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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

www.pharmaprocessforum.com
Part 1
Latest Fluid Bed Systems for Granulation and Coating for Hotmelt Applications

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

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

<table>
<thead>
<tr>
<th>Process data</th>
<th>Hot Melt process</th>
<th>Standard process</th>
</tr>
</thead>
<tbody>
<tr>
<td>Process time</td>
<td>1h</td>
<td>5 h</td>
</tr>
<tr>
<td>Quantity of air</td>
<td>6000 m³/h</td>
<td>6000 m³/h</td>
</tr>
<tr>
<td>Inlet air temp.</td>
<td>Not heated</td>
<td>70 °C</td>
</tr>
<tr>
<td>Melt temp./liquid temp.</td>
<td>90 °C</td>
<td>20 °C</td>
</tr>
<tr>
<td>Temp. of spray air</td>
<td>90 °C</td>
<td>60 °C</td>
</tr>
</tbody>
</table>

Calculation basis:

- $c_p$ wax/fat: 2,7 J/g/K
- Melt enthalpy $H$ wax/fat: 160 J/g
**Hotmelt Advantages: Energy Consumption**
in a Romaco Innojet V 400 (400 ltr. process batch)

<table>
<thead>
<tr>
<th></th>
<th>Hot Melt process</th>
<th>Standard process</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heating up the inlet</td>
<td>- - -</td>
<td>5 h x 125 kW = 500 kWh</td>
</tr>
<tr>
<td>air</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heating up the</td>
<td>10,5 kWh</td>
<td>- - -</td>
</tr>
<tr>
<td>melt/wax</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Melting energy wax</td>
<td>200 kg wax = 8,8 kWh</td>
<td>- - -</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spray air heating</td>
<td>1 h x 15 kW = 15 kW</td>
<td>5 h x 10 kW = 50 kWh</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tube/ house/ nozzle</td>
<td>1 h x 2 kW = 2 kW</td>
<td>- - -</td>
</tr>
<tr>
<td>heating</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>36, 3 kWh</td>
<td>550 kWh</td>
</tr>
</tbody>
</table>
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
Starter: 250 g granules
50 % coating -> 125 g fat/wax
Spray rate: 7 g/min
Process time: 18 min

Taste masking with polymer dispersion:
15% polymer in dispersion
125 g polymer – 833 g dispersion
Spray rate: 7 g/min
Process time: 120 min
(5 g/min - 170 min)
Product Sample: Taste masking of bitter tasting API

Process parameters

Starter material: 500 g crystals

Final product: 1000 g coated crystals

Proces time: 115 min
Spray rate: 3.6 – 8 g/min
Product Sample: Malic Acid Crystals protected against humidity

• +30% fat, size 200µm – 500µm
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

<table>
<thead>
<tr>
<th>Laboratory scale</th>
<th>Pilot scale</th>
<th>Production scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>V 2.5 - 1</td>
<td>V 10</td>
<td>V 600</td>
</tr>
<tr>
<td>V 5</td>
<td>V 25</td>
<td>V 800</td>
</tr>
<tr>
<td></td>
<td>V 50</td>
<td>V 1000</td>
</tr>
</tbody>
</table>
Romaco Innojet VENTILUS® Granulation & Coating System
Romaco Innojet VENTILUS®
3-in-1 System for Drying, Granulation & Coating

int. pat., developed by Dr. h.c. Herbert Hüttlin
Romaco Innojet VENTILUS®
Hotmelt device IHD

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

Laboratory scale

Production scale
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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Romaco Innojet VENTILUS®
1st Controlled Particle Movement – Homogeneous Temperature Supply
Booster ORBITER type IBO

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

air guiding blades – rear side

int. pat., developed by Dr. h.c. Herbert Hüttlin
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
Romaco Innojet VENTILUS®
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 %

int. pat., developed by Dr. h.c. Herbert Hüttlin
Romaco Innojet VENTILUS®
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.

int. pat., developed by Dr. h.c. Herbert Hüttlin
Romaco Innojet VENTILUS®
Booster ORBITER

The Innojet Booster Orbiter
int. patented
Romaco Innojet VENTILUS®
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)
int. pat., developed by Dr. h.c. Herbert Hüttlin
Romaco Innojet VENTILUS®
2\textsuperscript{nd} Controlled and Precise Spray Supply
Comparison spray nozzle ROTOJET vs. conventional nozzles

ROTOJET (all sizes)         Two-substance spray nozzles

Droplet size

Spray pressure

Prod. Scale (center diameter 1.2 – 1.8 mm)
Lab. Scale (center diameter 0.5 – 0.8 mm)
Romaco Innojet VENTILUS®
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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Romaco Innojet VENTILUS®
Spray nozzle ROTOJET
Romaco Innojet VENTILUS®
Functional principle of booster ORBITER and spray nozzle ROTOJET

Product movement and nozzle spray work into the same direction

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Romaco Innojet VENTILUS®
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
Romaco Innojet VENTILUS®
3rd Controlled and Permanent Powder Recovery System SEPAJET

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

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

simple and fast change of filter set
Romaco Innojet VENTILUS®
3rd Controlled and Permanent Powder Recovery System SEPAJET

Stainless steel carrier basket with textile filters

int. pat., developed by Dr. h.c. Herbert Hüttlin
Romaco Innojet VENTILUS®

3rd Controlled and Permanent Powder Recovery System SEPAJET

Comparison conventional filters vs. SEPAJET

- 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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Romaco Innojet VENTILUS®
Powder recovery system SEPAJET
Romaco Innojet VENTILUS®
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
Romaco Innojet VENTILUS®
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
Romaco Innojet VENTILUS®
Laboratory System – Pilot Plant – Production Scale
Romaco Innojet VENTILUS®
Laboratory System – Pilot Plant – Production Scale

Machine opened
GMP compliant access to inner parts of the machine

Contamination free loading – unloading
Discharge container (closed discharge)
Romaco Innojet VENTILUS®
Laboratory System – Pilot Plant – Production Scale

GMP compliant access to inner parts of the machine

GMP compliant change of spray nozzle – available in-process
Romaco Innojet VENTILUS®
Laboratory System – Pilot Plant – Production Scale
Romaco Innojet VENTILUS®
Laboratory System – Pilot Plant – Production Scale

3-in-1 Multi Purpose System

Endproduct

Enteric Coating

API

Starter

Micro Tablets

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

EXAMPLE:
MUPS – Multi Unit Particles Systems implemented in RDT or in Capsules, Stick Packs
Romaco Innojet VENTILUS®
Laboratory System – Pilot Plant – Production Scale

EXAMPLE: Film Coating, Crop Protection

Flower Seeds Coating
• homogeneous & fast
• gentle & reproducible
• no agglomerations
Romaco Innojet VENTILUS®
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
Contact:
e-mail: innojet@romaco.com
Romaco Innojet GmbH
Daimlerstr. 7
79585 Steinen | Germany
Int. Pat. Granulation & Coating Technology
www.romaco.com
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Part 2

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

New Taste Masking Technology
to Facilitate User-Friendly Pharmaceuticals

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

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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

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

**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)
QTPP
Formulation Development Strategy

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 β-form)
→ Additional: lower process temperatures applicable
Screening DoE (Frac Fac Res IV) for linear interactions

Definition of Critical Process Parameters as Input Parameters:

- Spray Rate (SR)
- Spray Pressure (SP)
- Coating Amount (CA)
- Emulsifier Content (EMU)
- Air Flow Rate (Air)
DoE
Interaction with Critical Quality Attributes

**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

![Graph showing the interaction between EMU and CA on dissolution rate](image-url)

- R2: 0.87
- Q2: 0.82
- Model validity: 0.57
- Reproducibility: 0.99
DoE
Interaction with Critical Quality Attributes

**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

R²: 0.92
Q²: 0.86
Model validity: 0.95
Reproducibility: 0.81
Coated Crystals
Polymorphic Behaviour

HMC-Process
„blooming“ of the surface
due to
α→β transformation

SEM picture of API-
Crystal without coating

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

Specification Limits:
85% in 30 min
HMC – Summary – Conclusion

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

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

Pharmaceutical Aspects

- Taste masking for user friendly Oral Solid Dosage 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
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