Probing the APSD Combination Products Foster® NEXThaler® and Seretide® Diskus® using SPAMS

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Introduction

- There is a need for a rapid, accurate way to determine physical/chemical microstructure of aerosols delivered from inhalation devices.
  - Single particle aerosol mass spectrometry (SPAMS)
  - Necessary information for truly representative generics
- Why current industry practices are inadequate
  - Impactor APSD gives only size and chemical information, no interaction information
  - Slow and time consuming limits what can be evaluated in a reasonable time.
  - Other technologies can be used to probe particle interactions

Key Quality Attributes - APSD

- How can we ensure APSD measurements reflect the product performance?
- Method and product variability
- Over product shelf-life
- Time consuming impactor testing
- Can we evaluate interactions in DPIs using any fast screening tools?

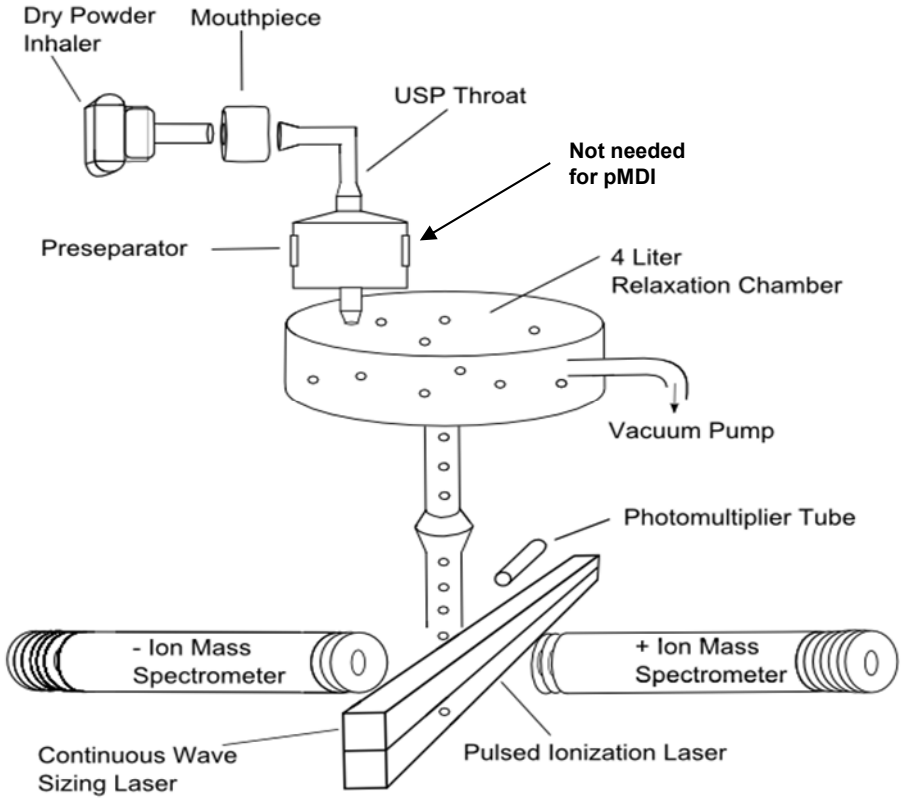
Single Particle Aerosol Mass Spectrometry (SPAMS)

- High interest in the development and routine use of more rapid techniques
- Aerodynamic diameters and chemical compositions of individual aerosol particles in real-time (API and excipient); Particle interactions in formulations
- Mass spectra give additional information on particle interactions and co-associations in combination products
- APSD data obtained by SPAMS can be correlated with NGI data
- Example: FP/SX in Advair

Source: Morrical et al. 2015, Fergenson et al. 2014, Jetzer et al. 2017, Jetzer et al. 2018

SPAMS: The instrument

SPAMS 3.0 basic principle of operation



Sampling rates up to 64 particle/sec acquisition

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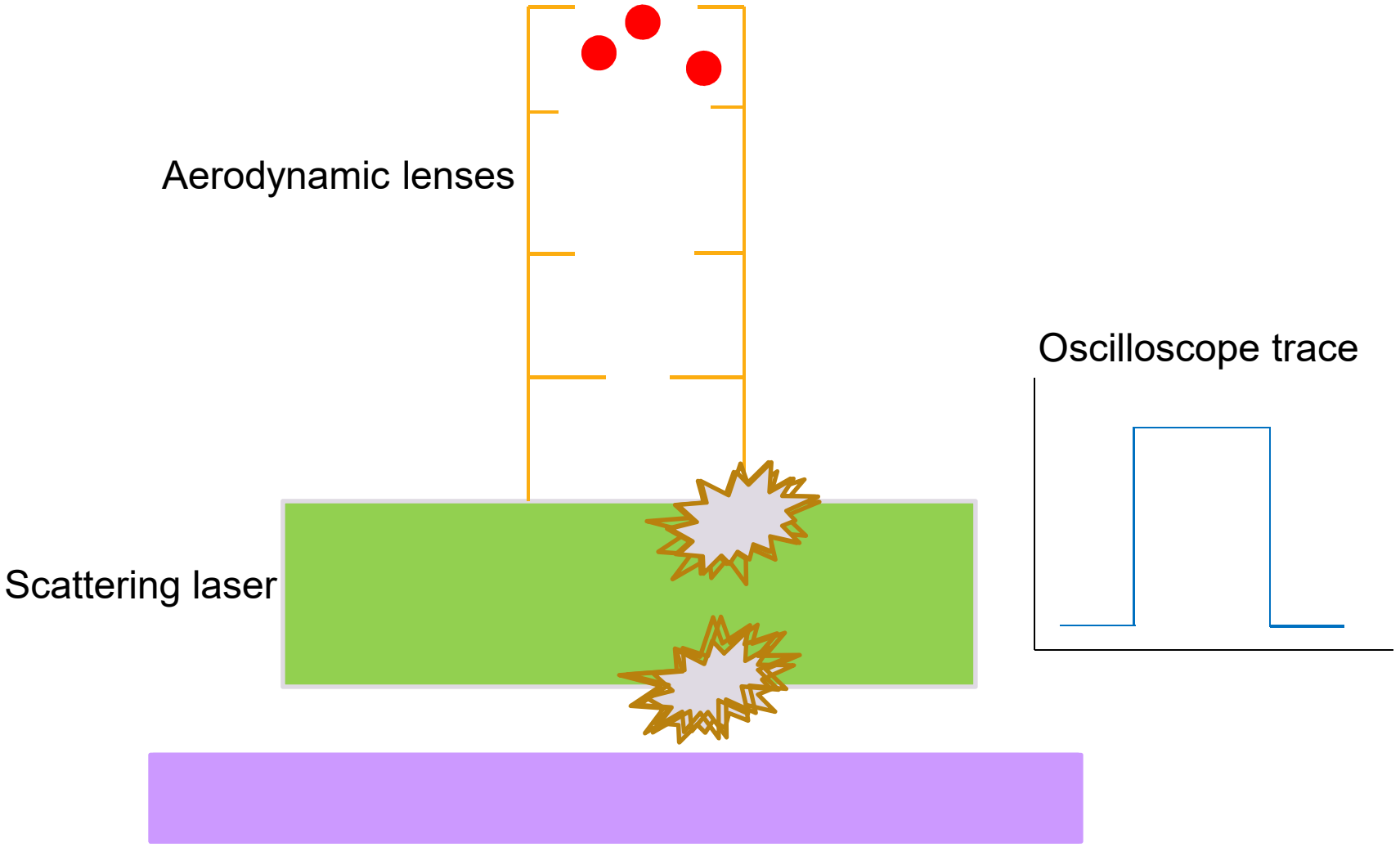
Particle interface in action

SPAMS 3.0 basic principle of operation



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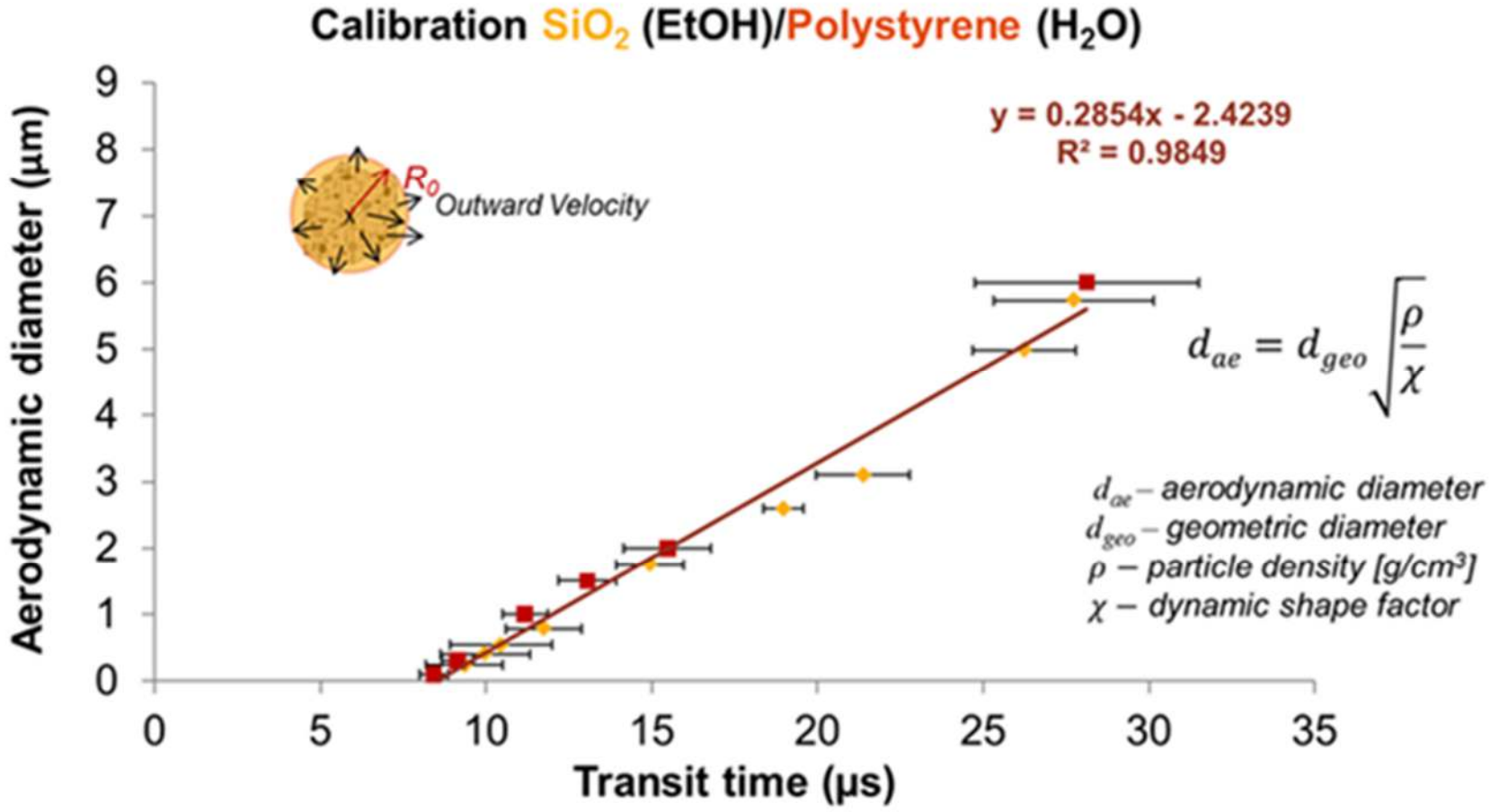
Calibration Curve: Linear behavior for sizing

Standard aqueous solutions of polystyrene and silica particles



Mass = Volume × density

$M_0 = {}^4/_3 \pi R_0^{\,3} \times \rho_0$

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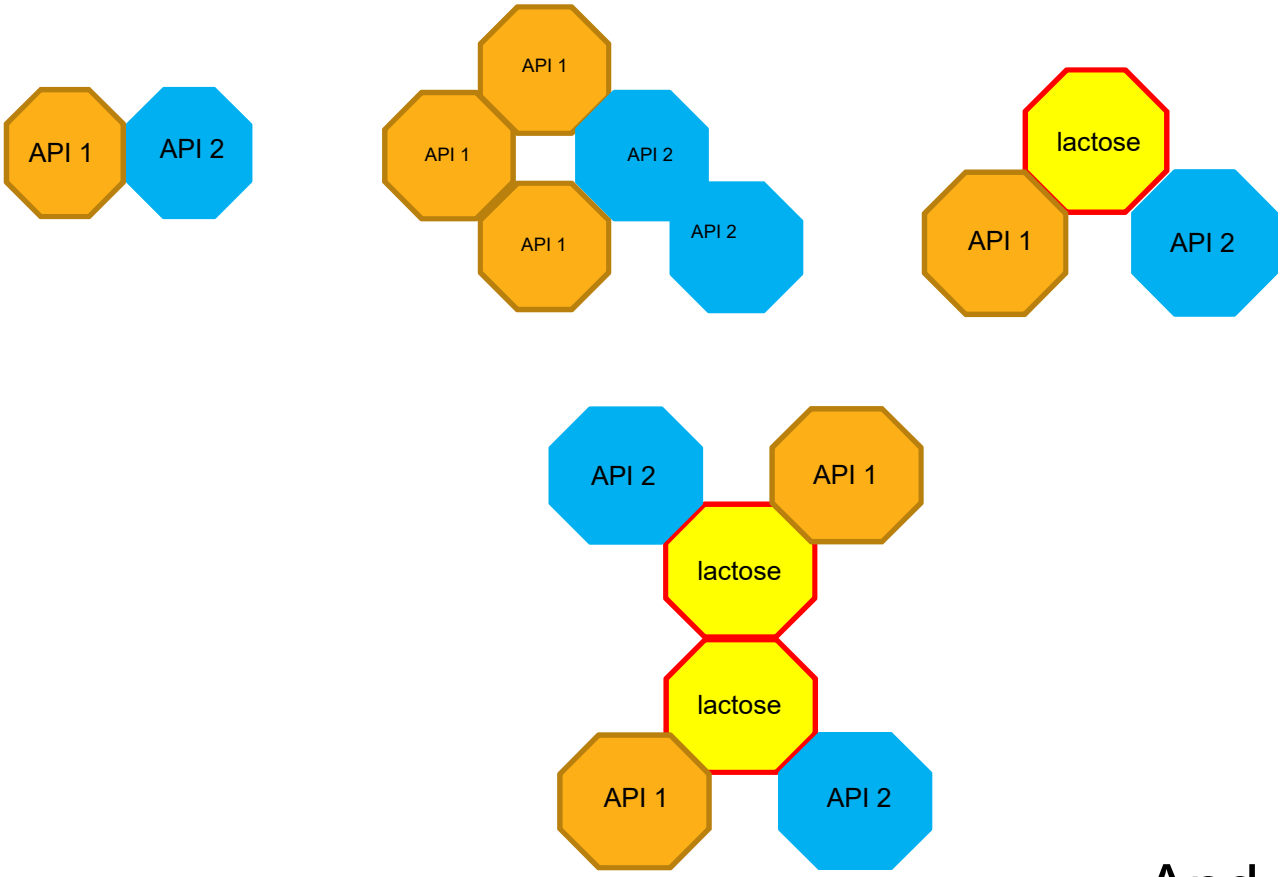
SPAMS in Innovation: Co-association

- Fixed dose combinations may not always behave clinically as separate single dose products taken sequentially (Taki et al. 2011)
- Is there a different dispersion pattern in the lungs where active particles deposit? (Leach et al. 2012)
  - Co-associated particles would co-deposit whereas separate doses would be less likely to be co-located
  - SPAMS can directly identify co-associated particles and determine the degree of co-association in a product
  - Due to rapid monitoring of batches, control over degree of co-association would be possible

What co-association can be – Multiple assemblies



And so on...

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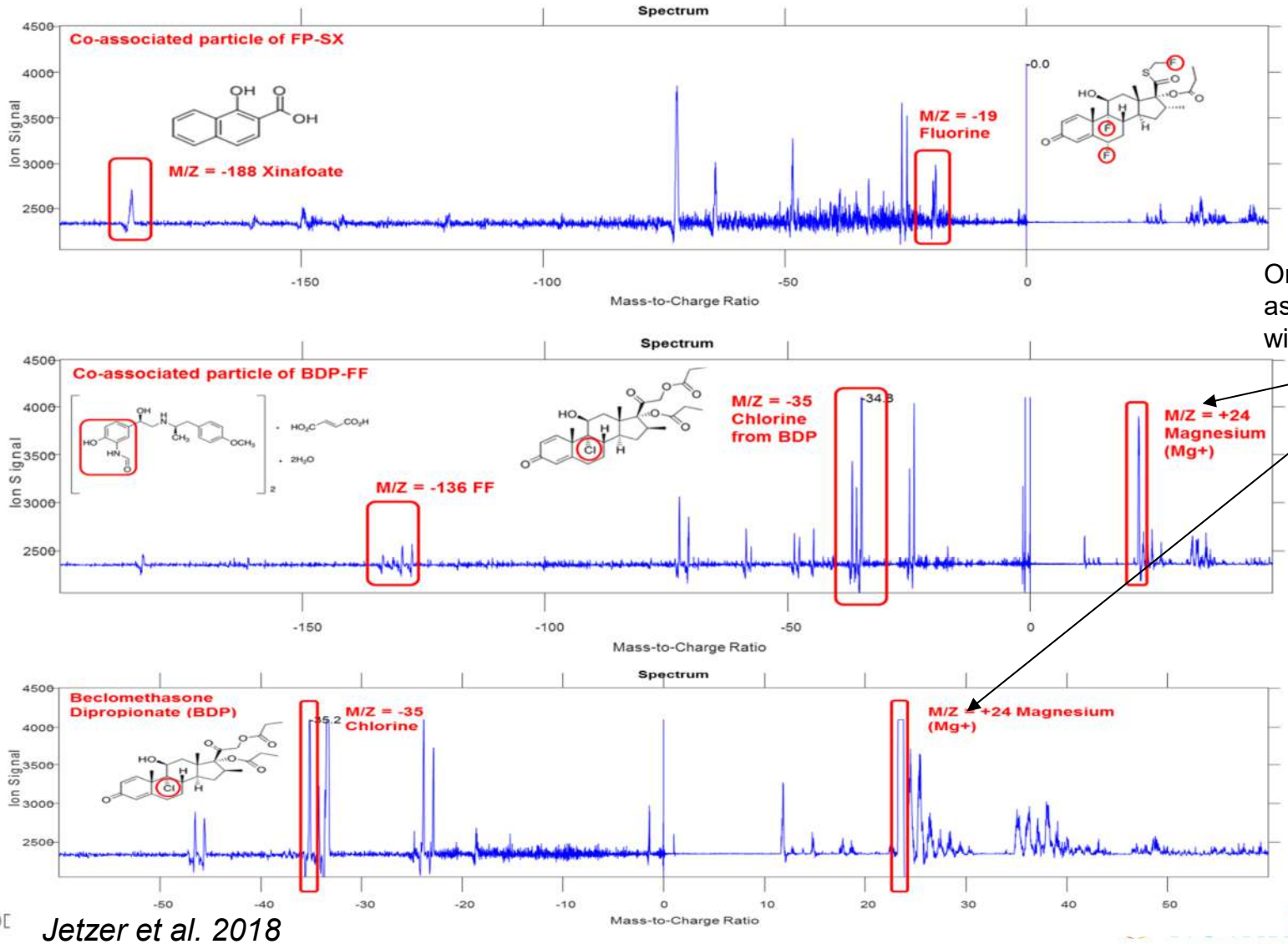
Example: Comparison of different formulations

- Recent publication by Jetzer et al., investigated differences in co-association between commercial DPIs
  - Foster® NEXThaler®
    - Contains beclomethasone dipropionate (BDP) and formoterol fumarate (FF)
  - Seretide® Diskus®
    - Contains fluticasone propionate (FP) and salmeterol xinafoate (SX)
- Differences in co-association were striking

Evidence of co-association for Seretide® and Foster®

Seretide® Diskus®

Foster® NEXThaler®



Only associated with the BDP

Jetzer et al. 2018

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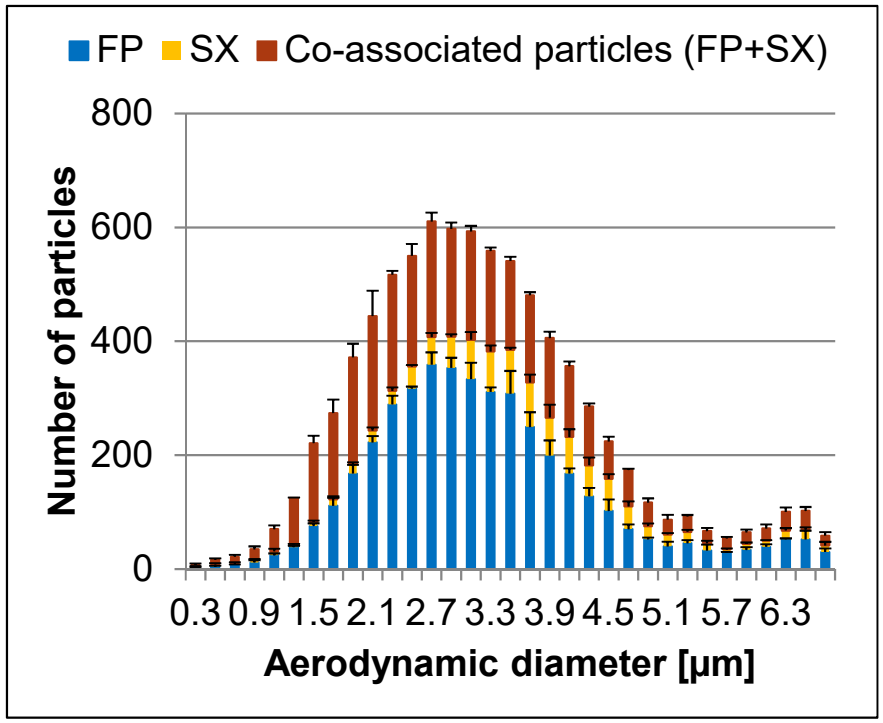
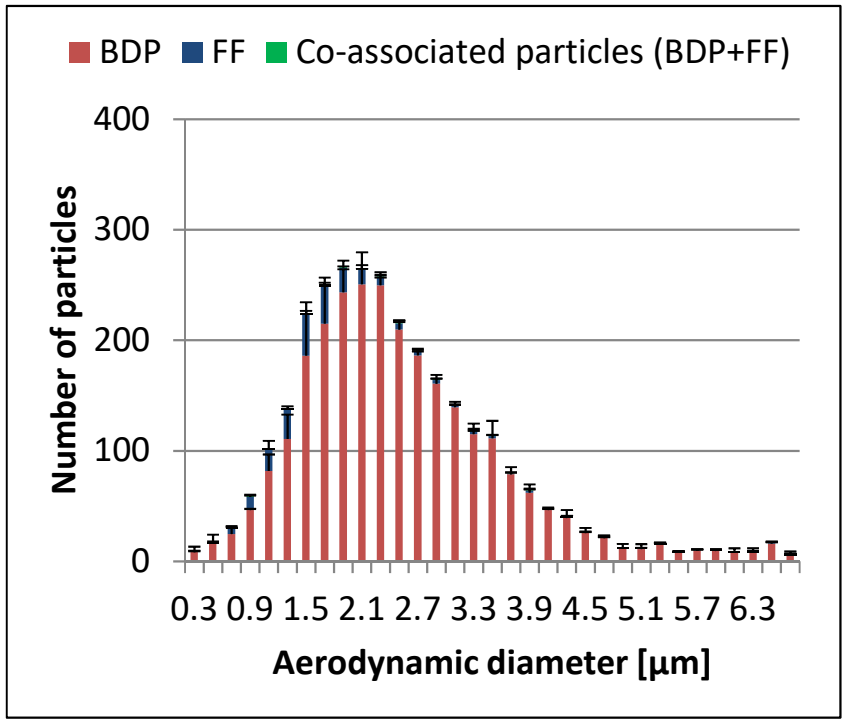
APSD profiles of the two DPIs





[%]	Seretide® Diskus®	[%]	Foster ® NEXThaler®
FP	51.3	BDP	92.6
SX	11.8	FF	7.0
FP-SX co-associated	36.9	BDP-FF co-associated	0.4

Jetzer et al. 2018

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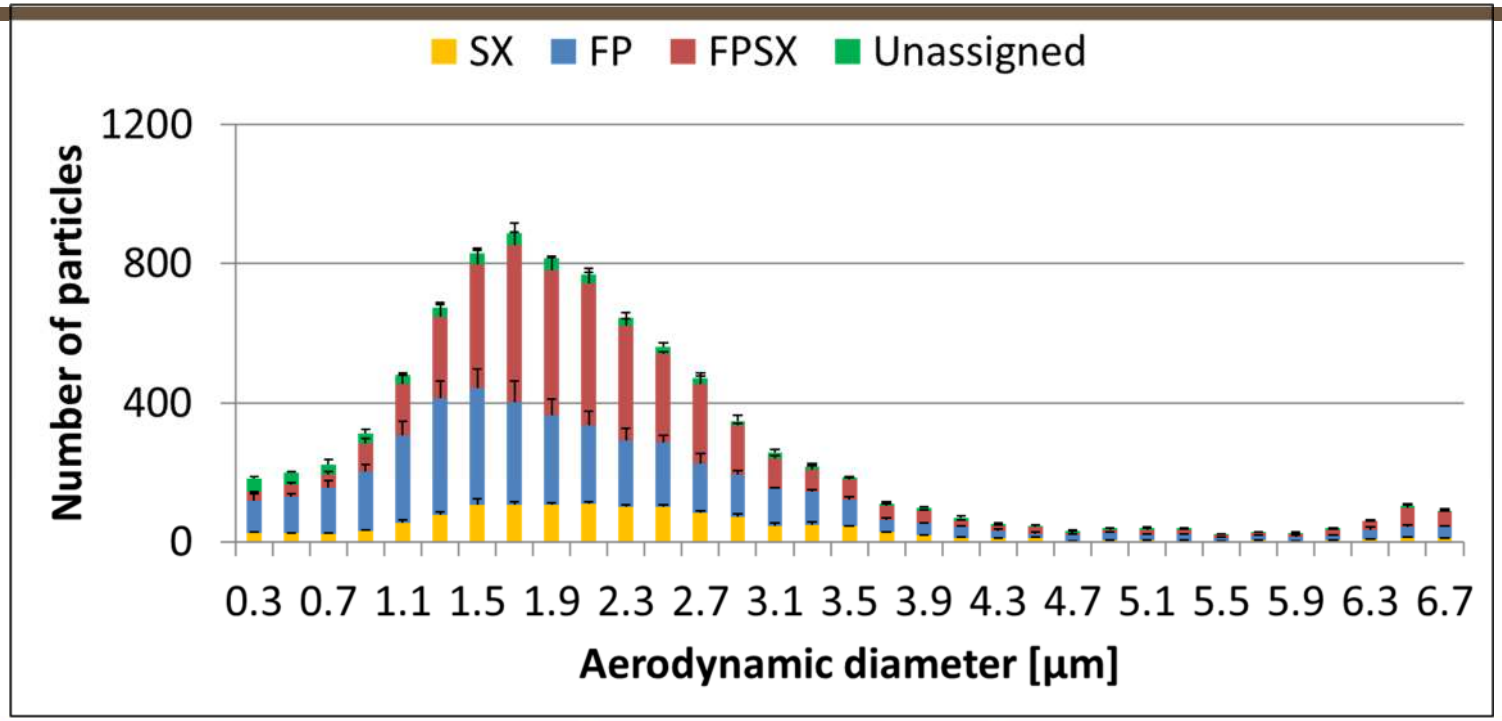
What's going on?

- Seretide contains only APIs and lactose
  - Normal adhesive cohesive behavior expected
    - High co-association expected
    - Little fine lactose so API/API interactions dominate fines
- Foster NEXThaler has an additional excipient: MgSt
  - Seems to be only associated with the BDP and not FF
    - Mass spec data shows FF only particles do not have large Mg+ peak
  - Is BDP and MgSt co-micronized or is MgSt coated on the API somehow?
  - Is MgSt inhibiting co-association due to particle engineering of BDP or is MgSt somehow being used differently here?

Investigation Advair vs. Mono therapies



[%]	Axotide Diskus® (FP)	Serevent Diskus® (SX)	Advair Diskus® (Combination)
FPSX	---	---	41.3
FP	79.1	---	38.8
SX	---	91.5	14.4
Unassigned	20.9	8.5	5.4

Jetzer et al. 2017

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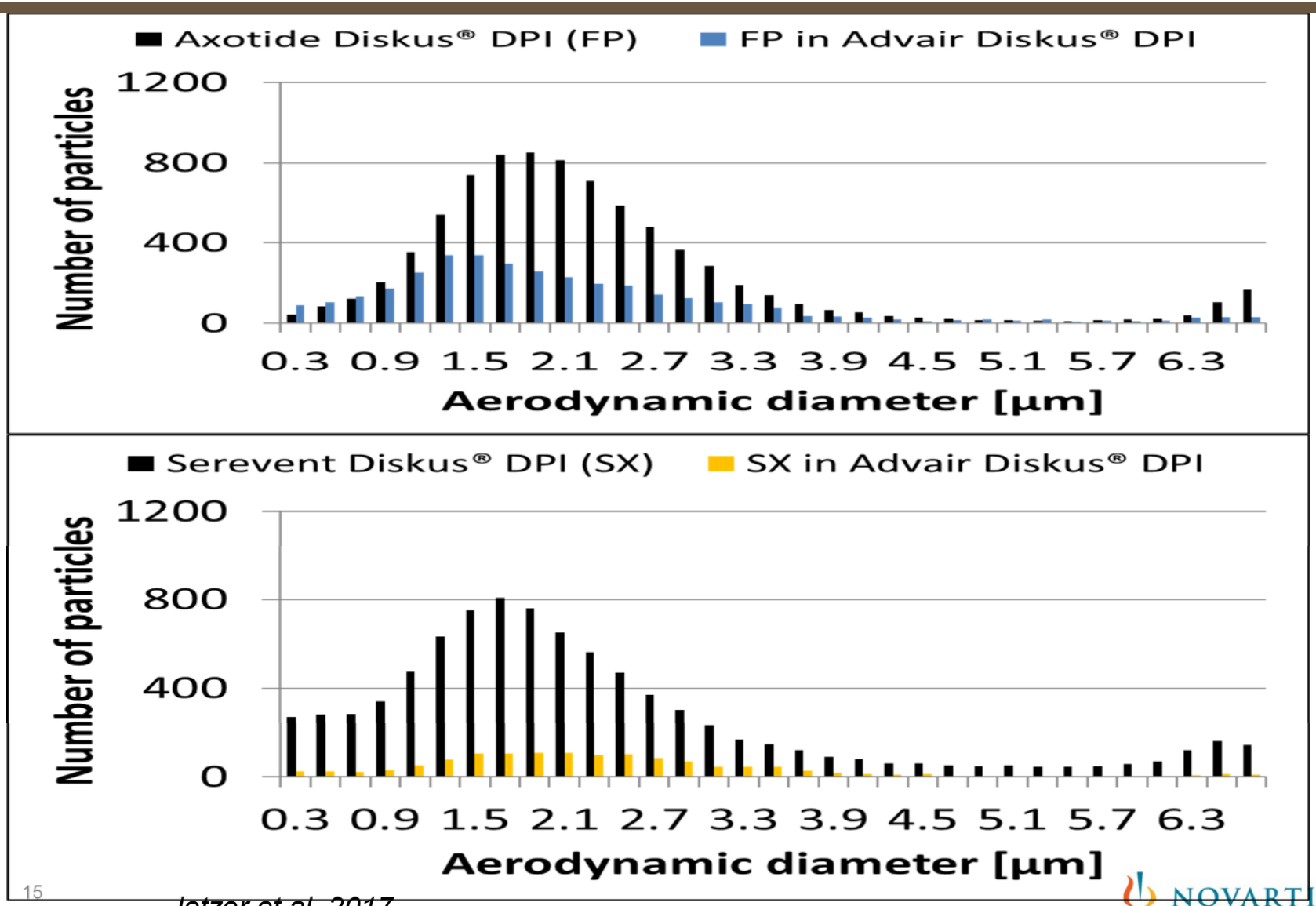
Examination of size distributions between formulations: Monos vs. Pure particles of combos



Jetzer et al. 2017

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Summary

- SPAMS has extremely rapid throughput (hours instead of weeks)
  - Can do things NGI cannot
  - Rapid screening of formulations and/or product development cycle
- SPAMS allows characterization of powder formulations on the single particle (agglomerate) level
  - SPAMS can demonstrate accurately the ratio of co-associated to mono particles in a formulation
  - SPAMS aids in formulation process optimization (blending, excipient distribution etc.)
  - Could be a strong aid in reverse engineering of originator products