Development of a population balance model for continuous twin-screw granulation in pharmaceutical manufacturing

Ashish Kumar, Krist V. Gernaey, Thomas De Beer, Ingmar Nopens

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Session: Agglomeration and Granulation Processes
Current solid-dosage manufacturing is slow and expensive

Product collected after each unit operation

Actual processing time = days to weeks
Traditional to new granulation method

- **High-shear mixer**
- **Drum**
- **Fluidised-bed**

**Batch**

**Continuous**

**From minutes to hours**

**Twin-screw**

**In seconds**
Easy to integrate with other unit operations of pharmaceutical manufacturing.
Continuous manufacturing line

Consigma™-25 system

Continuous twin-screw granulator

Segmented Fluid bed dryer

Granule conditioning module

Semi-Continuous
Both geometry and process conditions drive constitutive mechanisms.
Understanding the role of screw design

Flow direction
Consigma™-1 system
(GEA pharma systems, Collette)

Open barrel of a twin screw granulator
**Consigma™ - 1 experiments**

Granulated Lactose monohydrate with distilled water

<table>
<thead>
<tr>
<th>Factors:</th>
<th>Parameters</th>
<th>Low</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Throughput</td>
<td>10 Kg/h</td>
<td>25 Kg/h</td>
<td></td>
</tr>
<tr>
<td>Liquid-solid ratio</td>
<td>4.58%</td>
<td>6.52%</td>
<td></td>
</tr>
<tr>
<td>Screw speed</td>
<td>500 RPM</td>
<td>900 RPM</td>
<td></td>
</tr>
</tbody>
</table>

Flow direction: 1: kneading block 1, 2, 3: kneading block 2, 4, 5

Responses: Particle characterization by Dynamic Image Analysis (Location 1, 3, 5)
Consigma™ - 1 experiments

Throughput: High

Liquid-solids ratio: High

Screw speed: Low

Flow direction

1. kneading block 1
2. kneading block 2
3. Kneeing block 3
4. Kneeing block 4
5. Kneeing block 5

Consigma™- 1 experiments

Throughput High
Liquid-solid ratio High
Screw speed High

Tracer concentration in granules produced was measured using NIR chemical imaging.
API Map was used to measure RTD

Measure of the mean of the distribution

\[ \tau = \frac{\int_0^\infty t \cdot e(t) dt}{\int_0^\infty e(t) dt} \]

Mean residence time, \( \tau \)

Population balance models can track granule attributes

\[ \frac{\partial n(t, x)}{\partial t} = \frac{Q_{in}}{\tilde{V}} n_{in}(x) - \frac{Q_{out}}{\tilde{V}} n_{out}(x) \]

**GSD balance**

**Aggregation term**

\[ + \frac{1}{2} \int_{0}^{x} \beta(t, x - \varepsilon, \varepsilon) n(t, x - \varepsilon) n(t, \varepsilon) d\varepsilon \]

**Breakage term**

\[ -n(t, x) \int_{0}^{\infty} \beta(t, x, \varepsilon) n(t, \varepsilon) d\varepsilon \]

\[ + \int_{0}^{\infty} b(x, \varepsilon) S(\varepsilon)n(t, \varepsilon) d\varepsilon \]

\[ -S(x)n(t, x) \]
Semi-empirical kernels

**Aggregation Kernel**

\[ \beta(x, y) = \beta_0 \]

(Constant kernel)

**Breakage Kernel**

\[ S(y) = S_0(y)^\mu \]

\[ h(x, y) = \frac{\phi y^{\gamma-1}}{y^\gamma} + \frac{(1-\phi)x^{\alpha-1}}{y^\alpha} \]

\[ = \frac{\phi y^\gamma}{y^{\gamma+1}} + \frac{(1-\phi)\alpha}{\alpha+1} \]

(Austin, 2002)

**Cell-average technique**
Experimental and simulated data have a good agreement.

RMSE = 4.3
R^2 = 0.98
Particle population dynamics during granulation
Including effect of granulator design on granule size distribution
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Significance</th>
<th>Location 1</th>
<th>Location 3</th>
<th>Location 5</th>
<th>End</th>
</tr>
</thead>
<tbody>
<tr>
<td>RMSE</td>
<td></td>
<td>16.25</td>
<td>2.72</td>
<td>2.14</td>
<td>4.3</td>
</tr>
<tr>
<td><strong>Aggregation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\beta_0$</td>
<td>Collision frequency (sec$^{-1}$)</td>
<td>1052.53</td>
<td>1632.92</td>
<td>820.79</td>
<td>5055.40</td>
</tr>
<tr>
<td>$S_0$</td>
<td>Selection function constant for breakage</td>
<td>0.07</td>
<td>0.99</td>
<td>2.40</td>
<td>3.31</td>
</tr>
<tr>
<td><strong>Breakage</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\alpha$</td>
<td>Width of fragment distributions</td>
<td>0.17</td>
<td>0.31</td>
<td>0.39</td>
<td>0.35</td>
</tr>
<tr>
<td>$\gamma$</td>
<td>width of fragment distributions</td>
<td>22.21</td>
<td>28.89</td>
<td>2.64</td>
<td>200.30</td>
</tr>
<tr>
<td>$\phi$</td>
<td>mass content of first breakage distributions</td>
<td>0.02</td>
<td>0.00</td>
<td>0.02</td>
<td>0.01</td>
</tr>
</tbody>
</table>

$\gamma$, $\phi$ and $\alpha$ are dimensionless material constants.

$\phi$ is the weight parameter to quantify the mass content of first breakage distributions.

$\gamma$ and $\alpha$ are the width of the fragment distributions $\phi$ and $1-\phi$, respectively.

Quadratic selection function, $S(y) = S_0 (y)^\mu$ where $\mu$ was $1/3$. 

Flow direction Start 1 2 3 4 5
Including effect of granululator design on granule size distribution

Flow direction

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
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<tr>
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<td>PMSE</td>
<td>16.25</td>
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- RMSE
- Data points for cumulative size distribution in %
- Graph with legend:
  - Initial condition
  - Sim. final condition
  - Exp. final condition
  - Exp. location 1
  - Exp. location 2
  - Exp. location 3
  - Exp. location 4
  - Exp. location 5
Including effect of granulator design on granule size distribution

Flow direction

1st kneading block

RMSE = 1.73

Flow direction

2nd kneading block

RMSE = 1.48

Cumulative size distribution Q.0 in %
Throughput High | Liquid-solid ratio High | Screw speed Low

1 mixing zone

2 mixing zones

Throughput High | Liquid-solid ratio High | Screw speed High

1 mixing zone

2 mixing zones
Investigating effect of screw speed and screw configuration

High throughput, high L/S

Low Screw Speed

<table>
<thead>
<tr>
<th>Zone</th>
<th>1-3</th>
<th>3-5</th>
<th>1-3</th>
<th>3-5</th>
<th>1-3</th>
<th>3-5</th>
<th>1-3</th>
<th>3-5</th>
</tr>
</thead>
<tbody>
<tr>
<td>$R^2$</td>
<td>0.989</td>
<td>0.987</td>
<td>0.984</td>
<td>0.983</td>
<td>0.989</td>
<td>0.983</td>
<td>0.97</td>
<td>0.982</td>
</tr>
</tbody>
</table>

High Screw Speed

1st kneading block

2nd kneading block

Flow direction

1
2
3

3
4
5

Mixing zones

1-3
3-5

Investigating effect of screw speed and screw configuration
Shear supported further breakage

Overwetted lumps breaking

Almost nothing happened

Throughput High

Liquid-solid ratio High

Location 1-3 Screw speed Low Location 3-5 Screw speed High

Screw speed Low

Screw speed High

Overwetted lumps breaking

Almost nothing happened

Location 1-3

Location 3-5

Screw speed Low

Screw speed High

Overwetted lumps breaking

Shear supported further breakage

Volume density (%)
Throughput High | Liquid-solid ratio High

**Location 1-3**

**Screw speed Low**

- Some aggregation occurred

**Location 3-5**

**Screw speed High**

- Breaking of the oversized along with aggregation of fines

- Aggregation dominated

- Breakage dominated
Conclusions

Along with experimental study, an improved insight can be obtained by model-based analysis.

Wetting kinetics requires a separate explanation in the twin-screw granulation modelling.

Aggregation and breakage are most dominant phenomena in the twin-screw granulation.

Particle population dynamics and screw geometry effect can be better understood by compartmental PBM, and can ultimately be used for predictive modelling of twin-screw granulation.
Acknowledgements

Ashish.Kumar@UGent.be