CRITICAL IMPORTANCE OF EXCIPIENTS IN GENERIC PRODUCT DEVELOPMENT-NOW AND IN THE FUTURE

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Speaker Disclaimer

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Objective

This session will describe how emerging technologies and innovative approaches in FDA-funded research have informed our understanding of excipients in orally inhaled and nasal drug products (OINDPs), which support FDA guidance development and regulatory decision-making for generic drug products.

Outline

- FDA GDUFA Research Program
- Excipient Differences in MDIs Affect in vitro Performance Characteristics
- Excipient Differences Affect in vivo Bioequivalence
- Manufacturing Differences Can Affect in vitro Bioequivalence
- Conclusions

Generic Drug User Fee Amendments (GDUFA)

- Passed in July 2012 to speed access to safe and effective generic drugs to the public, reauthorized in 2017
- Requires user fees to supplement costs of reviewing generic drug applications and provides additional resources, including support for **regulatory science research**
- User fee program which directly supports regulatory science research activities

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

https://www.fda.gov/drugs/resourcesforyou/consumers/buyingusingmedicinesafely/genericdrugs/ucm567695.htm

Locally-Acting Orally-Inhaled and Nasal Drug Products (OINDPs)

- Performance is governed by complex interactions between formulation, device, and patient factors
  - In vitro methods have limited predictability
  - Bioequivalence (BE) demonstration is very challenging
  - In vivo studies are time-consuming and expensive
- Current regulatory pathway for BE demonstration utilizes the weight-of-evidence approach
- The Office of Generic Drugs continues to explore new methods to make development and BE demonstration more cost- and time-effective

Research Initiatives for 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

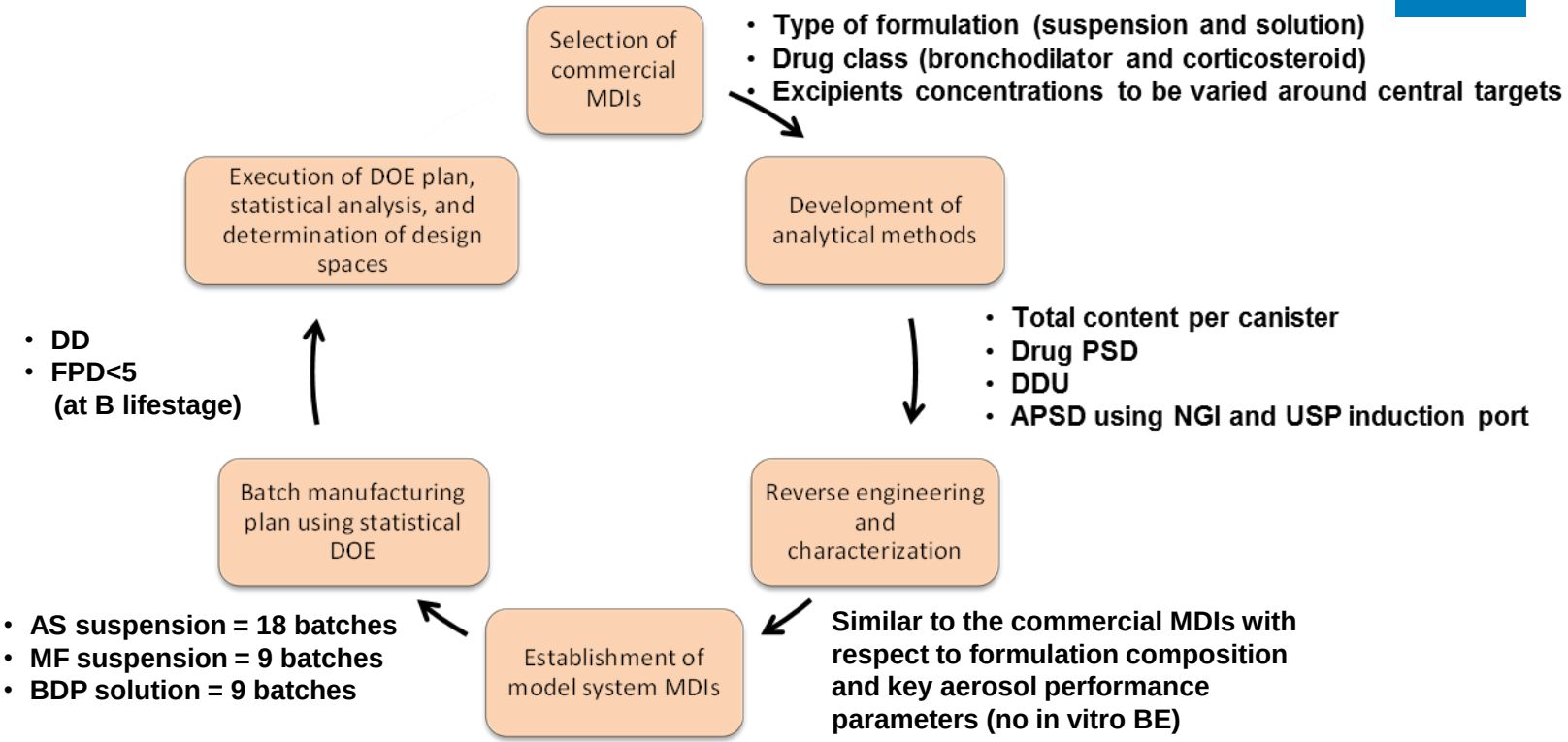
https://www.fda.gov/downloads/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/GenericDrugs/UCM582777.pdf

Comprehensive Evaluation of Formulation Effects on MDI Performance

- FY-13 grant # U01FD004943
  - Awarded to Cirrus Pharmaceuticals (Recipharm)
  - Expanded to University of Florida
- This project investigated the effect of excipient concentrations on aerosol performance of HFA-based MDI formulations and evaluated sensitivity of in vitro methods to detect excipient concentration changes

https://grants.nih.gov/grants/guide/rfa-files/RFA-FD-13-013.html

Overview of the Systematic Approach



Sheth, P.; Sandell, D.; Conti D. S.; Holt J. T.; Hickey, A.; Saluja, B. "Influence of Formulation Factors on the Aerosol Performance of Suspension and Solution Metered Dose Inhalers: A Systematic Approach." 2017. AAPS Journal; 19 (5): 1396-1410.

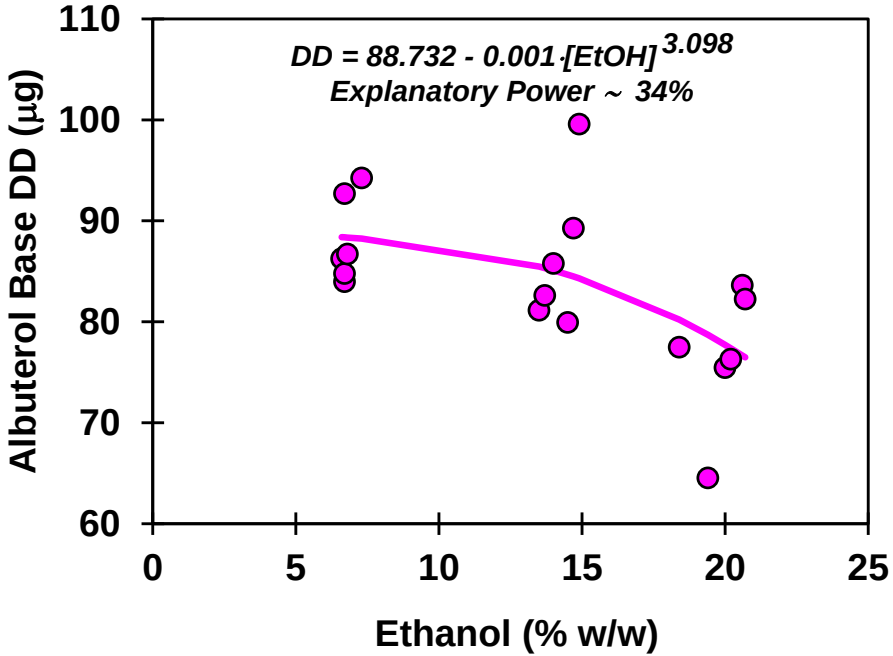
MDI Batch Manufacturing Plan

The levels of excipients [ethanol (EtOH) and oleic acid (OA)] and drug PSD D50 were varied according to a reduced factorial statistical design of experiments (DOE) approach. The following ranges were studied:

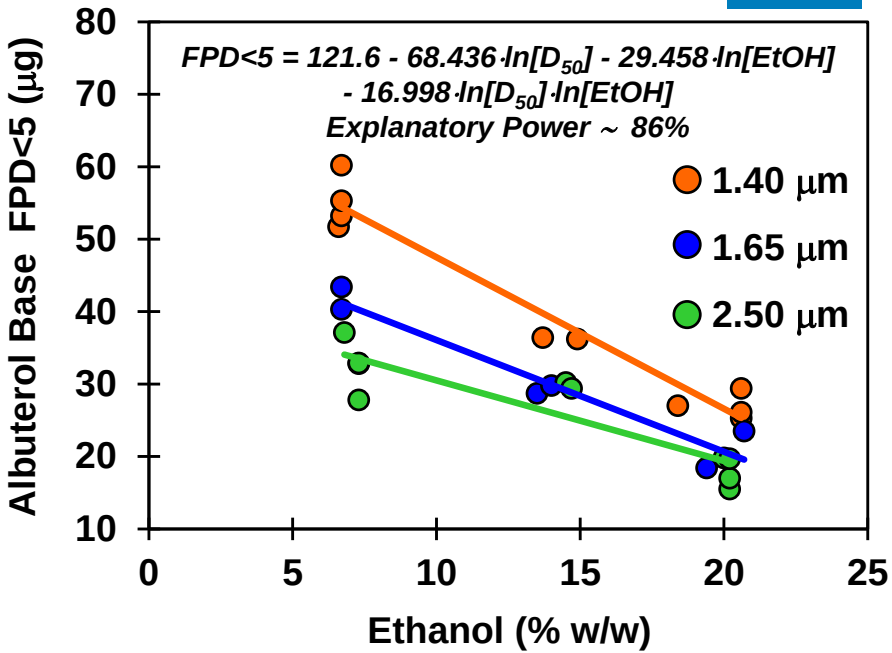
MDI Formulation	PSD D50 (µm)	EtOH (% w/w)	OA (% w/w)
AS suspension	1.4 – 2.5	7 – 20	0.005 – 0.1
MF suspension	1.1 – 2.0	0.45 – 3.6	0.001 – 0.025
BDP solution	N/A	7 – 9	0 – 2

Sheth, P.; Sandell, D.; Conti D. S.; Holt J. T.; Hickey, A.; Saluja, B. "Influence of Formulation Factors on the Aerosol Performance of Suspension and Solution Metered Dose Inhalers: A Systematic Approach." 2017. AAPS Journal; 19 (5): 1396-1410.

Albuterol Sulfate Suspension



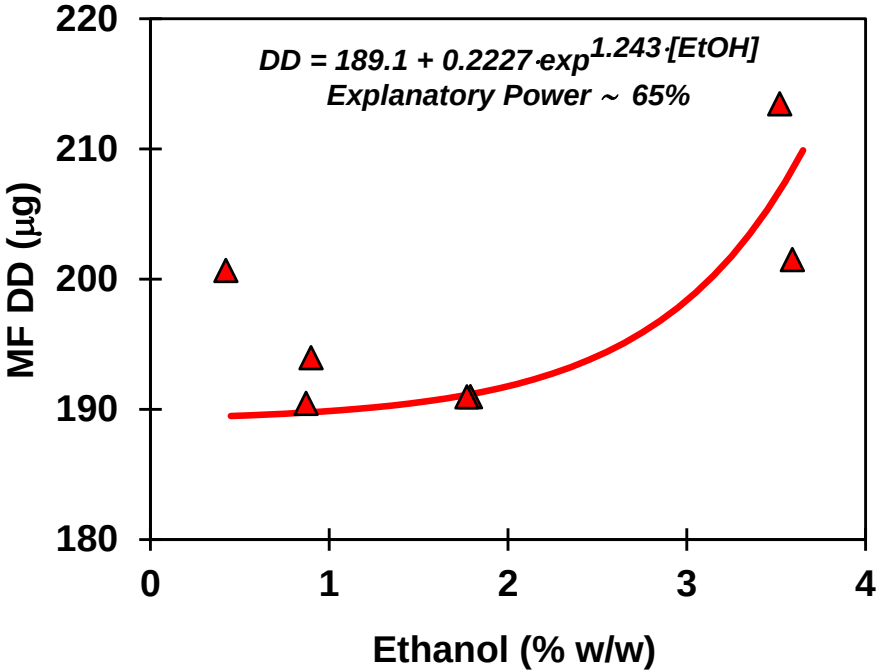
As the level of ethanol increased from 7% to 20% w/w, the DD of albuterol decreased by 13%.



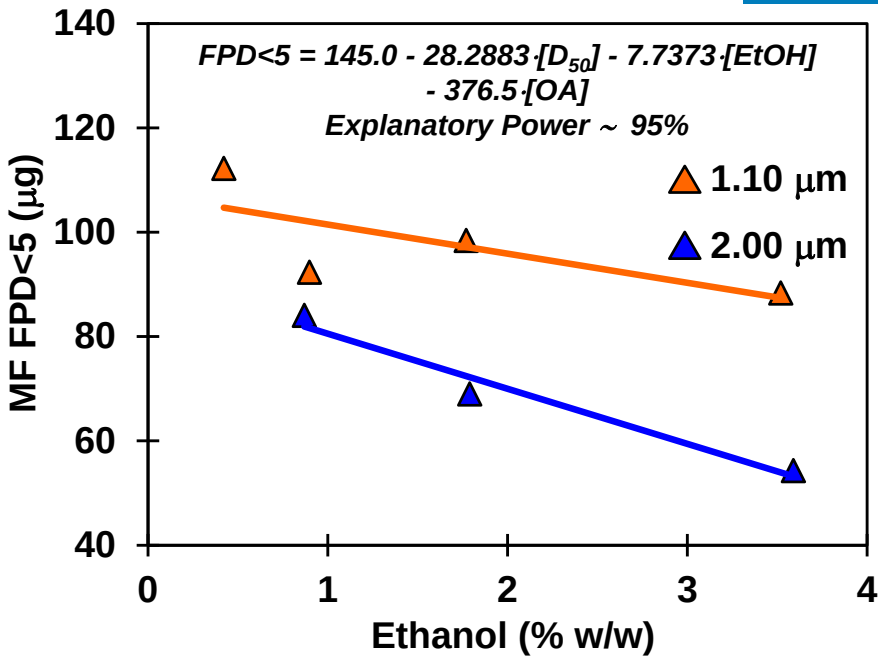
As the level of ethanol increased from 7% to 20% w/w, the FPD<5 of albuterol decreased by 51% (1.40 µm), 50% (1.65 µm) and 45% (2.50 µm).

Schroeter J.D., et al. "Effects of Formulation Variables on Lung Dosimetry of Albuterol Sulfate Suspension and Beclomethasone Dipropionate Solution Metered Dose Inhalers." AAPS PharmSciTech 2018; 19 (5): 1-11.

Mometasone Furoate Suspension



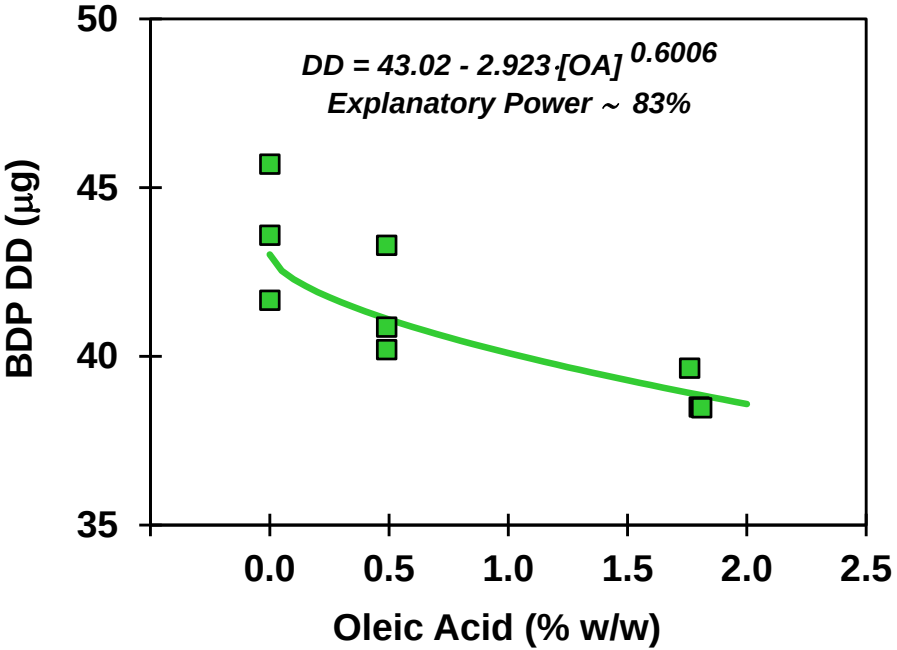
As the level of ethanol increased from 1.8% to 3.6% w/w, the DD of MF increased by 9%.



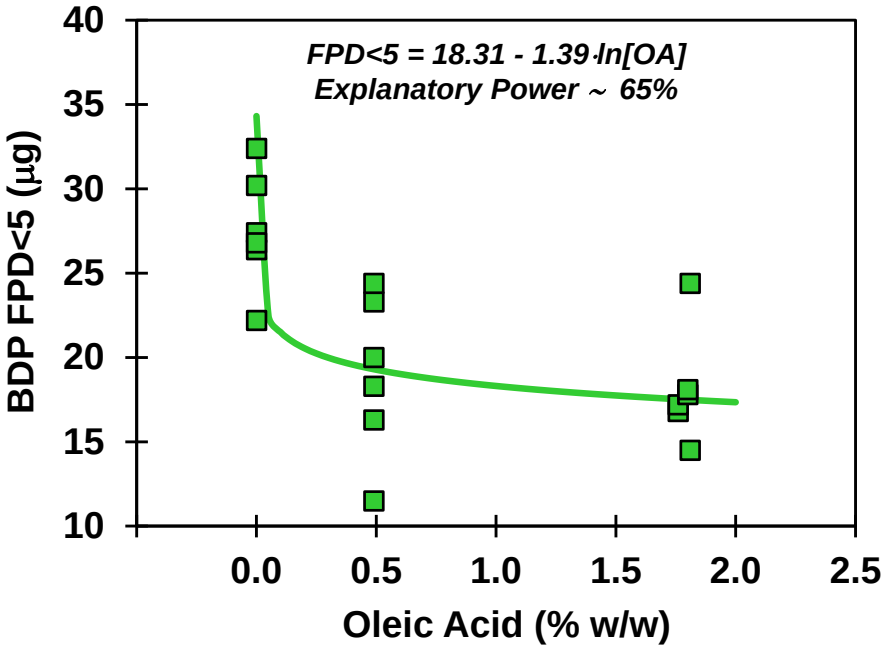
As the level of ethanol increased from 0.45% to 3.6% w/w (1.1 µm) and from 0.90% to 3.6% (2.0 µm), the FPD<5 of MF decreased by 21% and 35%.

Conti, D. S.; Holt, J.; Sheth, P.; Sandell, D.; Hickey, A.; Saluja, B. "The Effects of Formulation Factors on the Aerosolization Performance of Metered Dose Inhalers." In: AIChe Annual Meeting, 2016, San Francisco, CA, United States. Poster presentation.

Beclomethasone Dipropionate Solution



As the level of oleic acid increased from 0% to 2% w/w, the DD of BDP decreased by 11%.



As the level of oleic acid increased from 0% to 2% w/w, the FPD<5 of BDP decreased by 34%.

Schroeter J.D., et al. "Effects of Formulation Variables on Lung Dosimetry of Albuterol Sulfate Suspension and Beclomethasone Dipropionate Solution Metered Dose Inhalers." AAPS PharmSciTech 2018; 19 (5): 1-11.

Research Conclusions

- The changes in API PSD had statistically significant effects on the APSD performance of suspension MDI formulations studied, but not on DD.
- The changes in concentrations of excipients (ethanol and oleic acid) showed, in some cases, statistically significant effects on DD and APSD performance of suspension and solution MDI formulations studied. However, several cases without effects were also found, despite some large changes in concentrations of inactive ingredients studied.
- The possible effects of varying these characteristics must be studied on a case-by-case basis.

PK Comparison of Locally-Acting DPI Products

- FY-13 contract # HHSF223201110117A
- FY-16 contract # HHSF223201610099C
  - Awarded to University of Florida
- The objective of this project was to evaluate whether PK profiles are sensitive to DPI formulations that differ in the central to peripheral (C/P) lung deposition ratio. A clinical study was conducted to evaluate the PK profiles of healthy adult subjects after a single-dose of different orally inhaled formulations is administered using a DPI.

https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM526210.pdf

Formulation Development

- In collaboration with University of Bath
- Three DPI formulations only differing in lactose fines

Product Name	Formulation (% w/w)	Formulation # MMAD
Fluticasone Propionate DPI (Active)	FP: 0.80 Respitose SV003: 96.72 Lactohale LH300: 2.48	C-3.7µm
Fluticasone Propionate DPI (Active)	FP: 0.80 Respitose SV003: 79.36 Lactohale LH201: 19.84	A-4.5µm
Fluticasone Propionate DPI (Active)	FP: 0.80 Respitose SV003: 89.28 Lactohale LH230: 9.92	B-3.8µm

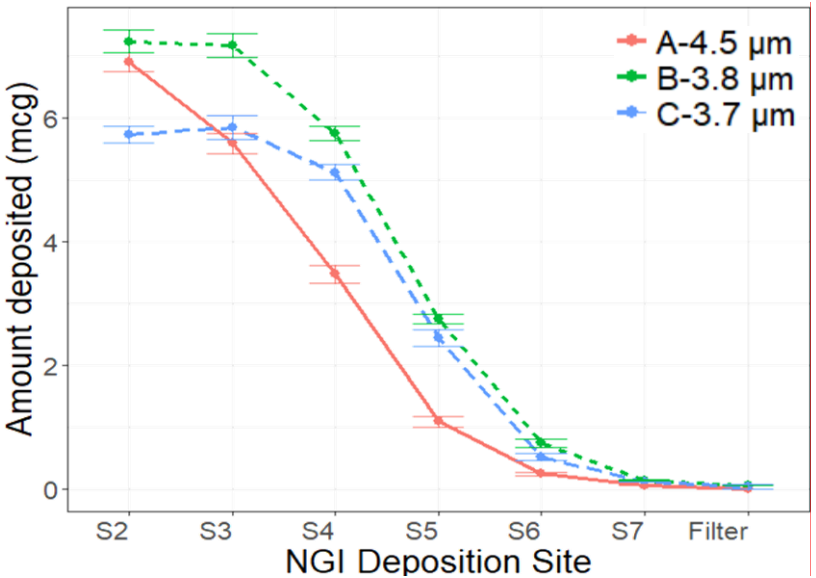
MMAD= Mass Median Aerodynamic Diameter

Günther Hochhaus and Jürgen Bullita. "Pharmacokinetic Comparison of Locally Acting Dry Powder Inhalers." In: DIA Meeting on Complex Drug-Device Generic Combination Products, Oct 9-10, 2018, Silver Spring, MD, USA. Podium Presentation.

In Vitro Characterization

- Cascade impaction performance of formulations (compendial NGI at flow rate of 60 L/min)

	A-4.5 µm	B-3.8 µm	C-3.7 µm
MMAD (µm)	4.5	3.8	3.7
GSD	1.9	2.0	2.1
FPD < 5µm (µg)	12.2	18.7	15.8
FPD < 3µm (µg)	5.3	10.0	8.6
Stage 2 to 3 (µg)	12.5	14.4	11.5
Stage 4 to 7 (µg)	4.8	9.4	8.1



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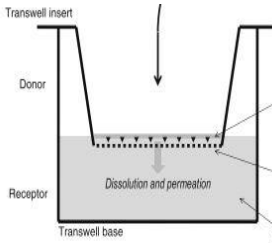
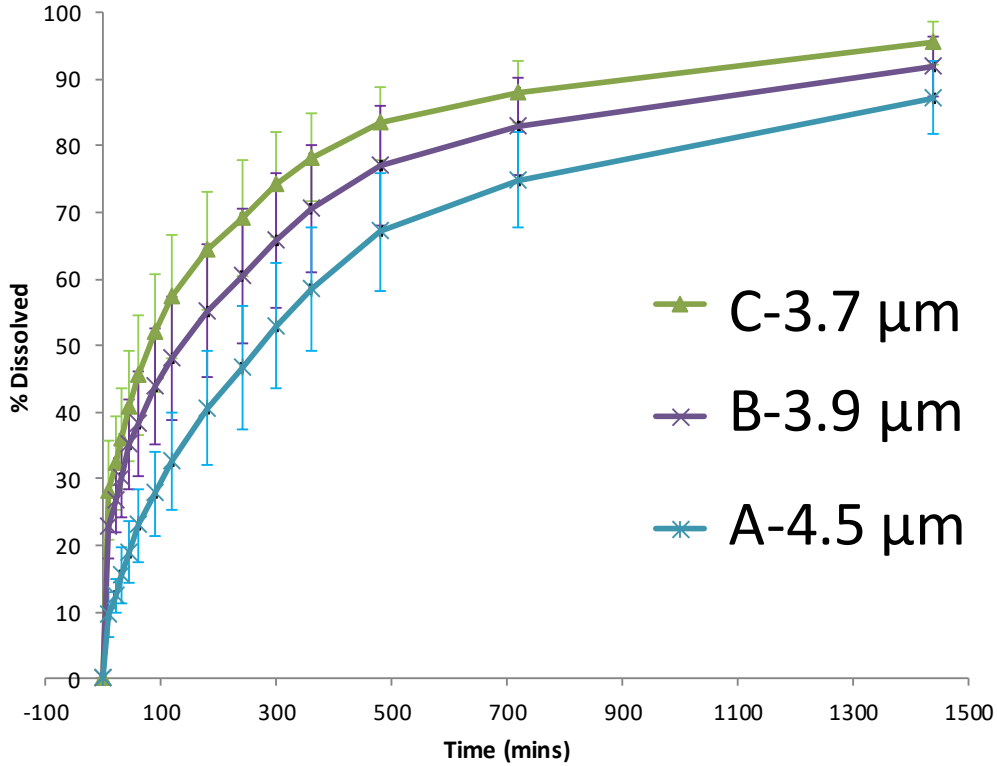
In Vitro Characterization

- Dissolution rate

Formulation	Parameter	Value
A-4.5 µm	MDT	15.4 hrs
B-3.9 µm	MDT	13.3 hrs
C-3.7 µm	MDT	10.3 hrs





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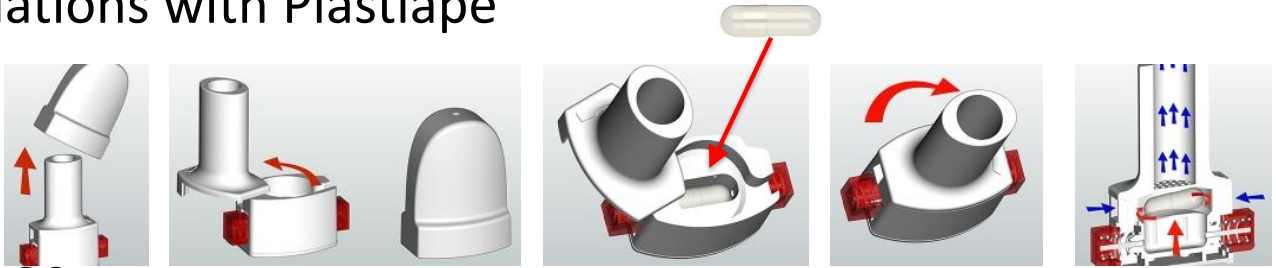
PK Study Design

- 4-way, double blind cross-over in 24 healthy volunteers (informs intra-subject variability)
- DPI formulations with Plastiape



http://plastiape.com/en/content/1635/dry-powder-inhaler-rs01-how-use

- Dose: 5 x 100 µg
- Record individual inhalation profiles
- LC-MS/MS Assay sensitivity: 1 pg/mL
- Non-compartmental Analysis + Compartmental Analysis (population-PK)

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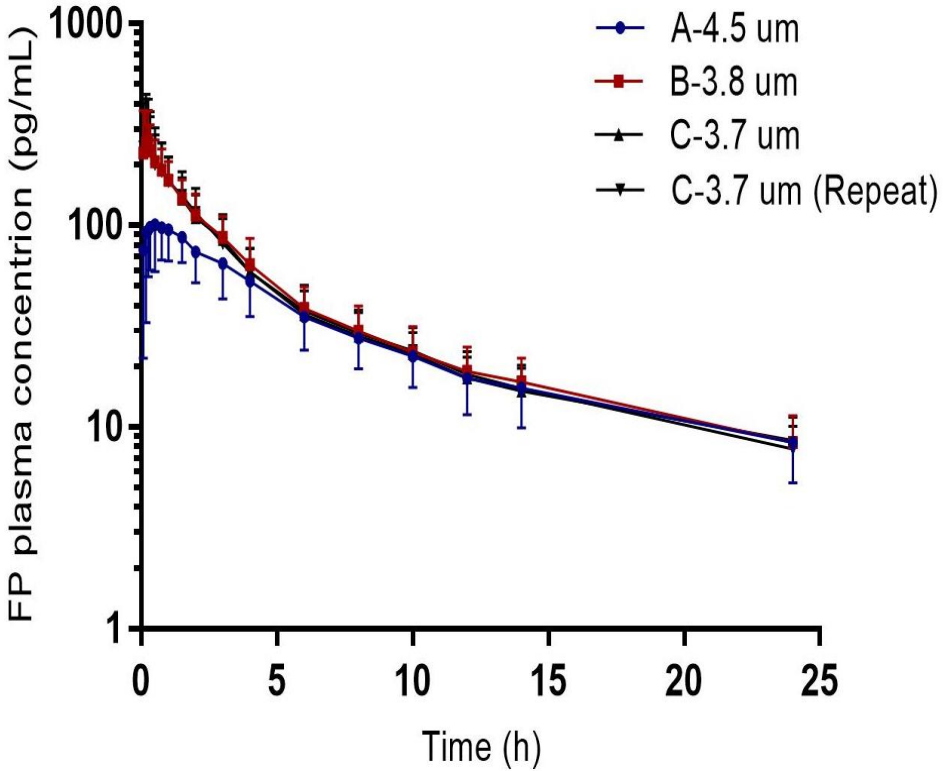
PK Profiles

Before dose normalization



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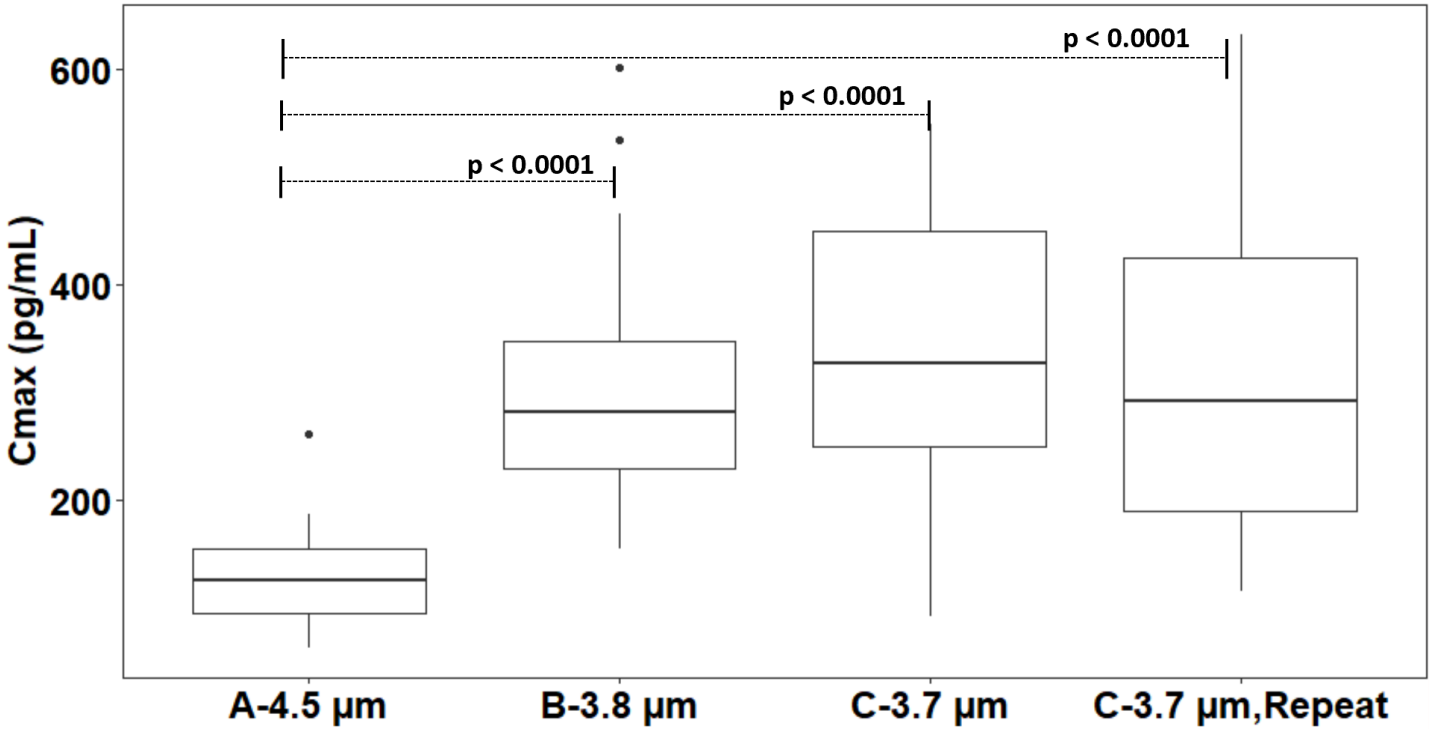
PK Properties - Cmax



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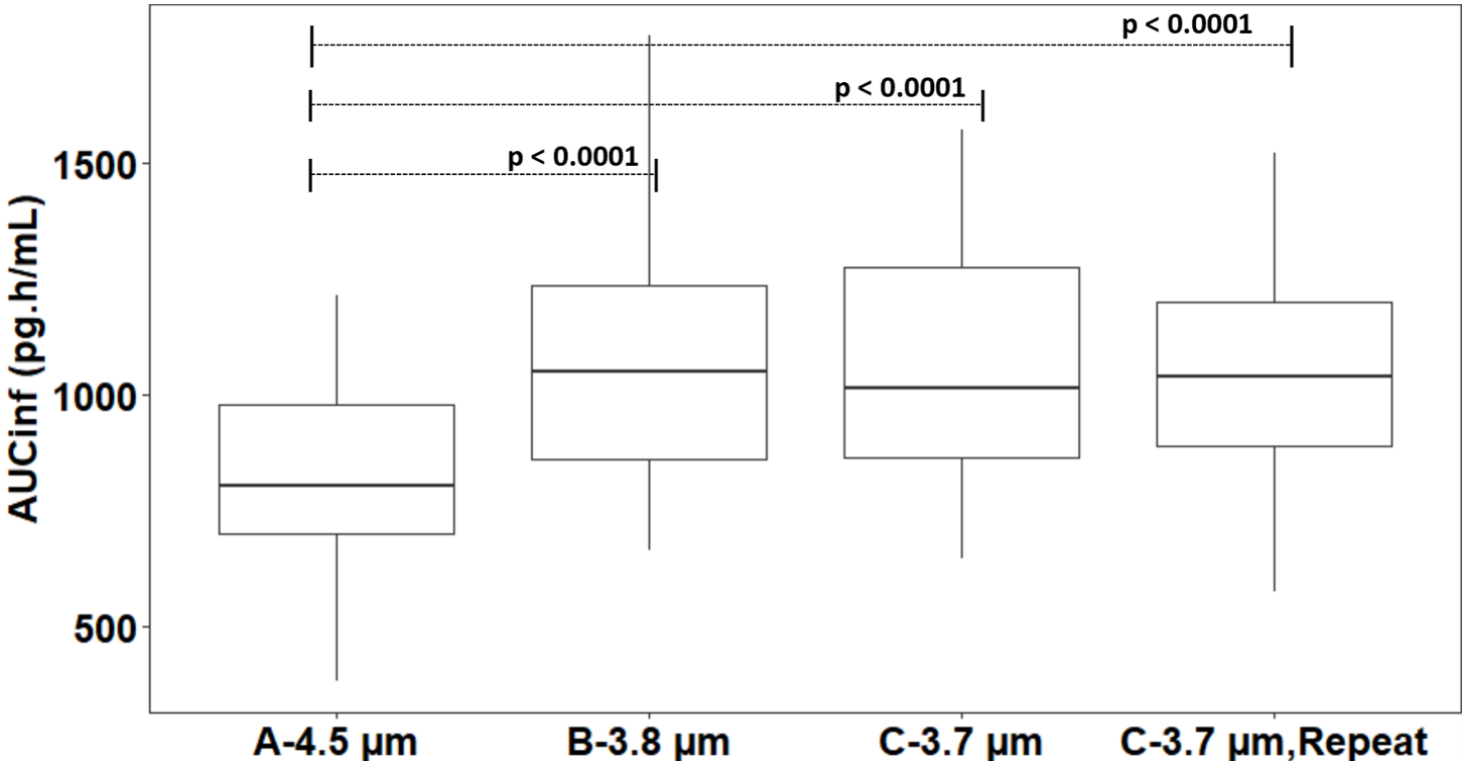
PK Properties - AUC



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Research Conclusions

- Given the same qualitative and quantitative excipient (lactose) concentrations, differences in lactose fines which impacted the MMADs were able to alter *in vitro* performance parameters and *in vitro* dissolution results.
- These differences in performance characteristics were measurable within *in vivo* PK profiles (Cmax and AUC).

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
- Morphologically Directed Raman Spectroscopy (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

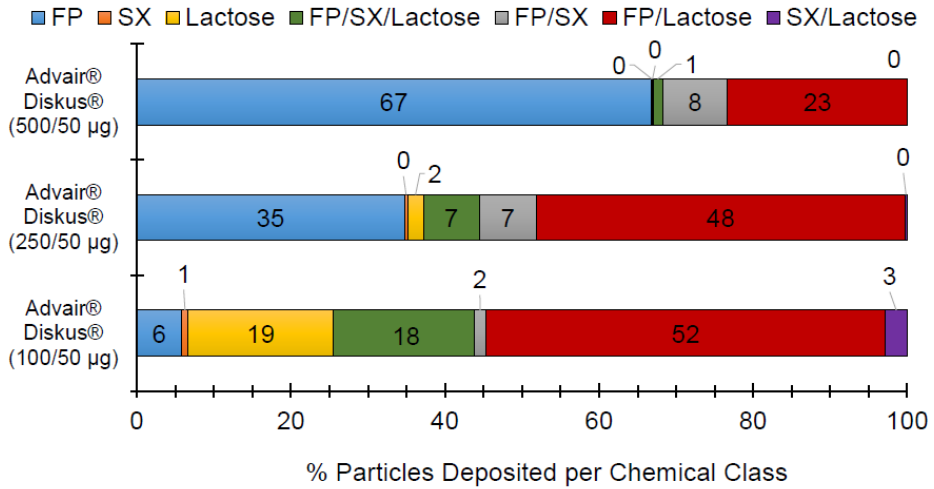

Figure 1: Particles deposited per chemical class (%) of the ISM of Advair® Diskus® (FP/SX; 100/50 µg), Advair® Diskus® (FP/SX; 250/50 µg), and Advair® Diskus® (FP/SX; 500/50 µg). These are presented as mean ± standard deviation (n=5).

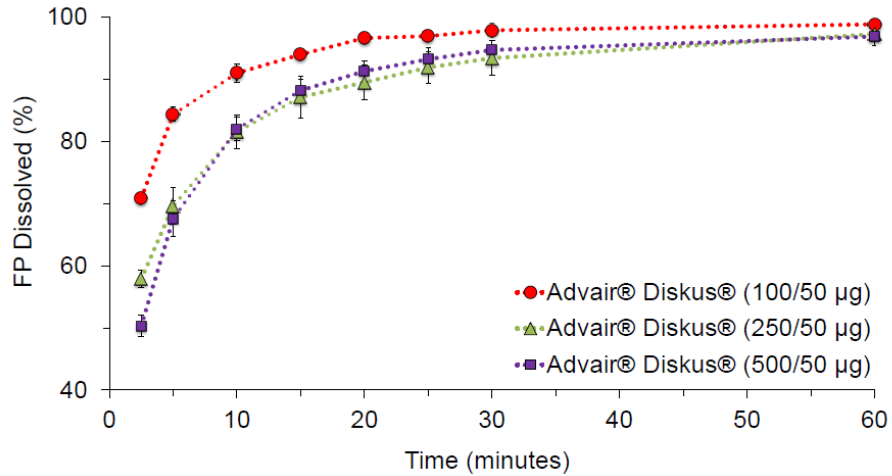

Figure 2: FP dissolved (%) from the ISM of Advair® Diskus® (100/50 µg) as Red Circle, Advair® Diskus® (250/50 µg) as Green Triangle, and Advair® Diskus® (500/50 µg) as Purple Square. These are presented as mean ± standard deviation (n=2).

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

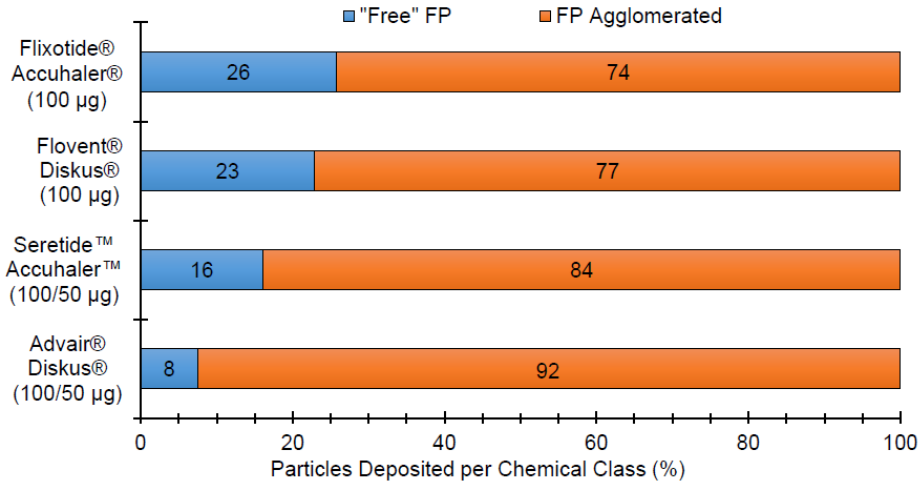

Figure 3: Particles deposited per chemical class (%) of the ISM of Advair® Diskus® (FP/SX; 100/50 µg), Flixotide® Accuhaler® (FP; 100 µg), Flovent® Diskus® (FP; 100 µg), and Seretide® Accuhaler® (FP/SX; 100/50 µg). These are presented as mean ± standard deviation (n=5).

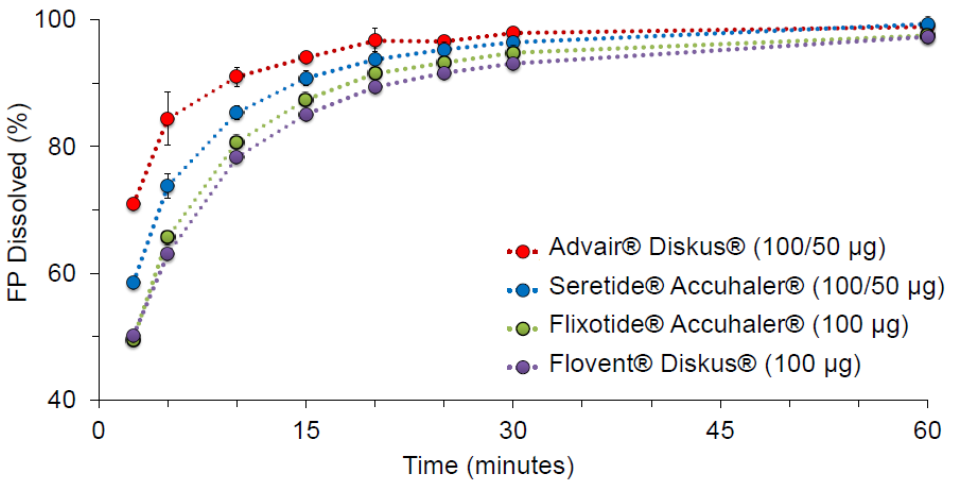

Figure 4: FP dissolved (%) from the ISM of Advair® Diskus® (100/50 µg), Flixotide® Accuhaler® (100 µg), Flovent® Diskus® (100 µg), and Seretide® Accuhaler® (100/50 µg). These are presented as mean ± standard deviation (n=2).

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 in different DPI products

FP microstructure vs. FP dissolved – good correlation

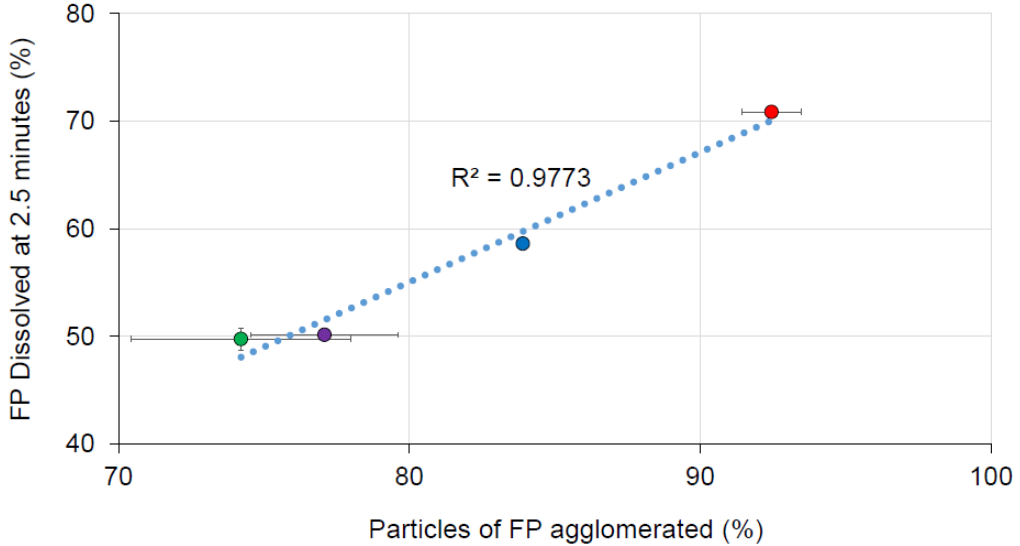

Figure 5: FP dissolved at 2.5 minutes (%) as a function of FP-lactose agglomerates (%) for Advair® Diskus® (100/50 µg, red circle); Flixotide® Accuhaler® (100 µg, green circle); Flovent® Diskus® (100 µg, purple circle); and Seretide® Accuhaler® (100/50 µg, blue circle).

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.

Research Conclusions

- The collected aerosolized fraction of DPI products were analyzed using MDRS and found to have different microstructures, despite formulation similarities.
- This may help to explain differences in dissolution performance between products.
- MDRS has the potential to serve as a new analytical tool to provide information on formulation and/or microstructure differences between DPI products.

Conclusions

- Small changes in excipient concentrations can lead to changes in *in vitro* characteristics
- Modifying excipient grade even while retaining Q1/Q2 can lead to product performance changes, as reflected in both *in vitro* and *in vivo* characterizations
- Similar formulations can have differing microstructural (drug-drug and drug-excipient) interactions, which may lead to differences in performance characteristics and dissolution rates
- Understanding Q1/Q2 excipients for inhalation is critical, but we need to understand the interactions within OINDPs as well
- FDA GDUFA research will continue to explore excipient interactions for their impact on complex generic OINDPs


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