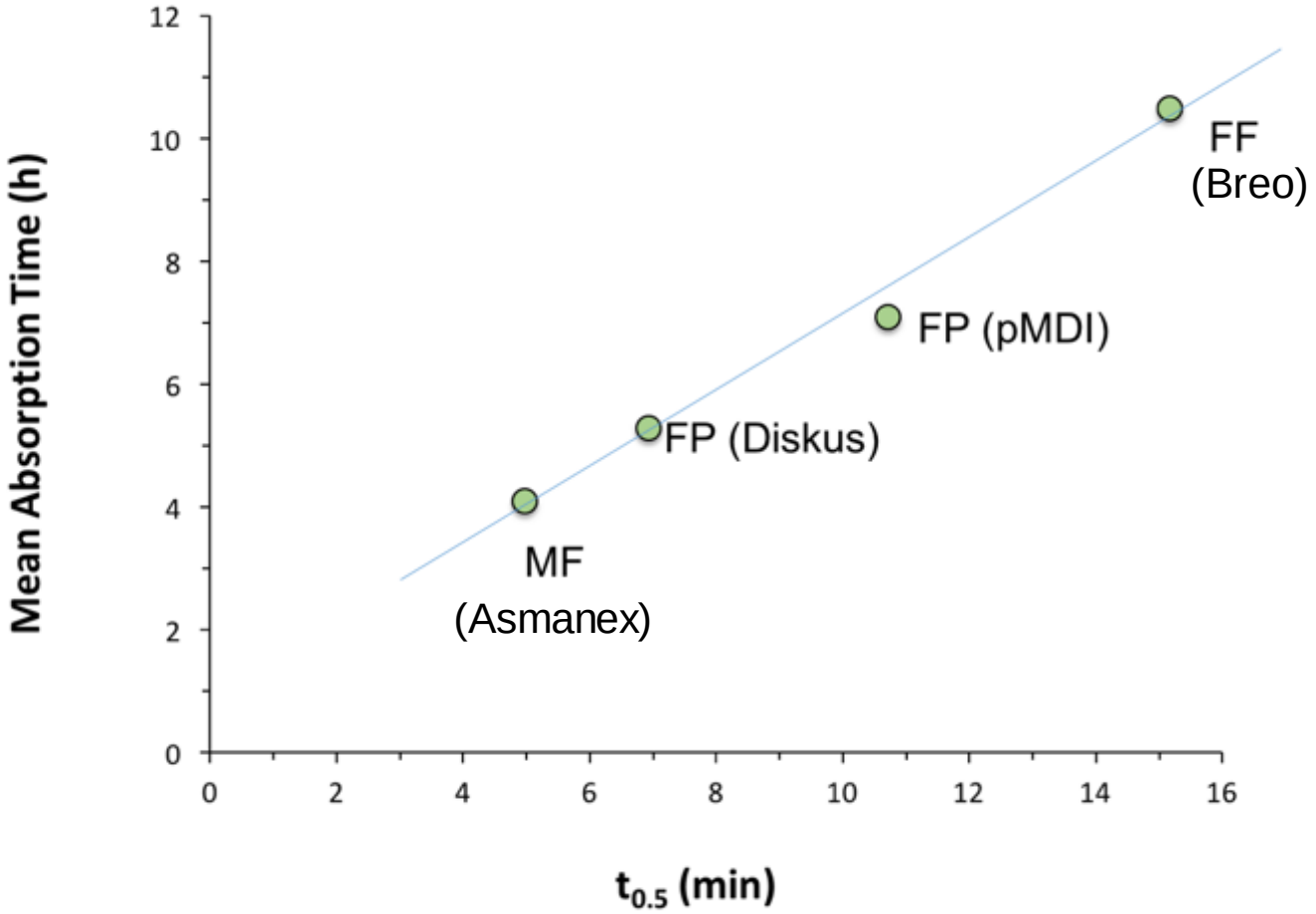
Relationship between in vivo MAT and dissolution half-life of the total lung dose of poorly soluble APIs



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Summary

- We have developed an aerosol collection system, that deposits the whole impactor stage mass (ISM) uniformly over a high surface area filter for dissolution studies.
- The system 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 conditions on formulation microstructure via dissolution.
- Utility to support formulation development and as an integrated QC tool for structure.

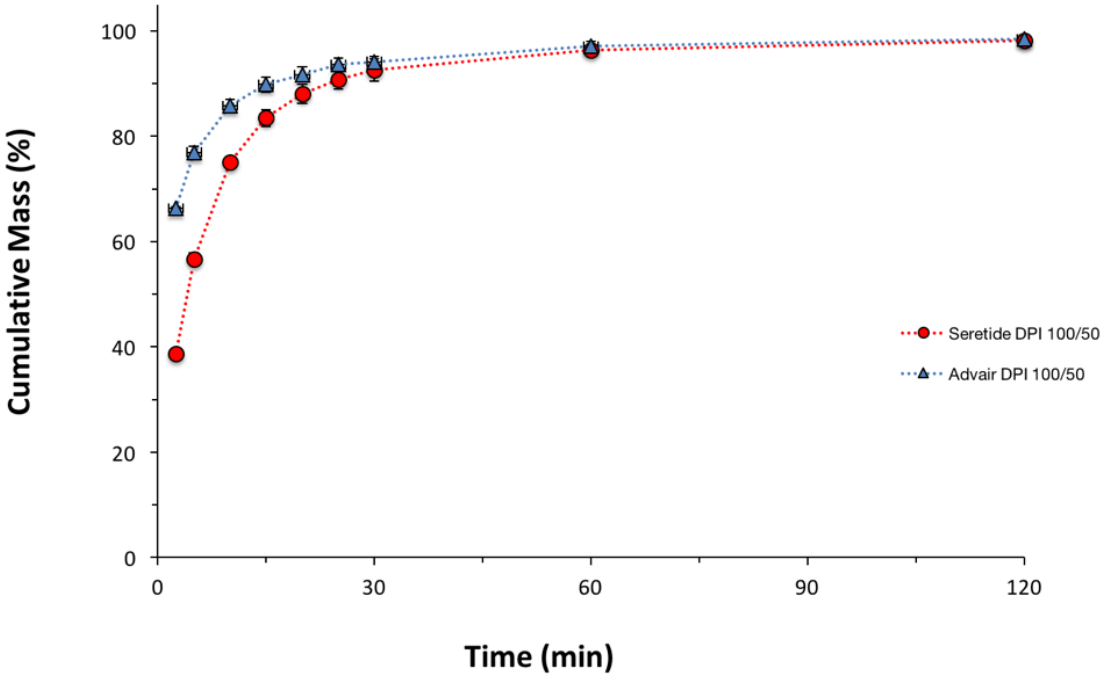
Future Directions

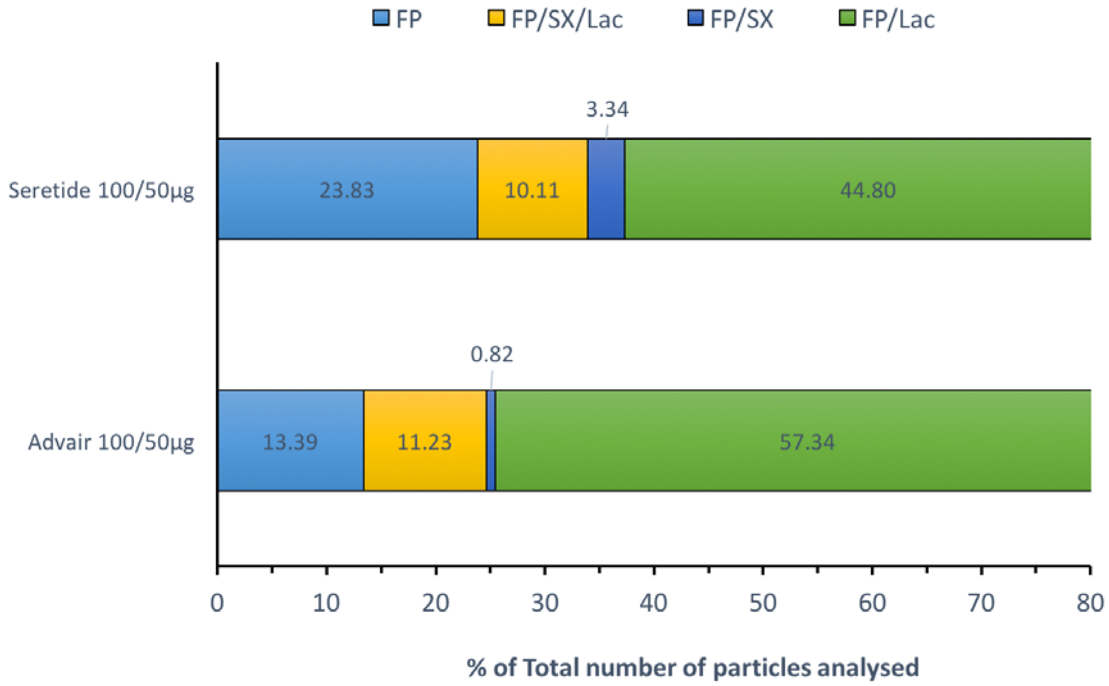
- The FDA have recently funded UoB (Grant No.: BAA-PMQWP#117) - Investigating a range of orthogonal in vitro techniques for the microstructural characterization of the state of aggregation of US RLD DPI products.

- The ultimate aim of the project is to provide the agency a range of validated in vitro based methods to assess the structural equivalence (Q3) within an aerosolized dose.

- Analytical methods under evaluation include in vitro dissolution/permeability, morphology directed and surface mapping Raman microscopy, in-line PSD and lactose concentrations within an aerosolized dose.

Orthogonal based approaches





Different principles suggest that the microstructure of a non-equilibrated powder may be critically important in achieving pharmaceutical equivalence

Acknowledgements

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