The World Leader in Serving Science

We are the leading provider of analytical instruments, equipment, reagents and consumables, software and services for research, analysis, discovery and diagnostics.

Leading Brands

- **Size and Scale**
  - $10.5 billion in revenues
  - 35,000 employees in 40 countries
  - Serving 350,000 customers in 150 countries
  - Fortune 300 company

- **Unmatched Capabilities**
  - Complete portfolio
  - World-class technologies
  - Commercial and service strength
The World Leader in Serving Science

Thermo’s world-class analytical technologies + New capabilities acquired from Fisher

- New brand stands for innovation and quality
- Thermo instruments plus new reagents, consumables and equipment
- Even better laboratory workflow solutions

Famous catalogs and supply-chain services

- Mark of choice and convenience
- Complete product portfolio of equipment & supplies
- One-stop, total lab supplier

All from Thermo Fisher Scientific
Historical brand names part of ThermoScientific:
Pharma Twin Screw Extruders 2010

Hot Melt Extrusion

Twin Screw Granulation

Information HME
Product Portfolio HME

Information TSG
Product Portfolio TSG

Customized Solutions
Introduction Hot Melt Extrusion
HME – What’s your challenge today?

- Limited by your API
- Poor solubility
- Taste masking
- New dosage concepts
- New delivery methods
- New capsule materials
Where is pharmaceutical Hot Melt Extrusion?

“For both the pharmaceutical industry and the academic community HME became an innovative drug delivery technology that is receiving increased attention. HME turned now into highly dynamic, interdisciplinary topics that provide a creative link between engineering and pharmaceutical sciences for the purposes of drug delivery.

Research in these vibrant research areas is making significant advances resulting in innovative, engineered drug delivery systems.”

Source:
What is Hot Melt Extrusion?

*Processing of polymeric materials above their glass transition temperature \( (T_g) \) in order to effect molecular level mixing of thermoplastic binders and/or polymers and active compounds*

Melt extrusion is a combination of melting and mechanical energy with advantages like:

- Continuous
- Reproducible
- Reasonably high throughput
- Dust reduction
- On-line-monitoring
Biopharmaceutics Classification Scheme

- **Class I**: High Solubility, High Permeability
- **Class II**: Low Solubility, High Permeability
- **Class III**: High Solubility, Low Permeability
- **Class IV**: Low Solubility, Low Permeability

- Permeability: 90%
- Solubility: 0.1 mg/ml
# Why Hot Melt Extrusion

<table>
<thead>
<tr>
<th>Problem</th>
<th>Solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Poor API stability during processing</td>
<td>Use of melt extrusion as alternative to wet agglomeration (no hydrolytic stress, no drying)</td>
</tr>
<tr>
<td>2 Poor (low/unreliable) bioavailability due to poor API solubility</td>
<td>Use of melt extrusion to prepare solid dispersion or SEDDS (=enhanced dissolution)</td>
</tr>
<tr>
<td>3 Poor compliance due to short dosing interval (=short half life of API)</td>
<td>Use of melt extrusion to prepare sustained release dosage form (single/multiple units)</td>
</tr>
<tr>
<td>4 Poor stability or tolerability of API in stomach</td>
<td>Use of melt extrusion to prepare enteric dosage form (single/multiple units)</td>
</tr>
<tr>
<td>5 Poor taste of API</td>
<td>Use of melt extrusion to prepare taste-masked pellets</td>
</tr>
<tr>
<td>6 Special dosage form designs (films, rods, hollow cylinders etc.)</td>
<td>Use of melt extrusion to achieve special shape</td>
</tr>
</tbody>
</table>
## Different Types of Solid Dispersions/Solutions

<table>
<thead>
<tr>
<th>Polymer:</th>
<th>Drug:</th>
<th>Thermo-dynamic Stability</th>
</tr>
</thead>
<tbody>
<tr>
<td>amorphous</td>
<td>crystalline</td>
<td>almost stable</td>
</tr>
<tr>
<td>amorphous</td>
<td>amorphous</td>
<td>unstable (kinetically controlled)</td>
</tr>
<tr>
<td>amorphous</td>
<td>molecularly dissolved</td>
<td>stable (drug below saturation solubility)</td>
</tr>
</tbody>
</table>
Pharmaceutical Development Needs

- Consistent, small scale production.
- Low consumption of expensive materials.
- Easy cleaning with simple verification.
- Flexibility for new product development.
- Reliable and repeatable operating conditions.
- Accurate process data for product audit.
How Extrusion Technology can support you…

- Hot melt extrusion supports you by establishing stable solid solutions which increase the availability of poorly soluble ingredients,
- A continuous steady state process monitored by process control allows you to minimize failed batches
- Extrusion technology allows you to produce new drug dosage forms e.g. mini implants
- Melt extrusion allows you to reduce the consumption of solvents - for instance in comparison with the wet granulation process
- and many other good reasons …

Extrusion technology is a mature process used in the polymer industry for more than 40 years and in the pharmaceutical for approx. >20 years known.
Validation Aspects

Regulatory aspects of melt extrusion:

Hot melt extrusion has a comprehensive documentation, which satisfy regulatory authorities

Melt extrusion is a mature technology

Measurable parameters such as feeding rate, equipment temperatures, discharge pressure, vacuum control, etc. can be monitored on-line with local sensors. Data logging provides supporting documentation to ensure the quality of production lots and simplify quality control.

Use of in-line sensors PAT provide a good basis for the FDA – QbD initiative
Product Portfolio Hot Melt Extrusion

Product Portfolio HME
Twin Screw Solutions for HME

16 mm Line

MiniLab

EuroLab

PharmaLab 16

PharmaLab 24

24 mm Line

MiniLab Pharma MiniLab
Phases of Pharmaceutical Development

Constraints
- Quantity of API
- Quality of API
- Consistent quality of Drug product
- Time

<table>
<thead>
<tr>
<th>Chemistry</th>
<th>Medicinal</th>
<th>Kilogramme Lab</th>
<th>Process Chemistry</th>
<th>Production Site</th>
<th>Production Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>API Batch Size</td>
<td>mg - g</td>
<td>0.2 - 10 kg</td>
<td>10 – 100 kg</td>
<td>1,000 kg</td>
<td>1,000 kg</td>
</tr>
<tr>
<td>Process Batch</td>
<td>10 g</td>
<td>0.2 - 5 kg</td>
<td>5 – 50 kg</td>
<td>100 – 500 kg</td>
<td>500 kg</td>
</tr>
<tr>
<td>Testing</td>
<td>In Vitro &amp; Animal</td>
<td>Safety in Human</td>
<td>Safety and Efficacy</td>
<td>Market</td>
<td>Market</td>
</tr>
</tbody>
</table>
# The Solution for your Phase

![Flowchart showing the phases of drug development](image)

<table>
<thead>
<tr>
<th>Chemistry</th>
<th>Medicinal</th>
<th>Kilogramme Lab</th>
<th>Process Chemistry</th>
<th>Production Site</th>
<th>Production Site</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>API Batch Size</strong></td>
<td>mg - g</td>
<td>0.2-10 kg</td>
<td>10 – 100 kg</td>
<td>1,000 kg</td>
<td>1,000 kg</td>
</tr>
<tr>
<td><strong>Process Batch</strong></td>
<td>10 g</td>
<td>0.2-5 kg</td>
<td>5 – 50 kg</td>
<td>100 – 500 kg</td>
<td>500 kg</td>
</tr>
<tr>
<td><strong>Twin Screw Granulator</strong></td>
<td>Pharma Minilab</td>
<td>PharmaLab 16</td>
<td>PharmaLab 16 PharmaLab 24</td>
<td>PharmaLab 24</td>
<td>PharmaLab 24 scale out</td>
</tr>
<tr>
<td><strong>Process Output</strong></td>
<td>10 g</td>
<td>0.2-5 kg/h</td>
<td>0.2 – 5 kg/h 1 – 50 kg/h</td>
<td>1 – 50 kg/h</td>
<td>1 – 50 kg/h 25 – 100 kg/h</td>
</tr>
</tbody>
</table>
The MiniLab

HAAKE MiniLab – suitable e.g. for

☞ Proof of concept studies
☞ Creating specimen for drug delivery systems
☞ Your advantages of a Micro Compounders

☞ Substantial cost savings for proof of concept studies due to compounding of small quantities of ingredients (5 ml)
☞ Understanding of material characteristics by documenting structural changes via integrated viscosity measurement

☞ Flexible process conditions for different materials by
  ☞ Using conical or co-rotating screws
  ☞ Automatic bypass operation for extrusion/recirculation
  ☞ Force feeder especially for continuous powder feeding
Pharma MiniLab for Small Scale Production

**HAAKE Pharma MiniLab**

- Allows you e.g. to produce clinical trial samples for e.g. phase 1 when only a few grams of clinical material is needed
- No time delay due to long process development on a larger twin screw extruder
- The characteristics of our GMP Version are:
  - Without backflow channel
  - Force feeder for powder and small pellets
  - Stainless steel materials without painted parts
  - Password protected Software
Pharma MiniLab Features

Housing

§ No Painted parts
§ All sheet metal is made of stainless steel 1.4301 (304)
§ Air supply connectors made of stainless steel
§ Force feeder for powder

New developments of our standard Pharma MiniLab:

We are currently working on our next generation model which will show improvements regarding cleaning features with an open outlet area.
MiniLab Force Feeder for continuous feeding

**Force Feeder**
- Stainless steel No. 1.4404 (316 L)
- Roughness electro polished better than 0,8µm

**Force Feeder Screw**
- Stainless steel No. 1.4112 (440 B) – Passivated
- Surface roughness 0,8 µm.
EuroLab Pharma
EuroLab Pharma - maximum flexibility...

... Feed ports...

... Length ...

... Screw design ...

... Split Barrel
EuroLab Pharma - maximum flexibility…

*flexible screw configuration*
EuroLab Pharma - maximum flexibility...

... Split Barrel
EuroLab Pharma - maximum flexibility...
Parallel twin-screw extruder - Screw Elements:

**Conveying elements:**

Profiles with open chambers are used:
- in the feeding sections
- for melt exchange (longitudinal mixing)
- for degassing (venting)

Profiles with closed chambers are used:
- for high pressure built up
- in front of kneading elements
Rheomex PTW – Conveying Elements
Mixing Elements:

- Mixing Elements are used to introduce shear energy to the extruded materials.

- The disks are arranged in different offset angles used for:
  - plasticizing
  - shearing
  - mixing
  - dispersing
Mixing elements

TWIN-SCREW MIXING

Material follows a figure '8' path as it is constantly transferred from one screw to the other across the intermesh.

The mixing action is a combination of compression and expansion with smearing effects between screw to screw and screw to barrel wall.

The energy to melt the polymer comes from the mechanical energy of the shafts, (i.e. from the motor).

Inter-particulate friction causes rapid melting, and high shear is imparted during the high viscosity transition from solid to molten phase.
Distributive Flow Elements:

- Distributive Flow Elements are special mixing elements, used for the distribution of small quantities of additives and shear sensitive materials.

- The shearing energy introduced to the polymer is significantly lower than that of the kneading elements.
Screw elements:

- **SINGLE LEAD EXTRUSION SCREW**
  - 0° 040-0126 - Front
  - 90° 040-0127 - Rear

- **TWIN LEAD DISCHARGE SCREW**
  - 040-0521 - Normal
  - 040-4284 - Reverse

- **FEEDSCREW**
  - 040-0107 - Normal
  - 040-1568 - Reverse

- **HALF FEEDSCREW**
  - 040-0274 - Normal
  - 040-2745 - Reverse

- **FEEDSCREW**
  - 041-6023 - Short helix
  - 041-6024 - Long helix

- **2D FEEDSCREW**
  - 041-1025 - Normal helix
  - 041-5898 - Short helix
  - 041-5899 - Long helix

- **MIXING ELEMENT**
  - 040-0104 - 0° offset
  - 040-0105 - 90° offset

- **D/2 MIXING ELEMENT**
  - 041-2631 - 0° Offset
  - 041-2632 - 90° Offset

- **DISTRIBUTIVE FLOW ELEMENT**
  - 041-9999 - Quarter depth
  - 042-0000 - Half depth

- **FLOW RESTRICTOR ELEMENT**
  - 045-0135 - Ø 15.1 mm
  - 045-0133 - Ø 15.6 mm
  - 045-0134 - Ø 14.6 mm

- **FLOW RESTRICTOR SPACER**
  - 040-0272
Screw configuration (Standard Layout 75%)

Feed Screw

- Conveying sample
- only partly filled
- low shear

Mixing Element

- Melting & mixing
- completely filled
- high shear
Dispersive and Distributive mixing

- For nearly all mixing applications a well dispersed and well distributed mixture is required.

- Distributive mixing can be achieved by splitting and reorienting the flow repeatedly.

- Dispersive mixing can be achieved by passing the mixture through small regions of intense deformation.
EuroLab Pharma Features

- Product contact parts made from pharmagrade steel
- Material certificates available
- Removable and segmented top barrel
- Touchscreen control
- Integrated feeding solutions
- Integration of PAT (e.g. NIR) possible
## PharmaLab 16 and 24 – Technical Specs

<table>
<thead>
<tr>
<th></th>
<th>Pharma 16 HME</th>
<th>Pharma 24 HME</th>
</tr>
</thead>
<tbody>
<tr>
<td>Part Number</td>
<td>554-1136</td>
<td>2145</td>
</tr>
<tr>
<td>Barrel Length</td>
<td>25:1</td>
<td>30:1</td>
</tr>
<tr>
<td>L/D</td>
<td>40:1</td>
<td>40:1</td>
</tr>
<tr>
<td>Barrel Bore Diameter</td>
<td>16 16 16 16</td>
<td>24 24 24 24</td>
</tr>
<tr>
<td>Screw Diameter</td>
<td>15.6 15.6 15.6 15.6</td>
<td>23.6 23.6 23.6 23.6</td>
</tr>
<tr>
<td>Channel Depth</td>
<td>3.3 3.3 3.3 3.3</td>
<td>5.2 5.2 5.2 5.2</td>
</tr>
<tr>
<td>Centre-line Spacing</td>
<td>12.5 12.5 12.5 12.5</td>
<td>18.75 18.75 18.75 18.75</td>
</tr>
<tr>
<td>Centre-line to Radius ratio</td>
<td>1.56 1.56 1.56 1.56</td>
<td>1.56 1.56 1.56 1.56</td>
</tr>
<tr>
<td>Maximum Screw speed</td>
<td>500 1000 500 1000</td>
<td>500 1000 500 1000</td>
</tr>
<tr>
<td>Power at Maximum Speed</td>
<td>1.25 2.5 1.25 2.5</td>
<td>5.5 11 5.5 11</td>
</tr>
<tr>
<td>Torque per shaft</td>
<td>12 12 12 12</td>
<td>52.5 52.5 52.5 52.5</td>
</tr>
<tr>
<td>Torque/ (C-line$^3$)</td>
<td>6.1 6.1 6.1 6.1</td>
<td>8 8 8 8</td>
</tr>
<tr>
<td>Barrel zones</td>
<td>6 6 10 10</td>
<td>6 6 8 8</td>
</tr>
</tbody>
</table>
PharmaLab 16 Hot Melt Extruder

PharmaLab 16 HME
Process development studies
Producing samples for Clinical Trials

Advantages of a Pharma HME
Substantial cost savings for process development from compounding of samples (from 200g)

Significant time savings from ability to process multiple samples in succession.

Flexible process configurations for different materials from segmented screws and barrels.

Opportunities for multiple feed streams to minimise use of expensive API.

Special feeding accessories for difficult to handle ingredients.
PharmaLab 16 Features

- Product contact parts made from pharmagrade steel
- Stainless steel housing
- Material certificates available
- Full validation documentation available
- Removable and segmented top and bottom barrel
- Touchscreen control
- Integrated feeding solutions
- Automated start-up procedure available
- Integration of PAT (e.g. NIR) possible
- Based on casters, movable
PharmaLab 16 – Barrel and Screws Removal

- Barrel clamps
- Barrel clamps removed
- Upper barrel removed
- Lower liner and screws removed
PharmaLab 16 – Barrel and Screws Removal
PharmaLab 16 – Design Features

Design features

Stainless steel GMP construction.
No external painted parts.
Sheet metal base is made of stainless steel.

Process contact parts from pharma-grade through-hardened surgical stainless steel

Easily removable screws and barrels for cleaning or reconfiguration.

Adjustment of effective process length to minimise residence time.
PharmaLab 16 – Segmented Barrel
PharmaLab – Screw Length Adaption Kit

Adjustment of effective process length to minimize residence time.
Pharma 16 Air Cooled Conveyor Belt
Pharma 16 – Varicut and Twin Servo Pelletiser
Pharma 16 – Strand Pelletising Line
PharmaLab 24 Hot Melt Extruder
PharmaLab 16 – Barrel Liners and Screws Removal

Barrel close-up

Barrel open

Barrel liners and plugs removed

All contact parts removed
Pharma 24 Chill Roll – The Compact Cooling Solution

Flaker parts removed

Belt cartridge removed
Pharma 24 Chill Roll

Flaker removed

Interlocked roll guard

Nip gap adjustment

Roll opening handles
Pharma 24 Chill Roll Belt Cartridge

Pharma 24 Chill Roll
Removing the Belt Cartridge.

Belt Cartridge removed
Pharma 24 Chill Roll Flaker Cleaning

Pharma 24 Chill Roll (Opening Flaker)

Flaker parts removed
Pharma 24 Hot Melt Discharge Die Nozzle

- Long Reach Die Temperature Probe
- Die Pressure Probe
- Vacuum Vent Stack
- Discharge Nozzle
Pharma 24 Vacuum Venting

Air Bleed Control

Vacuum Gauge

Blocked Vent Indicator

Vacuum Vent Stack
Pharma 24 Feeding Solutions

Discharge Tube, Fitted with Flexible Bellows

Hopper Extension

Load Cell

Feeder Controller

Extruder Touch Screen
Pharma 16 and 24 Feeder Plattforms
Pharma 16 and 24 Feeder Arrangement
Pharma 24 HME Line with Chill Roll

Pharma 24 Chill Roll/Flaker

Vacuum Vent

Pressure Probe

Gravimetric Screw Feeder

PharmaLab 24 HME Twin Screw Extruder
Twin Screw Granulation

Introduction TSG
Reasons for Granulation

- To prevent segregation of the constituents of the powder mix
- Aid downstream processing by improving the physical characteristics of the mix in terms of:
  - Flow
  - Density
  - Dustiness
  - Compressibility
  - Etc.
Granulation

- **Wet granulation** involves the agglomeration of a mix of dry primary powder particles using a granulating fluid.
- The fluid, which is added during the granulation step, must be pharmaceutically safe and volatile enough so that it can be evaporated by a subsequent drying step.

- In **Melt granulation** the binding fluid is created by heating the formulation and causing one or more of the dry ingredients to become molten. Cooling the mix at the end of the granulation step solidifies the molten binder.
Pharmaceutical Batch Granulation

- Traditional batch processes
  - High speed wet granulation (like APV, GEA, Fielder.)
  - Roll Compaction
  - Fluidised bed granulation
- Risks of Batch to batch variation require careful and complex procedures and controls.
  - Method and order of charging ingredients
  - Time and technique for introduction of binders
  - Definition of end point
- Large scale equipment needed in development to reduce risk of scale-up.
- Large quantities of expensive API (Active Pharmaceutical Ingredient) required
- Difficulty to produce small samples on production scale equipment.
Continuous Granulation

- Controlled continuous process
  - Suitable for PAT
  - No batch to batch variation

- Small inventory of in-process materials
  - Reduced risk of product loss
  - Reduced Powder risks

- On demand production
  - Reduced scale-up risk
## The Clinical Trials Development Cycle

<table>
<thead>
<tr>
<th>STUDY PHASE</th>
<th>Number of Patients</th>
<th>Duration</th>
<th>Primary Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 1</td>
<td>20 – 100 normal, healthy patients</td>
<td>Up to one year</td>
<td>Safety</td>
</tr>
<tr>
<td>Phase 2</td>
<td>Up to several hundred patients</td>
<td>One to two years</td>
<td>Safety and efficacy</td>
</tr>
<tr>
<td>Phase 3</td>
<td>Several hundred to several thousand patients</td>
<td>Two to four years</td>
<td>Efficacy and cost benefits</td>
</tr>
<tr>
<td>Phase 4 (Post Launch)</td>
<td>Several hundred to several thousand patients</td>
<td>Two to ten years</td>
<td>Cost benefits and outcomes</td>
</tr>
</tbody>
</table>
Batch vs. Continuous Granulation

- **3-10 litre**
- **65-150 litre**
- **300-600 litre**

**Phase 1**
- **Phase 2**
- **Phase 3**

**Pharmalab 24mm**

**Pharmalab 16mm**

**Pharmalab 24mm and Phase 3**
# Equivalent Production Capacities

<table>
<thead>
<tr>
<th>Batch Granulating Equipment</th>
<th>Daily output of Granulate</th>
<th>Continuous Granulating Equipment</th>
</tr>
</thead>
<tbody>
<tr>
<td>65 Litre Batch Mixer 15 kg batch</td>
<td>60 kg Based on 4 batches per 12h day</td>
<td>Pharma 16 TSG 0.2 – 6 kg/h</td>
</tr>
<tr>
<td>300 Litre Batch Mixer 75 kg batch</td>
<td>225 kg Based on 3 batches per 12h day</td>
<td>Pharma 24 TSG 1 – 60 kg/h</td>
</tr>
<tr>
<td>600 Litre Batch Mixer 150 kg batch</td>
<td>300 kg Based on 2 batches per 12h day</td>
<td>Pharma 24 TSG 1 – 60 kg/h</td>
</tr>
</tbody>
</table>
# Equivalent Production Capacities

<table>
<thead>
<tr>
<th>Equipment Volume</th>
<th>Process Evaluation Samples</th>
<th>Daily Production Rates</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Batch Mixer</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total Tank Volume</td>
<td>Working Volume</td>
</tr>
<tr>
<td></td>
<td>Litre</td>
<td>Kg</td>
</tr>
<tr>
<td>3 Litre</td>
<td>3</td>
<td>1.5</td>
</tr>
<tr>
<td>10 Litre</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>65 Litre</td>
<td>65</td>
<td>32.5</td>
</tr>
<tr>
<td>150 Litre</td>
<td>150</td>
<td>75</td>
</tr>
<tr>
<td>300 Litre</td>
<td>300</td>
<td>150</td>
</tr>
<tr>
<td>600 Litre</td>
<td>600</td>
<td>300</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Continuous Mixer</strong></th>
<th>Extruder Free Volume</th>
<th>Maximum Inventory</th>
<th>Minimum Batch Size</th>
<th>Batch Materials Cost</th>
<th>Minimum Sample Size</th>
<th>Number of process samples per Minimum Batch</th>
<th>Single Sample Materials Cost</th>
<th>Output Kg per Hour</th>
<th>Typical Continuous Daily (24h) Output</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minilab</td>
<td>0.007</td>
<td>3.5</td>
<td>5</td>
<td>$5</td>
<td>0.005</td>
<td>1</td>
<td>$5</td>
<td>0.1</td>
<td>2.4</td>
</tr>
<tr>
<td>Pharmalab 16 25:1</td>
<td>0.068</td>
<td>34</td>
<td>500</td>
<td>$500</td>
<td>0.170</td>
<td>3</td>
<td>$170</td>
<td>4</td>
<td>96</td>
</tr>
<tr>
<td>Pharmalab 16 40:1</td>
<td>0.109</td>
<td>54.5</td>
<td>900</td>
<td>$900</td>
<td>0.273</td>
<td>2</td>
<td>$273</td>
<td>4</td>
<td>96</td>
</tr>
<tr>
<td>Pharmalab 24 25:1</td>
<td>0.228</td>
<td>114</td>
<td>2000</td>
<td>$2,000</td>
<td>0.570</td>
<td>5</td>
<td>$570</td>
<td>20</td>
<td>480</td>
</tr>
<tr>
<td>Pharmalab 24 40:1</td>
<td>0.365</td>
<td>182.5</td>
<td>3000</td>
<td>$3,000</td>
<td>0.913</td>
<td>4</td>
<td>$913</td>
<td>20</td>
<td>480</td>
</tr>
</tbody>
</table>

Based on:
- **Formulation Density g/ml**: 0.50
- **Formulation Cost per Kg**: $1,000
Batch Granulation Population Balance

Diagram showing the stages of granulation:
- "Dry" Free Flowing Powder
- "Crumb"
- Steady Growth
- Rapid Growth
- Slurry/Over-Wet Mass

The diagram illustrates the increasing ease of deformation on impact as the saturation of the particle with binder progresses from 0% to 100%.
Comparison of materials – example of batch mixed granules

- Characteristic peak at 90-150 microns
- Fines variable 2-18%
- Variable quantities of coarse material between 2-14% @ 500 micron

Source: ISPE Conference
John Robertson GlaxoSmithKline
Comparison of materials – example of batch mixed granules

Potential for more consistent process!

Source: ISPE Conference
John Robertson GlaxoSmithkline
Motivation for adopting continuous granulation

• **Financial and business drivers**
  • Reduced footprint
    • facilities cost
  • No or little scale up from development to commercial
    • reduced tech transfer costs and risks
    • reduced FTE requirements
    • reduction in API requirements through development
  • Potential for common platform throughout development and commercial network
  • Reduced capital and OPEX costs
  • Lights out operation
  • Containment of high actives
  • Potential for modular construction approach
  • Reduced inventory – scope for just in time delivery

• **Technical Drivers**
  • Implementation of PAT
  • Scope for improved control and consistency

Source ISPE Conference
*John Robertson GlaxoSmithKline*
Product Portfolio Twin Screw Granulation

Product Portfolio TSG
PharmaLab 16 TSG

Gravimetric Screw Feeder

Liquid Feeding Pump

Pharma16 TSG Twin Screw Granulator
PharmaLab 16 with powder bridge braker
PharmaLab 16 TSG showing discharge area
PharmaLab 16 TSG dismantled for cleaning
PharmaLab 24 TSG

- Gravimetric Screw Feeder
- Gravimetric Liquid Feeding Pump
- Crammer Feeder
- Pharma16 TSG Twin Screw Granulator
PharmaLab 24 TSG with feeder platforms
PharmaLab 24 TSG showing barrel clamps
Pharma16 and 24 Feeder Platforms
Customized Solutions

Examples of Customized Solutions
EuroLab in Isolator

EuroLab extruder and spheronizer in Isolator (Glove-Box)

Motor EuroLab and Feeder outside

Touchscreen outside

Modified extruder base, splash-proof

Electronics integrated in isolator-base
EuroLab in Isolator
Customized 24 mm Chill Roll

- Gravimetric Screw Feeder
- Clear protection cover
- Modified belt take-off
- Discharge valve
- Electronic modification to allow control via 3rd party extruder control
- Collection bins
Special Sheet Layering Application

Sheet layering with release tape

Twin bore ram feeder to feed sticky or pasty materials
Modified EuroLab with open discharge

- Special shroud with access to feed ports
- Open discharge
- Active cooling for each zone
- Integrated feeder control
- Extruder barrel made from pharma grade steel
Parallel twin-screw extruder

Twin-Screw Compounding
Twin Screw Compounding

- Output (Kg/h)
- Screw Speed (rpm)
- Temperature ($T_m$)
- Power (Kw)
- Feed (Kg/h)
- Nm (Torque)
- Vacuum Vent
- Heat/Cool
Variables in Twin Screw Processing

- **Independent variables**
  - Continuous
    - Screw speed
    - Feed rate
    - Barrel temperature
  - Step change
    - Screw design
    - Barrel design
    - Die design

- **Dependent variables**
  - Process parameters
    - Melt temperature
    - Residence time
  - Quality Control parameters
    - Dispersion
    - Colour
Illustration of degree of fill inside the twin screw.
Degree of fill dependent on number of mixing stages.

Residence Time (typical)

- 60 secs: Degree of Fill Single Stage Mixing with Residence Time (typical) 60 secs, Degree of Fill (typical) 30%
- 90 secs: Degree of Fill Two Mixing Stages with Residence Time (typical) 90 secs, Degree of Fill (typical) 50%
- 120 secs: Degree of Fill Three Mixing Stages with Residence Time (typical) 120 secs, Degree of Fill (typical) 60%
Melt temperature vs. Screw speed

Melt discharge temperature (PP : PTW24)

\[ R^2 = 0.9993 \]
Effect on Melt-Temperature

Feedrate, kg/hr vs Screw Speed, rpm

- Q_{max}
- 100% Torque
- 100°C
- 110°C
- 115°C
- 120°C
- 130°C
- 140°C

Thermo Fisher Scientific
Residence time in a twin-screw

Residence time (PTW24)

Residence time [s] vs. Feed rate [kg/h]

- Blue diamonds: 250 l/min
- Pink squares: 500 l/min
Effect on Residence time

Feedrate, kg/hr

Screw Speed, rpm

$Q_{\text{max}}$

$N_{\text{max}}$

100% Torque

10 sec

30 sec

60 sec

100 sec

Feedrate, kg/hr vs Screw Speed, rpm graph showing the effect on residence time for different time periods.
Twin Screw Primary Variables

Feed Rate, kg/hr

Screw Speed, rpm

Q max

100% Torque

N. max

Feed Rate, kg/hr

Screw Speed, rpm

Q max

N. max

100% Torque

ThermoFisher SCIENTIFIC
Quality by Design

Knowledge Space

Design Space

Controlled Space
Quality by Design - Twin Screw Extruders

Knowledge Space

Control Space

Design Space

Specific Energy

Feedrate

Screw Speed

100% Torque

Temperature limit

Residence time limit

Thermo Fisher Scientific
Quality by Design - Twin Screw Extruders