Discrete Element Modeling of a Pharmaceutical Blending Process

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PURPOSE

Scale-up of blending unit operations from the laboratory scale to commercial scale can be challenging. Use of predictive tools for simulation of blending processes can be valuable in drug product manufacturability. We provide a mechanistic model based on Discrete Element Method (DEM) for a pharmaceutical blending processes. This model can successfully predict the operating ranges *a priori* to running the actual process and avoids a trial-and-error approach. This predictive model allows for the calculation of critical process parameters and performance early in the blending process.

OBJECTIVES

Our objectives in developing this mechanistic modeling of a blending process were two-fold:

1. Develop a systematic DEM model parameter calibration method by training an artificial neural network (ANN) on laboratory scale data for a spray-dried dispersion of a model compound, Z160,
2. Use the validated DEM model to simulate a V-blender process to identify the critical material attributes, process parameters and to evaluate the change of operating space during scale-up.

METHODS

The simulation of a pharmaceutical blending unit operation is developed based on a visco-elastoplastic frictional adhesive DEM model. First, an FT4 powder rheometer (Freeman Technologies) was used to characterize the mechanical properties of the powders in the Z160 formulation. The FT4 test was replicated using EDEM software (DEM Solutions Ltd.), and the contact model parameters of each powder were optimized to reproduce the experimental measurements using a space-filling design of experiments (DOE) as shown in Figure 1. Leveraging machine learning techniques, a response model based on an artificial neural network (ANN) was trained on the results from 180 FT4 simulations. This response model was used to determine the input parameters that provided the best fit to the experimental measurements. This validated DEM model was then used to simulate a laboratory-scale V-blender containing the Z160 formulation. Changes in operating space that occur during the scale-up process were then identified by modeling a Pilot-scale V-blender.

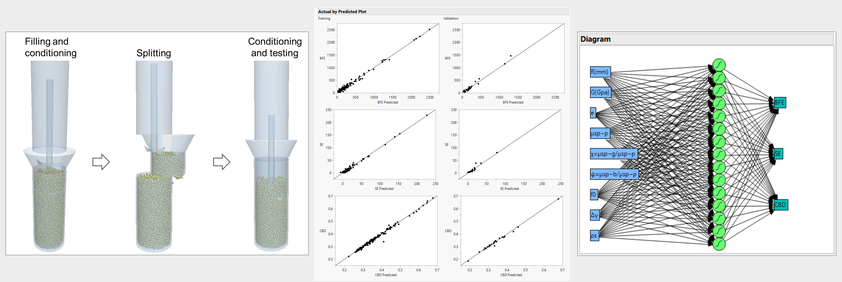


Figure 1. DEM simulation of the FT4 powder rheometer (left). Prediction accuracy of the ANN model (middle). Structure of the single-layer ANN model with 15 hidden nodes and TanH activation functions (right).

RESULTS

The experimental FT4 test results include Basic Flow Energy (BFE), Specific Energy (SE) and Conditioned Bulk Density (CBP). Using ANN we trained a model on DEM FT4 simulation which had high R^2 values > 0.98 for the training and validation tests shown in Figure 1 (middle). The effects of each variable on the flow characteristics of the powder are shown in Figure 2.

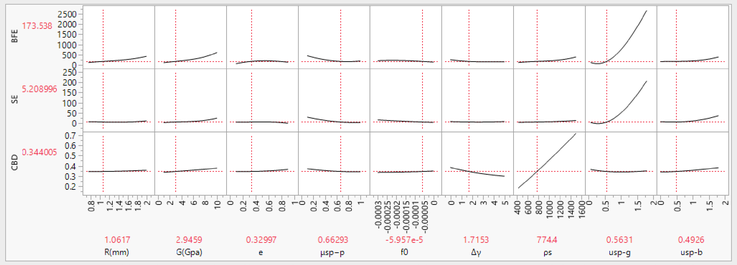


Figure 2. Prediction profiler showing the effects of independent variables, Particle radius (R), Shear modulus (G), Restitution coefficient (e), Particle-particle static friction (μsp−p), Constant pull-off force (f0), Cohesive surface energy (Δγ), Particle solid density (ps), Particle-wall static friction (μsp−g) and Particle-blade static friction (μsp−b) on the FT4 responses.

Calibrated DEM models based on FT4 simulations were used to simulate a 1.2L laboratory-scale V-blender for the formulation of Z160 (Table. 1). These simulations are shown in Figure 3. Images in the top row show the state of the final blend after 1-minute blending time at RPM 15 with fill levels of 30, 50 and 75%. Images at the bottom show the concentration of API by the means of bin analysis, with red representing the highest Z160 concentration. An obvious deviation was identified between fill level 30% to 75%. This indicates that *fill level* is a critical process parameter that impacts blend uniformity. These same results can also be quantified by the Coefficient of Blending (CBP) Performance which is a computational micro-scale index.

Table 1. Z160 model compound prototype formulation

Z160 Formulation	Unit Comp.
Component	wt%
40:60 Z160:PVP-VA64 SDD	49.0%
Lactose Monohydrate FlowLac 90	30.0%
Microcrystalline Cellulose (Avicel PH-105)	14.0%
Kollidon CL (Crospovidone)	5.0%
Colloidal Silicon Dioxide (Cab-O-Sil M-5P)	1.0%
PRUV Sodium Stearyl Fumarate (SSF)	1.0%
Total:	100.0%

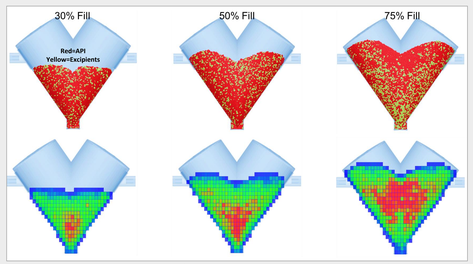


Figure 3. Snapshots of the final blends in 1.2 L V-Blenders after 1min blending with RPM=15 and various fill levels (top). Concentration of API, with red representing the highest concentration (bottom).

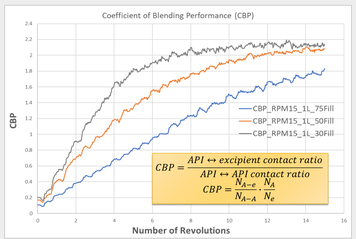
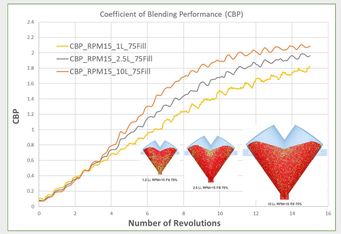
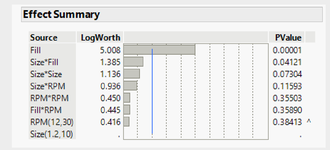


Figure 4. CBP vs. number of revolutions across different fill levels in 1.2 L V-blenders with RPM=15.

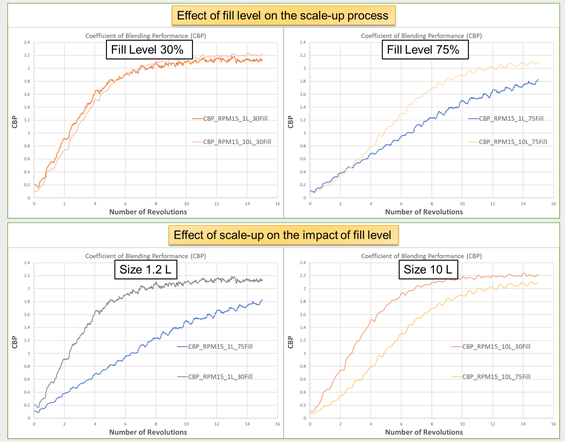
CBP provides information on the contact number of similar and dissimilar particles. As illustrated in Figure 4, after 1 min of blending with RPM 15, the CBP shows better mixing quality for the 30% fill level.

Simulated design of experiments were conducted to evaluate process scale-up for the V-blender from 1.2L to 2.5L and 10L as shown in the following figures.





The low p value indicates a significant effect. The most significant interaction was Size × Fill (p=0.04) indicating size dependence of the fill effect in mixing performance.



Scaling-up from 1.2L to 10L blender at constant rotation rate (RPM 15) has a larger impact on the blending performance (20% increase) at a 75% fill level (right) compared to a 30% fill level (left).

This figure shows the mixing performance of 1.2L and 10L blenders when increasing the fill level from 30-75%. Increasing fill level has a larger impact in the 1.2L blender when compared to the 10L blender.

CONCLUSIONS

- This work demonstrates the utility of DEM for modeling of pharmaceutical blending unit operations. This approach enables process simulation and mapping prior to experimentation and aids in optimization and scale-up.
- The DEM model was validated using a combination of experimental results from FT4 measurements and machine learning methods. Critical material properties were identified that play a significant role in blending performance.
- Critical process parameters were identified by statistical studies and showed dependence on blender size, fill level and the rotation rate.

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