Model-based Process Development and Operation of a Fluid Bed Granulation Unit to Manufacture Pharmaceutical Tablets

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Abstract

Fluid bed granulation is a complex yet versatile operation in the manufacturing of pharmaceutical oral solid dosages. A model was derived from the mass and energy balances on the unit while considering the available measurements. The model is built with considerations for pressure driven flow and the use of the temperature dependant drying equilibrium conditions as the driving force. The model was parametrized with available data across multiple operating conditions. Results from an estimability analysis were used to guide the parametrization of the model. The model was then utilized as the basis to build an Extended Kalman Filter (EKF) for the operation, the EKF approach is used to provide a real-time prediction (soft sensor) of the water content in the powder bed. The effectiveness of the EKF is demonstrated with batches operated at the commercial unit. These results clearly illustrate the benefits of an EKF approach over an on-line simulation specifically to provide estimates of unmeasured states.

**Keywords**: Fluid Bed Drying, Pharmaceuticals, soft sensor, extended Kalman filter, Process Modelling.

* 1. Introduction

Granulation is an important unit operation in the manufacturing of pharmaceutical oral dosage forms. The main objective of granulation is to increase the overall particle size and bulk density of a powder system. This drastically modifies its bulk behavior and allows the powder mixture to be further processed into an oral dosage (i.e. a tablet or a capsule). Wet granulation platforms span from those that use a relatively high shear processes in either a batch or a twin screw, to those that granulate using gentle shear phenomena imposed by a liquid spray and the fluidization of particles.

The fluid bed granulation unit (figure 1) utilizes the same chamber to create the granules by the addition of a binding liquid; and to dry them. The unit specifically studied consists of a cylindrical chamber where powder resides. In the bottom a perforated plate allows the drying air to come through and in the top a series of filters allow the air to escape the chamber while keeping the powder inside the unit. The binding liquid is atomized and sprayed with two-fluid nozzles located in the bottom of the chamber. The typical operation of the unit consists in the following steps: *a*) loading of the powders, *b*) spraying of a fixed and pre-determined amount of binder solution, *c*) drying of the granules until an acceptable level of moisture is reached, *d*) discharge the material from the unit.

 

Figure 1. Schematic of a fluid bed granulation chamber

The unit is equipped with a series of sensors that provide real-time data as the machine is operating. These measurements include the temperature and humidity of the incoming and outgoing air, the temperature of the powder bed, the volumetric air flow, and the spray rate. Additionally, during the development of the process, samples of granules are taken throughout the process to be analyzed for water content using a Loss on Drying analyzer (LOD) (Figure 2). The available manipulated variables to operate this unit are a) The flowrate of the drying air during the spraying and the drying phase, b) temperature of the incoming air and d) spray rate. The incoming air is dehydrated by a chiller prior to entering the unit.



Figure 2. LOD Measurements taken throughout the fluid bed granulation process.

As any other process, this operation is subject to the effect of disturbances that can come through variations in raw materials, variations in the humidity of the incoming air or other environmental conditions affecting the agglomeration or the drying.

* 1. Modeling of the powder-water system

A mass and energy model for the fluid bed granulation process was proposed by (Ochsenbein, Billups et al. 2019). We implemented this model with some modifications to the driving forces for air flow and drying rate. From a physical properties standpoint, our implementation of this model requires the parametrization of the GAB equation with temperature dependent terms as proposed by (Quirijns, Van Boxtel et al. 2005) and the consideration that this equilibrium is also a function of the binder concentration that changes as spray is added. The energy balance is implemented with a small modification: due to the difficulty in measuring a representative temperature of the wall; the heat transfer between wall and powder bed was neglected. This energy transfer was included in a second version of the model after analyzing the real-time adjustments of the model parameters by the EKF.

The interface between the bed and the surrounding systems is the surface of each particle, as such, the total amount of surface area is a critical parameter that brings full coupling between the granule growth phenomena and the water intake/loss phenomena. We assume this available surface area does not change throughout the process. Albeit this is not true during granule growth; this assumption is easy to defend during the drying phase of the process since the granules are already formed and any changes in size distribution are due to potential attrition of fine particles in the filters and the unlikely breakage of granules. When the drying phenomena is at its strongest, it is reasonable to assume that the surface area per unit of mass is constant and pre-determined since this model does not account for granule growth.

* 1. Estimability and Parametrization

The full model construct includes nine parameters to be estimated from data (Tables 1 and 2). There were two data sets executed at opposite corners of the granulation phenomena. One set (Over granulation) was carried out at conditions that would promote granule growth and yield particles of large size; while the other set (Under granulation) was executed at conditions that grow smaller granules. Measurements for the final particle size were available for both scenarios.

Two parameter estimation (PE) exercises were initially carried out (Table 1), one per data set. Along with this initial PE, an estimability analysis (McLean and McAuley 2012) was also conducted to rank the model parameters from the most estimable one, to the least. At this point: two parameters were fixed to the average value obtained between the sets given their poor estimability from the data; two parameters were fixed to the average due to the small differences in the obtained values; and four parameters were re-estimated.

After the second round of PE, the estimated heat transfer coefficients between air and wall, and wall and the environment were fixed since these parameters should be agnostic to the granule properties. And after one last round of PE we are left with six parameters with common values for the over and under granulation sets, and three highly correlated parameters (Table 2). The correlated parameters are reflective of the high level of coupling between granulation and drying as the heat transfer between the bed and air, and the time constant for the evaporation rate are both correlated to the particle specific surface are (which the mechanistic part of the model cannot predict).

Table 1. First Round of Estimated Model Parameters and Estimability Results



Table 2. Final values of Parameters post-Estimability adjustments



* 1. The Extended Kalman Filter

To streamline the operation of the unit, a soft sensor for the LOD is desired to avoid the need of sampling material. This was implemented using the commercial solution by Siemens Process Engineering using gPROMS Digital Applications. The Extended Kalman Filter (EKF) uses real-time data from all manipulated variables along with data from the bed temperature, outlet air temperature and the outlet air humidity to provide an updated estimate for the LOD. The EKF is also adjusting 6 parameters to keep the model contemporary with the last observed state of the process. The EKF was tuned to achieve optimal performance for the nominal operating conditions (center-conditions). This EKF implementation was then challenged by testing the behaviour of the EKF when the process was operated at opposite corners of the design space (slight under and slight over granulation). The estimated profiles for the unmeasured values of LOD are shown in figure 3, the end-point errors are between 0.46% and 1.32%. This uncertainty in the estimate is considered adequate for this application.



Figure 3. Estimated vs measured LOD for three test lots.

The model appears to also have exquisite tractability to predict the measured states, namely the temperature of the bed, and the temperature of the exhaust humidity (Figure 4). And despite small temporary deviations in one of the batches, the LOD estimate remains stable. The accuracy of the LOD prediction at the point that is needed is well withing the required uncertainty for the application.

All the model parametrization and initial testing of the EKF was conducted in a unit located in the pilot facilities in R&D. The process was later transferred to a commercial manufacture site, to a unit of the same brand and model (like for like). As an additional test of robustness, the EKF was applied to data acquired from the commercial site. These tech transfer lots are common practice to ensure the robustness of process conditions in ensuring product quality.



Figure 4. Predictions for measured model outputs.



Figure 5. LOD estimated vs measured for 6 independent lots

And although the fluid bed granulation units are like-for-like, there were known differences in the utility lines that condition the air to the unit, aside from the environmental conditions from one geography to the other. No data from this commercial unit had been used in any way to parametrize the model or the EKF. The performance of the LOD estimates against the measured values of LOD in the commercial unit are shown in Figure 5. The implementation delivered remarkable results. The application of State estimation in pharmaceutical manufacture is in its early days, in pharma the use of a deterministic model in real-time is commonly interpreted as an on-line simulation exercise where real-time values of the manipulated variables are fed to a model to produce a result. Figure 6 illustrates the difference between on-line simulation (where the measured model outputs are neglected) with the results from a state estimation solution where the measured outputs are also considered hence bringing information about the effect of disturbances onto the system and thus providing superior estimates for the unmeasured states (the LOD in this case).



Figure 6. Comparison of results using on-line simulation vs state estimation



Figure 7. Main diagnostics from the EKF implementation

One notable behaviour from the EKF across all batches tested is the consistent increase of the heat transfer from the wall to the environment at the end of the batch (Fig 6). This diagnostic led us to review the energy flows and to add the transfer of energy from the wall to the powder. This heat transfer was initially neglected due to the inability to measure a representative temperature for the wall. The model was further refined with an additional term to the energy balance to account for the heat transfer between wall and powder bed. Upon re-parametrizing the model (and unsurprisingly) the $u\_{wall \leftrightarrow bed} $is the parameter with the least desirable statistical properties.

* 1. Concluding remarks

For industrial applications, the mathematics for a model needs to be established considering the available measurements and the potential estimability of the model parameters. The model built was adequate to be used as the basis for an extended Kalman filter to provide predictions of the LOD, the diagnostics from the proof of concept from the EKF were quite informative to refine the model. The EKF implementation provided accurate estimates for the unmeasured states (LOD) even when tested on data acquired in a different like to like unit. This illustrates the benefits from an optimization-based approach capable of updating the model with the most contemporary measurements, as opposed to a simple on-line simulation exercise.

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