PURE BREAKAGE PBM CALIBRATION IN PHARMACEUTICAL WET GRANULATION

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7-9 May 2018
6th International Conference on Population Balance Modelling
Ghent, Belgium
Twin-screw granulator:

- **Continuous** production of granulated pharmaceutical material for oral solid dosage production
  - pharmaceutical powder mixed with liquid
  - conveyed between co-rotating Archimedes screws alternated with kneading zones

- **Drying after granulation:**
  - formation of solid bonds by crystallisation of solubilised material (binder)

Figure 1. Twin-screw granulator schematic (screw configuration with 12 kneading discs), *(Eur. J. Pharm. Sci.,* 90(2016), 25–37).
Figure 2. Slice from μCT scan of pharmaceutical granule (obtained at UGCT, Centre for X-ray Tomography)
System: the ConsiGma™ continuous granulation line

Figure 3. ConsiGma™ containing twin-screw granulator, fluid bed dryer, dry transfer line and hopper (GEA Pharma systems).

Figure 4. Fraction of fines, yield and oversized for experiments F–I (filling time 180s) on the vertical set-up, in function of drying time (Eur. J. Pharm. Sci., 115(2018), 223–232).
System: the ConsiGma™ continuous granulation line

Data collection:

- Dryer variation:
  - drying time, inlet air temperature and flow

- PSD
  - QICPIC™ Dynamic Image analysis system (Sympatec, Clausthal-Zellerfeld, Germany)
  - equipped with a vibrating feeder system (Vibri/L™)
  - Samples of 20g in duplicate

- Moisture content
  - Loss-on-drying (LOD) with moisture analyser (Mettler LP16, Mettler-Toledo, Zaventem, Belgium)
    (infrared dryer and balance, sample of 1g)
“Contradictory” number- and volume-based PSD evolution

![Graphs showing number- and volume-based PSD evolution](image)

Figure 5. Number- (left) and volume-based PSD of wet granules and granules dried for different time periods, at inlet air temperature of 40°C, inlet air flow of 360m³/h and cell loading of 1kg. PSDs were obtained with QICPIC™ system (Sympatec, Clausthal-Zellerfeld, Germany)
Population balance model

Fragment distributions:

- **Attrition**: lognormal distribution:
  \[ b_{\text{attr}}(x, y, s, \mu) = \frac{1}{\exp(\mu) s x \sqrt{2\pi}} \exp\left(-\frac{1}{2} \left(\frac{\log(x/\exp(\mu))}{s}\right)^2\right) + \frac{1}{\exp(\mu) s (y-x) \sqrt{2\pi}} \exp\left(-\frac{1}{2} \left(\frac{\log((y-x)/\exp(\mu))}{s}\right)^2\right) \]

- **Fragmentation**: equisize distribution:
  \[ b_{\text{frag}}(x, y) = \delta \left(x - \frac{y}{p}\right) p \quad \text{with : } p = \frac{y(D)}{y(D)} \]

- **Combined** fragment distribution:
  \[ b = z b_{\text{attr}} + (1 - z) b_{\text{frag}} \]

Breakage rate: power law combined with sigmoid threshold function:

\[ S(x, \alpha, \beta, S_0) = S_0 \frac{1}{1 + e^{\alpha(x_{\text{thres}}-x)} x^\beta} \]
Population balance model

Fragment distributions:

- **Attrition**: lognormal distribution:

\[ b_{\text{attr}}(x, y, s, \mu) = \frac{1}{\exp(\mu)s\sqrt{2\pi}} \exp\left( -\frac{1}{2} \left( \frac{\log(x/\exp(\mu))}{s} \right)^2 \right) + \frac{1}{\exp(\mu) s(y-x)\sqrt{2\pi}} \exp\left( -\frac{1}{2} \left( \frac{\log((y-x)/\exp(\mu))}{s} \right)^2 \right) \]

- **Fragmentation**: equisize distribution:

\[ b_{\text{frag}}(x, y) = \delta \left( x - \frac{y}{p} \right) p \quad \text{with} \quad p = y \left( \frac{D}{y(D)} \right) \]

- **Combined** fragment distribution:

\[ b = z b_{\text{attr}} + (1 - z) b_{\text{frag}} \]

Breakage rate: **power law** combined with sigmoid **threshold** function:

\[ S(x, \alpha, \beta, S_0) = S_0 \frac{1}{1 + e^{\alpha(x\text{thres}-x)}} x^\beta \]
Step-wise, for each experiment:

1. Calibration of attrition parameters to number fraction distribution
   - PBM: version with only attrition \((z = 1)\)
   - Objective function: SSE between simulation and data in number-based distribution
   - Algorithm: L-BFGS-B (local)

2. Calibration other parameters
   - PBM including attrition and fragmentation
   - Objective function:
     - SSE between simulation and data in volume-based distribution
     - weighted in function of size \(u\): \(W(u) = \frac{1}{\log_{10}(u)}\)
   - Algorithm: brute-force (global)
Results: attrition

Parameters lognormal distribution:

mean diameter and shape correlated with moisture content (LOD), and temperature
Results: simulated vs experimental PSDs

Inlet air temperature: 40°C
Inlet air flow: 360 m³/h
Drying time: 300 s
Results: simulated vs experimental PSDs

Inlet air temperature: 40°C
Inlet air flow: 360 m³/h
Drying time: 700 s
Results: simulated vs experimental PSDs

Inlet air temperature: 60°C
Inlet air flow: 360 m³/h
Drying time: 300 s
Calibrated parameter values

Ratio $z$

Threshold

Power

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Study of granule breakage phenomena on different length scales

- needed to capture breakage in detail

- kernels still to be evaluated $\Rightarrow$ parameter identifiability
  - objective function (beware of over-fitting)
  - model validation to be performed

- breakage related to granule moisture content after drying
Thank you for your attention

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Results: simulated vs experimental PSDs

Inlet air temperature: 40°C
Inlet air flow: 440 m³/h
Drying time: 300 s
Results: simulated vs experimental PSDs

Inlet air temperature: 40°C
Inlet air flow: 360 m³/h
Drying time: 400 s