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EMERGING CONCEPTS AND NEW TECHNOLOGIES FOR BIOEQUIVALENCE OF ORALLY INHALED AND NASAL DRUG PRODUCTS

Emerging Concepts and New Technologies for Bioequivalence of Orally Inhaled and Nasal Drug Products

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Outline

- GDUFA Regulatory Science Program
- Research initiatives for locally acting orally inhaled and nasal drug products (OINDPs)
  - A **novel technique** for particle size measurement in nasal suspension products and formulation/microstructure characterization in dry powder inhalers
- Conclusions

GDUFA Regulatory Science Program

- Competitive research grants and contracts are awarded yearly
- GDUFA funds are specifically allocated to stimulate innovation and growth in the generic drug field
  - Identify, study, and implement new methodologies and tools
  - Development and evaluation of quality and equivalence of new generic drug products
  - All therapeutic areas and product categories
- FDA annual public meeting provides stakeholder input on research priorities for generic drug development and regulation
  - Industry, Academia
  - Patient advocates, Professional societies

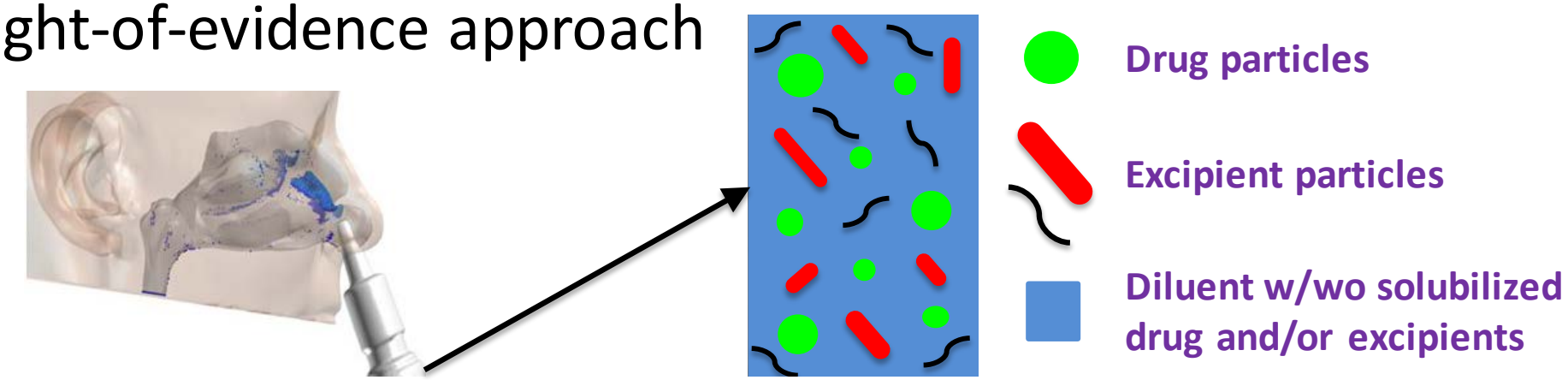
Research Initiatives for Locally Acting Orally Inhaled and Nasal Drug Products (OINDPs)

- Identification of **formulation** and device variables
- Development of clinically relevant in vitro methods for prediction of in vivo drug deposition and dissolution
- Development of computational fluid dynamic (CFD) and physiology-based pharmacokinetic (PBPK) models for prediction of the fate of drugs
- Identification, validation, and standardization of **novel techniques** that may have the potential to reduce the burden of current BE requirements

https://www.fda.gov/downloads/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/GenericDrugs/UCM626329.pdf

Locally Acting Nasal Suspension Sprays

- Current regulatory pathway for BE demonstration utilizes the aggregate weight-of-evidence approach

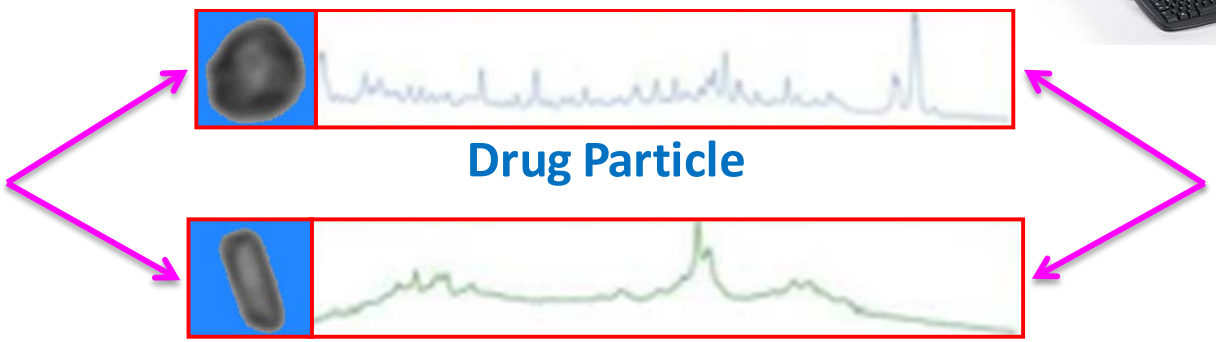


- Drug particle size distribution (PSD) in suspension formulations has the potential to influence **the rate and extent of drug availability** to nasal sites of action and systemic circulation
- Inability to adequately characterize drug PSD in aerosols and sprays using **common analytical methods**

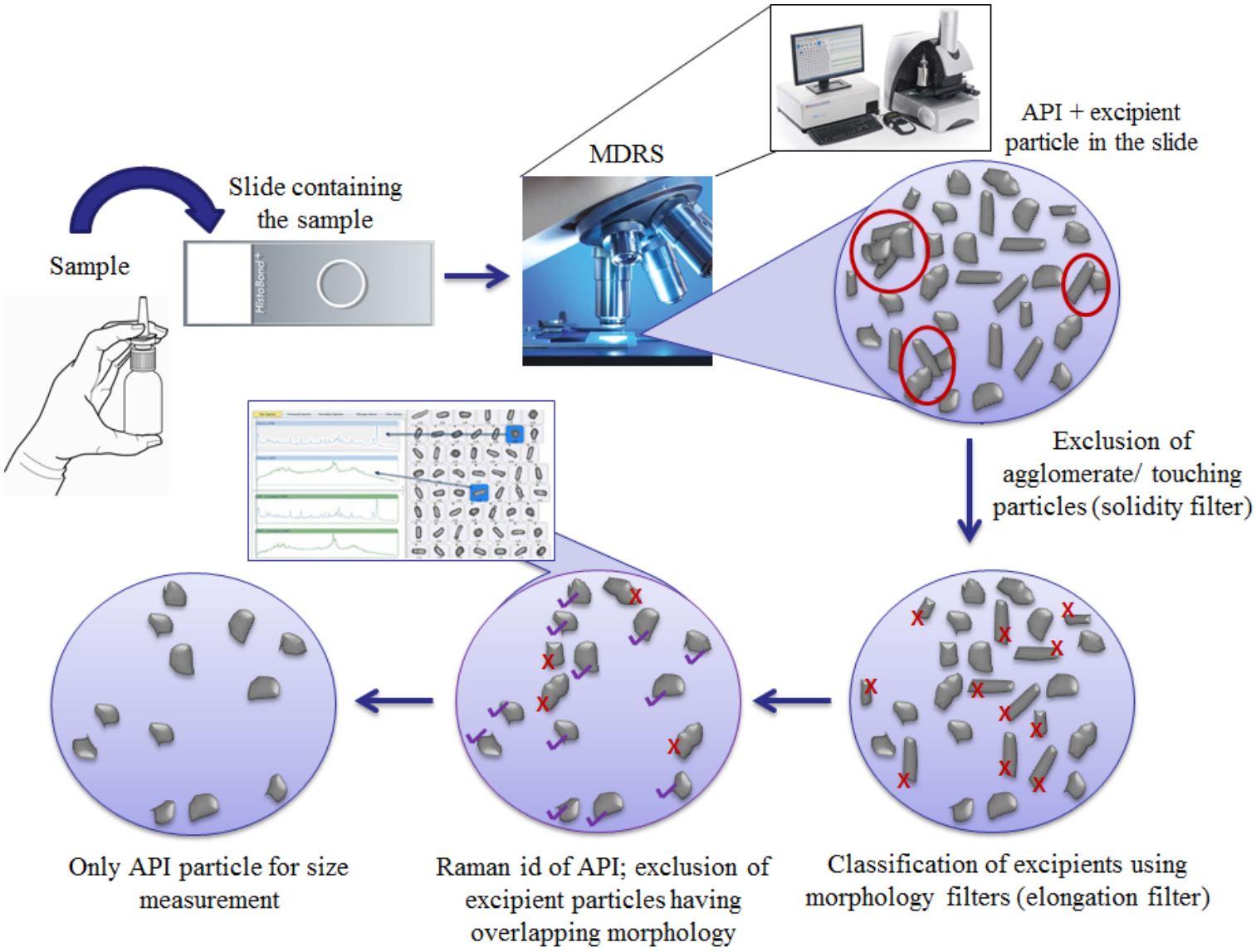
MDRS for Nasal Suspension Sprays

- If drug PSD in test and reference products can be accurately measured using a validated **advanced analytical method**, generic applicants may submit comparative drug PSD data
- The **Morphologically-Directed Raman Spectroscopy (MDRS)** opens this possibility
  - Novel in vitro technology
  - Enables drug PSD comparison

http://www.news-medical.net/news



MDRS: How does it work?

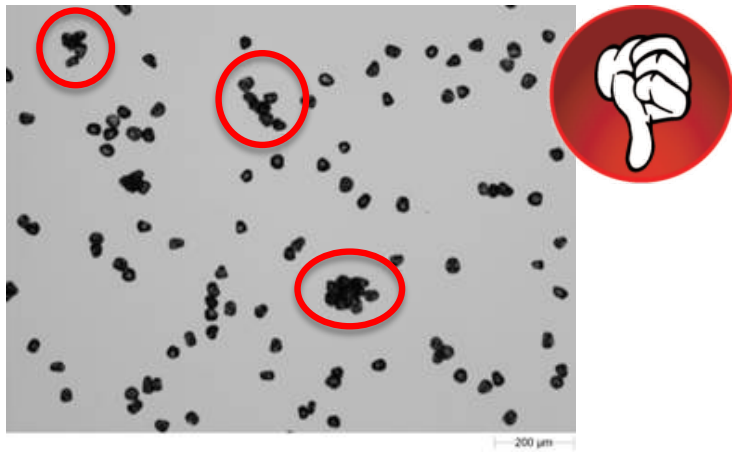


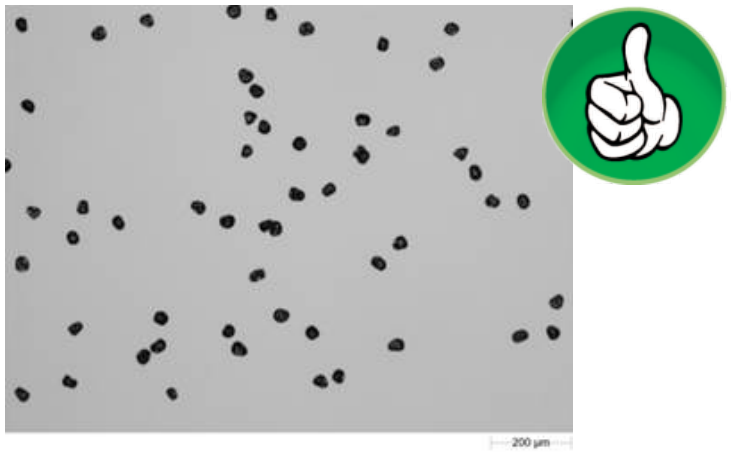
Courtesy of Dr. Abir Absar, Ph.D. (FDA/OCP)

Removal of Agglomerates and Touching Particles

- May consist of
  - Excipient-excipient particles
  - Drug-drug particles
  - Drug-excipient particles

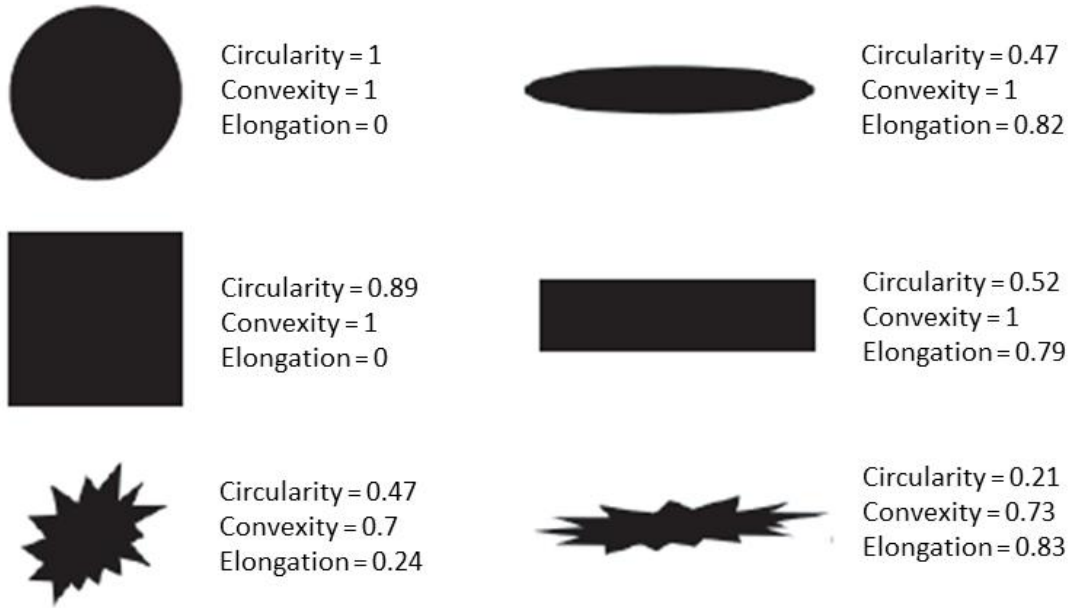
- Sample preparation – Can give misleading data





Particle Classification Using Morphology Filters

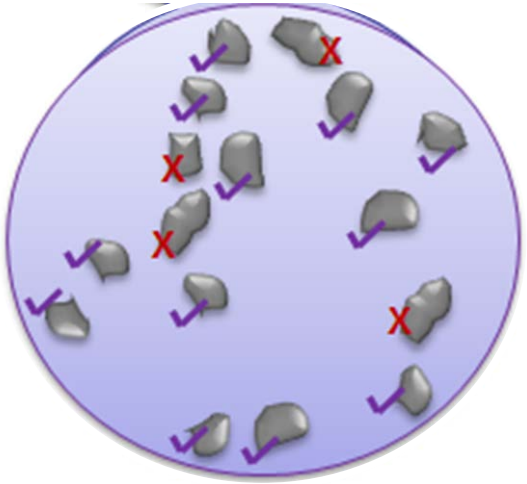
- Should exclude as many excipient particles as possible
- Should not exclude drug particles
- Morphology filters
  - Size
    - Circular equivalent (CE) diameter
  - Shape
    - Aspect ratio
    - Elongation
    - Circularity
    - Convexity
    - Solicity



<u>Disadvantage</u>: Cannot completely separate API and excipient particles due to particles with overlapping morphological features.

Chemical Identification by Raman Spectra

- Identifies particles with overlapping morphological features
- API/Excipient particles typically show different Raman profiles
  - Each molecule has a unique spectrum



Disadvantage:
Slow measurement, time-consuming.

GDUFA Research Has Informed ANDA Review Process and PSG Development

- We have been able to use MDRS
  - to support **BE review** for complex nasal suspension products, which precluded an applicant from repeating a comparative clinical endpoint study, and led to ANDA approval for the first generic Mometasone Furoate Nasal Suspension [RLD: Nasonex® NDA 20-762]
  - in PSGs as **alternate approach** to the comparative clinical endpoint study for other nasal suspension products
    - Fluticasone Propionate
    - Fluticasone Propionate and Azelastine Hydrochloride
    - Triamcinolone Acetonide

Microstructure of DPIs Using Orthogonal Analytical Approaches

- FY-17 contract # HHSF223201710116C
  - Awarded to University of Bath
- The objective of this project is to evaluate a range of orthogonal analytical techniques and utilize a combination of them to support the development and validation of methods in characterizing microstructures of an array of reference listed drug (RLD) dry powder inhaler (DPI) formulations

https://www.fda.gov/downloads/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/GenericDrugs/UCM582981.pdf

Methods

- Product selection: all products were commercially manufactured by the same pharmaceutical company
- Aerosolized fraction collection (impactor-sized mass, ISM): Unidose® aerosol collection system via USP inlet port at a fixed flow rate of 60 L/min for 4 seconds
- MDRS: filter substrate with ISM from one actuation mounted on the sample stage of a Morphologi G3-ID®
- In vitro dissolution: modified USP Apparatus V, samples taken at 2.5, 5, 10, 15, 25, 30, 60, 120, 180, 240 min, ISM collected from equivalent 500mcg fluticasone

Mangal, S.; Conti, D. S.; Delvadia, R.; Oguntimein, O.; Shur, J.; Price, R. "Microstructural Mapping of Dry Powder Inhalers (DPIs) using Morphologically Directed Raman Spectroscopy (MDRS): A Novel Analytical Tool for DPI Characterization." In: AAPS Annual Meeting, 2018, Washington DC, USA. Poster presentation.

Results: Same DPI product, but different FP fractions

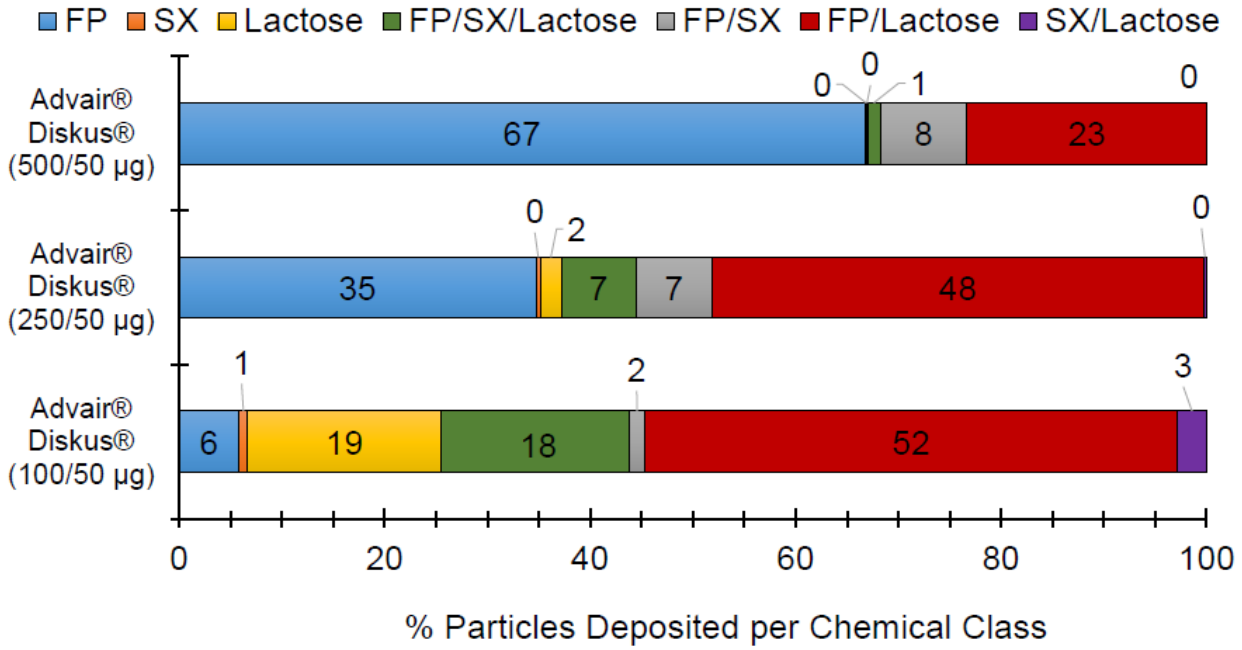


Figure 1: Particles deposited per chemical class (%) of the ISM of Advair® Diskus® (FP/SX; 100/50 µg), Advair® Diskus® (FP/SX; 250/50 µg), and Advair® Diskus® (FP/SX; 500/50 µg). These are presented as mean ± standard deviation (n=5).

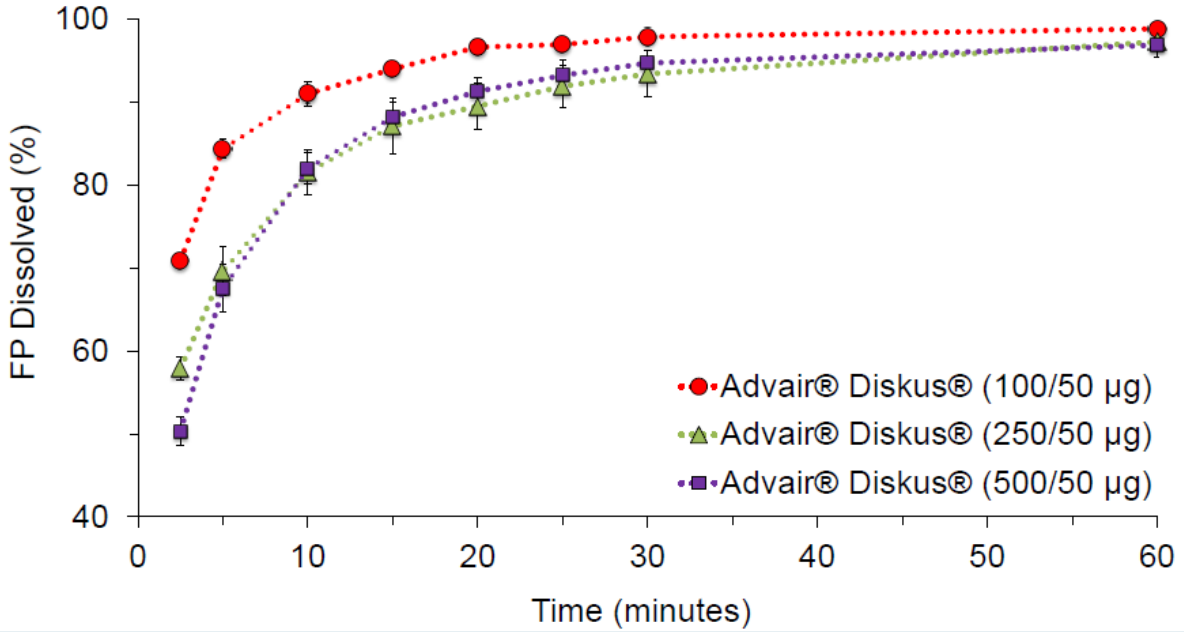


Figure 2: FP dissolved (%) from the ISM of Advair® Diskus® (100/50 µg) as Red Circle, Advair® Diskus® (250/50 µg) as Green Triangle, and Advair® Diskus® (500/50 µg) as Purple Square. These are presented as mean ± standard deviation (n=2).

Mangal, S.; Conti, D. S.; Delvadia, R.; Oguntimein, O.; Shur, J.; Price, R. "Microstructural Mapping of Dry Powder Inhalers (DPIs) using Morphologically Directed Raman Spectroscopy (MDRS): A Novel Analytical Tool for DPI Characterization." In: AAPS Annual Meeting, 2018, Washington DC, USA. Poster presentation.

Results: FP fractions across DPI products

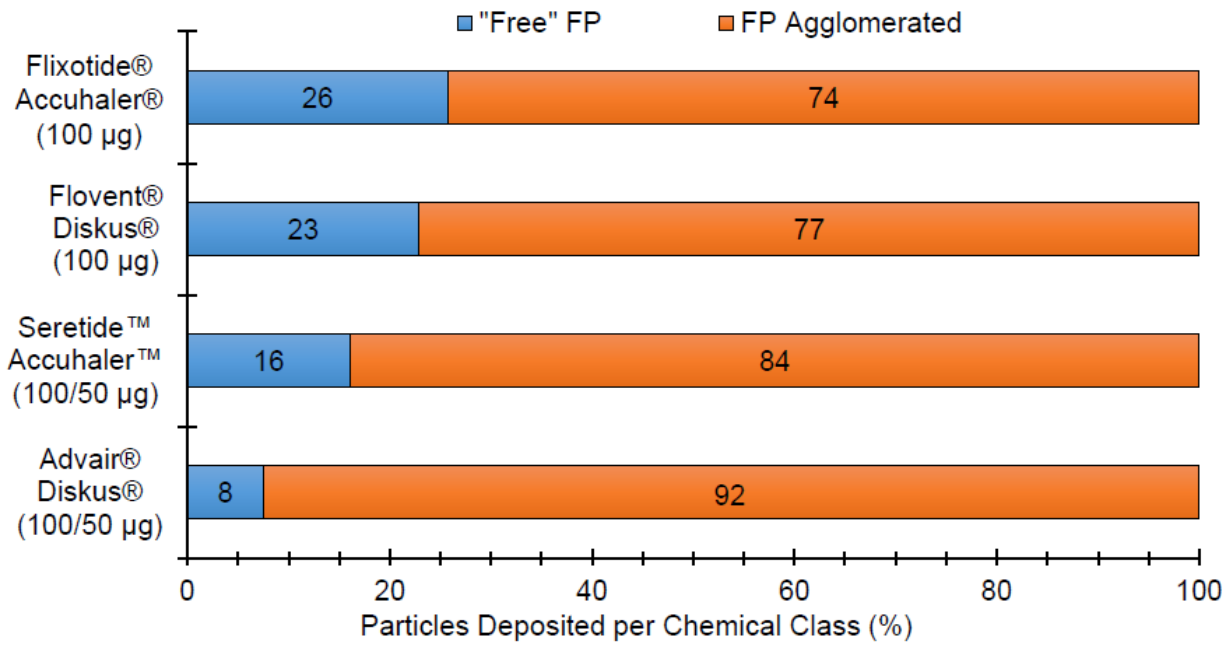


Figure 3: Particles deposited per chemical class (%) of the ISM of Advair® Diskus® (FP/SX; 100/50 µg), Flixotide® Accuhaler® (FP; 100 µg), Flovent® Diskus® (FP; 100 µg), and Seretide® Accuhaler® (FP/SX; 100/50 µg). These are presented as mean ± standard deviation (n=5).

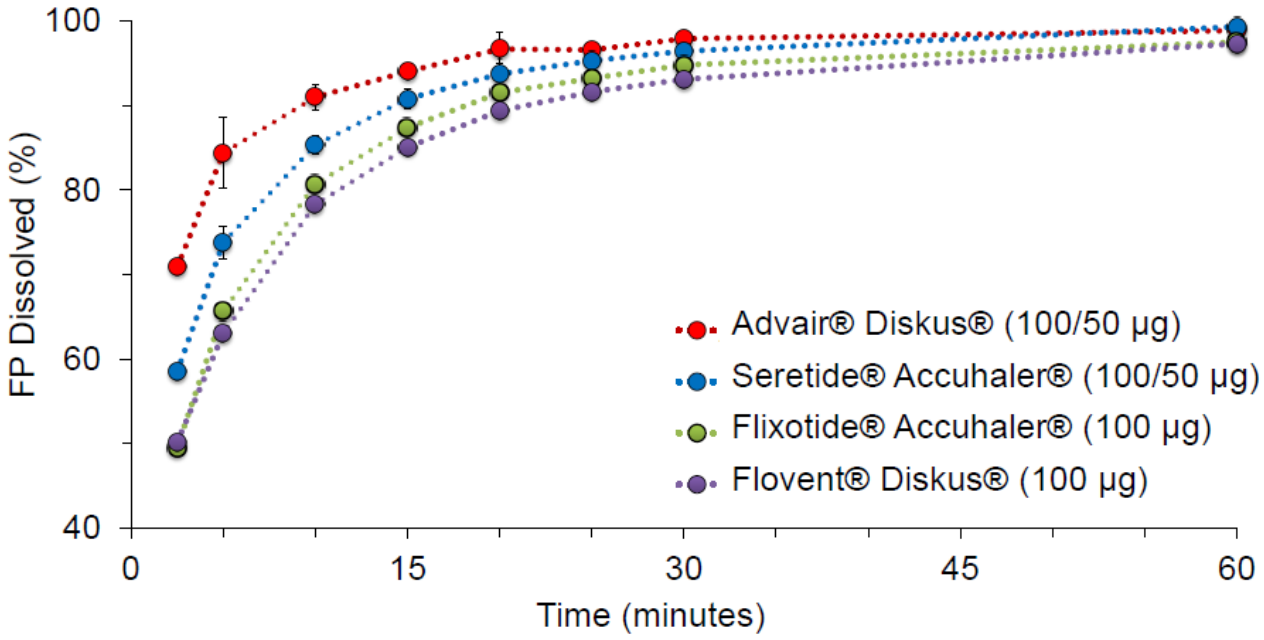


Figure 4: FP dissolved (%) from the ISM of Advair® Diskus® (100/50 µg), Flixotide® Accuhaler® (100 µg), Flovent® Diskus® (100 µg), and Seretide® Accuhaler® (100/50 µg). These are presented as mean ± standard deviation (n=2).

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Results: FP in different DPI products

FP microstructure vs. FP dissolved – good correlation

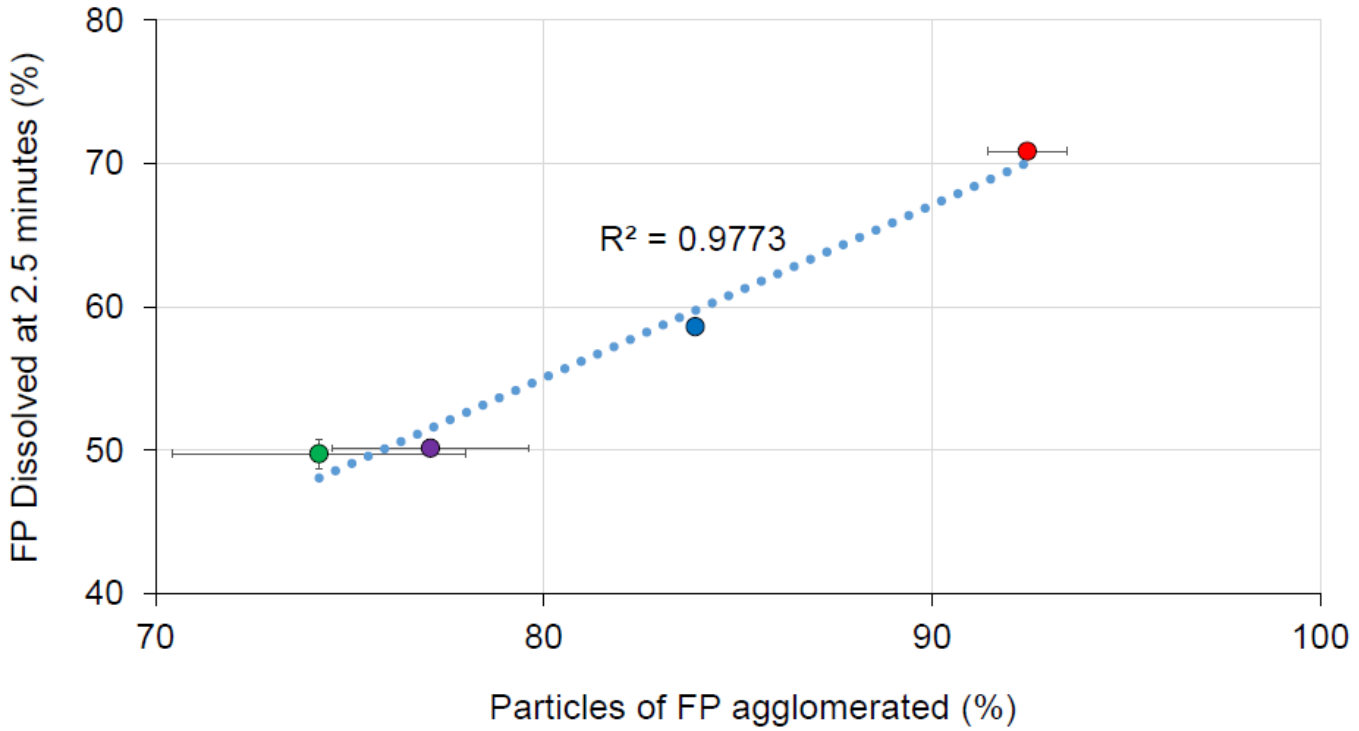

Figure 5: FP dissolved at 2.5 minutes (%) as a function of FP-lactose agglomerates (%) for Advair® Diskus® (100/50 µg, red circle); Flixotide® Accuhaler® (100 µg, green circle); Flovent® Diskus® (100 µg, purple circle); and Seretide® Accuhaler® (100/50 µg, blue circle).

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Conclusions

- GDUFA Regulatory Science Research supports ANDA review, approval and guidance development
- Research initiatives for locally-acting OINDPs explore new techniques to make generic product development and BE demonstration faster and more cost-effective
- An advanced analytical method, such as MDRS:
  - enables a comparison of drug PSD in generic and reference nasal spray suspension products
  - has the potential to provide information on formulation and/or microstructure differences between DPI products

Acknowledgements

- Abir Absar, Ph.D. — FDA
- Jason Rodriguez, Ph.D. — FDA
- Changning Guo, Ph.D. — FDA
- Kimberly Witzmann, M.D. — FDA
- Markham Luke, M.D., Ph.D. — FDA
- Robert Lionberger, Ph.D. — FDA
- Jag Shur, Ph.D. — University of Bath
- Robert Price, Ph.D. — University of Bath
- Sharad Mangal, Ph.D. — Pearl Therapeutics (former ORISE at FDA)


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