EQUIPMENT AND PROCESSING
Fluid Bed Granulation

Maroglou, 1986
EQUIPMENT AND PROCESSING
Psychrometric Chart
EQUIPMENT AND PROCESSING
Fluid Bed Granulation Process

- Particles are suspended in the hot air stream.
- The atomized liquid is sprayed
- Top spray granulation
- Tangential spray granulation
  - rotary granulation
EQUIPMENT AND PROCESSING
Fluid Bed Top Spray Granulation Process
EQUIPMENT AND PROCESSING
Top Spray Fluid Bed Granulation Process

Vector Inc
EQUIPMENT AND PROCESSING
Fluid Bed Rotor (Tangential Spray) Granulation Process
EQUIPMENT AND PROCESSING
Fluid Bed Rotor (Tangential Spray) Granulation Process

Glatt GRG 120/200 Rotor
1400 mm dia disc
5 - 25 m/s circumf. Speed
70 - 340 rpm
6000 m³/h air flow

Glatt Brochure
EQUIPMENT AND PROCESSING
Assessment of Fluid Bed Granulation

- Single process step for mixing, granulating, drying
- Relative ease of process control and validation
- Lighter granules (dissolution, chewable tab.)

- Limitation:
  - cohesive material
  - dust explosion potential
<table>
<thead>
<tr>
<th>Binder</th>
<th>Characteristics of primary particles</th>
<th>Process parameters of the Fluid Bed</th>
<th>Granule growth stages</th>
<th>Balance between bonding forces and breakup force to control growth</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nucleation</td>
<td>Transition</td>
<td>Ball growth</td>
<td></td>
</tr>
</tbody>
</table>
EQUIPMENT AND PROCESSING
Fluid Bed Granulation Equipment Variables

• Air Distributor Plate
  – low density drug requires low fluidizing velocity
• Fliter Bag Shaker
• Granulator Bowl Geometry
EQUIPMENT AND PROCESSING
Fluid Bed Granulation Process Variables

- Linear relation between size of granules & droplets
- Granule size increases with increasing binder concentration
- Inlet Temperature
- Air Volume
- Dew Point
- Droplet size
  - Spray rate
  - Atomization air pressure/volume
- Solids content
- Product Temperature
- Exhaust Temperature
EQUIPMENT AND PROCESSING
Fluid Bed Granulation End Point

Combination of:

- Exhaust temperature
- Bed temperature
- Drying time
EQUIPMENT AND PROCESSING
Scale-Up Fluid-Bed Processes

• Process air temperature
  – Selected to achieve desired product temperature
  – Adjusted with process air volume

• Process air volume
  – Produces fluidization pattern
  – Delivers heat to the product
  – Changes should be at the same time and magnitude (batch to batch)
EQUIPMENT AND PROCESSING
Spray Drying Granulation Process

Process to convert pumpable liquid into a free flowing powders

Spray drying is instant moisture removal
EQUIPMENT AND PROCESSING
Spray Drying Granulation Process

1. Source of hot gas
2. Atomized liquid
3. A place to mix them in
4. A device to separate the powders
EQUIPMENT AND PROCESSING
Spray Drying Co-current Process
EQUIPMENT AND PROCESSING

Spray Drying Two Fluid Nozzle

Two Fluid Nozzle

Good for small particles 5 - 50µm

Quantity and pressure of atomization
air controls particle size
Spray Drying Two Fluid Nozzle
EQUIPMENT AND PROCESSING
Spray Drying Pressure Nozzle

Pressure Fluid Nozzle

Narrow particle size distribution

Large particles, less fines (30->100μm)

High pressure pump required (500-2000 psi)

May need a larger tower for larger particles
EQUIPMENT AND PROCESSING
Spray Drying Rotary Nozzle

Rotary Nozzle

- Narrowest particle size distribution
- Largest particle size range (15-100 µm)
- Good Scalability
  - Less potential for plugging
  - More complex system
## EQUIPMENT AND PROCESSING

**Particle Size From Spray Drier - Nozzle Type Combination**

<table>
<thead>
<tr>
<th>Size</th>
<th>Nozzle Type</th>
<th>Particle Size</th>
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<tbody>
<tr>
<td>1</td>
<td>Rotary</td>
<td>30 um</td>
</tr>
<tr>
<td></td>
<td>2 Fluid</td>
<td>30 um</td>
</tr>
<tr>
<td>2</td>
<td>Rotary</td>
<td>40-50 um</td>
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<tr>
<td></td>
<td>2 Fluid</td>
<td>60-80 um</td>
</tr>
<tr>
<td>4</td>
<td>Rotary</td>
<td>80-100 um</td>
</tr>
<tr>
<td></td>
<td>2 Fluid</td>
<td>80-100 um</td>
</tr>
<tr>
<td></td>
<td>Press</td>
<td>&gt;100 um</td>
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</table>
EQUIPMENT AND PROCESSING
Spray Dried Powder

- Free Flowing
- Dust Free
- Controlled Particle Size Distribution
EQUIPMENT AND PROCESSING
Spray Drying Advantages

Amorphous Powders

Molecular to Colloidal Drug Substance Dispersion
  Dissolution/Bioavailability
  Content Uniformity

Enhanced Physical Properties
  Flow
  Compressibility
EQUIPMENT AND PROCESSING
Spray Drying Applications

Drug Matrix Formation

Solid Dispersions
  Solids Solution

Modified Release
  Taste Masking
  Enhanced Solubility/Bioavailability
EQUIPMENT AND PROCESSING
Drying Unit Operation

Tray Drying

Fluid Bed Drying

Microwave Drying
Moisture bonding mechanisms

- bonded on the surface of the granules
- bonded inside the granules (capillary attraction)
- hygroscopically / chemically bonded...
EQUIPMENT AND PROCESSING
Tray Drier

• Heated, inlet air enters chamber from bottom
• Paper-lined trays hold granules
  - Spread evenly to promote uniform drying
• Perforated trays to improve air flow through granule bed
• Exhaust air emitted through top
EQUIPMENT AND PROCESSING - Fluid Bed Drier

- **Filter Housing**
  - Traps product which has become entrained in the exiting air stream
  - Agitated to allow particles to return to the product container

- **Expansion Chamber**
  - Cylindrical in shape
  - Area of fluidization/drying

- **Product Container**
  - Conical in shape
  - Bottom screen to retain product while allowing air flow through the product bed
EQUIPMENT AND PROCESSING
Critical Process Parameters

- Humidity of Inlet Air
- Inlet Air Volume
- Inlet Air Temperature
EQUIPMENT AND PROCESSING
ΔT Drying

- From Development Work It’s Been Established That a Δt of Correlates to an Acceptable Endpoint LOD
- In Example, the Product Is Dried to a Product Temperature of 47.9°C to Achieve an LOD of 4.1%

<table>
<thead>
<tr>
<th>Drying Time</th>
<th>Incoming Air Temperature</th>
<th>Product Temperature</th>
<th>Wet Bulb Temperature</th>
<th>Product Temperature Difference</th>
<th>LOD</th>
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</thead>
<tbody>
<tr>
<td>[min]</td>
<td>[°C]</td>
<td>[°C]</td>
<td>[°C]</td>
<td>[°C]</td>
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</tr>
<tr>
<td>0</td>
<td>60</td>
<td>-</td>
<td>24</td>
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<tr>
<td>15</td>
<td>60</td>
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<td>0</td>
<td>27.9</td>
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<td>30</td>
<td>60</td>
<td>27.1</td>
<td>24</td>
<td>3.1</td>
<td>17.4</td>
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<tr>
<td>50</td>
<td>60</td>
<td>36.3</td>
<td>24</td>
<td>12.3</td>
<td>7.5</td>
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<tr>
<td>60</td>
<td>60</td>
<td>47.4</td>
<td>24</td>
<td>23.4</td>
<td>4.5</td>
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<td>62</td>
<td>60</td>
<td>47.9</td>
<td>24</td>
<td>23.9</td>
<td>4.1</td>
</tr>
</tbody>
</table>
EQUIPMENT AND PROCESSING
Microwave Drying Techniques

- Microwave - Vacuum Drying
- Combination of Microwave Plus Gas Assisted Drying
In an electric field, the charges of dipolar material are polarized and oriented according to the direction of the field.

The used microwave frequency (2450 MHz) creates a rapidly alternating electric field.

At 2450 MHz, the field is alternating at a rate of 2450 million times per second.

At this rate, the orientation polarization effect gives rise to internal friction phenomena, producing heat.
**Microwave Drying Principles**

P = \(2\pi f v^2 E_0 E_r \tan \delta\)

- **P** = energy absorbed by material exposed to microwave energy (Watt/m³)
- For a given electrical field strength \(v\), \(2\pi f v^2 E_0\) is constant and **P** (power absorbed) is proportional to: \(E_r \tan \delta\)

**Known as:** LOSS FACTOR

**Transparent material:** low loss factor

**Absorbers:** high loss factor

**Microwave Properties**

- **Reflection**: e.g. Metals
- **Transmission**: e.g. Rubber
- **Absorption**: e.g. Rubber
EQUIPMENT AND PROCESSING
Microwave Drying Principles

Additional energy supply by microwaves:

Preferential heating of products with a high loss factor (water, solvents), negligible heating of products with a low loss factor (most pharmaceutical excipients)

Result: faster evaporation, reduced drying times
EQUIPMENT AND PROCESSING
Vacuum Drying Principles

The boiling point of liquids is lower at lower pressures.

By applying vacuum in the bowl, the boiling point of the granulation liquid used is significantly decreased.

Lower energy supply and lower temperatures needed for drying
EQUIPMENT AND PROCESSING
Vacuum Drying - Temperature and Pressure Relationship

Temperature (°C)

Pressure (mili bar)

- ETHANOL
- METHANOL
- I-PROANOL
- ACETONE
- METHYLENE CHLORIDE

water
EQUIPMENT AND PROCESSING
Vacuum Drying Principles

Is Influenced by the Solvent Used

Enthalpy of vaporization (kJ/kg)

- Water 20 mbar
- Water
- Isopropanol
- Ethanol
- Methanol
- Acetone
- Methylene chloride

organic solvents will evaporate 4 to 5 times quicker than water (on fixed energy input)
EQUIPMENT AND PROCESSING
Vacuum Drying Scale-up

– Limited energy supply and thus long drying time
– Scale up of drying time not linear due to difference in ratio of working volume and contact surface
EQUIPMENT AND PROCESSING
Gas Assisted Drying

During Vacuum Drying, Inert Gas Is Passed Through the Product in Order To:

- Improve the Transport of Moisture From the Granules to the Vacuum System
- Increase the Partial Pressure Drop Across the Vessel
- Improve the Heat Transport Through the Bed
- Mix the Product Gently When It Becomes Dry and Fragile
EQUIPMENT AND PROCESSING
End-Point Analysis

Composition:
- Lactose: 72.7%
- Corn Starch: 18.2%
- Prejel PA5: 9.1%
- Water: 17.5%

Graph showing LOD [%] over time for Microwave, Gas Assisted and Vacuum, and Pure Vacuum processes.
EQUIPMENT AND PROCESSING
Characteristics of the Collette Vacuum System

- Highly efficient vacuum system (roots blower + vacuum pump)*
- Energy supply through heated jacket of lid and bowl
- Liquid recovery unit (1 or 2 condensers)

* The roots blower is integrated for machines ≥ ULTIMA 75
EQUIPMENT AND PROCESSING
Collette Vacuum System
EQUIPMENT AND PROCESSING
Collette Vacuum System

Removable inserts

Product

water jacket
Control of drying process by means of product temperature and power detection
EQUIPMENT AND PROCESSING
Melt Extrusion

Melt Extrusion is a suitable process for preparation of solid dispersions and for the enhancement of dissolution for poorly water-soluble drugs.

Melt Extrusion is a versatile application with precise monitoring systems:
- Feeding
- Melting Temperature control
- Mixing

Melt Extrusion is relatively new to the pharmaceutical industry.
Global Technical Research & Development

EQUIPMENT AND PROCESSING
Melt Extrusion

POORLY WATER-SOLUBLE DRUG

Tablet/Capsule
Disintegration
Large Solid Particles (Usually 5-100 microns)
Lower Dissolution Rate
Absorption into Body Systems

Dosage Form

Drug in G.I. Tract

Solid Dispersion/Solution
Disintegration
Colloidal Particles/Fine Oily Globules (Usually <1 micron)
Higher Dissolution Rate

Serajuddin, 1999
EQUIPMENT AND PROCESSING
Melt Extrusion

Carrier materials: PVP, PEG, Eudragit, HPMC, etc.

- Polyethylene Glycols (PEGs) - Crystalline
  Molecular weights of 4000 - 6000 are most common

- Polyvinylpyrrolidone (PVPs) - Amorphous
  Molecular weights of 2500 to 3000000 (K value)

Plasticizers: Water, PEGs, triethyl citrate (TEC), Sorbitol
  Lower Tg of material and torque

Surfactants: Sodium Lauryl Sulfate, Poloxamer

Antioxidants: BHT, BHA
EQUIPMENT AND PROCESSING
Melt Extrusion
EQUIPMENT AND PROCESSING

Melt Extrusion
EQUIPMENT AND PROCESSING
Melt Extrusion - 16 mm Twin - Screw Extruder
EQUIPMENT AND PROCESSING
Melt Extrusion - 16 mm Clam Shell Design
EQUIPMENT AND PROCESSING
Particle Coating - Fluid Bed

• Applying Polymeric Coating to Spheres Containing or Layered with Drug

• Layering Spheres with Drug Substances
EQUIPMENT AND PROCESSING
Particle Coating - Coating

- Coating Droplets
  - water evaporation

- Substrate Contact
  - water evaporation

- Close Packed Spheres
  - water evaporation
  - droplet coalescence

- Polymer Film
EQUIPMENT AND PROCESSING
Particle Coating - Layering

Layering Particles
water evaporation

Substrate Contact
water evaporation

Layered Particles
water evaporation
polymer film formation
Sugar Starch Spheres (Nu-Pareils)  
60 - 80 mesh (215 um),  
16 - 18 mesh (1000 um)
Particle Coating - Fluid Bed Basic Design Layout
Particle Coating - Theoretical Considerations

Coating Equations $\Delta H = 0$

$$m_{a1}h_{a1} + m_{v1}h_{v1} + m_{liq}h_{liq} = m_{a2}h_{a2} + m_{v2}h_{v2}$$

$m_{a1}$ = mass of dry air in
$h_{a1}$ = enthalpy of air in
$m_{v1}$ = mass of water vapor in
$h_{v1}$ = enthalpy of water vapor in
$m_{liq}$ = mass of water in
$h_{liq}$ = enthalpy of water in
$m_{a2}$ = mass of air out
$h_{a2}$ = enthalpy of air out
$m_{v2}$ = mass of water vapor out
$h_{v2}$ = enthalpy of water vapor out

Ebey, G., Pharm. Tech., April 1987, pages 40-50
EQUIPMENT AND PROCESSING
Particle Coating - Formulation Variables

- Substrate (Sugar/Starch Spheres)
- Substrate Particle Size
- Substrate Density
- Coating Composition (latex, suspension, solution)
- Coating Concentration
- Coating Viscosity
EQUIPMENT AND PROCESSING

Particle Coating - Process Variables

- Inlet temperature
- Outlet temperature
- Inlet/Outlet Air flow
- Spray Rate
- Atomization Pressure
EQUIPMENT AND PROCESSING
Particle Coating - Equipment Variables

Type Spray (Top, Bottom & Tangential)

Top Spray - Location in Expansion Chamber
Design of the expansion Chamber

Bottom Spray - Width of Column Partition
Length of Column Partition
Gap of Column Partition
Bottom Plate Design

Tangential Spray - Size of Disc
Texture of the Disc
Speed of the Disc
Nip between Disc and Wall
EQUIPMENT AND PROCESSING
Particle Coating - Top Spray Process

Glatt Company Brochure
EQUIPMENT AND PROCESSING
Particle Coating - Top Spray Process
EQUIPMENT AND PROCESSING
Particle Coating - Bottom Spray (Wurster) Process

Glatt Company Brochure
EQUIPMENT AND PROCESSING
Particle Coating - Bottom Spray Process
EQUIPMENT AND PROCESSING
Particle Coating - Tangential Spray Rotor Process
EQUIPMENT AND PROCESSING
Particle Coating - Tangential Spray Rotor Process

Glatt Fluid Bed Rotor Granulator, Type GPG 120/200
In 2 bar pressure shock resistant construction
EQUIPMENT AND PROCESSING
Particle Coating - Top Spray Process

Granulated pharmaceutical  Top spray enteric coated pharmaceutical

Glatt Company Brochure
EQUIPMENT AND PROCESSING
Particle Coating - Bottom Spray (Wurster) Process

Wurster HS latex coated pharmaceutical (particle size < 150 μm)
Wurster layered and coated
Wurster HS latex coated pharmaceutical (particle size < 150 μm) (cross-section)
EQUIPMENT AND PROCESSING
Particle Coating - Bottom Spray (Wurster) Process
EQUIPMENT AND PROCESSING
Particle Coating - Bottom Spray (Wurster) Process
EQUIPMENT AND PROCESSING
Particle Coating - Tangential Spray Rotor Process

Glatt Brochure
EQUIPMENT AND PROCESSING
Particle Coating - Spray Systems

Single Head Nozzle

Uni-Glatt/Versa-Glatt Nozzle
(Granulation)
EQUIPMENT AND PROCESSING
Particle Coating - Nozzle Droplet Size Distribution
# Equipment and Processing

## Particle Coating - Equipment Application Assessment

<table>
<thead>
<tr>
<th>Property</th>
<th>Top</th>
<th>Bottom</th>
<th>Tangential</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Process:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simplicity</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Nozzle Access</td>
<td>3</td>
<td>1</td>
<td>2</td>
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<tr>
<td>Scale-Up</td>
<td>3</td>
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<tr>
<td>Mechanical Stress</td>
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<td><strong>Product:</strong></td>
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<tr>
<td>Film Quality</td>
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<td>Coating Uniformity</td>
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<td>Coating Efficiency</td>
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<tr>
<td>Layering Capacity</td>
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<tr>
<td>Equipment Cost</td>
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Rubino, O., Pharm. Tech., June 1999