Varying Particle Size and Excipient Levels for Three MDIs: Effects on In-Vitro Performance

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Outline

- Background
- Approach
- A selection of results
- The future

Background (1)

- In 2013 FDA advertised Grant U01FD004943-01 ”Comprehensive Evaluation of Formulation Effects om Metered Dose Inhaler Performance”
- See http://grantome.com/grant/NIH/U01-FD004943-01
- Primary aims:
  - Evaluation of effects of varying co-solvent and surfactant on product in-vitro performance
  - Develop multivariate mathematical model
  - Use model to explore process design space within and outside the Q2 acceptance limits of ±5%

Background (2)

- Cirrus Pharmaceuticals (a Kemwell company) awarded grant
- I was involved to help with general planning, designing experiments and statistical evaluations
- Work started in late 2013 – still ongoing!
- This is a cooperative grant (U01) where a project officer from FDA assigned to the grant was directly involved in the project
  - Regular update/discussion TCs with FDA
  - One F2F meeting at FDA

Approach

- Select a ”model product”
- Determine key performance (DDU, APSD)
- Use ”reversed engineering” to determine model product formulation
  - Primary particle size
  - Concentrations of active(s) and excipients(s)
- Try to make a ”copy product”
  - Also need can, valve and actuator...
- Compare in-vitro performance of copy product to that of model product
- Several attempts needed before ”good enough”
- Not aiming for perfect match, only ”reasonable similar” clinically relevant system (we are *not* making a generic)

Approach (2)

- Develop statistical (factorial) design varying particle size and excipient levels
- Manufacture design batches
- Characterize all batches
  - Confirm manufacture (content of API and excipients)
  - DDU, APSD, laser diffraction
- Evaluate data!
  - Effect of design factors
  - Models
  - Address questions

Model products

- Year 1
  - Proventil 100
  - QVAR 50
- Year 2
  - Dulera 200/5 (on-going)

Results

- Some results already published
  - From Q2 to QbD: The Influence of Formulation Changes on MDI Performance (RDD Asia 2014)
  - Influence of Formulation Variables on the Performance of a Beclomethasone Metered Dose Inhaler (RDD Europe 2015)
  - Systematic Evaluation of Formulation Factors on Aerolization Performance of Metered Dose Inhalers (FDA Science Forum 2015)
- Will only present some snapshots from each study

Proventil/Albuterol

- Proventil formulation (based on three lots):

Albuterol Sulfate	EtOH	Oleic Acid	HFA-134a
0.38%	14.4%	0.03%	85.20%

D10	D50	D90
0.7 μm	1.5 μm	3.4 μm

- Container closure for copy product
  - 17 mL uncoated cans (Presspart)
  - 28 μL valves (Aptar)
  - Actuators from Proventil

Experimental design

- Assess effect of primary particle size (D50), EtOH and oleic acid content
- Wanted levels well apart to ensure effects
- Some guessing involved when selecting factor levels

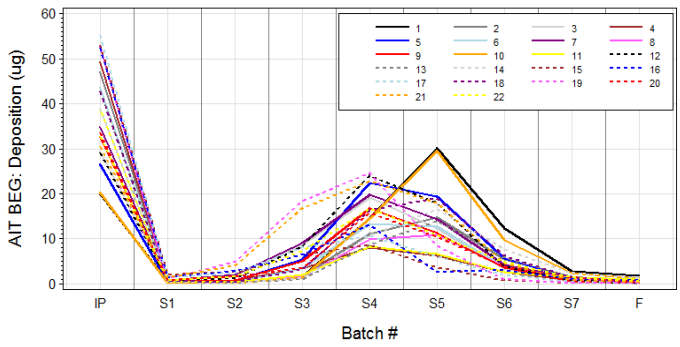
Level	API D50 (μm)	EtOH (% w/w)	Oleic Acid (% w/w)
High	2.5	20	0.10
Medium	1.65	14	0.02
Low	1.4	7	0.005

- 3 x 3 x 3 = 27; too many batches - reduced to 18
- Four extreme ”corner batches” manufactured first to confirm design
- Four more batches later manufactured in add-on design to explore lower EtOH and higher OA

Test plan

- 14±2 days equillibration
- EtOH & OA
- Total can content
- Moisture content
- Volumetric PSD by laser diffraction
- Delivered dose uniformity
  - 1 can/batch: 2B+2M+2E (3 cans for corner batches)
- Aerodynamic particle size distribution (NGI at 30 L/min)
  - 1 can per batch
  - B and E with Alberta Idealized Throat (AIT)
  - B with USP inlet
- One can per batch is based on formal power considerations!

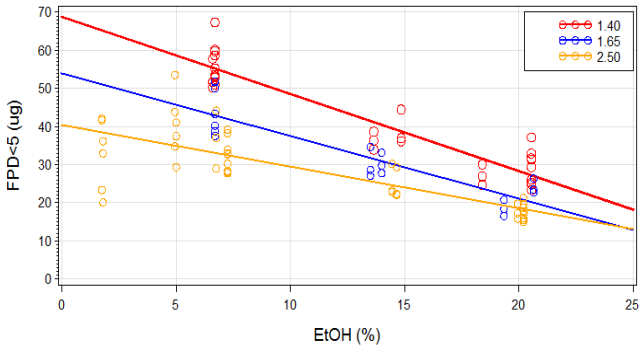
APSD AIT beginning of can



- Graph shows average profiles for all 22 batches
- Clearly something is happening...

Effects on FPD<5

- Both D50 and EtOH (strongly) affect FPD<5
- Decrease in either increases FPD<5
- Substantial effect: 3-fold increase from (2.5, 20) to (1.4, 7)
- Similar findings for USP & AIT, and for BEG and END of can



Model for FPD<5

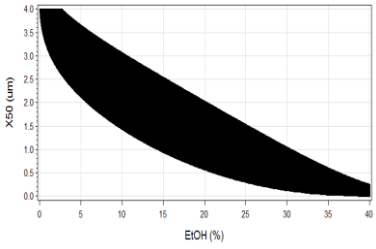
$FPD<5 = d_1 + d_2 \cdot \ln(D50) + d_3 \cdot \ln(EtOH) + d_4 \cdot \ln(D50) \cdot \ln(EtOH)$

Using this

- a ”banana” design space can be determined
- the effect by a ±5% change can be estimated

D50 (µm)	EtOH (%)	FPD<5 (µg)	UL/LL
1.501 – 1.659	14.4	31.34 – 33.65	1.07
1.58	13.68 – 15.12	31.41 – 33.58	1.07
1.501 – 1.659	13.68 – 15.12	30.32 – 34.81	1.15

- 15% change in FPD<5 may be too much?

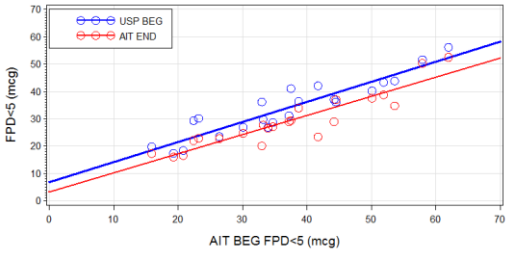


AIT vs. USP?

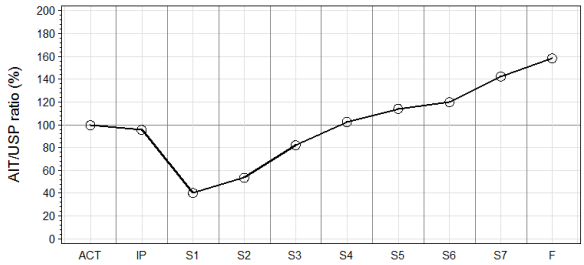
- Is the throat used affecting FPD<5?

End-point	USP BEG	AIT BEG	AIT END
FPD<5	34.0	36.9	29.1
Throat	39.5	38.0	30.2

- Not much: BEG AIT FPD<5 is 9% higher than with USP throat
- Throat depositions are almost identical
- Both throat deposition and FPD<5 less at END of can
- Correlations AIT/USP and BEG/END good



BEG AIT/USP ratio by stage



- APSD clearly depends on throat used
- Less coarse with Alberta throat
- ...and more fines with AIT
- Actuator deposition of course not affected

Albuterol summary

- Beginning DD and NGI TD only affected by EtOH
- Strong effects by D50 and EtOH on FPD<5
- FPD<5 increases with decreasing D50 and EtOH
- 3-fold FPD<5 change between extreme factor combinations
- Modelling indicates changing factor levels within 95-105% of targets result in up to 15% change in FPD<5
- Very similar findings for AIT & USP, BEG & END
  - Reduction of testing for next product
- Laser diffraction data also show strong effect by EtOH
  - No effect by D50 but some by OA

QVAR/BDP

- QVAR formulation (based on three lots):

BDP	EtOH	HFA-134a
0.0820%	8.0%	91.92%

- Solution formulation: primary particle size irrelevant
- Container closure for copy product
  - 17 mL uncoated cans (Presspart)
  - 50 μL valves (Aptar)
  - Actuators from QVAR

Experimental design

- Boring with only one factor (EtOH)
- We added oleic acid despite not present in model product!
- Due to strong EtOH effect for albuterol smaller range explored here
- Due to no effect for oleic acid, very wide range studied for BDP

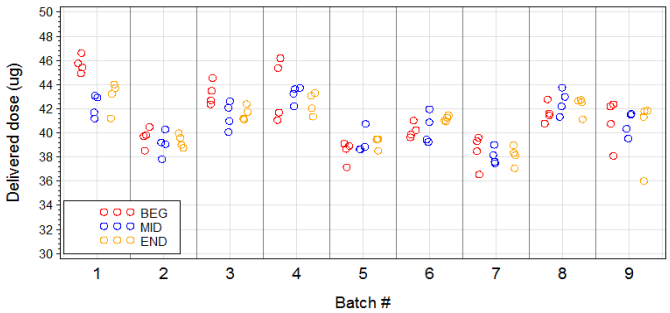
Level	EtOH (% w/w)	Oleic Acid (% w/w)
High	9	2.0
Medium	8	0.5
Low	7	0.0

- 3 x 3 = 9 batches OK

Test plan

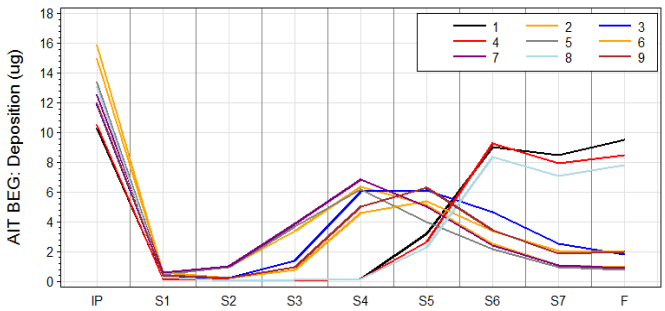
- 7±2 days equillibration
- EtOH & OA
- Total can content
- Moisture content
- Volumetric PSD by laser diffraction
- Delivered dose uniformity
  - 2 cans/batch: 2B+2M+2E
- Aerodynamic particle size distribution (NGI at 30 L/min)
  - 2 cans per batch
  - Alberta throat and USP inlet
  - Beginning of can only

Delivered dose uniformity



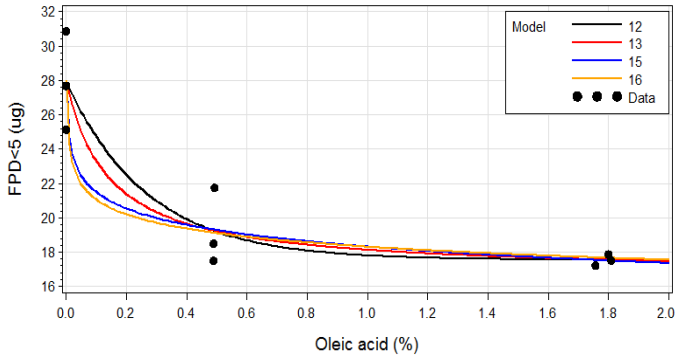
- Very low dose variability; all within 36-47 µg (90-118% LC) RSD ~ 3%
- Some batch differences
- Only oleic acid has statistically significant effect (!)
- Practically relevant (?): DD decreases from 43 to 38 µg (12%) when OA increases from 0 to 2%

APSD AIT beginning of can



- Graph shows profiles for all 9 batches
- Clearly something is happening...
- Three groups of profiles, defined by OA level
- Most fines with no oleic acid (as for model product)

FPD<5 vs. oleic acid



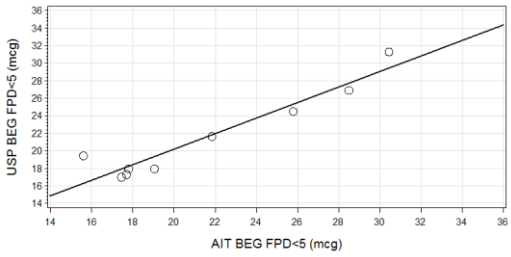
- Effect clearly nonlinear
- FPD<5 = $e_1 + e_2 \cdot \ln(OA)$ reasonable & simple model (blue)
- Hard to identify best without data between 0 and 0.5%

BDP: AIT vs. USP?

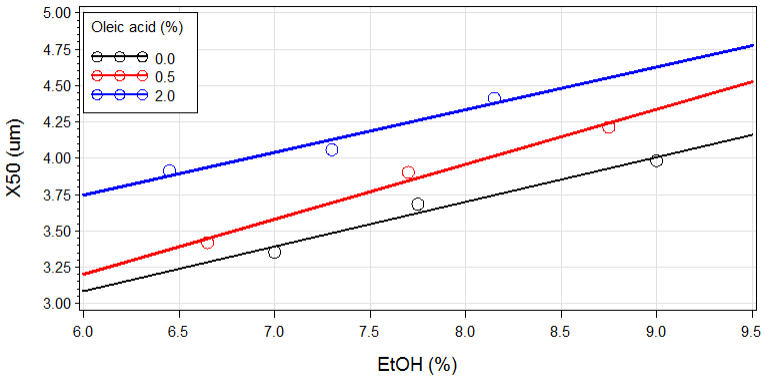
- Is the throat used affecting FPD<5?

End-point	USP BEG	AIT BEG
FPD<5	21.6	21.6
Throat	12.7	12.7

- For BDP both FPD<5 and IP deposition are identical regardless of throat used!
- Again correlation AIT/USP is good



Laser diffraction



- Both EtOH and OA have significant effect on X50
- About 0.35 µm increase in X50 when either increases 1%

BDP summary

- DD marginally affected by oleic acid
- No effect by EtOH (7-9% too narrow range?) on FPD<5
- Strong non-linear effect by oleic acid on FPD<5
- Results consistent between AIT or USP throats
- X50 by laser diffraction affected by both EtOH and OA
- Good model can be found for X50
  - ±5% change in EtOH corresponds to ±3.5% change in X50
  - If EtOH = 8%, OA ≤ 3% ensures X50 within 3.0-5.0 µm

Dulera/Mometasone

- Wanted to do Asmanex but not launched
- Decided to do Dulera without FFD
- Dulera formulation (based on three lots):

Mometasone fuorate	Formoterol fumarate	EtOH	Oleic Acid	HFA-227
0.3231%	0.0024%	1.81%	0.0049%	97.8596%

D10	D50	D90
0.8 μm	1.7 μm	3.6 μm

Experimental design

- Return to wide range for EtOH
- More levels for better models if non-linear

Batch	D50 (μm)	EtOH (%)	Oleic Acid (%)	Manufacturing order
1	1.1	0.45	0.001	1
2	2.0	0.45	0.025	4
3	2.0	0.90	0.001	3
4	1.1	0.90	0.025	7
5	2.0	1.80	0.001	6
6	1.1	1.80	0.025	5
7	1.1	3.60	0.001	8
8	2.0	3.60	0.025	2

- 2 x 4 x 2 = 16 batches
- Simple to reduce to 8

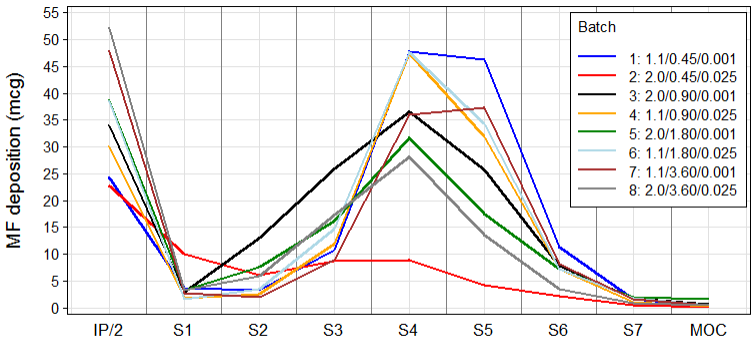
Slightly revised goals

- Still want to understand how excipients affect in-vitro performance
- Still want to develop models linking key performance parameters to composition
- Want to use models to ”design” two different formulations with same FPD<5 (for example)
- Then we should manufacture these...
- ...and compare them in a PK study
- Will same in-vitro performance imply same PK, despite differences in formulations?

Other changes

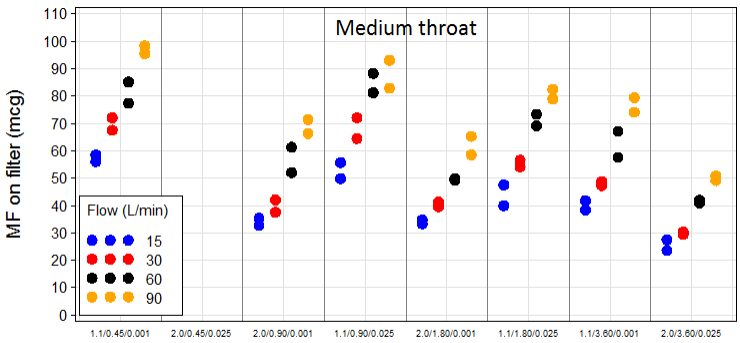
- Grant transfered to University of Florida
  - Cirrus still doing development, manufacturing & testing
- Günther Hochhaus at Department of Pharmaceutics
  - New grant: 5U01FD04943-05
  - UF will do dissolution for MF batches
  - Managing PK planning and execution
- Stability testing (1 month 40/75)
  - Due to PK
- Emmace Consulting joined to contribute with ”lung dose” testing
  - Small, medium & large throat
  - 15, 30, 60 & 90 L/min
  - Dose on filter after throat

Initial APSD testing



- Batch 2 (red) very odd. All OA not soluble in 0.45% EtOH?
- Low D50 gives as expected more fines
- More EtOH increases throat deposition
- Substantial batch differences also without #2: 3-fold difference for S5

Lung dose with medium throat



- Batches are different
  - Only D50 and EtOH have significant effect on lung dose
- Strong flow rate effect
- More drug escapes throat at higher flow rate

Overall (tentative) summary

- (Based on albuterol and BDP studies)
- Primary particle size influence FPD<5 but not DD
- Small/no effect by EtOH or OA on DD
- More EtOH reduces FPD<5
- OA: only presence, not amount, affects FPD<5
- Reasonable models to predict in-vitro performance can be developed to support QbD
- Changing excipients within ±5% may result in up to 15% change of FPD<5

Next steps

- Complete MF MDIs 1 month 40/75 data collection
- Analyse all data
- Develop models
- Determine and select formulations for candidate PK batches
- Manufacture pilot PK batches using candidate formulations
- Update models and finalize selection of formulations
- Manufacture PK batches and run the study!
- What will we find??? Will different formulations with same in-vitro performance differ in PK???

Acknowledgements

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- Study team:
  - Diane Centeno-Deshields, Denise Conti, Bhawana Saluja, (Sau Lee) (OGD, CDER, FDA)
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  - Dennis Sandell (S5 Consulting)
  - Mårten Svensson (Emmace Consulting)
  - Günther Hochhaus (University of Florida)