Population balance modeling of a continuous conical screen milling process: Parameter estimation and model validation using gPROMS

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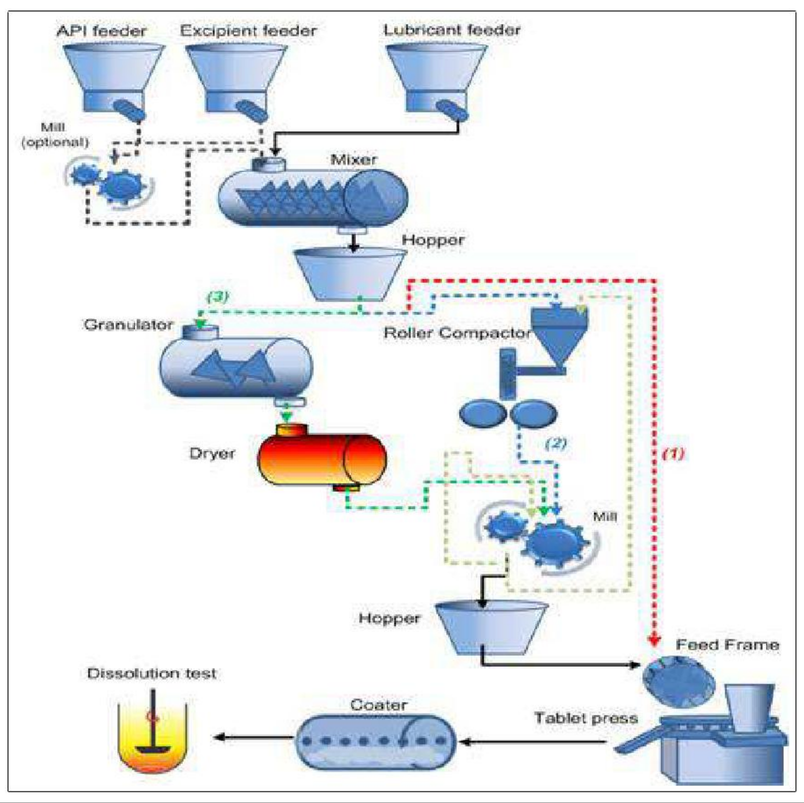
Overview

- Continuous processing has demonstrated advantages over batch processes for pharmaceutical applications: cost, scalability, controllability, efficiency.
- A model-based approach is taken to determine the effects of process parameters on critical quality attributes of a continuous milling process. A better process understanding is needed to define a design space, implement QbD, and validate the process.
- Milling is a size reduction step following roller compaction or wet granulation. Product size distribution is important.

Objectives

- Characterize milling as a continuous unit operation to be able to effectively predict the particle size distribution as a function of process parameters.
- Develop a predictive model that enables the design and optimization of a continuous milling process.
- Use experimental data to calibrate and validate the model.

Continuous tablet manufacturing



Experimental Approach

- Use roller compaction to produce ribbons at two ribbon densities.
- Mill ribbons continuously using a conical screen mill.
- Vary screen aperture at three levels and impeller speed at two levels for each ribbon density.
- Measure hold up and particle size distribution (using sieve) after mill reaches steady state, within a few minutes of start-up.

Ribbon material

Avicel PH-200
MgSt

Compaction conditions

Roll speed: 9 RPM
Roll pressure:
28 bars (low density ribbon)
70 bars (high density ribbon)

Design of Experiment

Screen / Speed	991 µm	1575 µm	3175 µm
3350 rpm			
4923 rpm			

- Performed separately for each ribbon density.

Model Development

- Model was developed to determine steady-state mass hold up and product size distributions, effects of screen size and impeller speed
- 1D population balance model tracks number of particles (F) over time of each size class (u)

$$\frac{dF(u,t)}{dt} = \Re_{break,form}(u,t) - \Re_{break,dep}(u,t) + \dot{F}_{in}(u,t) - \dot{F}_{out}(u,t)$$

- Formation and depletion due to breakage depend on number of particles, breakage kernel, and breakage distribution

$$\Re_{break,form}(u) = \int_u^\infty K(v)F(v)b(u,v)dv \qquad \Re_{break,dep}(u) = K(u)F(u)$$

- Breakage kernel is proportional to impeller speed and particle size, with two adjustable parameters (P_1, P_2) [1]

$$K(u) = P_1 v_{imp}\left(\frac{u}{u_{ref}}\right)^{P_2}$$

- Log normal fragment size distribution, with two adjustable parameters (n,σ)

$$b(u,v) = \frac{C(v)}{u\sigma}\exp\left[-\frac{(\log u - \mu(v))^2}{2\sigma^2}\right] \qquad \exp\mu(v) = \frac{v}{n}$$

- Screen model describes outflow of particles with one unknown parameter (δ)

$$\dot{F}_{out} = (\Re_{break,form}(u) - \Re_{break,dep}(u) + \dot{F}_{in}(u))(1 - f_d(u))$$

$$f_d(u) = \begin{cases} 0 & \text{for } d(u) \le (1-\delta)d_{screen} \\ \frac{d(u)-(1-\delta)d_{screen}}{\delta\, d_{screen}} & \text{for } (1-\delta)d_{screen} \le d(u) \le d_{screen} \\ 1 & \text{for } d(u) > d_{screen} \end{cases}$$

Parameter Estimation

- Used experimental size distributions and mass hold-up to calibrate model.
- Performed using gPROMS Parameter Estimation feature, using SQP algorithm to minimize objective function [2].

$$\Phi = \frac{N}{2}\ln(2\pi) + \frac{1}{2}\min_\theta\left\{\sum_{i=1}^{NE}\sum_{j=1}^{NV_i}\sum_{k=1}^{NM_{ij}}\left[\ln\left(\sigma_{ijk}^2\right) + \frac{(\tilde{z}_{ijk} - z_{ijk})^2}{\sigma_{ijk}^2}\right]\right\}$$

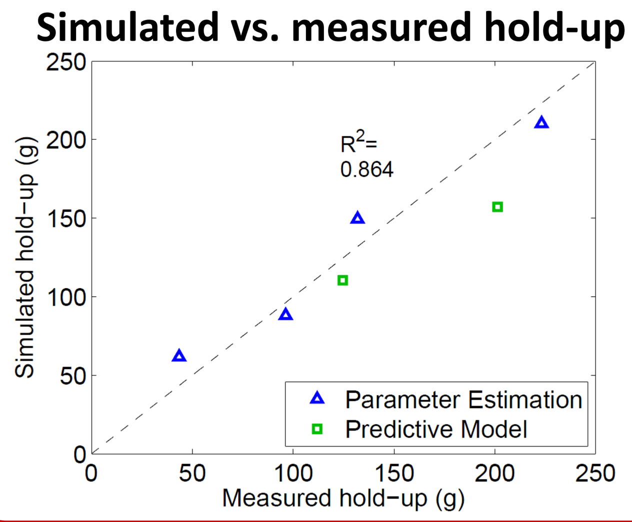
- Estimated five model parameters and three variances parameters (two in linear variance model for sieve data, one in constant variance model for mass hold-up).
- Each ribbon density was considered separately, material properties resulted in different empirical parameters.
- Four of six experimental runs were used for each ribbon density. Both runs at the medium screen size were omitted from PE and used for comparison with calibrated model.

Results for Low Density Ribbon

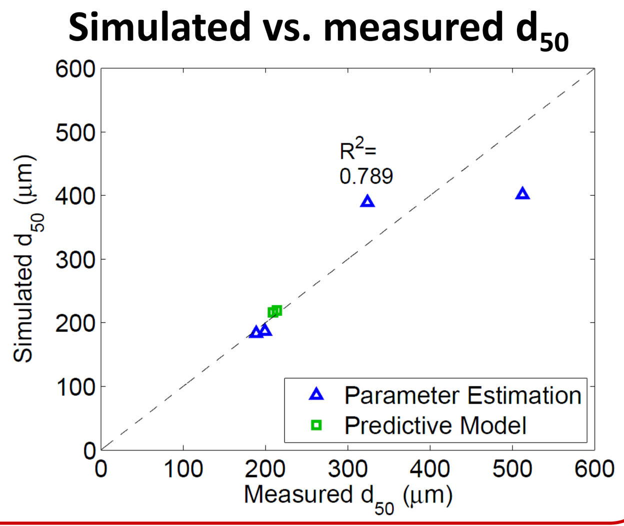
Parameter	Value	Std. Dev.	t-value
Critical screen size ratio , δ	0.44	0.07	3.04*
Breakage kernel coefficient, P_1	8.82×10^{-6}	1.01×10^{-6}	4.30*
Breakage kernel size dependence, P_2	0.34	0.08	2.16*
Breakage distribution parameter, n	2.68×10^5	1.64×10^5	0.80
Breakage distribution std. dev., σ	2.10	0.12	8.66*
Sieve data variance slope, A	0.067	0.28	0.12
Sieve data variance intercept, B	0.029	0.043	0.32
Mass hold-up variance, σ_2^2	14.9	7.9	0.93

- Four parameters were estimated with statistical significance (t>1.69).
- Model successfully describes trends in mass hold-up and median diameter with impeller speed and screen size.

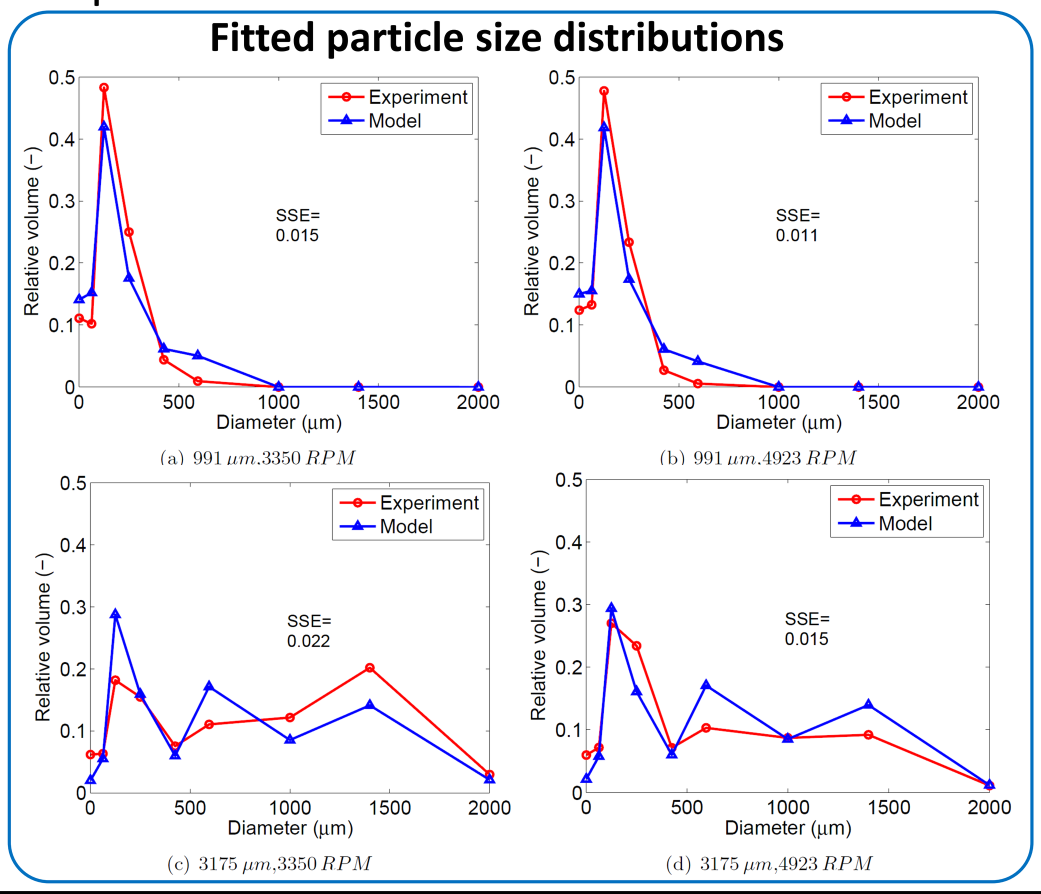
Simulated vs. measured hold-up



Simulated vs. measured d_{50}

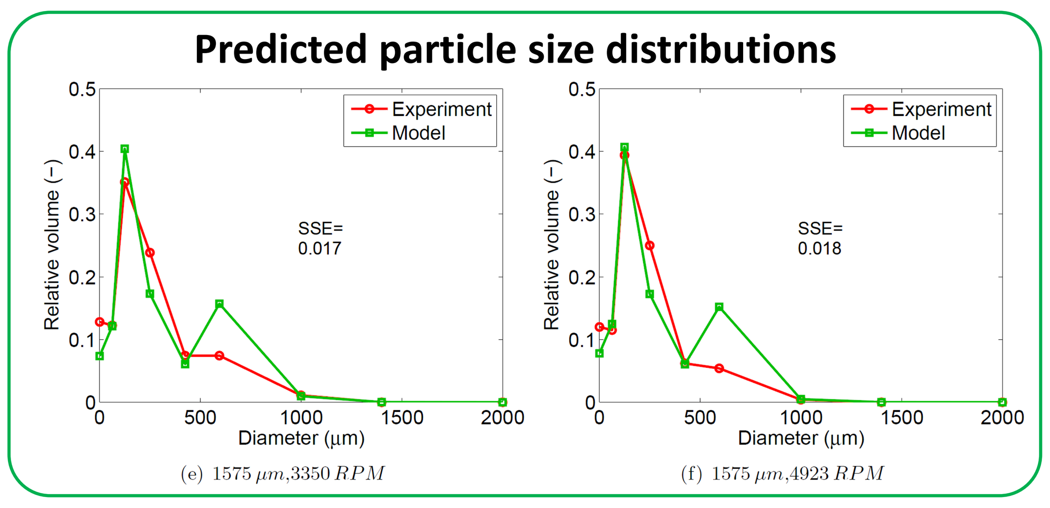


Fitted particle size distributions



- Simulated size distributions are a good fit to experimental results.
- Predictive capability was demonstrated using calibrated model and data at medium screen size (not used in parameter estimation).

Predicted particle size distributions



Conclusions and Future Work

- Validated model can be used to predict critical quality attributes based on process parameters.
- Model-based approach can be used to implement QbD and facilitate process design and optimization, resulting in labor and cost savings.
- Future work will involve developing more mechanistic kernels and accounting for material properties in the model.

Acknowledgements and References

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[1] Pandya, J., Spielman, L., 1983. Floc breakage in agitated suspensions: Effect of agitation rate. Chemical Engineering Science 38 (12), 1983-1992.

[2] Process Systems Enterprise, Ltd., 2012. gPROMS Advanced User Guide. Vol. 3.6.