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PHARMAprocess

Innovation Forum in Pharmaceutical Process

High Sophisticated Technologies for Oral Solid Dosage Forms:

Hotmelt Granulation and Coating

Part 1 – by Romaco Innojet

Latest Fluid Bed Systems for Granulation and Coating for Hotmelt Applications

Part 2 – by Hermes Pharma

R&D of High Sophisticated OSD and Hot Melt Coating Processing

Part 1

Latest Fluid Bed Systems for Granulation and Coating for Hotmelt Applications

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Quality By Design approach is essential:

To chose the right technology and the corresponding equipment for R&D from the Laboratory to Pilot Plant – Production Scale

Hot-Melt-Coating (HMC)

which is: Spraying with melted materials (Granulation, Coating)

- fast up-coming as a high profitable solution for production in Food and Pharma
- looking to avoid the shortfalls of solvent-based granulation and coating
- to better control taste (masking) and release (efficacy) parameters
- requires special know-how and insight expertise to develop the suitable technical solution

Obstacles

- there are pretty rare so called Ready-To-Use materials
- just few or no materials registered for Pharma and Food applications in comparison to Polymer Coatings (aqueous or for organic solvents)
- conventional Fluid Bed Devices (Top-Spray or Bottom Spray) are very limited or even unable to perform a robust, reproducible and high efficient granulation or coating process due to their physical characteristics

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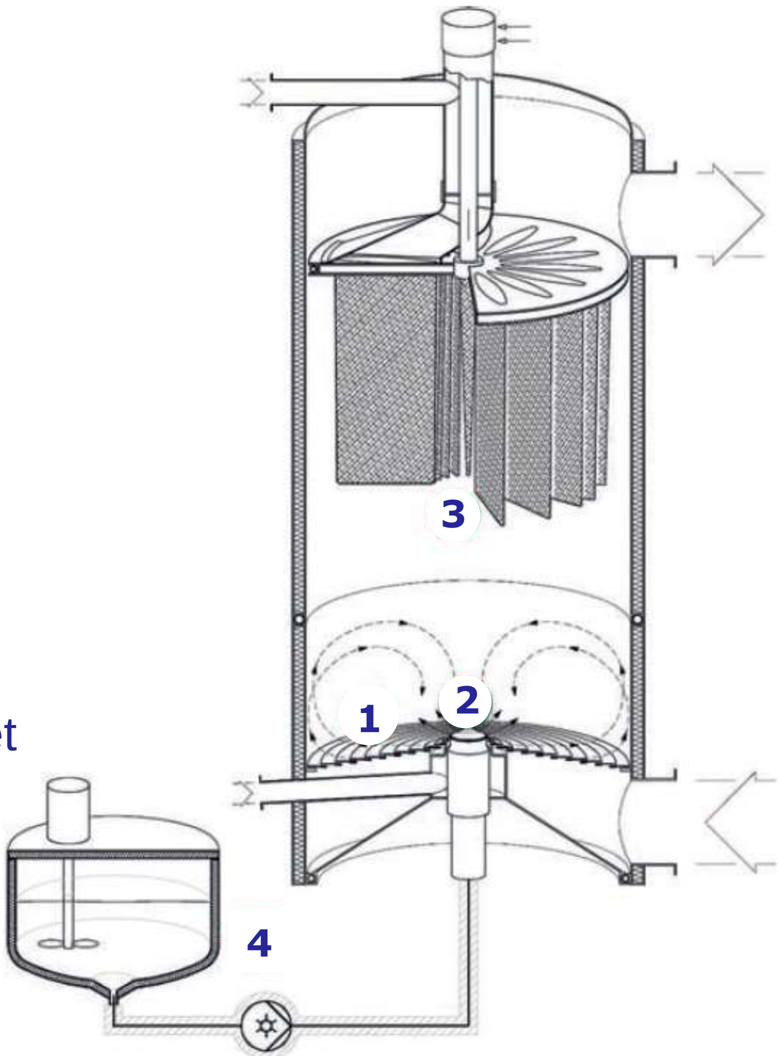
Hot-Melt-Coating (HMC)

Functionality Of HMC-System

3 Major Functional Core Components to achieve required physical conditions

1. **Fluid Bed** for high precisely controlled and homogeneous particle movement (int. pat Romaco Innojet ORBITER)
2. **Spray Nozzle** (int. pat. Romaco Innojet ROTOJET) – controlled, high precisely spray supply
3. **In-Process Filters** (int. pat. Romaco Innojet SEPAJET) – permanent product recovery
4. Melting Device with heated pump and dosage system



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Hotmelt Advantages: Process Time
in a Romaco Innojet V 400 (400 ltr. process batch)

Process data	Hot Melt process	Standard process
Process time	**1h**	**5 h**
Quantity of air	6000 m³/h	6000 m³/h
Inlet air temp.	Not heated	70 °C
Melt temp./ liquid temp.	90 °C	20 ° C
Temp. of spray air	90 °C	60 °C

Calculation basis:

c_p wax/fat: 2,7 J/g/K

melt enthalpy H wax/fat: 160 J/g

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Hotmelt Advantages: Energy Consumption
in a Romaco Innojet V 400 (400 ltr. process batch)

	Hot Melt process	Standard process
Heating up the inlet air	**- - -**	**5 h** x 125 kW = 500 kWh
Heating up the melt/wax	10,5 kWh	- - -
Melting energy wax	200 kg wax = 8,8 kWh	- - -
Spray air heating	**1 h** x 15 kW = 15 kW	**5 h** x 10 kW = 50 kWh
Tube/ house/ nozzle heating	**1 h** x 2 kW = 2 kW	- - -
Total	**36, 3 kWh**	**550 kWh**

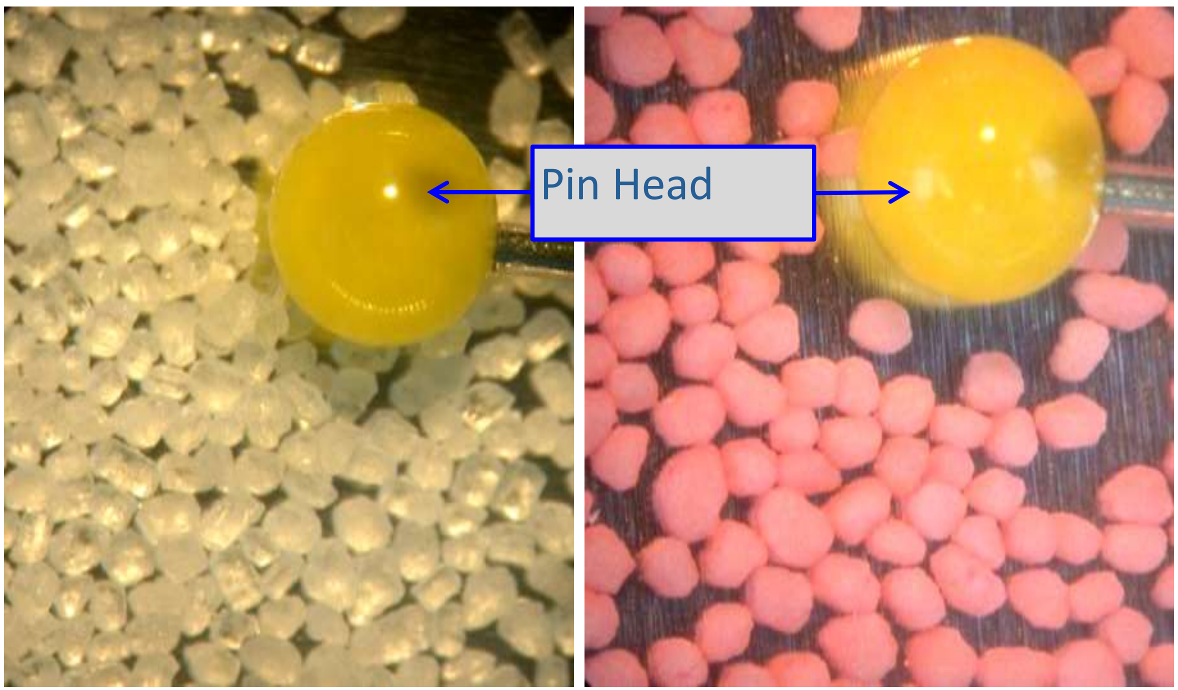
Hotmelt: Advantages

- No liquid / moisture in the system
- No evaporation of aqueous solution
- Very short process times
- Green Pharma – no organic solvents – natural materials

Application example:

HMC – Taste masking of granules	Taste masking with polymer dispersion:
Starter: 250 g granules	15% polymer in dispersion
50 % coating -> 125 g fat/wax	125 g polymer – 833 g dispersion
Spray rate: 7 g/min	Spray rate: 7 g/min
Process time: 18 min	**Process time: 120 min**
	(5 g/min - 170 min)

Product Sample: Taste masking of bitter tasting API



Process parameters

Starter material:
500 g crystalls

Final product :
1000 g coated crystalls

Proces time: 115 min
Spray rate: 3,6 – 8 g/min

Product Sample: Malic Acid Crystals protected against humidity

- +30% fat, size 200µm – 500µm

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Product Sample: Encapsulation of Alginate Capsules
made by Coacervate Method

Encapsulation: 1st pre-drying in Ventilus® System – 2nd Hotmelt Coating

- liquid API-s
- flavors
- to provide handling of liquids as a dry product

Application Example: Encapsulation of Probiotics

Unique Multiple-Layered Micro-Encapsulation – a Single-Pot-Process

- started with granulation and completed with multi-layer coating – non-stop just the spray nozzle got changed while product was under control
- to provide Pro-Biotic Bacteria with maximum heat resistance
- to ensure highest biological efficacy in the lower GIT
- to achieve Healthy Food Comprising THEM 25847-WO-09

Yellow – probiotics granules (the core)
Blue – moisture barrier coating layer
Pale blue – subcoating-intermediate layer
Brown – acid-resistant layer (enteric coating)
Pale brown – heat-protection layer

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Romaco Innojet VENTILUS®

3-in-1 Drying, Granulation & Coating System

Laboratory scale

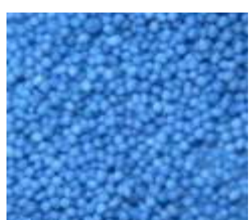
- V 2.5 - 1
- V 5

Pilot scale

- V 10
- V 25
- V 50

Production scale

- V 600
- V 800
- V 1000



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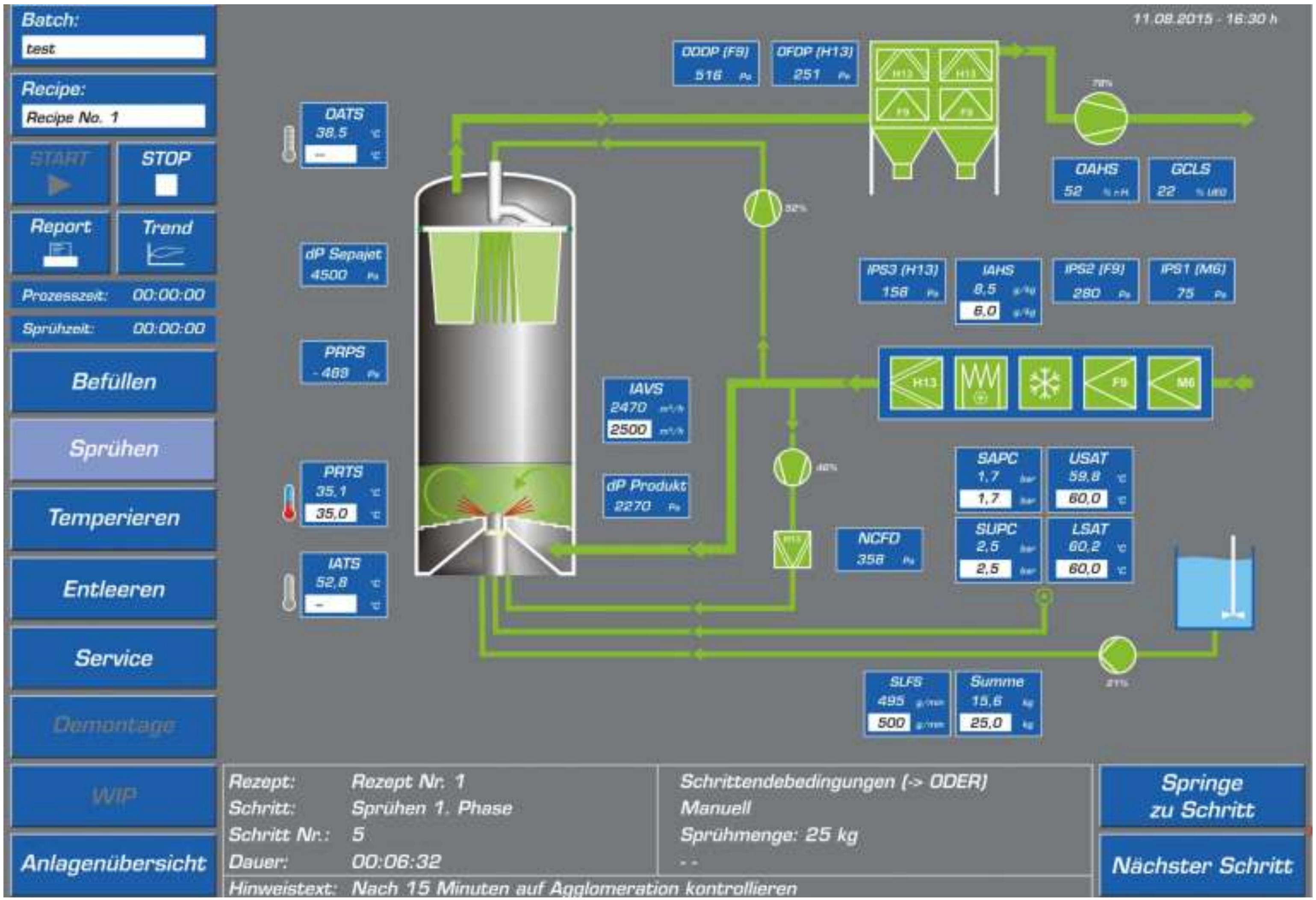
Romaco Innojet VENTILUS® Granulation & Coating System



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Romaco Innojet VENTILUS®

3-in-1 System for Drying, Granulation & Coating

int. pat., developed by Dr. h.c. Herbert Hüttlin

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Romaco Innojet VENTILUS®
Hotmelt device IHD

Laboratory scale

VENTILUS® equipment is working with only one centrally placed spray nozzle ROTOJET Hotmelt which forms the basis for successful Hotmelt Applications

Production scale

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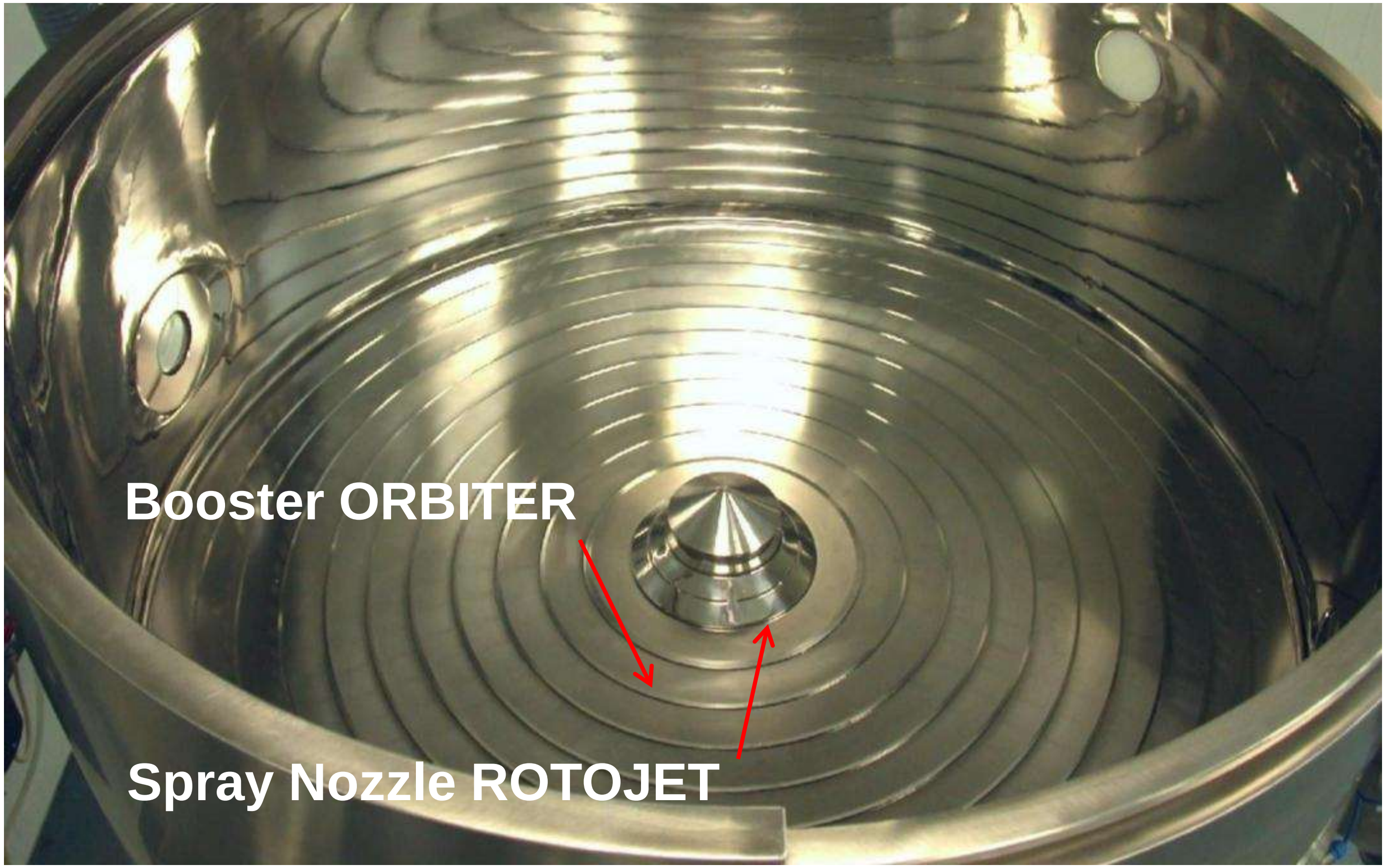
Romaco Innojet VENTILUS®

1st Controlled Particle Movement – Homogeneous Temperature Supply
Booster ORBITER type IBO



Example: Production scale unit 800 liters batch size

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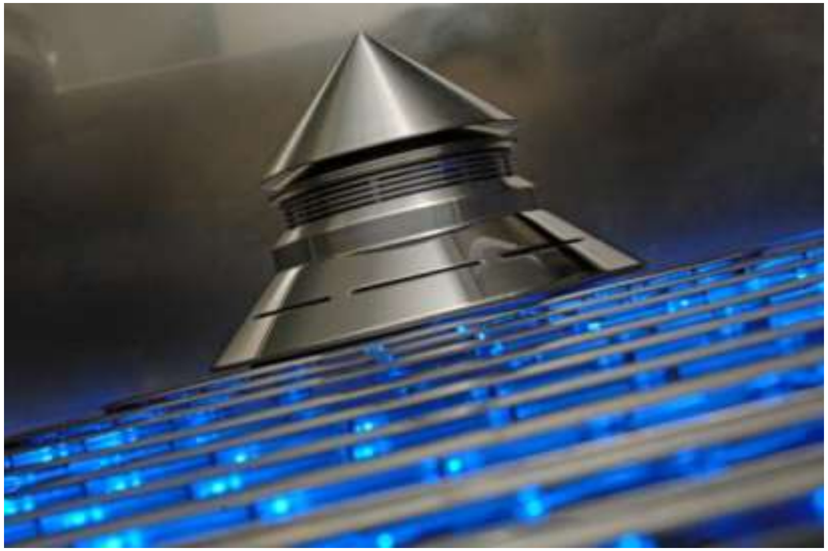
1st Controlled Particle Movement – Homogeneous Temperature Supply Booster ORBITER type IBO



Romaco Innojet booster ORBITER (side view, open air gaps highlighted).

air giding blades – rear side

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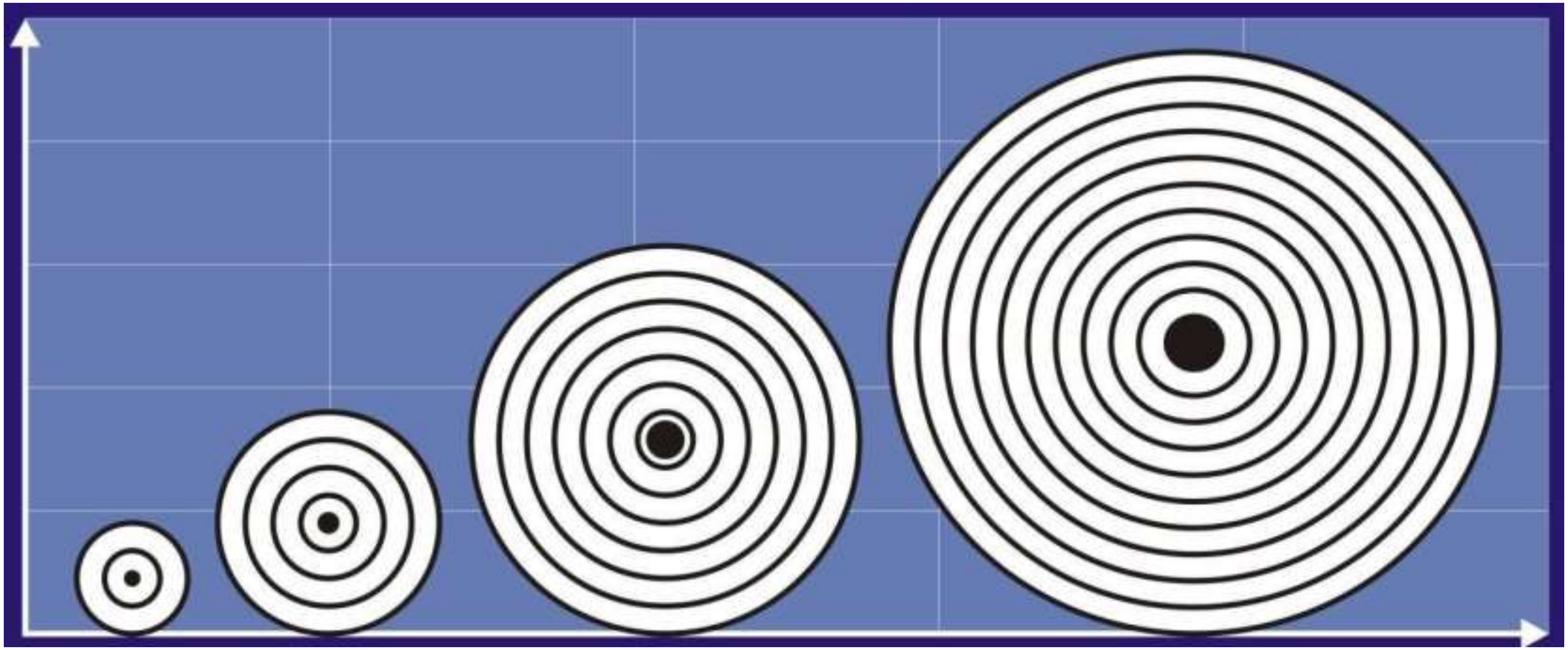
Romaco Innojet VENTILUS®

1st Controlled Particle Movement – Homogeneous Temperature Supply

Booster ORBITER type IBO



V 1 V 25 V 200 V 800

The relative number of air-gaps per Booster surface is constant

‣The relative air-quantity per product-volume is constant

‣Nearly linear up-scaling characteristic

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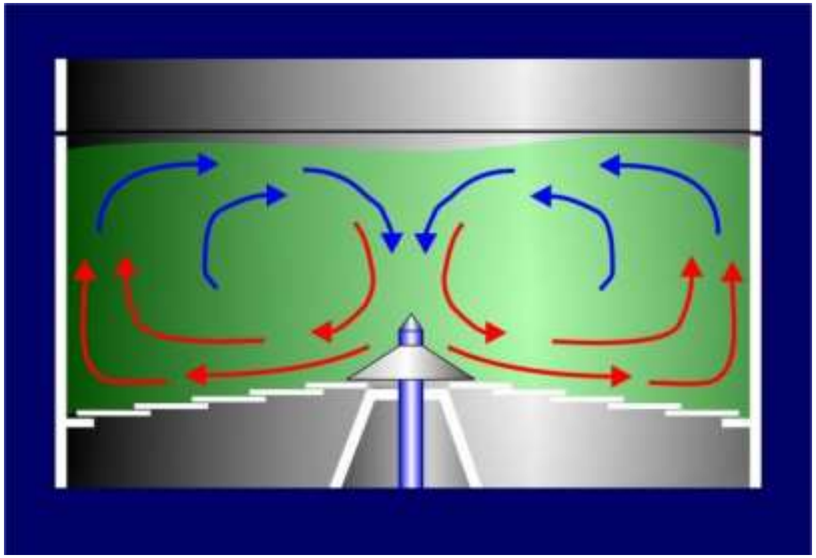
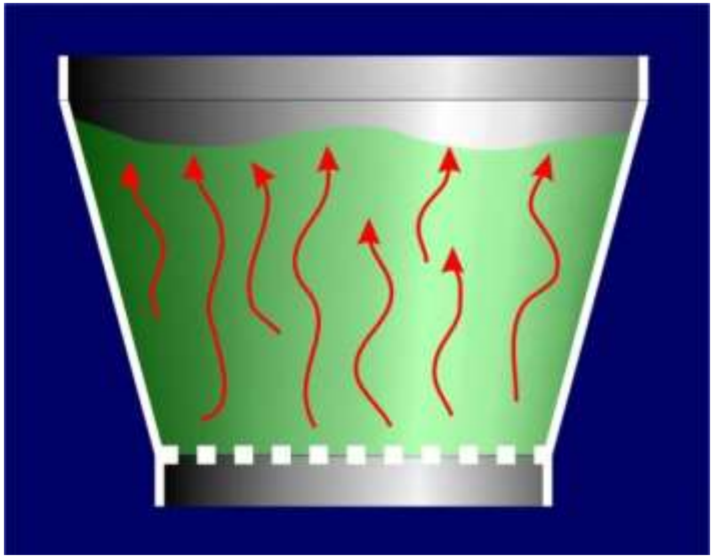
1st Controlled Particle Movement – Homogeneous Temperature Supply

Booster ORBITER type IBO



Romaco Innojet booster ORBITER:
Horizontal – vertical air stream



Sieve, Conidur and slot bottoms:
Only vertical or tangential air stream

The prolonged path of the process air on the booster ORBITER enhances **the drying efficiency by 25 %**

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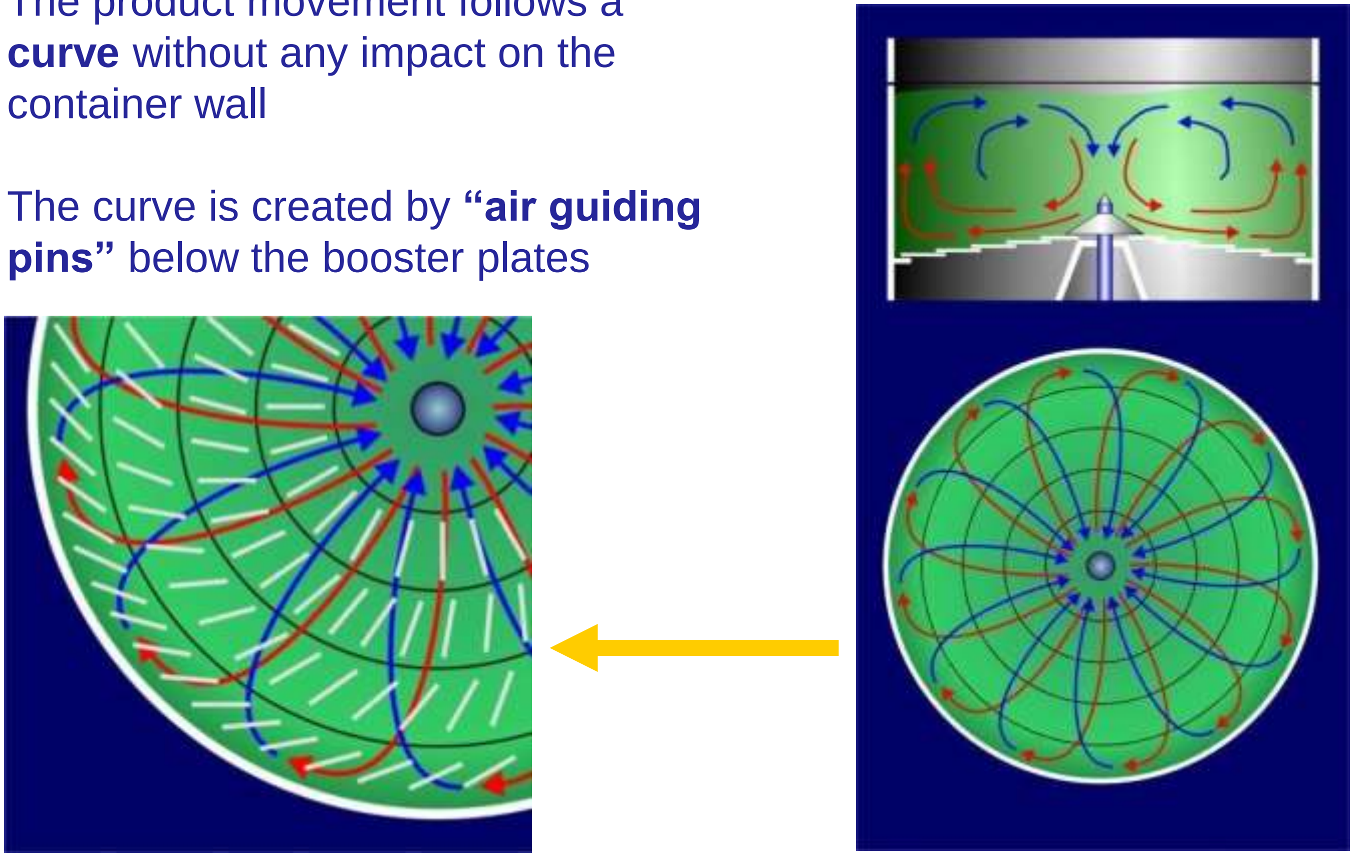
Functional principle of booster ORBITER

The product movement follows a **curve** without any impact on the container wall

The curve is created by **"air guiding pins"** below the booster plates



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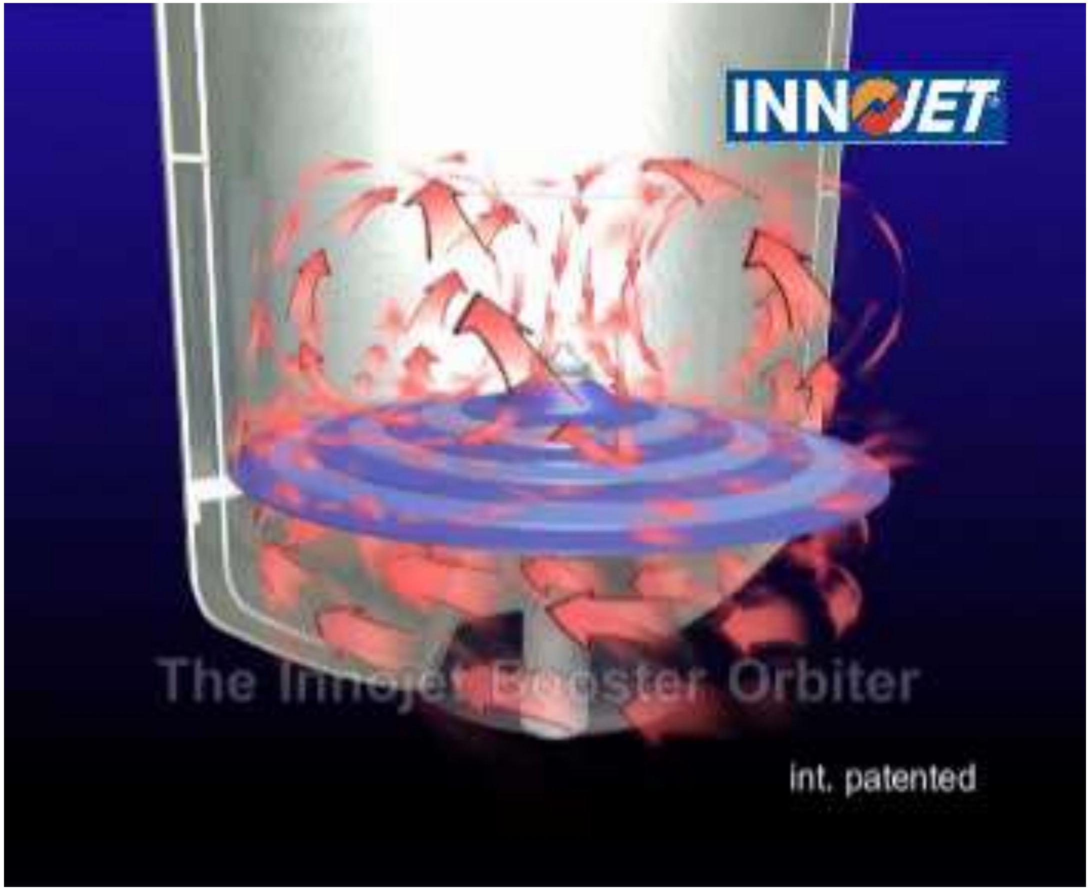
Romaco Innojet VENTILUS®
Booster ORBITER



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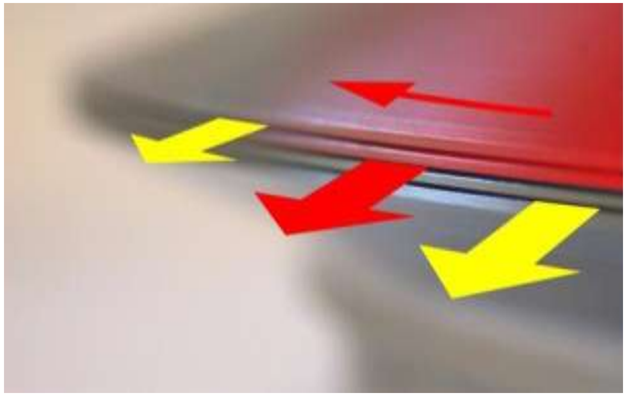
2nd Controlled and Precise Spray Supply

Spray nozzle ROTOJET



Detailed view on spray liquid gaps

Individual ROTOJET parts

Laboratory- and pilot scale (e.g. type INR 10/25)

Production scale (type INR 50/75/100/125)

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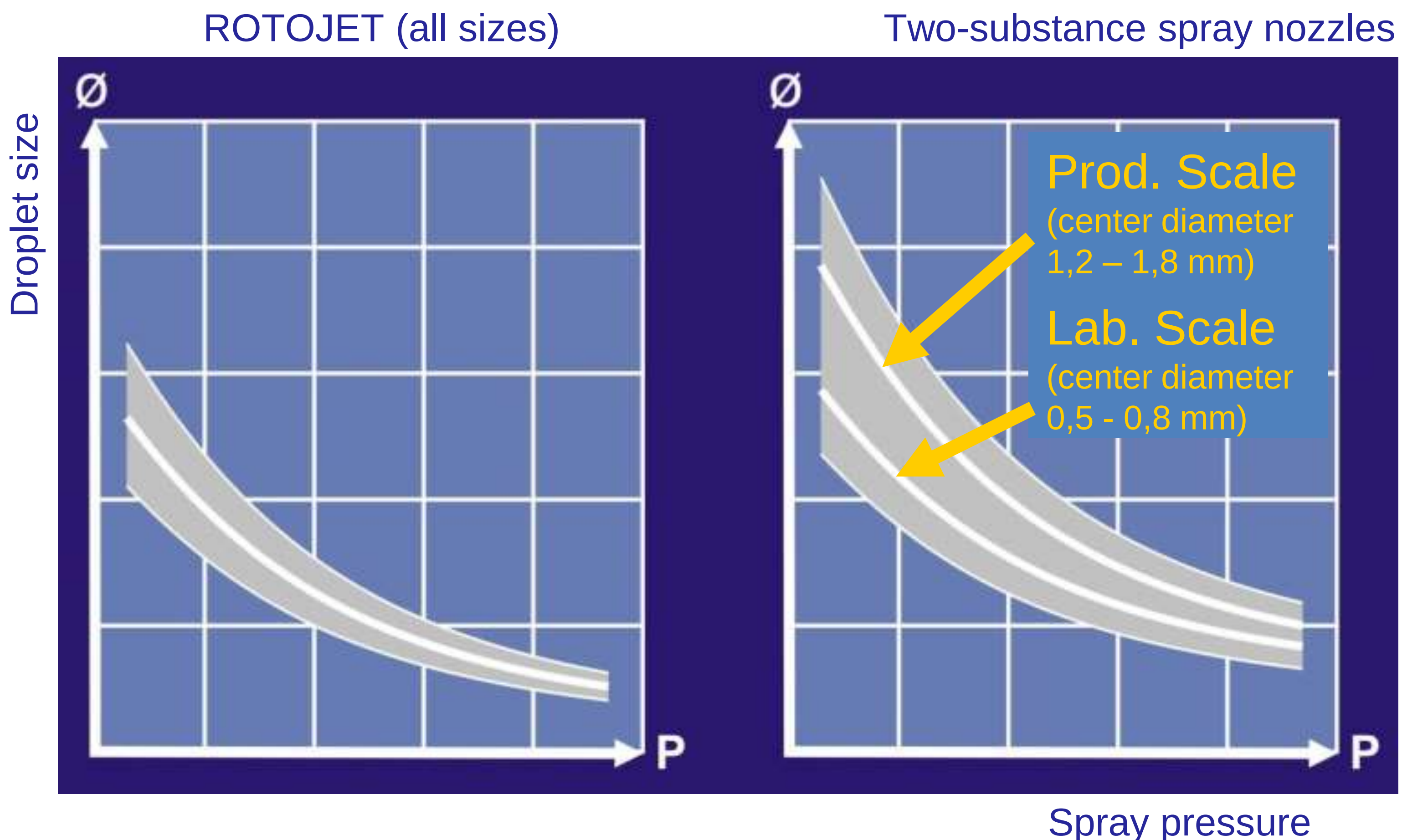
2nd Controlled and Precise Spray Supply

Comparison spray nozzle ROTOJET vs. conventional nozzles



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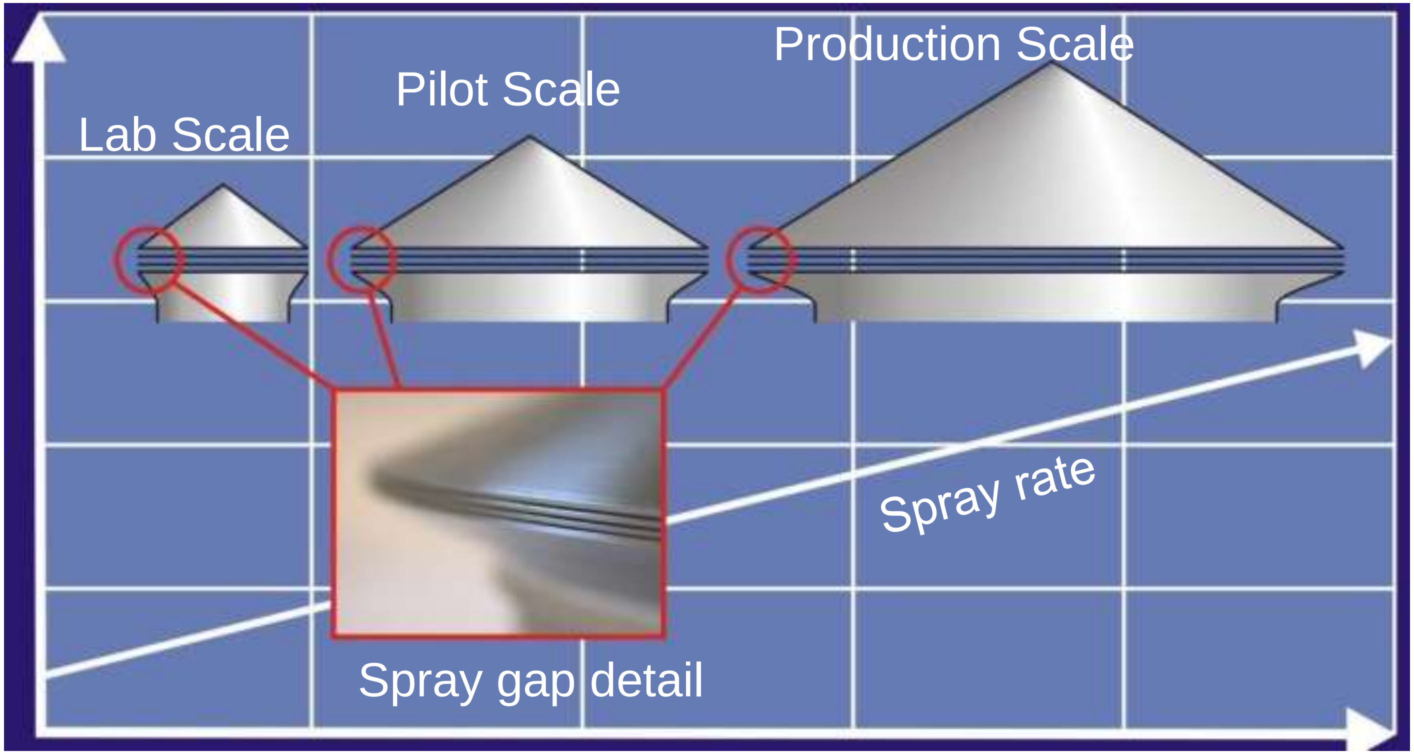
2nd Controlled and Precise Spray Supply

Scale-Up of spray nozzle ROTOJET



Spray gap geometry remains the same, independent of the nozzle size

- Scale-up is the basic philosophy

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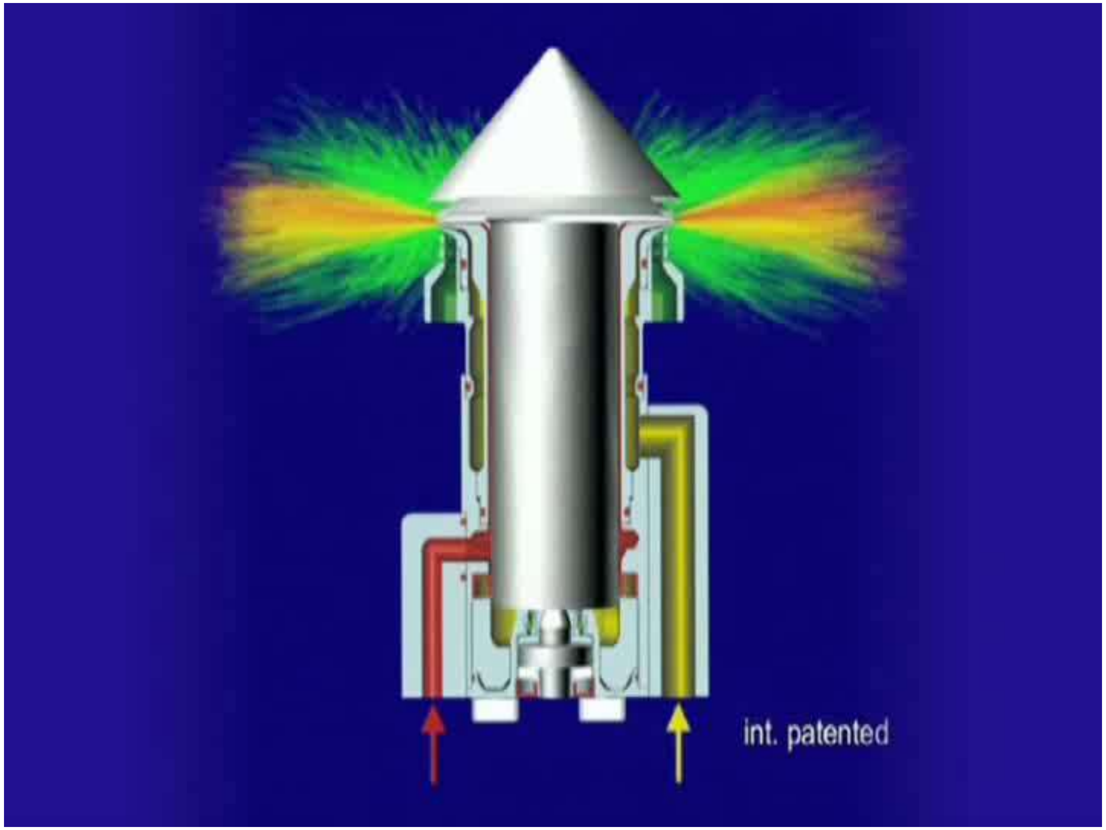
Spray nozzle ROTOJET



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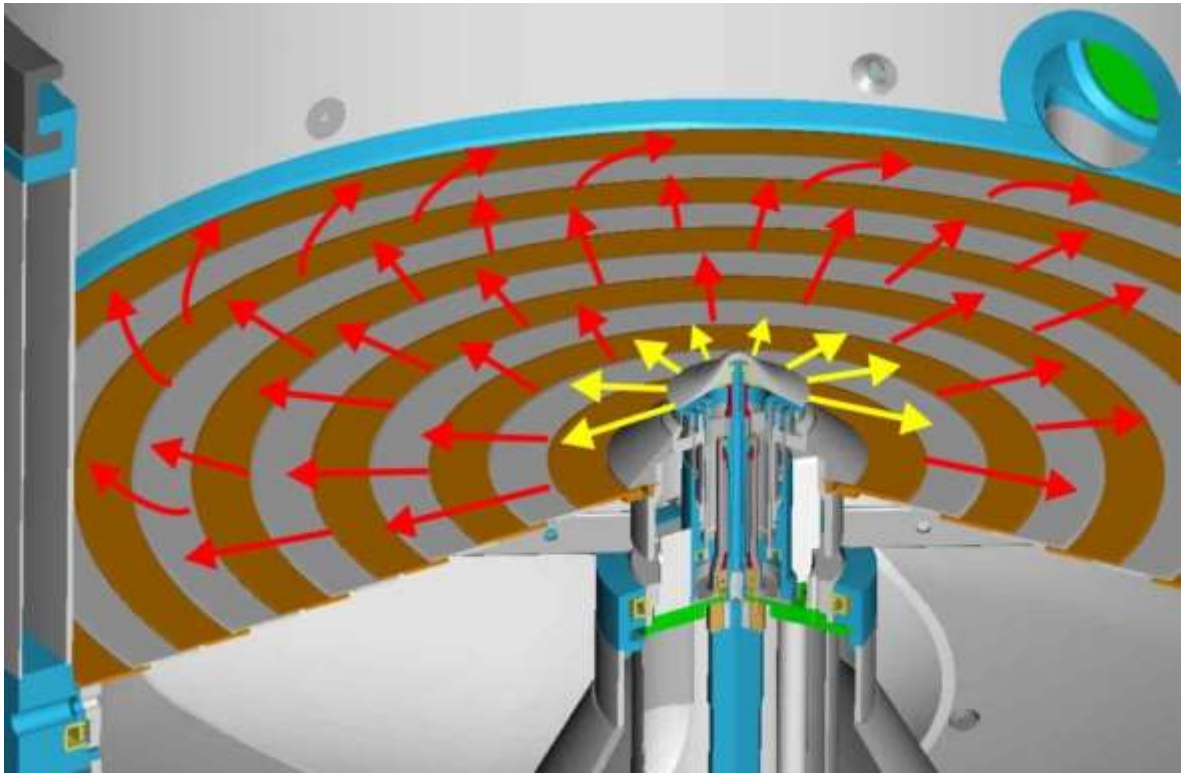
Functional principle of booster ORBITER and spray nozzle ROTOJET



Product movement and **nozzle spray** work into the same direction

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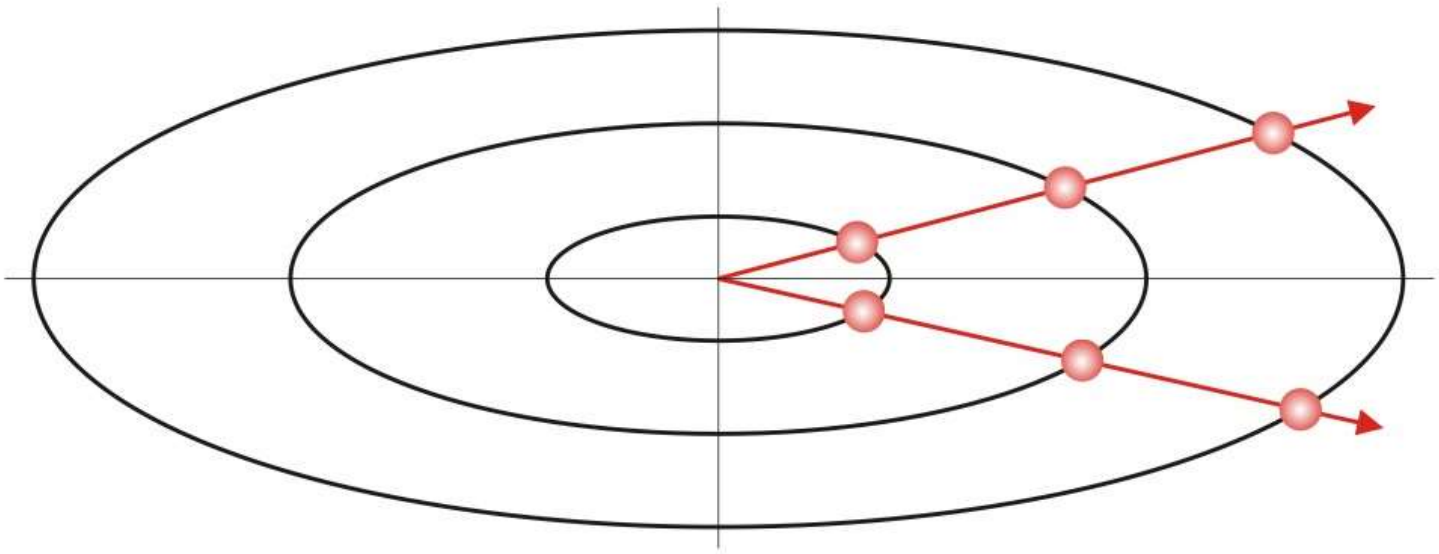
Functional principle of booster ORBITER and spray nozzle ROTOJET



- Spraying and moving **from the center** make the particles disperse
- Very high spray rates are possible

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3rd Controlled and Permanent Powder Recovery System SEPAJET

view into the filter dome from working position with product container opened

simple and fast change of filter set

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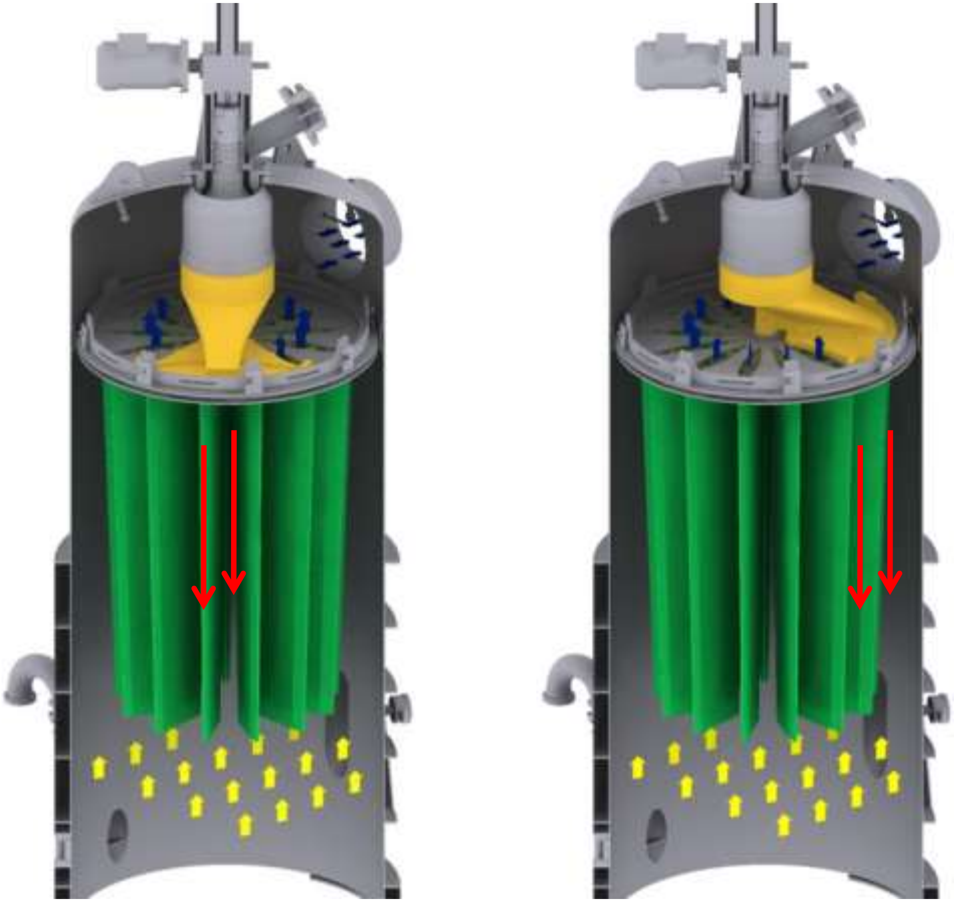
3rd Controlled and Permanent Powder Recovery System SEPAJET

Stainless steel carrier basket with textile filters



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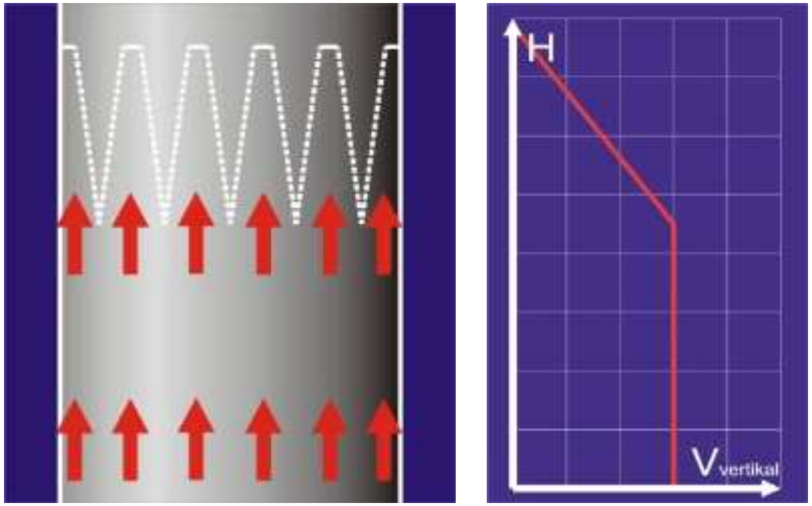
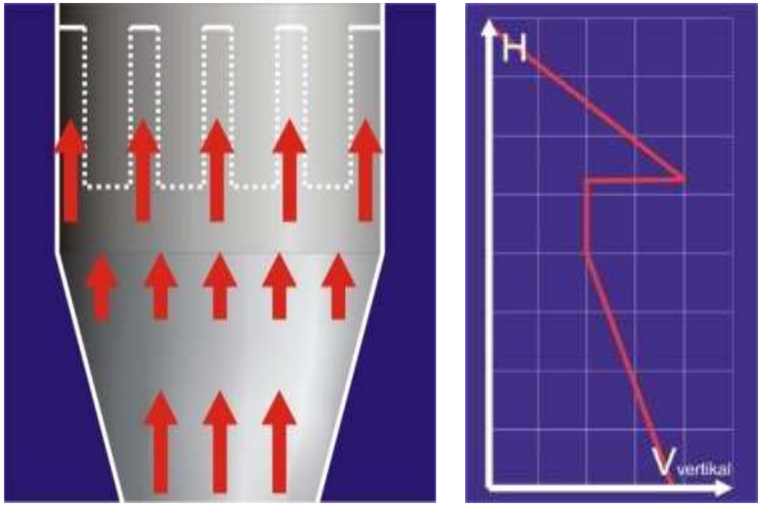
3rd Controlled and Permanent Powder Recovery System SEPAJET

Comparison conventional filters vs. SEPAJET



SEPAJET filter with
cylindrical product container



Conventional filter with conical
product container

- Conventional filters accelerate the process air at the filter tubes' lower edge or in single chamber systems the process is stopped for filter cleaning/shaking
- ▸ Fine material stays in the filter
- ▸ Non-stop and permanent powder recovery and filter cleaning

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Powder recovery system SEPAJET

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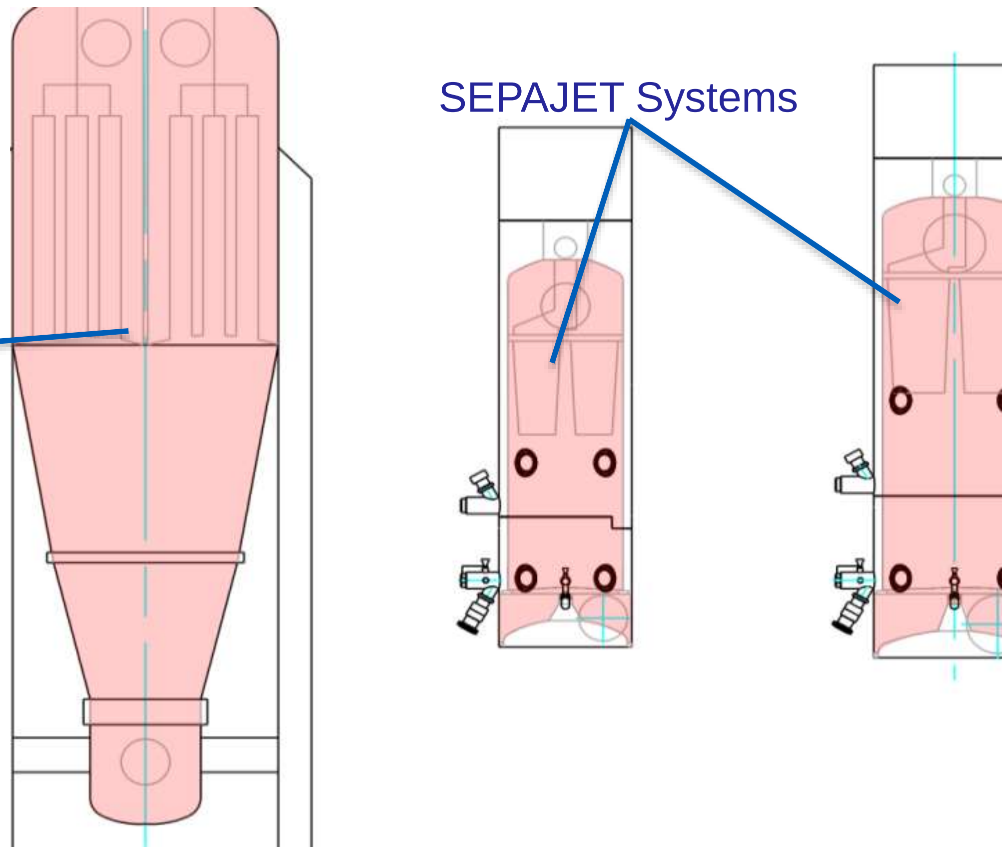
3rd Controlled and Permanent Powder Recovery System SEPAJET
Comparison conventional filters vs. SEPAJET

Inner surface area in contact with the product (including filters)

Conventional Double Chamber Tube-Filter system



Inner surface area: FBD 60: 50 m² V 50: 8 m² V 100: 12 m²

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Laboratory System – Pilot Plant – Production Scale

Nearly linear up-scaling from laboratory up to production scale

Excellence due to Physical Features of Patented Design

+ 99% dust free granules
+ homogeneous film coating
+ exactly controlled process
+ hot melt coating
+ reduced process time
+ increased yield

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Laboratory System – Pilot Plant – Production Scale

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Laboratory System – Pilot Plant – Production Scale

Contamination free loading – unloading

Discharge container (closed discharge)

Machine opened

GMP compliant access to inner parts of the machine

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Laboratory System – Pilot Plant – Production Scale

GMP compliant access to inner parts of the machine

GMP compliant change of spray nozzle – available in-process

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Laboratory System – Pilot Plant – Production Scale

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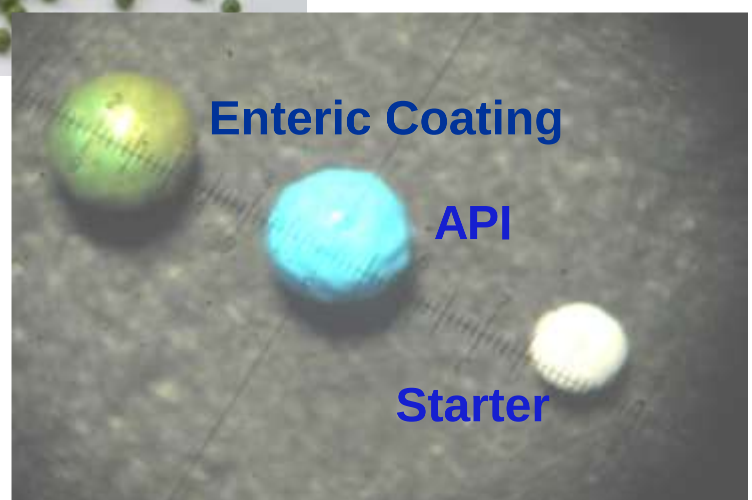
Laboratory System – Pilot Plant – Production Scale

3-in-1 Multi Purpose System

1. Granulation – 2. Film Coating Micro Tablets – 3. Pellets Layering and Coating

Endproduct

Starterpellets



Micro Tablets

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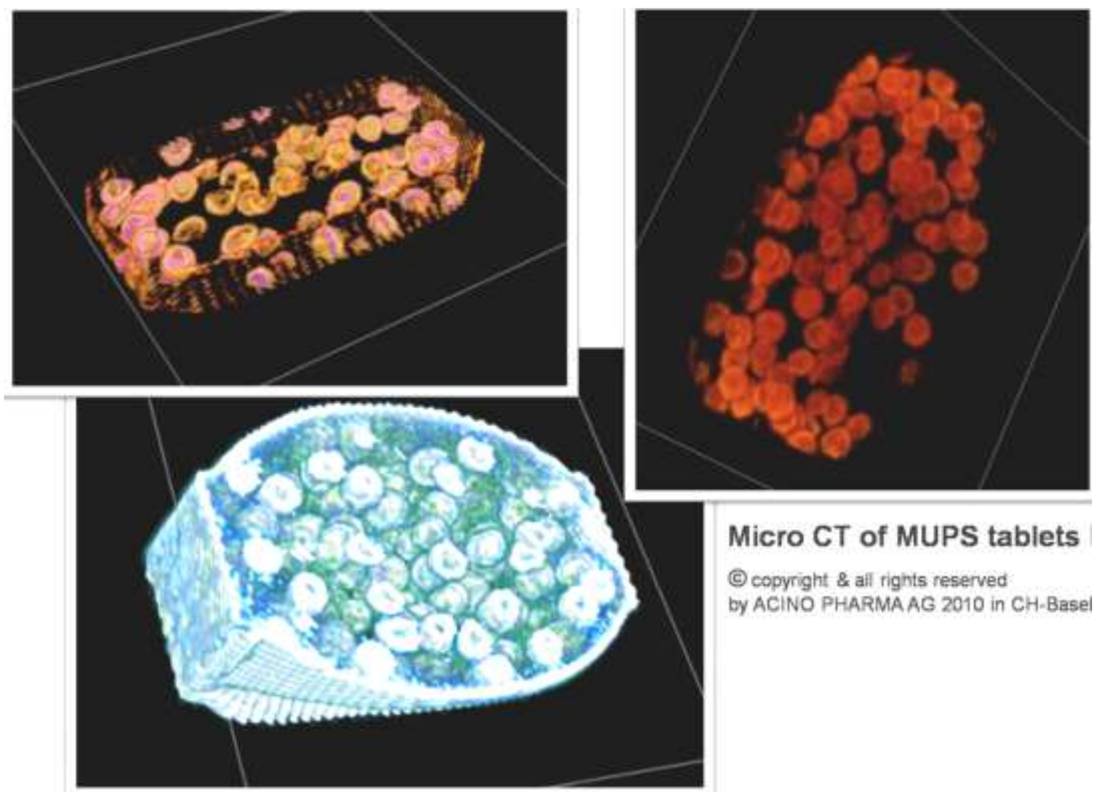
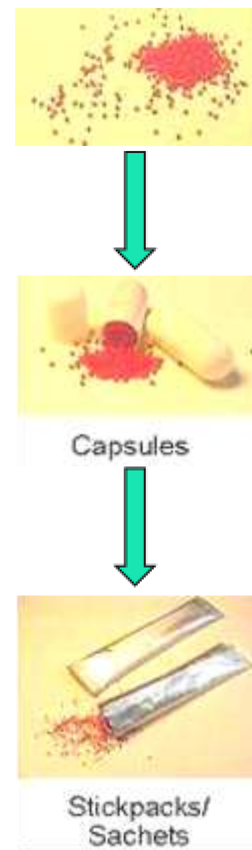
Laboratory System – Pilot Plant – Production Scale

EXAMPLE:

MUPS – Multi Unit Particles Systems implemented in RDT or in Capsules, Stick Packs



Micro CT of MUPS tablets



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Romaco Innojet VENTILUS®
Laboratory System – Pilot Plant – Production Scale

EXAMPLE: Film Coating, Crop Protection

Flower Seeds Coating
- homogeneous & fast
- gentle & reproducible
- no agglomerations

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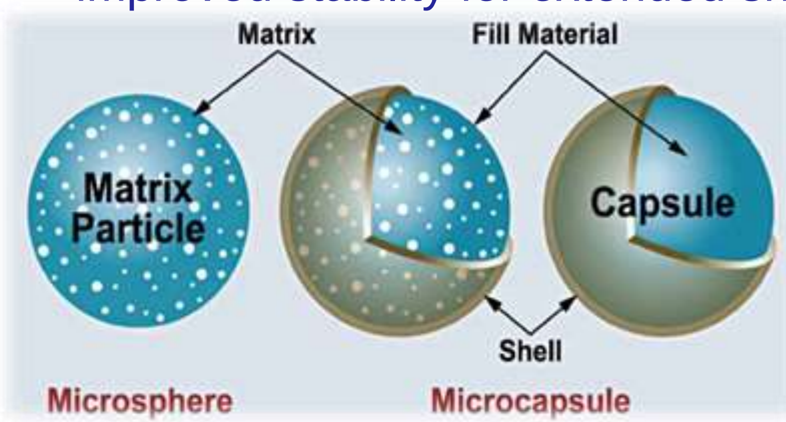
Laboratory System – Pilot Plant – Production Scale

EXAMPLE: Solidification and Unique Encapsulation and Preservation

Multiple-Layered Micro-Encapsulation

- to provide sensitive natural oils with a superior stability
- preservation against oxygen and humidity
- improved stability for extended shelf life



- ➢ Flavoring Agents (e.g. Lemon Oil, Peach Oil, etc.)
- ➢ Poly-Unsaturated Fatty Acids (PUFA , e.g. Omega 3, etc.)

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Romaco Innojet VENTILUS®
Granulation & Coating – Aqueous – Organic Solvents – Hotmelt Applications

Fast and Reproducible – Direct Granulate
Single-Pot Processing, yield >98% of batch

1st Granulation

2nd in-process change of the single Spray Nozzle

3rd application of a sub-coating

4th application of Enteric Coating

5th after total process time: Final sieving of ready-made product for packing into Stick Packs

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www.romaco.com

HERMES PHARMA

Get the dose right™

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Part 2

R&D of High Sophisticated OSD and Hot Melt Coating Processing

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New Taste Masking Technology to Facilitate User-Friendly Pharmaceuticals

Hermes Pharma, INNOJET Herbert Hüttlin,
RCPE and Karl-Franzens University

Aim

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Aim

- Development of taste masked powder or granulate with an immediate release profile
- Packaging and sales in a Stick Pack

Why Oral Solid Dosage in a Stick Pack?

- Medicine-To-Go: Convenient Stick Pack
- Ready and easy to use – taking without water
- Faster liberation than tablets: Improved bio-availability
- Easy to swallow – pediatrics, geriatrics

Hurdles and Approach

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Hurdles

- Amount of single dose approx. 2 g (salivation sufficient)
- Taste masking with matrix not enough
- Amount of matrix limited

Approach

- Hot Melt Coating of API-crystals with lipid excipients
  → taste masking with immediate release profile

Hot Melt Coating with Lipid Excipients

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Advantages

- Short process times (saving of solvent evaporation step)
- Coating materials toxicologically uncritical and from natural sources (Green Pharmacy)
- Dissolution pH-independent (compatible with acidic matrix components)
- Lipids: Pleasant taste, odor and feeling in the mouth
- Applicable for processing with implemented PAT

Disadvantages

- Polymorphic changes during storage
- Retardation of dissolution profile (sustained release)

Romaco Innojet VENTILUS® Laboratory System V 2.5/1
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QTPP
Formulation Development Strategy

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Quality Target Product Profile

Storage Stability:	Climate zone IV b (30° C, 75 % r.h.) 12 months
Fast Dissolution:	85 % in 30 min
Taste Masking:	1 min

Storage Stability:

Avoiding of polymorphic changes

→ Adding of modifiers (emulsifiers):

- Induction of the stable β-form:
  Increasing of emulsifier content 10 % to 30 %
  (21 h vs. 2 h to achieve stable ß-form)
  → Additional: lower process temperatures applicable

DoE

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Screening DoE (Frac Fac Res IV) for linear interactions

Definition of Critical Process Parameters as Input Parameters:

Input parameter:

- Spray Rate (SR)
- Spray Pressure (SP)
- Coating Amount (CA)
- Emulsifier Content (EMU)
- Air Flow Rate (Air)

DoE

Interaction with Critical Quality Attributes

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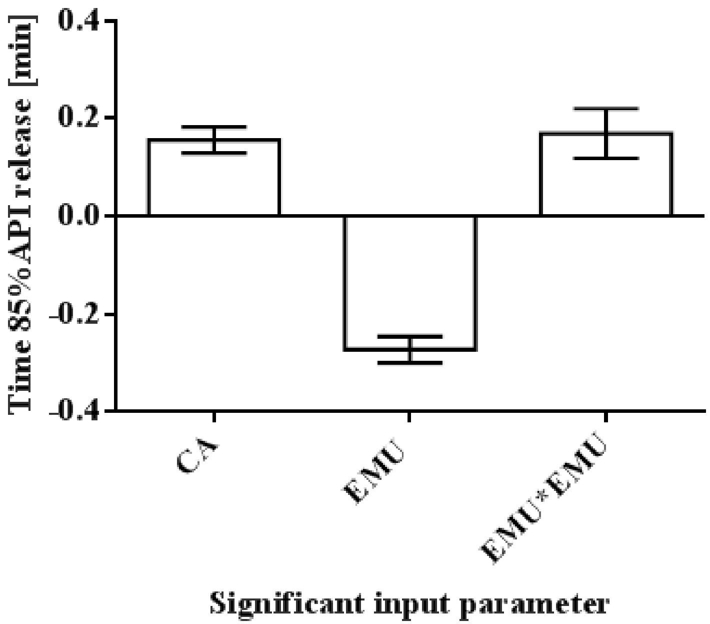
Output parameter: Dissolution rate

- **Emulsifier Content (EMU):**
  Increasing EMU:
  faster dissolution
  and shorter transformation
  time to the stable β-form

- **Coating Amount (CA):**
  Increasing CA:
  Slower dissolution



R2: 0.87
Q2: 0.82
Model validity: 0.57
Reproducibility: 0.99

DoE
Interaction with Critical Quality Attributes

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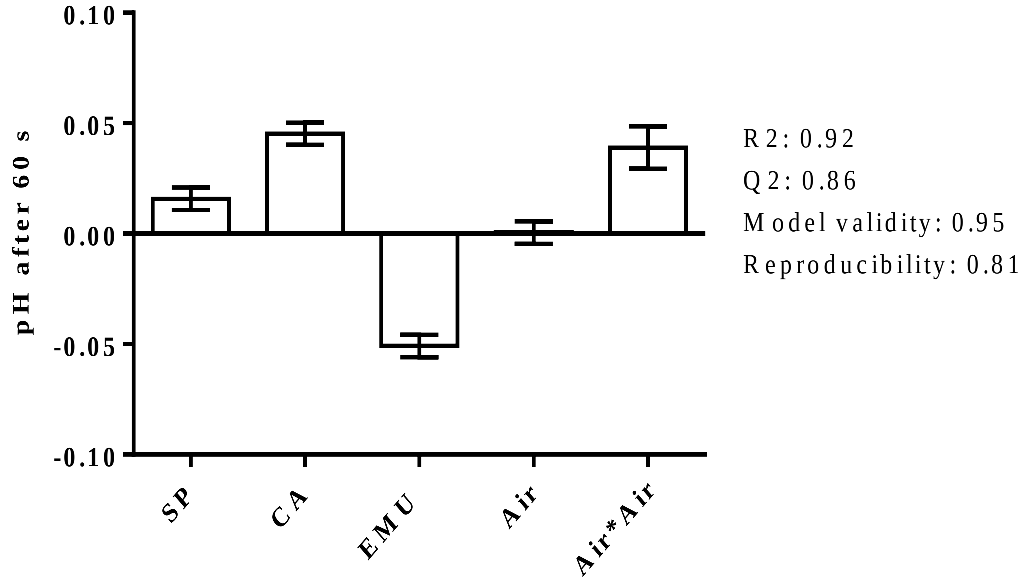
Output parameter: Taste masking efficiency (in vitro pH measurement)

- **Coating Amount (CA)**
- **Air flow rate – quadratic term (Air²)**
- **Spray Pressure (SP)**
  Increasing CA/Air/SP:
  improved taste masking

- **Emulsifier Content (EMU)**
  Increasing EMU:
  degraded taste masking



Coated Crystals
Polymorphic Behaviour

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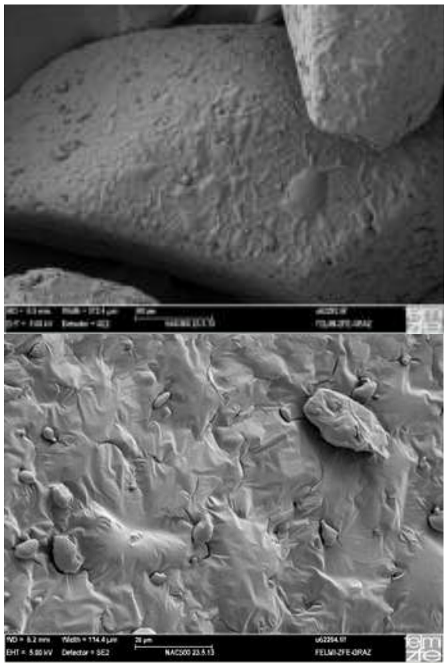
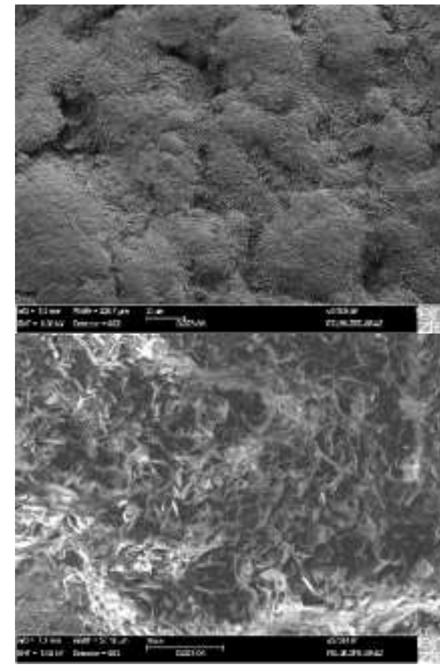


SEM picture of API-Crystal without coating

HMC-Process
„blooming“ of the surface due to
$\alpha \rightarrow \beta$ transformation



SEM picture of API-Crystal coated with a lipid/emulsifier mixture

Significant changes in the dissolution profile during storage induced?

Stability Study

Dissolution immediate release

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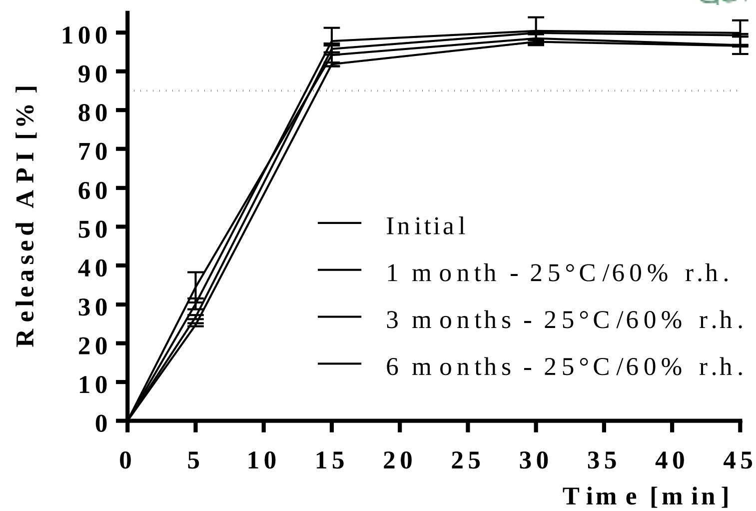
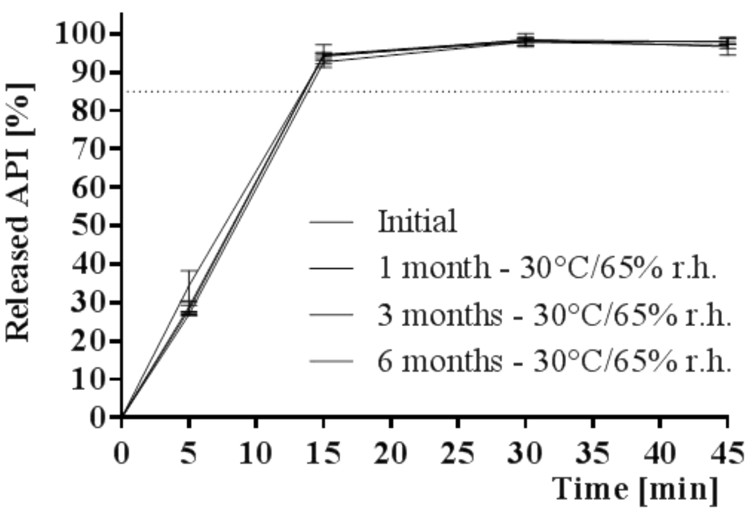
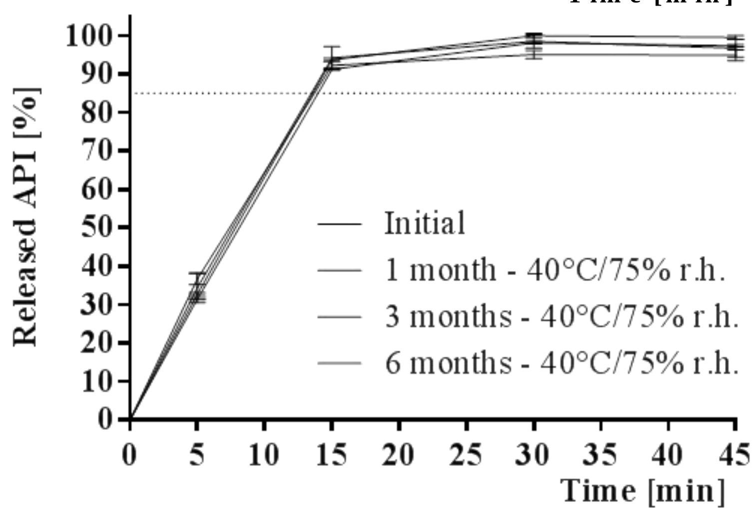
Specification Limits:
85% in 30 min







HMC – Summary – Conclusion

Hot-Melt Coating: An available and proved alternative technology to replace conventional Polymer Coatings

HERMES PHARMA
Get the dose right.™

Process Technology

- Very short processing times in comparison to conventional coatings
- Robust and reproducible process
- Easy/simple scale-up
- PAT solutions to control and determine the product quality
- No window fouling on probe in pilot and production plant
- PAT controls the endpoint of the coating process in real time

HMC – Summary – Conclusion

Hot-Melt Coating: An available and proved alternative technology to replace conventional Polymer Coatings

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Pharmaceutical Aspects

- Taste masking for user friendly **O**ral **S**olid **D**osage forms achievable
- Excellent bio-availability
- Increased customers convenience
- Stable product over shelf life
- Immediate release profile and reliable taste masking
- Significant cut of business costs and increase of profitability
- Solvent free – Green Pharma
- Sustained and controlled release (Enteric Coating) achievable

PHARMAprocess

Innovation Forum in Pharmaceutical Process

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