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Model Based Process Development and Operation of a Fluid Bed Granulation Unit to Manufacture Pharmaceutical Tablets.

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ABSTRACT

A hybrid model for the fluid bed granulation operation was built. The deterministic component focuses on the mass and energy balances representing the water ingress and egress from the powder bed. The empirical one does on granule growth. Estimability techniques were used to determine which parameters to regress from the available data. A partial least squares approach was used to better understand the impact of the model parameters onto key model responses and sensitivity plots were made to aid operational decisions and support pharmaceutical development.

Keywords: Process Operations

INTRODUCTION

Fluid bed granulation is a common operation in the manufacture of pharmaceutical oral solid dosage forms (i.e. tablets and capsules). The aim of the operation is to agglomerate the blend of primary particles in the incoming powder blend to increase particle size and density. This operation becomes necessary when simpler approaches (e.g. direct compression) are unfeasible due to the poor flowability of the unprocessed powder mixture. The operation typically consists of a closed chamber where powder is loaded, an aqueous solution of a binding polymer is sprayed onto the powder as drying air is fed through the bottom of the chamber fluidizing the powder and aiding the incorporation of the spray into the powder bed. The operation consists of two main phases after the powder is loaded, a *spray* phase where a pre-defined amount of solution is sprayed onto the powder and a *drying* phase where the spray is stopped, and air continues to be fed to fluidize and dry the agglomerates (granules) to a desired level of humidity (Figure 1).

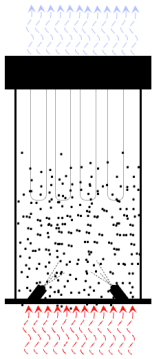

Figure 1. Schematic of a fluid bed granulation chamber

The common manipulated variables (MV) in this operation are i) the amount of spray added ii) the spraying rate, iii) the temperature of the drying air, iv) the air flow during the spraying phase and *v*) airflow during the drying phase. A typical constraint is the composition of the powder blend since this is determined to satisfy a desired dose in the final product.

The aim of this study is to approach the design of the operating conditions for this unit for a specific product, utilizing scientific understanding rather than solely through empiricism. We do this through the formulation of a mathematical expression (a model) that captures the combined effect of the multiple driving forces affecting the in the system. Once the model is formulated, we use in-sillico studies to define a design space for commercial manufacturing.

MODEL DESCRIPTION

Detailed studies [1] demonstrate the strong coupling between granule growth and drying mechanism. Both mechanisms are tied since the granule size will determine the particle specific surface area available for water intake and drying. Some researchers have focused on studying the granule growth solely [2], while others focus the study on the water intake an egress [3] under the hypothesis that controlling one mechanism will result in control of the other.

Our work approaches the drying phenomena through mechanistic modeling while addressing the granule size through an empirical model.

Mass and Energy Conservation

Our approach follows that of Ochsenbein et. al [3] with some differences that are discussed. The considered flows of water across the system are illustrated in figure 2. Three distinct phases are considered: spray, powder bed, and chamber (gas phase). Liquid water ingresses the system through the spray and most of it assumed to be immediately transferred to the powder bed. Water vapor is assumed to be lost directly from the spray to the gas phase through an efficiency and transferred between the powder bed and the gas phase through a drying expression.

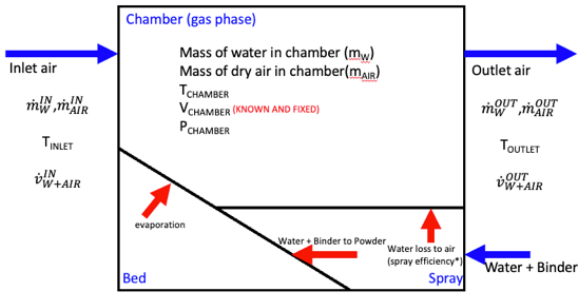

Figure 2. Mass flows across phases

Several key differences separate our work from that of Ochenbein et al. [3]. The way we calculate the outlet airflow is discussed first. The only inlet of bone-dry air is the inlet air flow. We assume that the volume of humid air leaving the chamber is a natural response to equalizing the pressure in the chamber as it can build up or down depending on the temperature or the water content in the gas phase. This approach is known as a pressure-driven simulation and would typically require complex momentum transfer calculations, we took a short-cut approach. In this work we calculate the pressure in the chamber as a function of temperature and water content using an ideal gas approach (the volume of the chamber is fixed). We determine the necessary volumetric flow of humid air leaving the chamber necessary to keep the pressure in the chamber steady at atmospheric conditions. This is calculated using the equations of a fictitious PI controller (Equations. 1 and 2) tuned to be fast but stable.

$$\dot{v}_{W+AIR}^{OUT} = K_p \varepsilon + \frac{1}{\tau_i} \int \varepsilon + \dot{v}_{W+AIR}^{IN} \quad (1)$$

$$\varepsilon = P_{CHAMBER} - P_{SP} \quad (2)$$

A second difference is the assumed driving force for the water transfer from powder to the gas phase. In our work we assume that the difference between the absolute humidity in the powder and the equilibrium humidity of the powder when exposed to the current conditions in the gas phase $\left(\Delta Hum = y_{bed}^{abs} - y_{bed}^{@eq\ w\ air}\right)$ is the drying driving force. This equilibrium condition can be obtained in the laboratory using a dynamic vapor sorption instrument. Typically, these equilibrium curves will be produced at ambient conditions, which are not reflective of the powder bed temperatures in the process. In our work we chose to consider the dependency of this equilibrium with respect to temperature. We include this in the model by measuring the water sorption isotherms at multiple temperatures and following the approach by Quirijns et. al. [4] to modify the GAB equation and thus be able to include the temperature effect on the equilibrium condition. This equilibrium is also a function of composition since each different ingredient has a different sorption curve and the composition of the bed changes as binder is added through the spray; a simple mass fraction weighted average is used.

We also consider the inclusion of a spraying efficiency (γ) equation (Equation 3) to capture the losses of water directly from the spray into the gas phase as a function of the absolute humidity of the powder bed. This expression introduces into the model the phenomena known as “wetting” where water permeation onto a dry powder is more difficult that onto a wet powder. We also consider the inclusion of a modifying scalar omega (ω) to the available surface area for drying (Equation 4). This scalar is less than one during the spray phase and equal to one during drying. During the spray phase, water is entering the powder bed, and it is assumed that the portion of the total surface area of the powder that is used for water intake cannot be used for drying. The evaporation rate coefficient (k_{evap}) is assumed to follow a first order exponential function with respect to the driving force. This allows k_{evap} to be a constant during the constant drying phase; and to decay when the drying is limited by mass transfer. This approximation Eq (5) enables the drying calculations without formally solving the intra-particle mass transfer problem.

$$\gamma = \left(1 - e^{(-\tau_s\, y_{bed}^{abs})}\right) \quad (3)$$

$$\dot{m}_{evap\ bed} = SA_{particles} k_{evap} * \omega \quad (4)$$

$$k_{evap} = \begin{cases} = K_{evap} & if\ \ \Delta Hum \geq \Delta Hum_{crit} \\ = K_{evap}\left(1 - e^{\left(-\tau_{evap}\Delta Hum\right)}\right) & if \Delta Hum < \Delta Hum_{crit} \end{cases} \quad (5)$$

The exchanges of energy across the unit are illustrated in Figure 3, they are the same transfers considered by Ochsenbein [3].

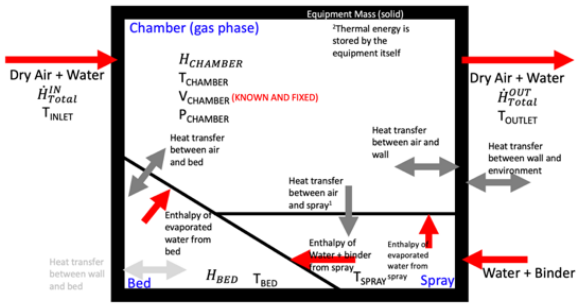

Figure 3. Energy transfers across phases

One final parameter to discuss is that of a correction factor for the measured absolute humidity of the outlet air. After discussions with the equipment vendor, it became clear that value reported by this sensor needed a multiplier to be reflective of the true value. This is an additional parameter considered in the model.

Parameter Estimability

The mass and energy portion of the model consists of 9 model parameters plus the initial wall temperature as quantities that need to be estimated from data.

Table 1: Model Parameters

Parameter	Estimability Measure	Rank
u wall_air	6.498	1
k_evap_rate.K	3.313	2
temp wall init	1.245	3
u wall_bed	1.028	4
omega_factor	0.551	5
u bed_air	0.372	6
spraying_efficiency.tau	0.155	7
k_evap_rate.tau	0.003	8
abs.humidity out correction factor	-0.004	9
u wall_env	-1.380	10

The fluid bed granulator unit is fitted with sensors that provide electronic data captured throughout the operation. Specifically for the airflow, the temperatures and absolute humidity for the air before and after the chamber, the temperature of the powder bed and the spray rate. Additional to these real-time measurements, samples are taken from the unit and analyzed for water content. This is reported in percent weight loss after drying (LOD). With these data available, we analyzed the estimability [5] of the model parameters to determine which parameters to estimate and which to fix. The absolute humidity correction factor and the heat transfer from wall to environment are the least estimable parameters from the data. The low estimability for the heat transfer coefficient from wall to environment was expected since the wall temperature is not measurable in the unit.

Three sets of parameters were obtained for nominal conditions that would incrementally create larger granule sizes (referred to as *under-granulation*, *nominal* and *over-granulation conditions*).

Obtained predicted vs measured values for the LOD and the bed temperature are shown in figure 4 for illustration purposes.

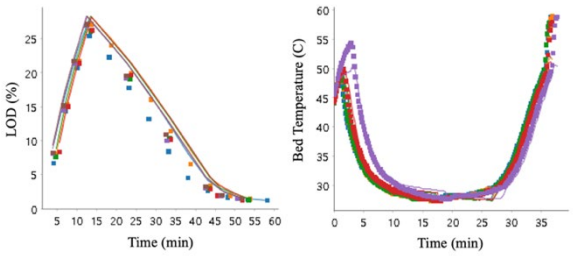

Figure 4. Predicted vs observed profiles

Hybrid component for total particle growth

Through all the mass and energy calculations a fundamental assumption is made that the particle size of the powder is constant. This also fixes the available particle specific surface area which is essential in the calculations of drying kinetics and heat transfers to/from the bed. This mimics the approach taken by Ochsenbein et. al. [3].

A hybrid component is added to the model to account for the effect of the process conditions onto the final granule particle size. This extension adds predictability to the granule size and particle specific surface area, bonding the granule growth and drying mechanisms. A Partial Least Squares (PLS) model is built to predict the final granule properties (including particle specific surface area) as a function of the recipe parameters that also dictate the drying behaviour. The particle specific surface area is predicted with an R^2 value of ~90%. The hybrid model proves to be adequate to predict the time varying values for the LOD, the powder bed temperature and the humidity of the outlet air. The PLS model was built with open-source code (https://github.com/salvadorgarciamunoz/pyphi).

The PLS model was implemented along with the

mass and energy balance using gPROMS (Siemens Industry Software, Ltd).

MODEL PARAMETERS EFFECT

Once a model is assembled and parametrized a natural question to further the understanding of the model is to explore the effect of the model parameters onto the predictions. We explore this dependency in two ways: a) the effect of parameter uncertainty and b) The effect of true statistically significant changes in the model parameters (beyond uncertainty) onto the responses of interest.

To explore the propagation of parameter uncertainty, a sensitivity analysis is done simultaneously varying the values of each model parameter by three standard deviations above and below the optimal value obtained at the parameter estimation step. The variation of LOD due to this parametric uncertainty is shown in figure 5. The variation is ~0.125 % which is acceptable for the application at hand.

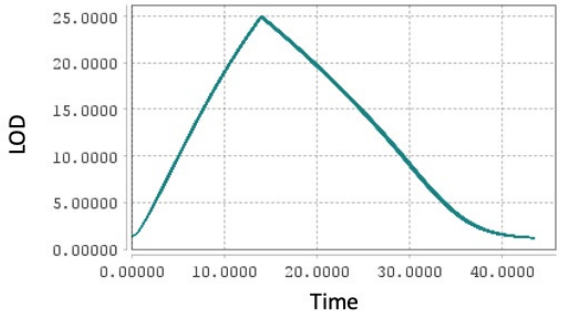

Figure 5. Variation in LOD prediction due to model parameter uncertainty.

A second sensitivity study was carried out to understand the numerical effect from meaningful changes to the model parameters onto the predictions of interest: the LOD, the absolute humidity of the outlet air, and the temperature of the powder bed. This analysis was done by simultaneously varying the 10 estimated parameters to random values within 20% (above and below) of its estimated one. Ten thousand simulations were conducted for each of the three scenarios of interest (under, nominal and over granulation). A PLS model was fitted to better understand the multivariate interactions between the model parameters and the time varying profiles for the responses. Three significant latent variables were found across the three scenarios. From the coefficients of correlation (Figure 6) one can conclude that the model parameters that cause the largest change across the time varying profiles for the three model outputs are: the time constant and the gain for the evaporation rate

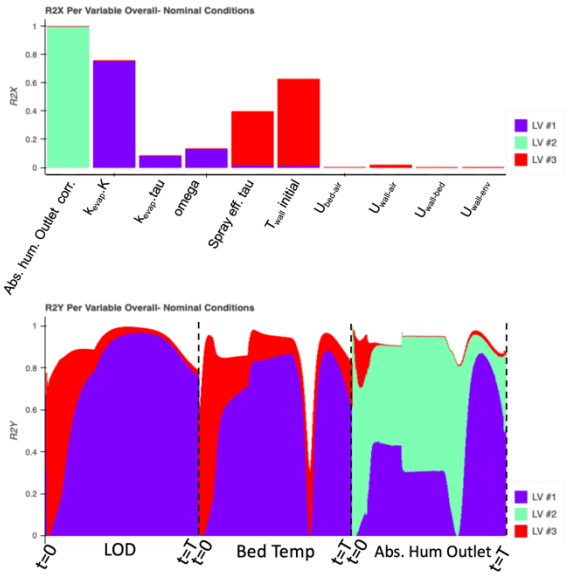

Figure 6. R^2X and R^2Y for the PLS model at nominal conditions fitted to meaningful variation in model parameters and its effect onto responses.

Coefficient (Equation 5), and the omega factor that controls the fraction of surface area available for drying during the spray phase. The second latent variable captures the influence of the time constant for the spray efficiency equation (Equation 3) and the initial temperature of the bed onto the LOD and the bed temperature. The third latent variable represents the effect of the outlet absolute humidity correction factor. Interestingly, this analysis also seems to indicate the almost negligible effect of the heat transfer coefficients. The trends and conclusions form Figure 6 are shared (with minor differences) across the three scenarios (*under*, *nominal* and *over* granulation). The overall ranking of importance for the model parameters can be summarized in the Very Important to the Projection (VIP) plot shown in Figure 7. This diagnostic considers the importance for each regressor accounting for the multivariate consequence onto the response.
The combined effect on the LOD from of these meaningful variations in model parameters with the necessary adjustments in the process parameters to go from under to nominal to over granulation are shown in Figure 8.

Beyond the correlations illustrated in Figure 6, the PLS model diagnostics could be further analyzed to also uncover the directionality in these correlations. This understanding is useful to determine necessary direction and magnitude for a change in a model parameter to create a positive of negative change in a model response. This information in the PLS model can be embedded with an optimization routine for example to find improved initial guesses for the model parameters for a new product.

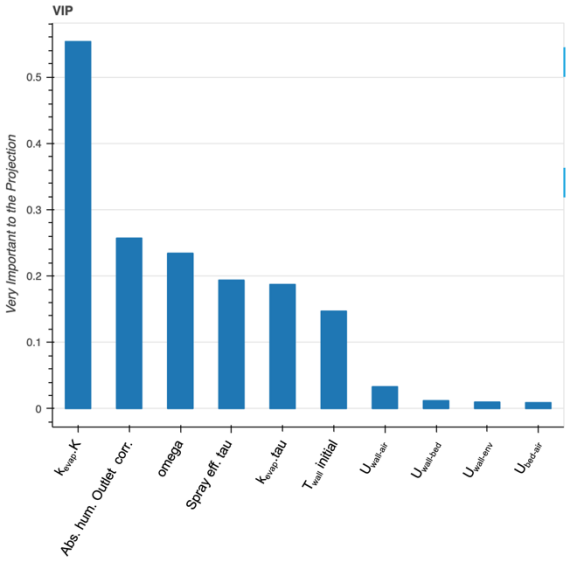

Figure 7. Very Important to the Projection (VIP) plot for the PLS model fitted to meaningful variation in model parameters and its effect onto responses

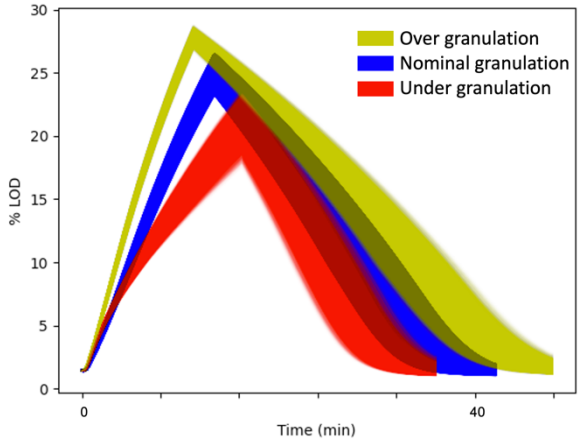

Figure 8. Variation in LOD prediction due to meaningful changes in model parameters at different operating regimes.

PROCESS PARAMETERS EFFECT

The pharmaceutical development process requires the study of the impact of all the MV in the operation of a process onto the quality of the final product. Regulatory agencies encourage practitioners to take a risk-based approach to optimize development efforts [6]. Although the granules produced from the fluid bed granulation operation can be the end-product [7]; more commonly these are intermediate materials to the final oral solid dosage form. As such, the study of this operation is customarily coupled with the study of all downstream operations in a systematic way [8]. Through a combination of experimentation and modeling described elsewhere [9] two intermediate process characteristics were identified

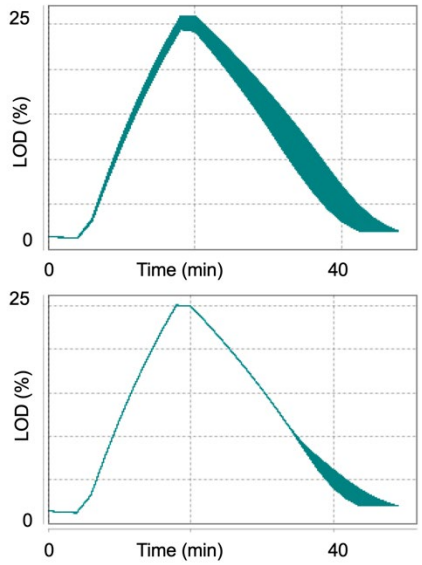

Figure 9. Variation in LOD due to changes in Airflow during the spraying phase (top) and drying phase (bottom)

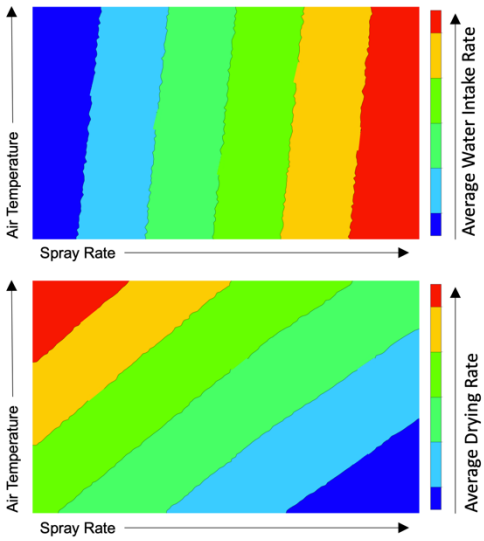

Figure 10. Sensitivity of the average water intake and drying by the poweder bed with changes in air temperature and spray rate.

as key for this operation: The average rate of water intake into the powder bed and the average rate of drying. These are as indicative of the downstream performance of the granule.

Univariate studies per MV are conducted to help identify initial criticality and isolate the effect per MV. For illustrative purposes, Figure 9 shows the LOD result from variations in volumetric airflow during spraying, and during drying (as two independent MV). Remarkably, the effect of the airflow during *spraying* has a stronger effect on the LOD during the *drying* period than the airflow during *drying*. A similar effect emerges in Figure 10 showing

the effect of the air temperature (which remains constant throughout the operation) and the spray rate onto the average rate of water ingress (top) and the average drying rate (bottom). These figures show that while the spray rate dominates the effect of the water ingress to powder bed, it also has a strong effect onto the drying rate. The strong impact of the manipulated variables defining the water ingress onto the drying rate is because these variables define the initial conditions for the drying phase. This follows what other researchers have also postulated: that the dynamics of water intake and egress from the powder bed are intrinsically coupled with the dynamics of granule grown and thus the final attributes of the granule [1]. The model described here was utilized to better understand the effect of the MV in the process as they affected these two rates. These sensitivity plots can be used in the definition of design spaces once constraints are given for the rates of water intake and drying.

CONCLUSIONS

The foundations for the assembly of a useful mathematical representation of a process are the initial articulation of the assumptions made, and the systemic enumeration of the driving forces to be considered. In a systemic approach, the latter exercise needs to be done in consideration to the available measurements that can help identify the individual contributions from the subsystems of the model, and their behavior upon interaction. After the euphoric task of postulating equations and equations to represent a process; the modeler must subject itself to the sobering exercise of statistics, such as performing an Estimability analysis [5] to better understand what level of rigor can be afforded by the available data for the parametrization of the model. This intersection of statistical and deterministic approaches is the key to the construction of a useful model with optimal level of parsimony.

Once a model is built and well parametrized two natural questions arise. One resulting from the need to make operational decisions, and one from the desire to better understand the interaction of the different sub-systems built onto the model. *What is the effect of the process MV onto key model outputs?* and *what is the impact of the model parameters onto the key responses?* And with coupled and non-linear effects at play, the answer to both questions is often of a multivariate nature. Herein we used simple graphical approaches to support operational decisions, these of course are limited to a small number of factors. We present the use of PLS as a useful tool to better understand the multivariable relations between model parameters and responses. In the authors opinion, the visual aids and diagnostics obtained by PLS are richer and provide a more intuitive way to uncover the complex relations represented by the model structure and its parameters, which ultimately represent the innermost fundamental understanding of the process.

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