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Technology selection for capsule-based inhalation product development

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Agenda

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- Design, Develop, Manufacture
- Why a Capsule-based Dry Powder Inhaler approach
  - The DPI “magic triangle”
- Options for particle engineering
  - Closer look: Spray drying
  - Closer look: Micronization
- Optimizing capsule critical parameters
- Speed-to-patient

Formulation and process development

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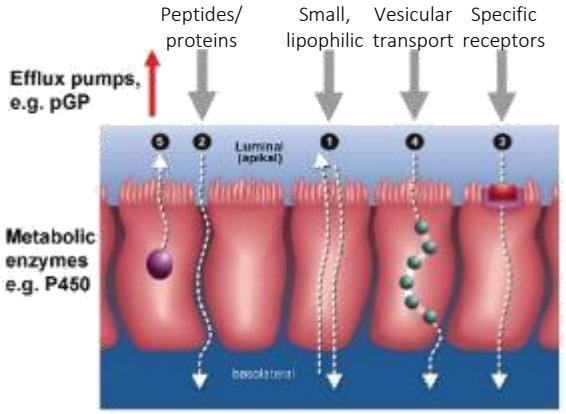
Typical workflow

- Understand your target product profile

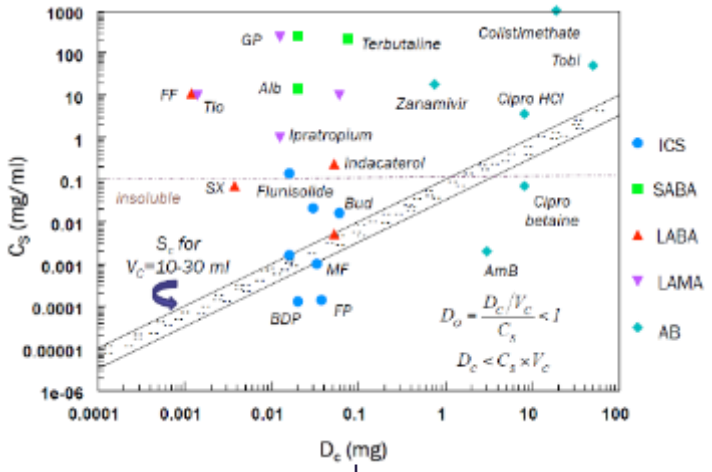
Design

Define product concept

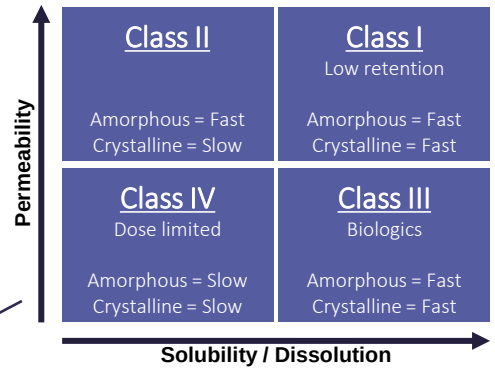
Mechanism of action



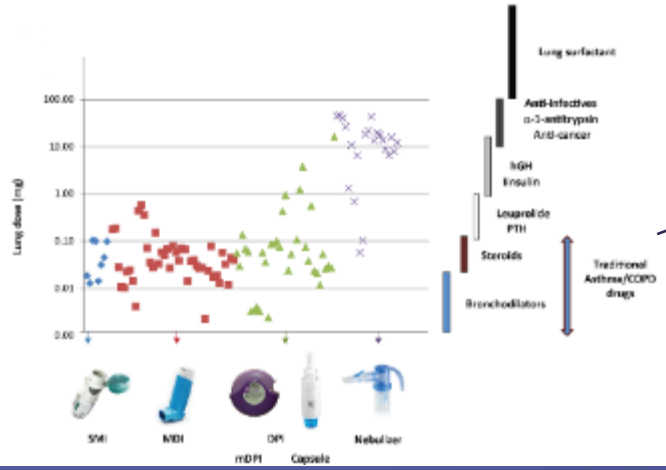
Solubility/Dose in Lung Fluid



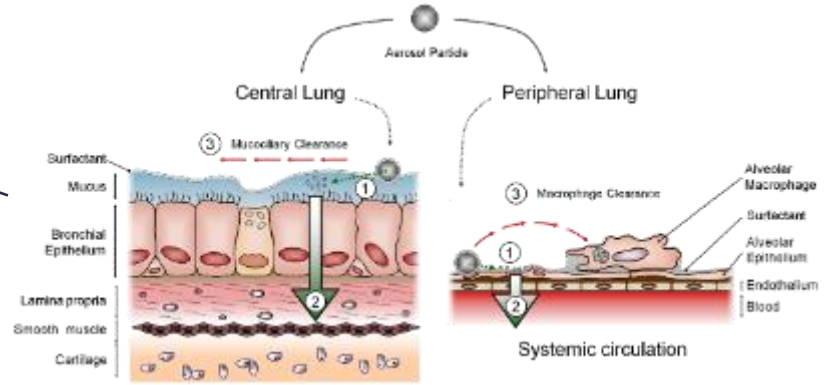
Permeability/Dissolution/Form



Dose/Technology



Location for deposition



Product Design/Profile

Figures adapted from:
Hastedt *et al*. *AAPS Open* (2016) 2:1
DOI 10.1186/s41120-015-0002-x

Formulation and process development

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Typical workflow

- Understand your target product profile
- Combination product – Not just the formulation, but interactions with the device
- Strategies to make the API aerosolizable and evaluation:
  - Nebulization for initial FIH studies (then reformulate to DPI)
  - Particle engineering with off-the-shelf capsule-based inhalers

Benefits of Capsule-based Dry Powder Inhalers

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Capsule-based DPI

Dry Powder Inhalation Technology

- **Patient compliance**: ease of use, commitment, self assessment of full medication dose delivered
- **Cost effective solution**, easy to manufacture (standard filling equipment)
- Compatible with **standard carrier based formulations and new engineered particles** (Jetmill, Spray-Dried), ideal platform for **combination drugs**
- Wide offer of **off-the-shelf devices**
- **Eco friendly solution**: re-usable device, biodegradable capsule

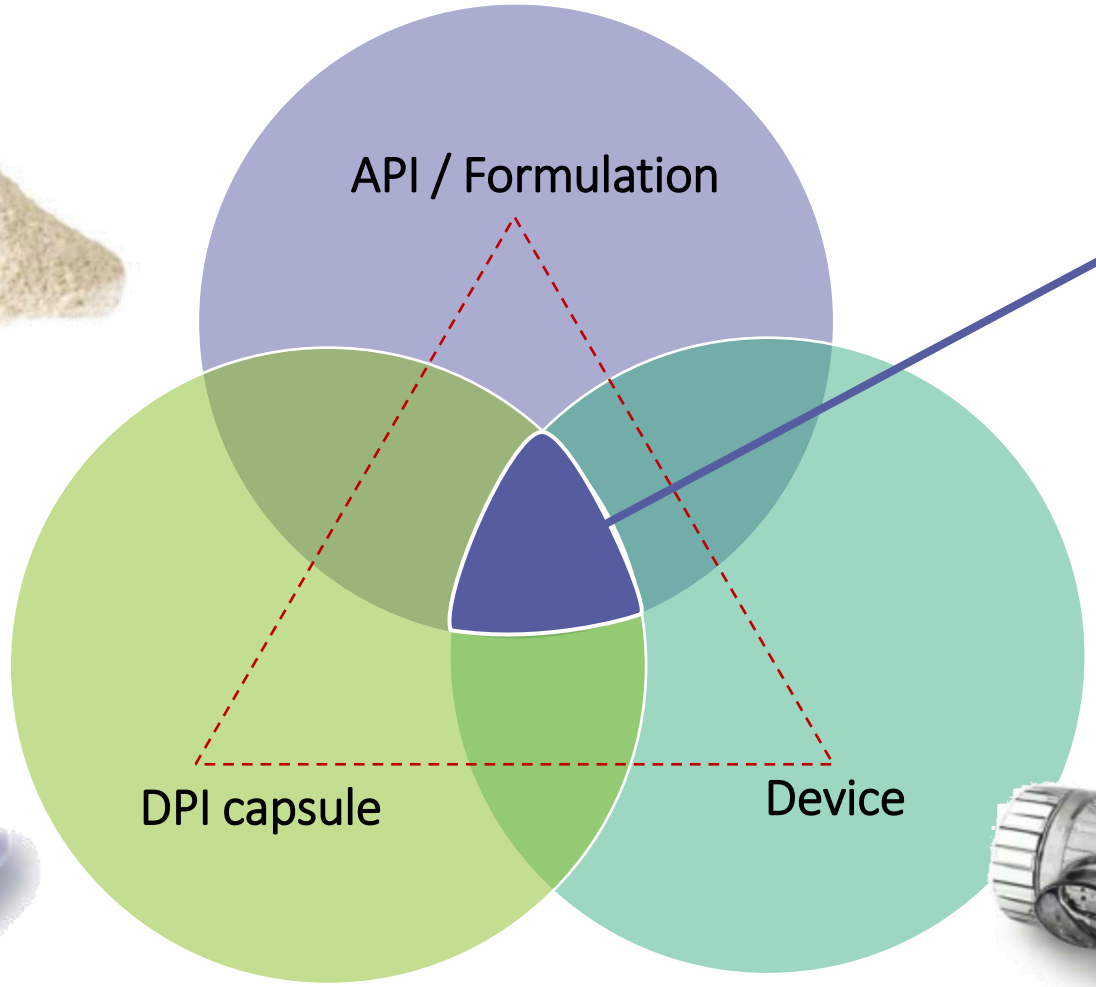
- **No need** for coordinated device **actuation and patient inhalation**
- **No propellants**
- Potential **drug stability** advantages
- **High dose** carrying capacity
- **Different level of sophistication** available
- Device **flow-rate/inhalation requirements can be adapted** to targeted patient population
- Open the path for **connected device and improved patient compliance**

The DPI "magic triangle"

Optimizing performance of inhalation capsule based products

All components contribute to product performance

Critical parameters:
- Particle size distribution and morphology
- Chemical stability
- Hygroscopicity
- Ability to deagglomerate



Optimal performance:
- Emitted dose
- Aerodynamic particle size distribution (APSD)
- Fine Particle Mass (FPM)

Critical parameters:
- Dimensions /weight
- Polymer
- Water content
- Powder retention
- Mechanical Resistance

Critical parameters:
- Opening principle
- Resistance
- Patient Handling
- Powder retention

Formulation and process development

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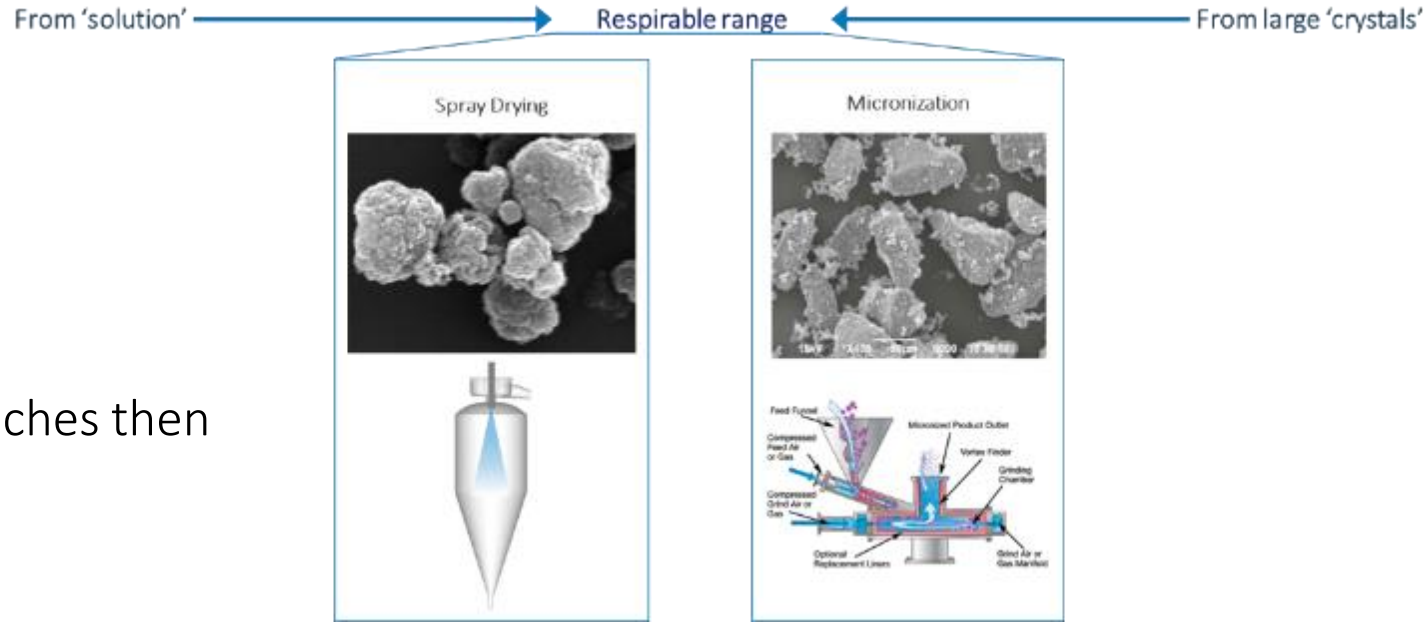
Typical workflow

- Understand your target product profile
- Combination product – Not just the formulation, but interactions with the device
- Strategies to make the API aerosolizable and evaluation:
  - Nebulization for initial FIH studies (then reformulate to DPI)
  - Particle engineering with off-the-shelf capsule-based inhalers
- What to look for in technology selection?
  - Speed to study
  - Scalable process for clinical trials / future commercial manufacturing

Particle engineering options

Bottom-up or top-down?

- Bottom-up or top-down approach?
  - No one-size-fits-all approach
- For new compounds, screen multiple approaches then decide best path forward
  - One approach may not be better



Formulation and process development

Typical workflow

- Device strategy – same mechanism (e.g. capsule based) or another type?

- Fine-tune process and/or composition with interactions of the entire system (capsule/device)

Develop

Particle engineering / formulation

- Some APIs have **higher therapeutic dose** requirements than small molecules
  - Typically biologics
  - Minimize excipient use – sufficient to stabilize formulation
  - Focus on morphology and physical state

- New APIs are designed to be more targeted – **lower therapeutic dose** required
  - Engineered particles to contain API with functional excipients
  - Micronization and blending with carriers
    - Use of additional excipients may improve performance

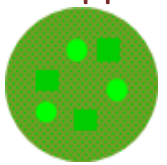
- Can a formulation be over engineered?

Neat API

Amorphous API/Excipient

Crystalline API/Excipient

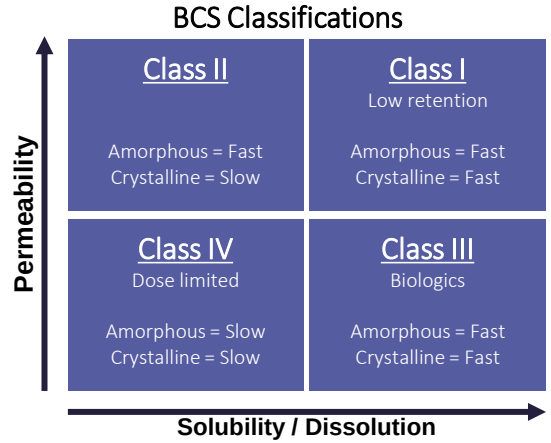
Mixed Approach



Closer look: Spray drying

How to utilize process to alter physical form or morphology

- Making amorphous form to modify PK profile / bioavailability
  - Potentially may push product profile outside the therapeutic window
  - Potentially may be unstable as it want to recrystallize
  - Potentially may have poor aerosolization properties with cohesive powders
- How to control the physical form?
- How does excipients play into the overall product profile?
- Can the API be dissolved with traditional solvents?



Possible approaches with spray drying

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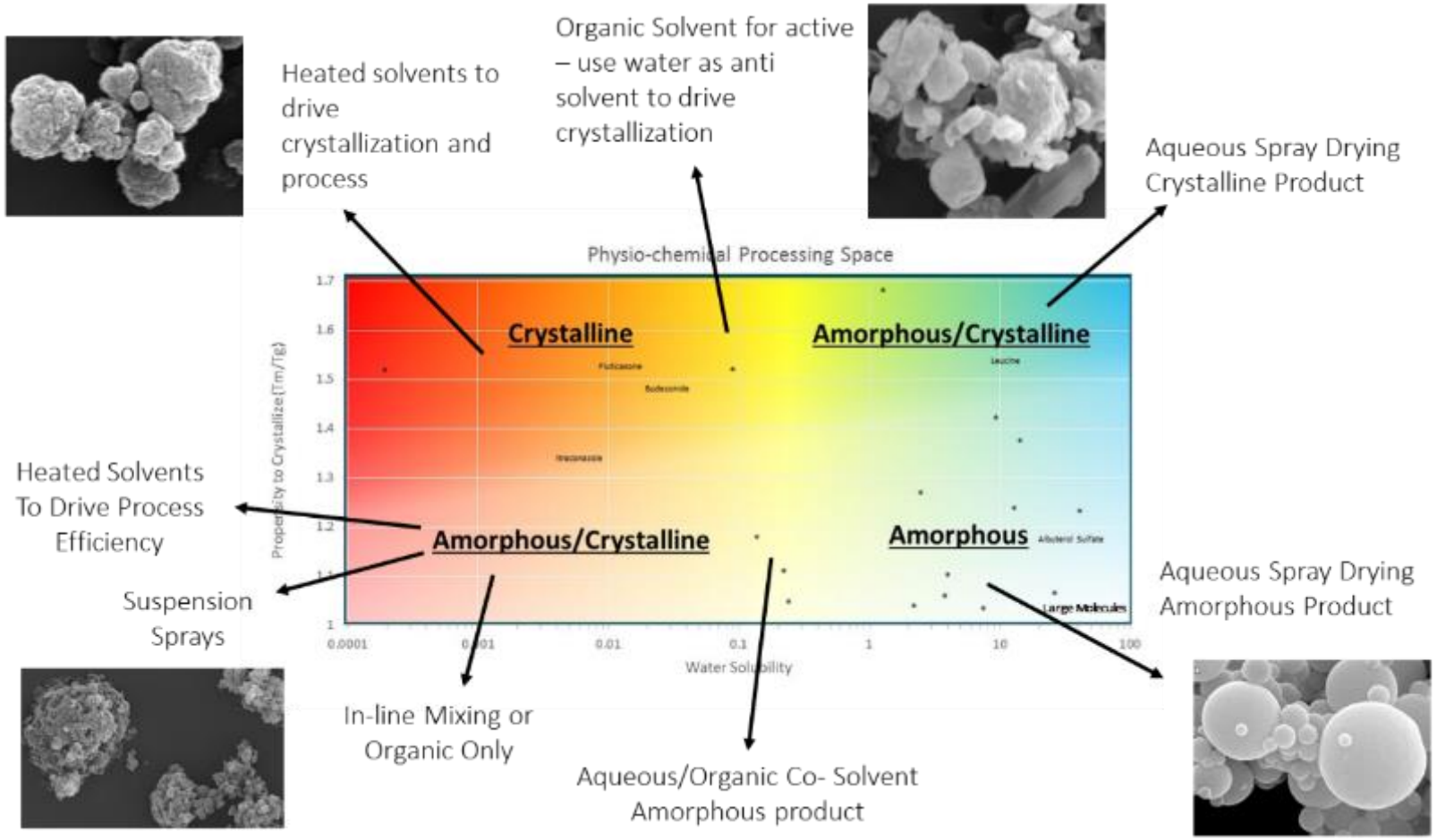
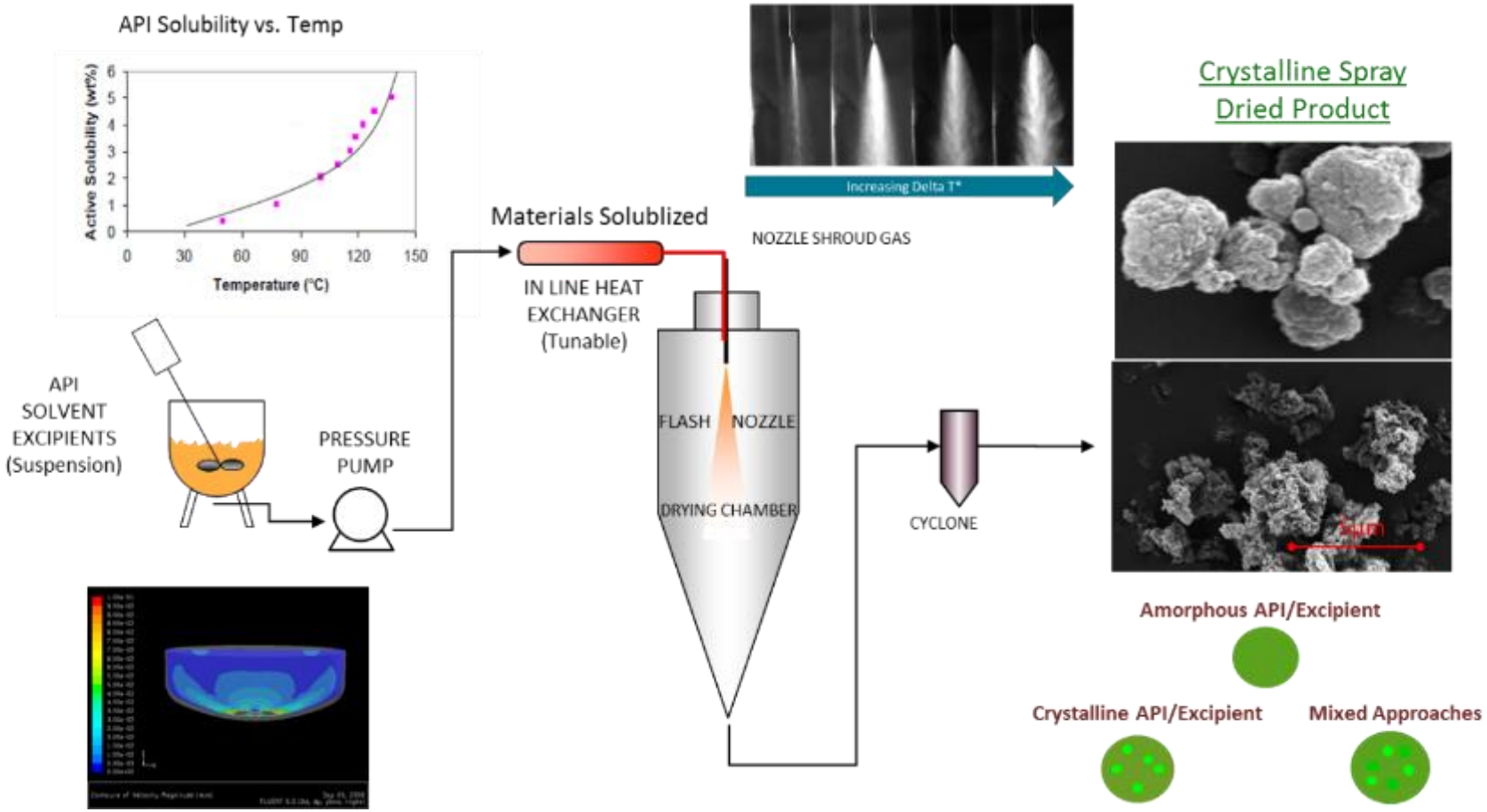
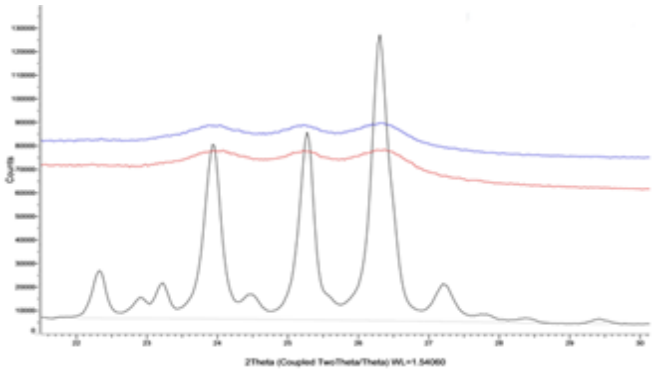
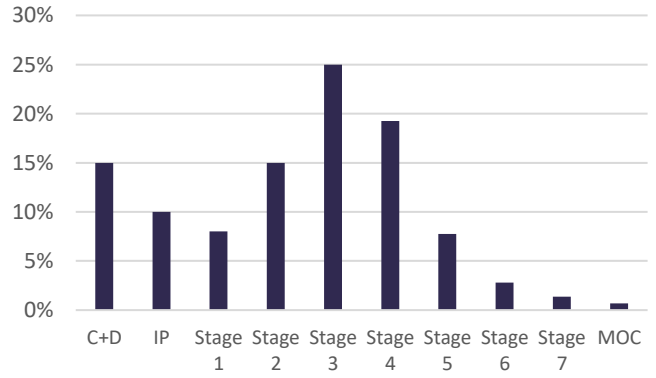


Flash solubilization spray drying





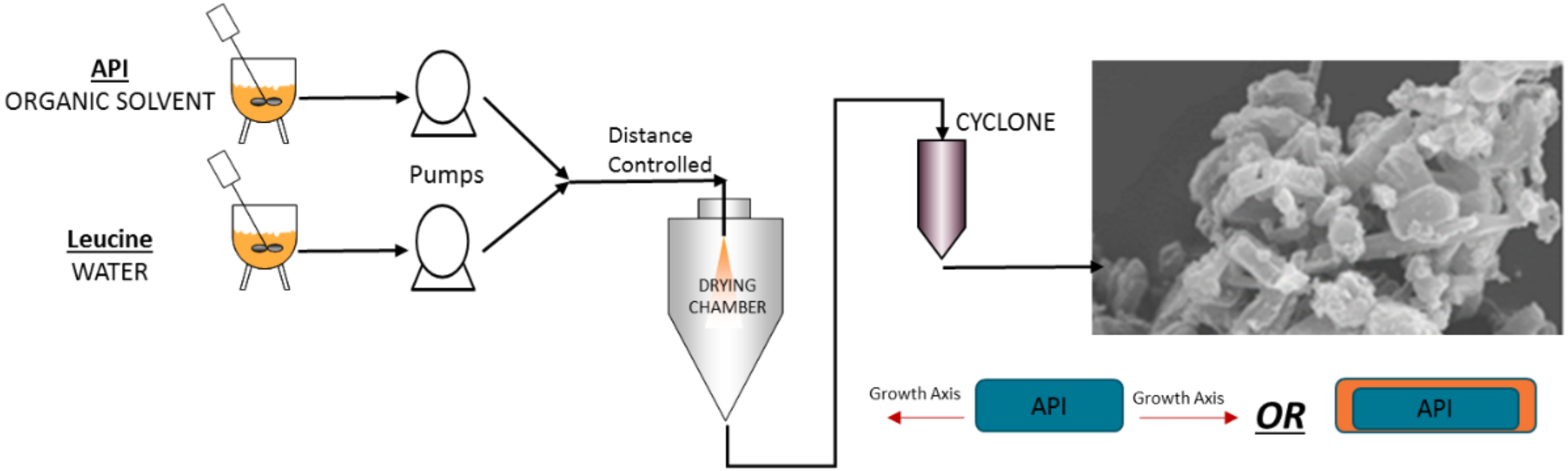


EF (C+D)	MMAD	GSD	FPF <5 µm
85.0	3.5	1.7	65.0%

Patents: US 20120015924A1, EP2411137B1, EP3130396A1

Precipitation spray drying

- Enabling process which aids stabilization by using a preferred solvent
- Generated a crystalline product with excipients by using anti-solvents
- High Dose



Spray drying vs. Micronization

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- Technology selection may not be as clear-cut
  - Depending on API properties

Example:

- API: Peptide
- Spray dry with, and without excipient
- Short-term feasibility stability: No change between formulations, all stable
- Micronization feasibility – able to micronize and aerosolize
  - Also stable
- Continuing with micronization path for this compound

Closer look: Micronization

Equipment differences (all achieve collisions between particles)

Fluidized bed opposed jet mill

- The particles are accelerated towards the center, impacting each other

Loop mill

- The fine fractions are exhausted from the top

Spiral jet mill

- The fine fractions are exhausted from the center

Different mill types

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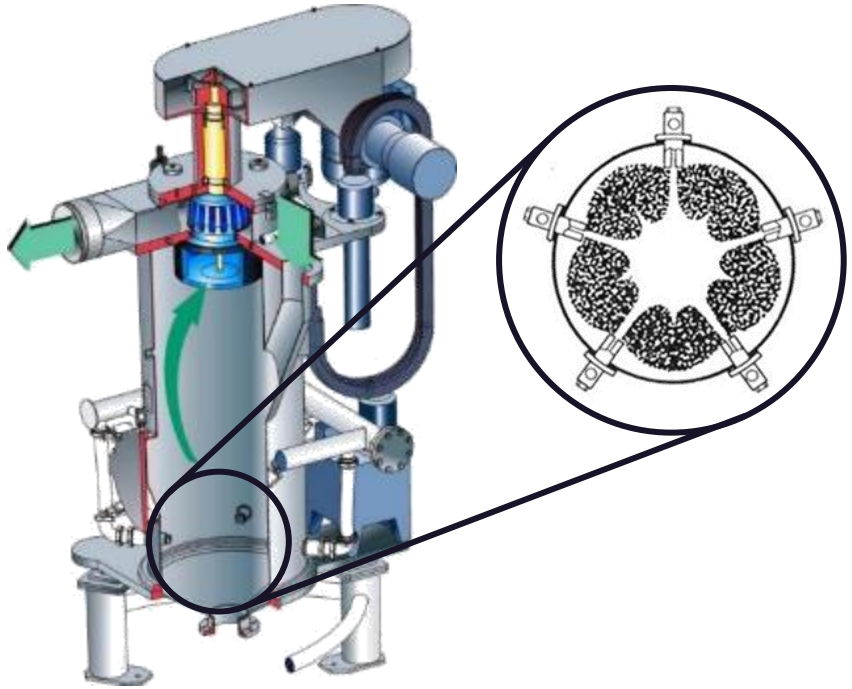
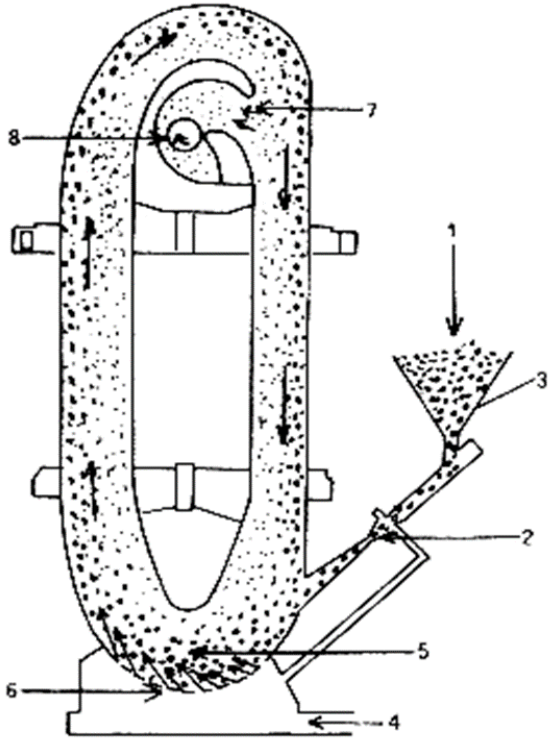
Fluidized bed opposite jet mill



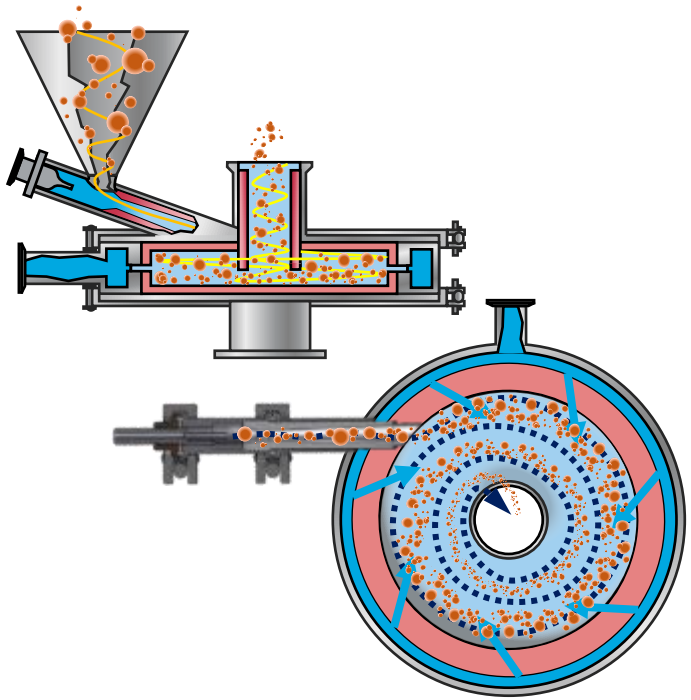
- Dynamic classifier
- Sharp cut of the coarse fraction of the PSD
- Applicable for coarse incoming material

Loop Mill



- Static classifier
- No mechanical moving parts
- High throughputs

Spiral jet mill



- Static classifier
- No mechanical moving parts
- High throughputs

How to select the proper size reduction technology

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Starting Material

Target Final Size *Range*

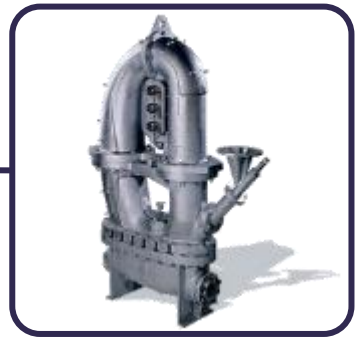
Incoming Material Size *Range*

2 µm – 10 µm

20 µm – 80 µm

80 µm – 500 µm

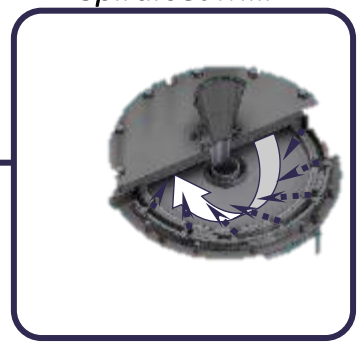
Loop Mill



Pin/Hammer Mills

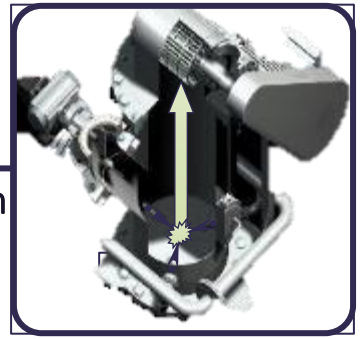
5 µm – 500 µm

Spiral Jet Mill



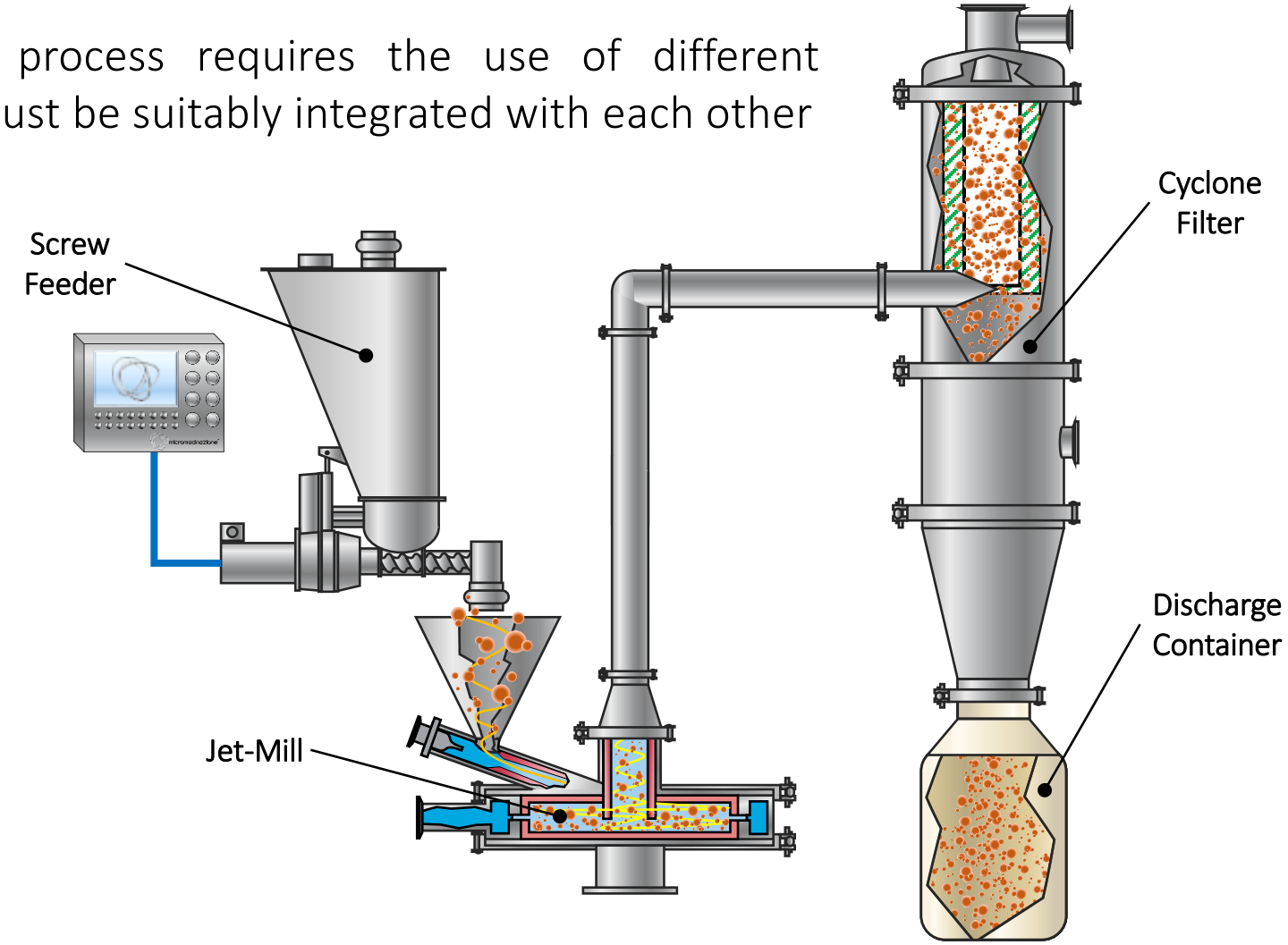
5 µm – 1.5 mm

Opposite Jet Mill



Micronization equipment

The micronization process requires the use of different components that must be suitably integrated with each other



Equipment choice

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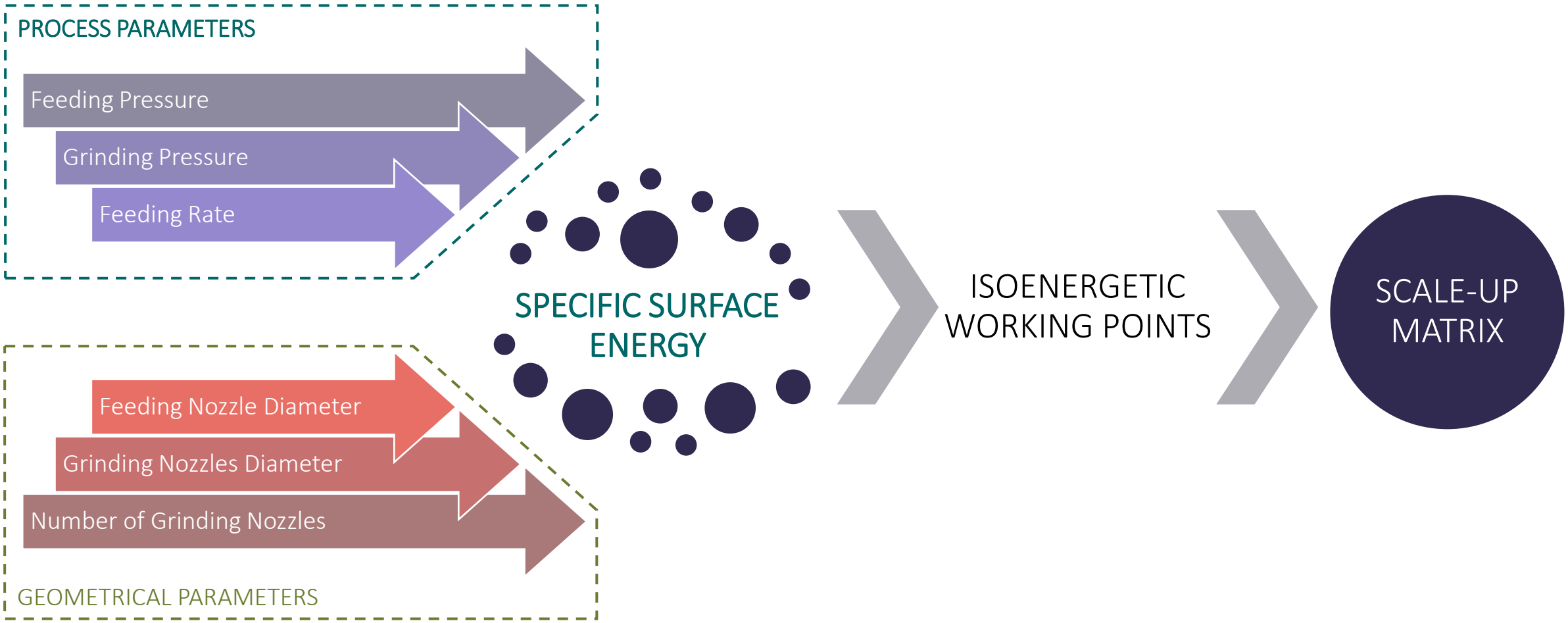
Material Characteristics
- Hardness
- Hygroscopic
- Particle size
- Melting point
- Thermolabile
- Flammable
- Fibrous
- Elastic

Accessories
- Powder collector
- Mechanical feeding
- Temperature control: cooling jacket, liquid N_2, air, dry ice
- Inert atmosphere: CO_2, N_2

Type of operation
- Desired scale
- Cleaning
- Sterility
- Versatility
- Capacity
- Dry, wet
- Feeding speed
- Costs
- Batch or continuous
- Space occupied

Safety
- Risk of explosion
- Irritability of the material
- Toxicity of the material
- Safety features of the equipment

Micronization Scale-up model



Product and Process

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PRODUCT

Product Properties = F(particles properties, formulation)

- **Particles Properties**: Particle size, morphology, superficial characteristics

PROCESS

Particles Properties = F(process parameter, raw/intermediate material properties)

- **Process Parameters**: Type of single step operation, operating parameters

Particles Properties - Potential Impact

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Product Properties = *F(particles properties, formulation)*

	PROCESSING BEHAVIOR				PRODUCT QUALITY FACTORS		
PROPERTY	**FLOW**	**BLENDING**	**WETTING**	**DRYING**	**MECHANICAL**	**DISSOLUTION**	**STABILITY**
Particle Size	X	X	X	X	X	X	X
Surface Area	X	X	X	X	X	X	X
Particle Shape	X						
Surface Energy	X	X	X				
Bulk Density	X		X		X		
Pore Size			X	X		X	
Internal Friction	X				X		
Wall Friction	X				X		
Hygroscopicity	X			X			X

Hlinak et al, Journal of Pharmaceutical Innovation, 1 (2006)

Co-micronization

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PURPOSE:

To achieve in a single step the mix & mill process co-feeding and concomitantly micronizing an API and an Excipient. This approach can support the mixing of low dosed API and can be used to migrate from a batch process to a continuous process.

Development Steps:

- Jet milling of the physical mixture and PSD controls
- Co-Micronization of the separate powders
- Trials execution according to DoE protocol

Co-micronization

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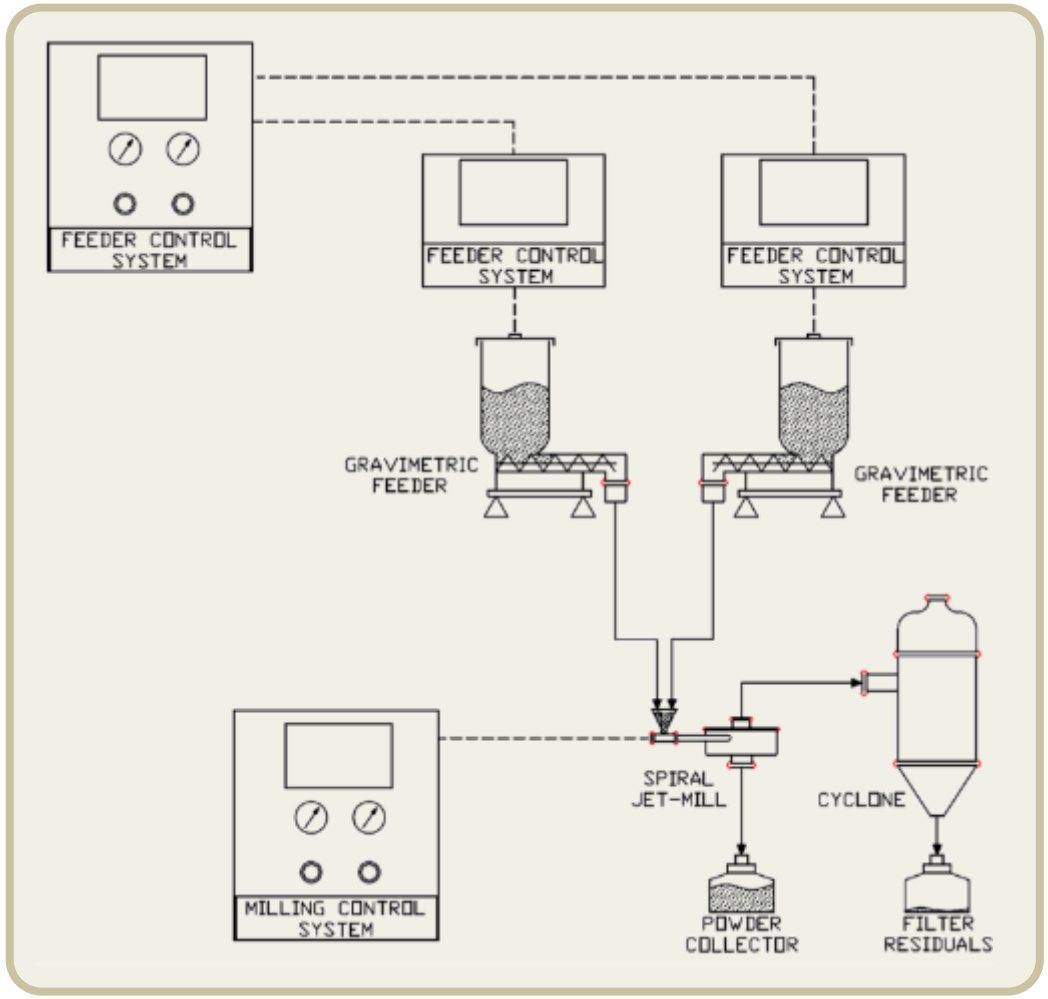
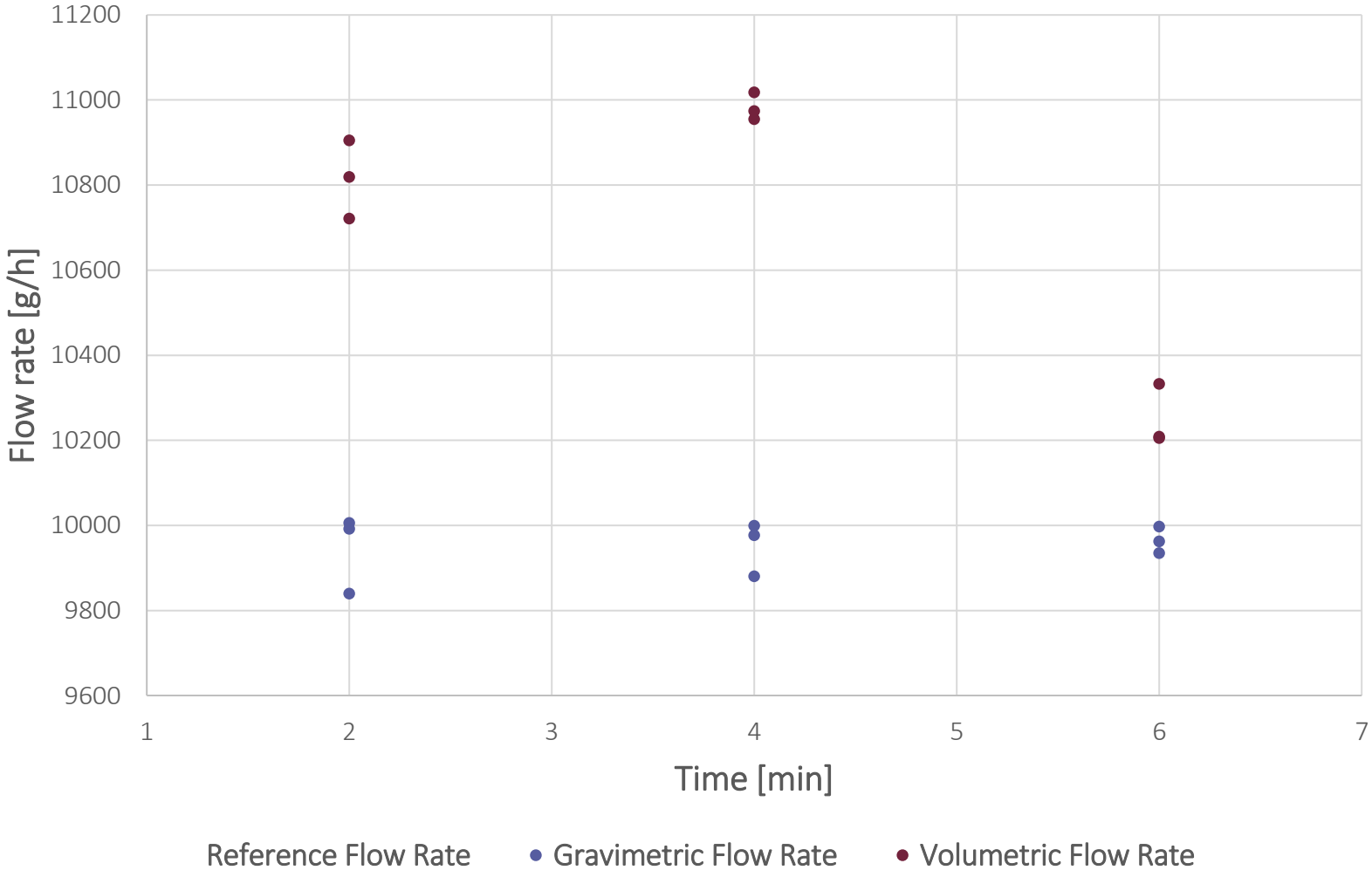
CO-MICRONIZATION PROCESS DIAGRAM



MACHINE SET-UP

Co-micronization

Gravimetric vs Volumetric Feeders



Co-micronization

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SCREENING DoE Definition:

- Two level full factorial plan:
  - 2 controlled factors (feeding rate, feeding pressure);
  - 1 derived factor (milling pressure);
  - 4 responses (according to customer request).
  - 7 trials (3 central points)

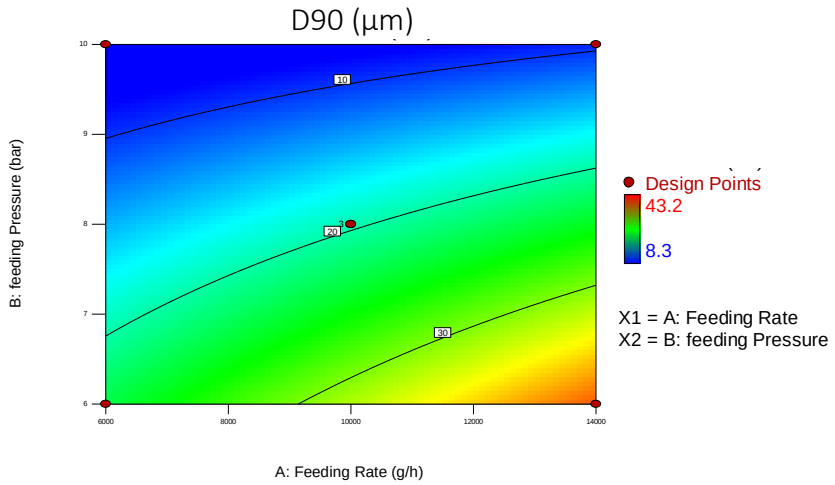
RESPONSE	NAME	M.U.	TARGET	CONSTRAINT LIMIT	
1	API Assay	[%]	2.48	2.33	2.63
2	Assay RSD	[%]	0	-6.00	6.00
3	D90	[µm]	-	0	63
4	D95	[µm]	-	0	100

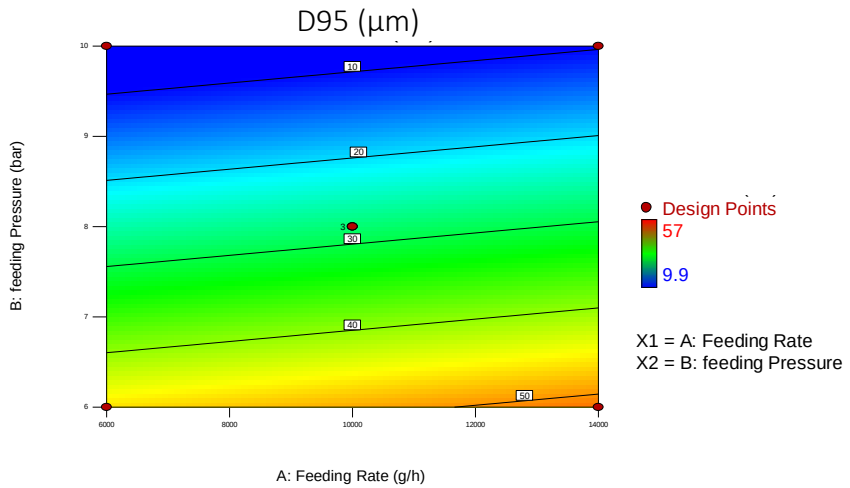
SCREENING DESIGN RESULTS

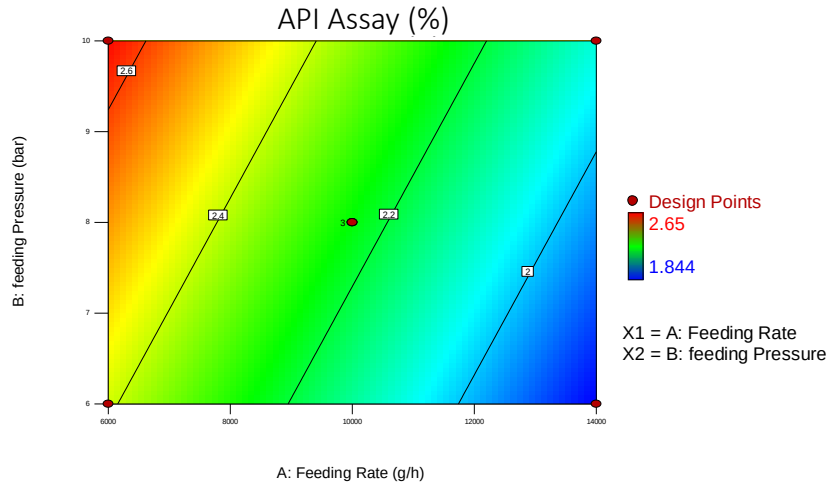
Run	Trial Name	Space Type	*Milling pressure [bar]	A: Feeding Rate [g/h]	B: Feeding Pressure [bar]	API Assay [%]	RSD [%]	D90 [µm]	D95 [µm]
1	0315.022-11	Factorial	2	14000	6	1.84	7.25	43.2	57.0
2	0315.022-12	Center	4	10000	8	2.25	3.15	15.2	19.3
3	0315.022-13	Factorial	6	6000	10	2.65	3.38	8.3	9.9
4	0315.022-14	Center	4	10000	8	2.37	1.93	15.8	21.1
5	0315.022-15	Factorial	6	14000	10	2.10	2.41	12.5	15.6
6	0315.022-16	Center	4	10000	8	2.03	0.64	15.5	20.6
7	0315.022-17	Factorial	2	6000	6	2.44	6.31	26.5	52.3

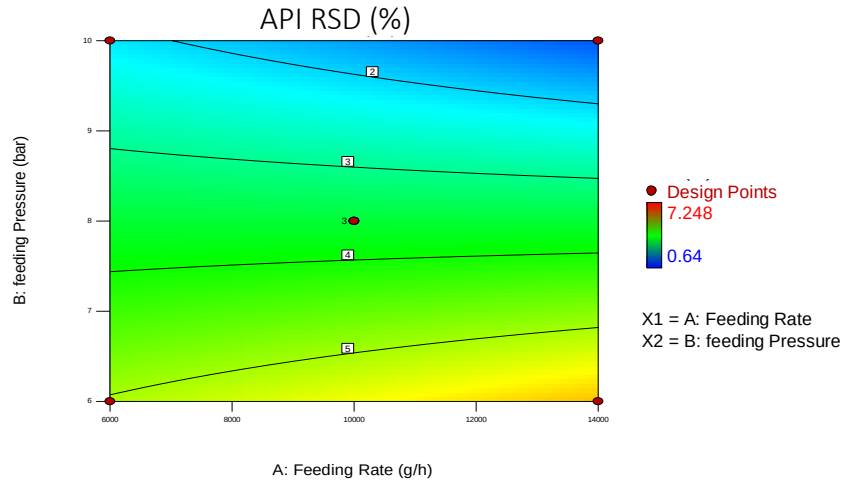
* The milling pressure was kept linked to the feeding pressure by a Δp of 4 bar

Co-micronization



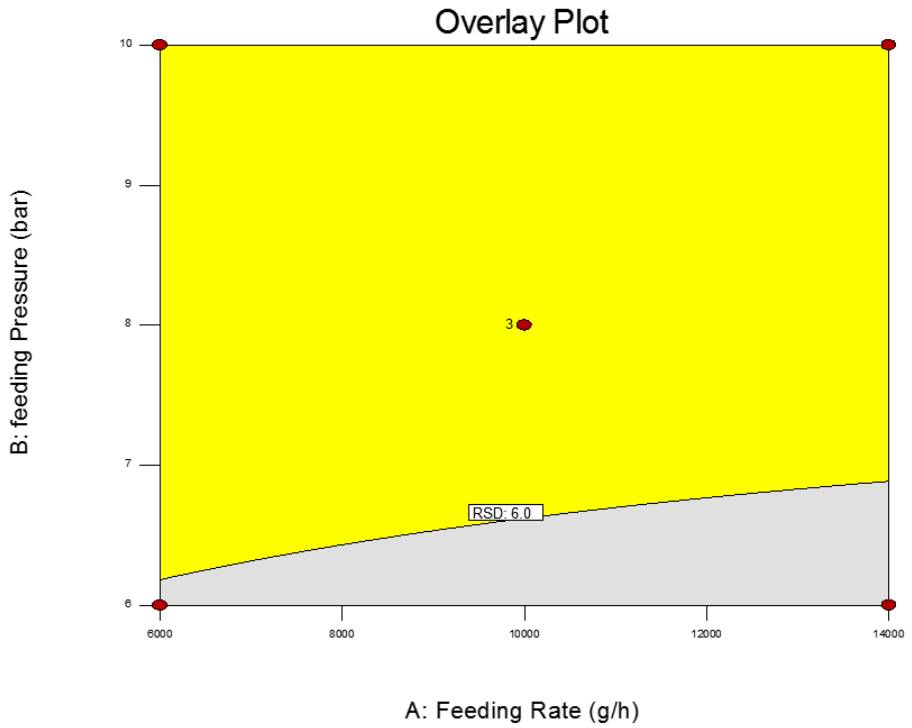






Co-micronization

DESIGN SPACE



A co-micronization process was successfully applied to replace a mix and mill process

Formulation and process development

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Typical workflow

- Device strategy – same mechanism (e.g. capsule based) or another type?

- Fine-tune process and/or composition with interactions of the entire system (capsule/device)
  - How does the capsule interact with the device and formulation?

The Capsule – Formulation Interaction

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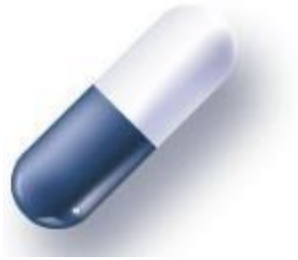
- Interactive powder mixture (API, powder blend, porous particles)
- Powder container/primary packaging (capsule, blister, reservoir)



Differences in capsules

Microbiological purity

- The only pharmacopoeia difference between capsules for oral use and inhalation use are the microbiological requirements
  - European Pharmacopeia 7.0, 5.1.4
  - USP <61>, <62>, <1111>

Test	Criteria
Total Aerobic Microbial Count	10^2 CFU/g
Total Yeast and Mold Count	10^1 CFU/g
Staphylococcus aureus	Absent in 1 g
Pseudomonas aeruginosa	Absent in 1 g
Bile-tolerant gram-negative bacteria	Absent in 1 g

Capsule compositions

Different options to choose from

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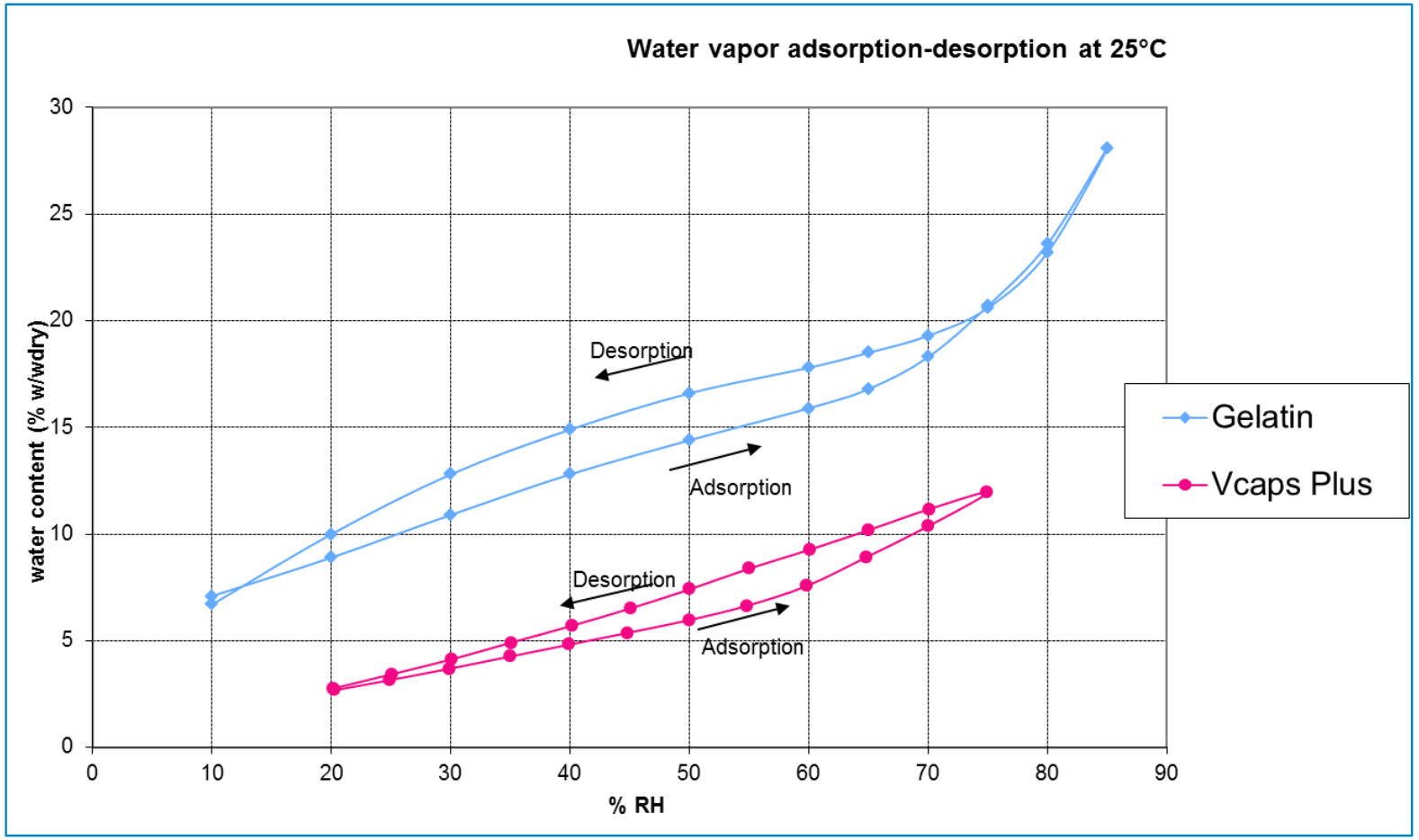
The following types of capsules are used for DPI:

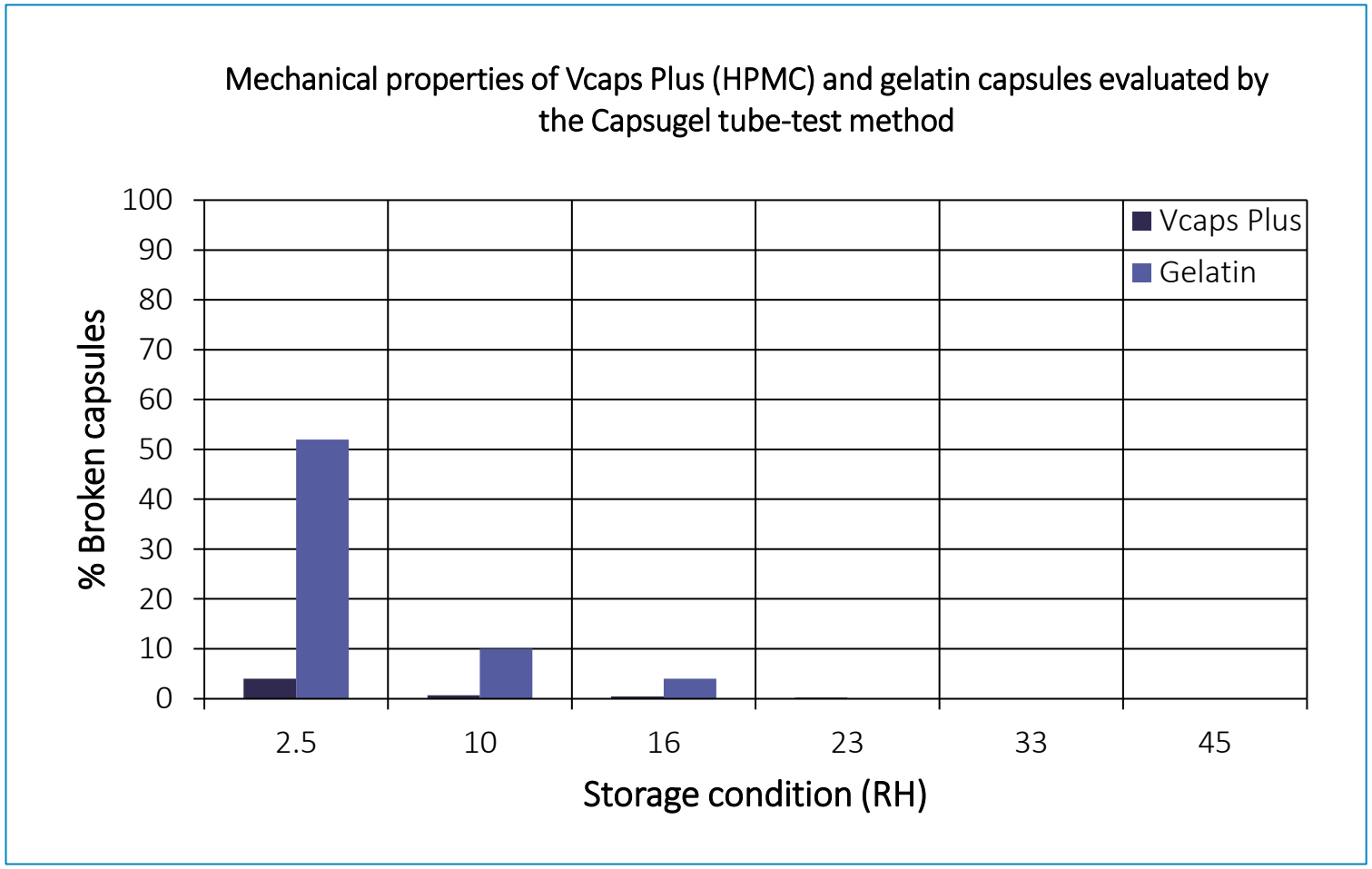
- Gelatin capsules
- Gelatin/PEG capsules
- HPMC + gelling agent
- HPMC only

DPI capsules: sorption isotherms

A significantly lower water content for HPMC-based capsules



DPI capsules: mechanical resistance



DPI capsule specification

Lubricant content

Capsugel Library

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Technical Reference File – Addendum
Dry Powder Inhaler Capsules

1st Edition

Specific Specifications *
Dry Powder Inhaler Capsules

Test	Specification	Method reference	
		Coni-Snap® Hard Gelatin Capsules	Vcaps® HPMC Capsules
Lubricant content	Less than 500 ppm	CP019b	VCP016b
Total viable aerobic count			
Total Aerobic Microbial Count	Less than 100 cfu per gram	CP031	VCP031
Total Yeasts/Moulds Count	Less than 10 cfu per gram	CP032	VCP035
Specified micro-organisms			
Bile-Tolerant Gram-Negative	Absence in 1 gram	CP048	VCP048

*: These DPI capsule specifications apply in addition to the specifications and information available in the Technical Reference File of Capsugel's Coni-Snap® Hard Gelatin Capsules and Vcaps® HPMC Capsules, as applicable.

DPI capsule powder retention

Reduced lubricant content impacts powder retention (NMT 500 ppm)

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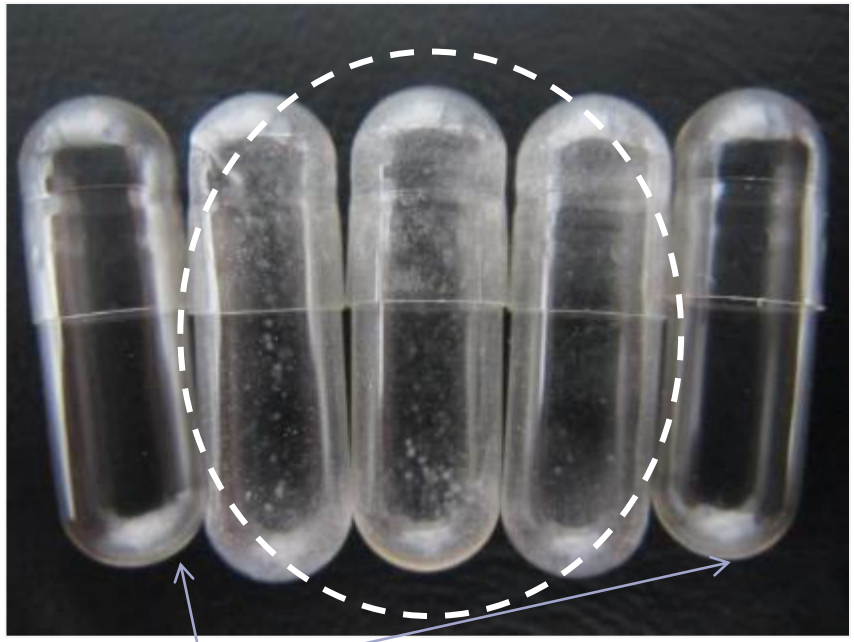
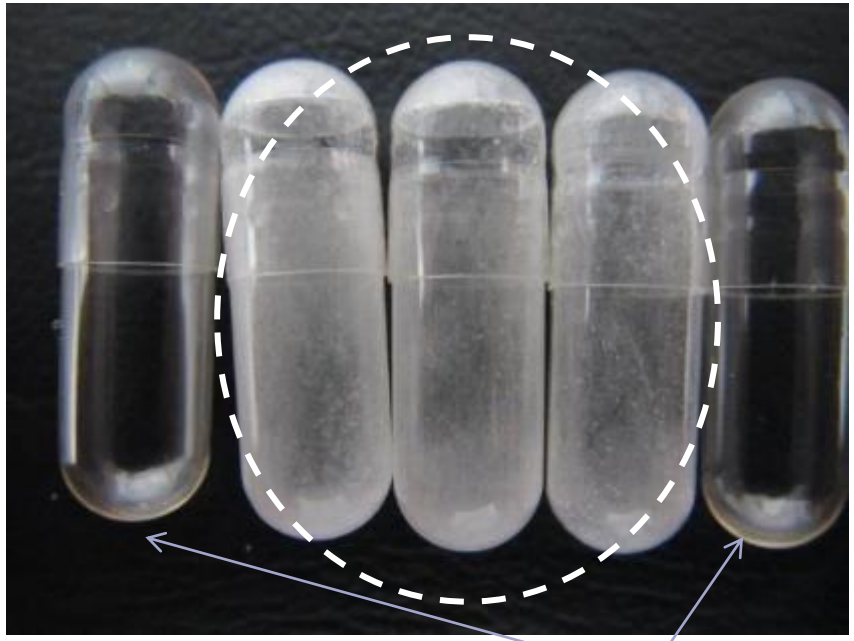
Vcaps Plus for DPI after test



Reference empty capsule

Std Vcaps Plus after test



Reference empty capsule

Capsugel Internal Data

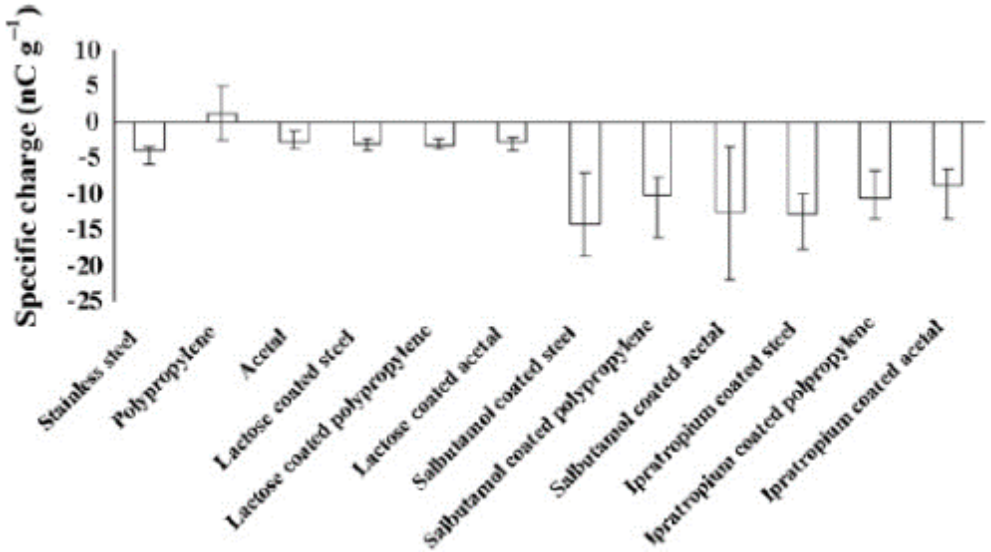
DPI capsules: Electrostatics

Impact of API / Formulation

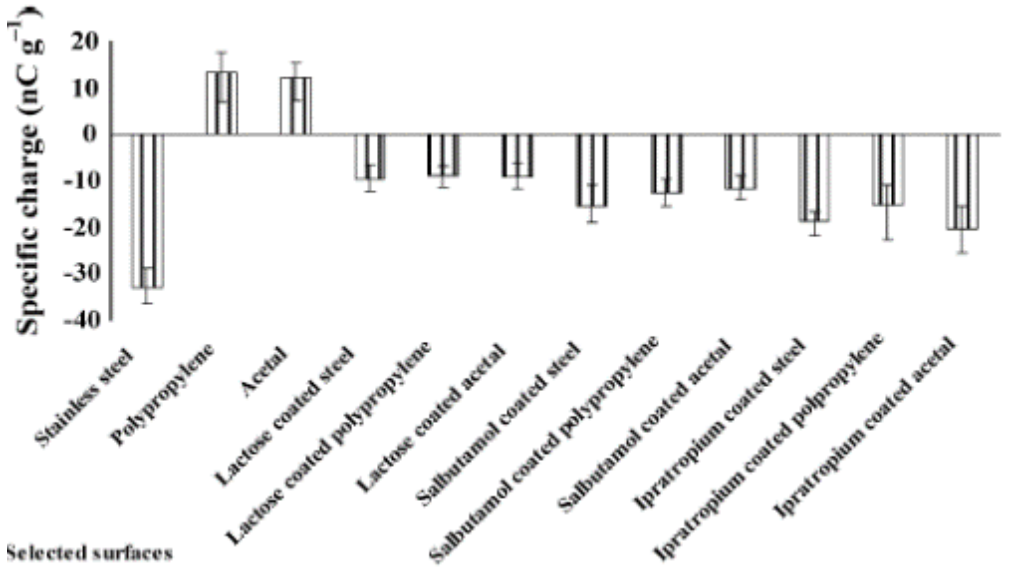
- Powder retention is not solely capsule related

- Electrostatic charges of carrier and API in blenders with different surface treatments.

Lactose



Salbutamol sulphate

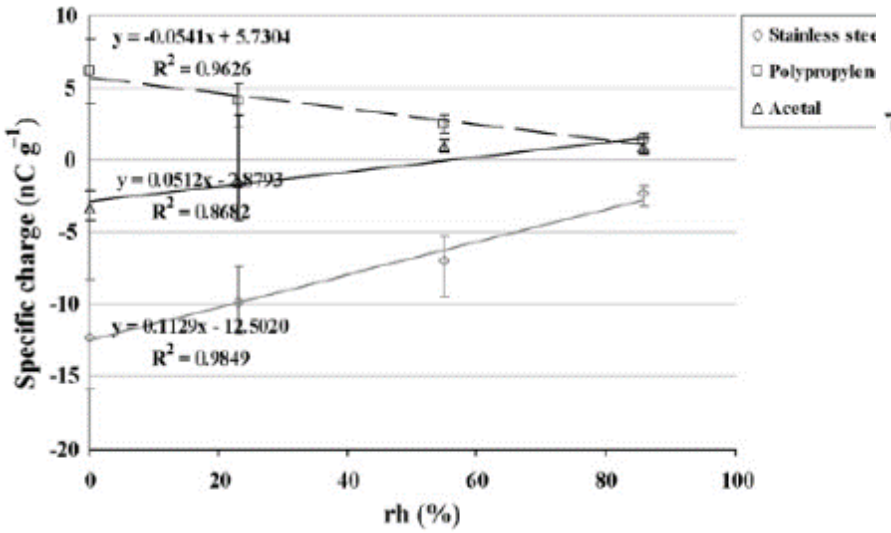


Elajnaf et al 2006

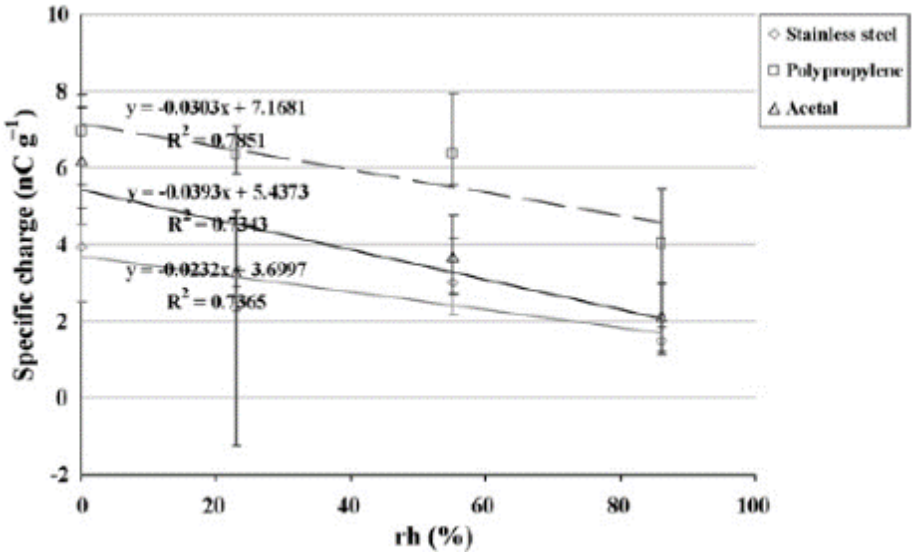
DPI capsules: Electrostatics

Impact of Moisture

- Increasing moisture reduces electrostatics of the API-carrier blend (stored from 0 – 86 % RH)
- Charging properties between salbutamol and ipratropium blends with lactose were different
- Higher moisture level increase adhesion due to capilary forces



Salbutamol-lactose mixture



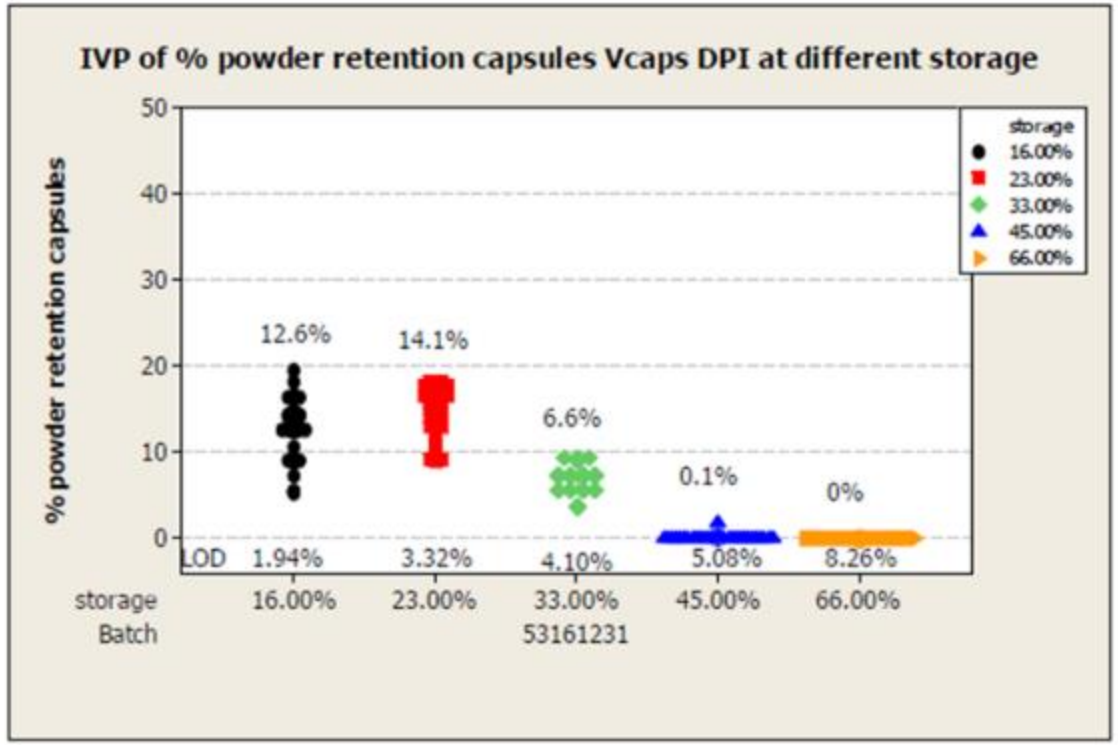
Ipratropium-lactose

Elajnaf et al 2006

DPI capsule powder retention

Impact of capsule water content

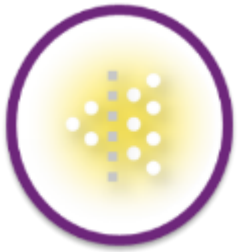
Powder retention and water content of HPMC capsules (Vcaps DPI) filled with 25.0 ± 1 mg 150 mesh lactose at different RH conditions (n=20)



Powder retention increased with decreased of LOD (static effect)

Capsugel Internal Data

Powder Retention



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The following parameters impact the powder retention (%):

- Capsule moisture
- Formulation water activity
- Morphology of the internal surface of the capsule
- Lubricant content
- Static and/or high energy relaxation (Blending & filling process conditions)

Capsule – Device interaction

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- Powder container/primary packaging (capsule, blister, reservoir)
- Device

Capsule opening principles

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Three basic principles of capsule opening by devices:

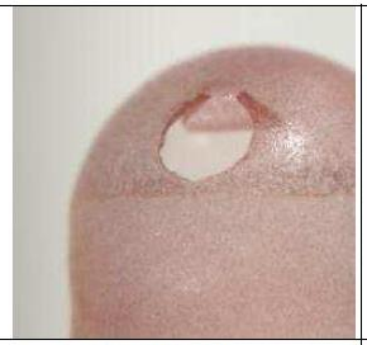
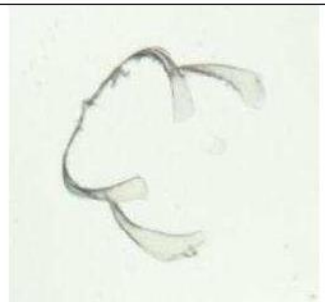
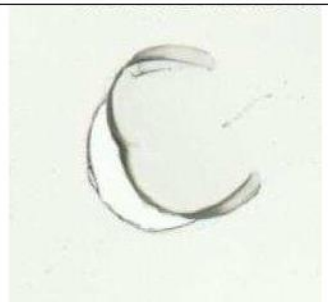
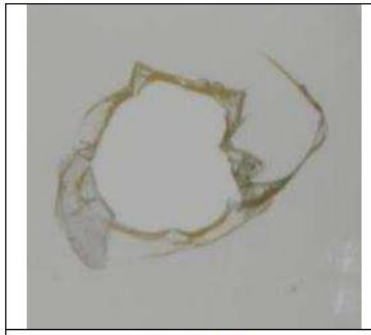
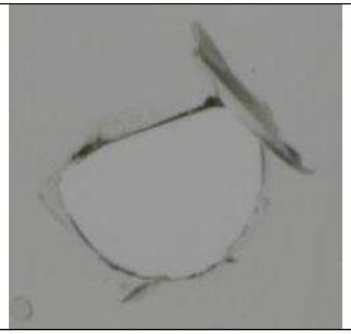
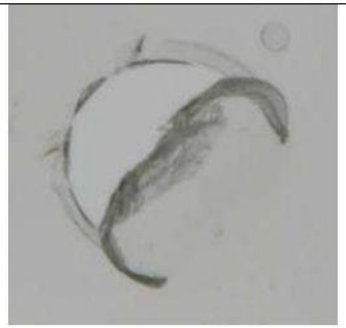
- Shear forces separating the body from the cap
  - E.g. Rotahaler

- Piercing the capsules from the top or the side
  - E.g. Cyclohaler / Handihaler

- Cutting by blades

DPI capsule puncturing

Impact of moisture with different capsule polymers

	23% RH	33% RH	45% RH	66% RH
HPMC + Gelling agent				
HPMC only				
Gelatin				

Inhalation device

Puncturing performance

- The devices tested performed similar on piercing performance
- For low RH products, HPMC capsules is recommended

	Puncturing		
Capsules conditioning	23 %RH	33 %RH	45 %RH
RS01	Good for HPMC capsules	Good for HPMC capsules	Good for HPMC, PEG & gelatin capsules
Capsuhale	Good for HPMC & PEG capsules	Good for HPMC & PEG capsules, acceptable for gelatin capsules	Good for HPMC, PEG & gelatin capsules
Handihaler	Good for HPMC capsules acceptable for other capsules	Good for HPMC & PEG capsules, acceptable for gelatin capsules	Good for HPMC, PEG & gelatin capsules

Puncturing: 15 capsules were tested and observed after use for absence of particle; when a minor particle is missing for a few capsules only, the test is rated “acceptable”

Higher doses with a capsule based inhaler

Challenges

- Would scaling up the inhaler and capsule allow a higher delivery

- How many inhalation maneuvers would be required?
  - Which is better: Multiple maneuvers from a single capsule vs single maneuver with multiple capsules?

- Are there sufficient energy to deagglomerate the formulation when scaled up?
  - Does the inhaler need to be modified to provide higher energy?

- Would the formulation need to be engineered for improved delivery?

Formulation and process development

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Typical workflow

- Ultimately, the goal is to bring the product to the patient (speed-to-patient)
  - At the design/develop stage, concurrently evaluate multiple particle engineering technologies
  - Example: Micronization, spray drying, micronization with spray drying.

- Is the particle engineering technology available to support commercial scale manufacturing?
  - If two particle engineering technologies provides similar product/clinical performance, price to patient should be considered.

Small Molecule Technologies Integrated Offer

Flexible Model Across the Product Development Cycle

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DESIGN	DEVELOP	MANUFACTURE
Small / Lab-Scale (non-GMP)	Clinical Scale	Commercial Scale
	> 300 Projects	*> 200 Products*

- Drug Substance Intermediates – early and GMP intermediates

- Drug Substances – full range of API inclusive of HPAPI, cytotoxic payloads for ADC's

- Drug Product Intermediates – multiparticulates (MP), micronized API, spray dried dispersions

- Drug Products – inhalation, tablets, encapsulated powder & MP, soft gels, liquid-fill hard caps

Key Focus Areas

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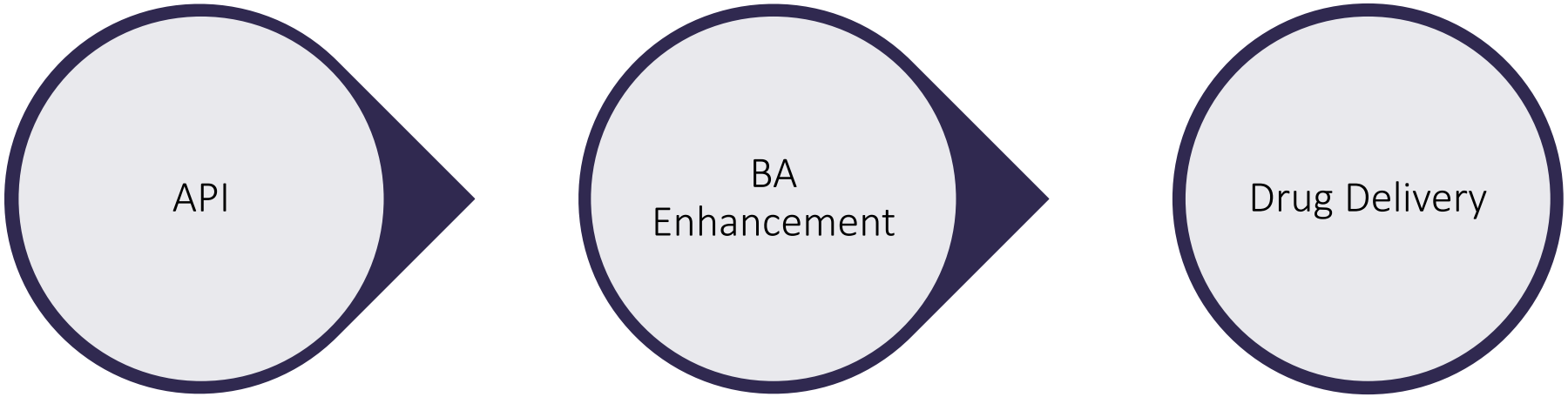

Early Intermediates
GMP Intermediates
HPAPI
ADC Payloads

Micronization
Nanotechnologies
Solid Dispersions
Lipid Based Formulations

Extended Release
Targeted Delivery
Osmotics / MP's
DPI Formulations

Capsule-based inhalation product development

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Take-aways

- Capsule-based inhaler product development consist of 3 major components
  - Capsule, Formulation, Device
  - All with equal importance – to be evaluated together
  - Each component are well understood and developable

- To reduce development risk and time, evaluate particle engineering technologies concurrently during design phase.

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Thank You

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