METHODOLOGY AND PITFALLS WHEN CALIBRATING A PBM: THE CASE OF TWIN-SCREW WET GRANULATION

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ABSTRACT

Traditional pharmaceutical processes comprise of a series of batch-wise operations. Nowadays, a shift is being made from these batch processes to continuous manufacturing, to cope with the inefficiencies and high cost involved in process development and manufacturing. Twin-screw wet granulation (TSWG) is an up-and-coming continuous granulation process that is being assessed for its performance in the solid dosage manufacturing. However, since these continuous processes are fairly new in the pharmaceutical industry, detailed process knowledge and understanding is still lacking. Application of mechanistic models can help in bridging this gap by assessing the experimental data and unravelling the underlying mechanisms. In this work, a compartmentalised Population Balance Model (PBM) is developed for predicting the granule size distribution inside the granulator starting from the pre-blend, up until the wet granules at the end of the process, also evaluating at intermediate positions in the barrel. Dedicated experiments were performed to collect sufficient data. Moreover, the PBM model was formulated in such a way that it is able to predict both the unimodal behaviour observed for high L/S ratios, as well as the bimodal behaviour observed at low L/S ratio using one set of kernel structures. This model-based approach provides significant insight in the driving mechanisms and operating conditions of the TSWG.

KEYWORDS

Modelling, twin-screw wet granulation, PBM, population balance modelling

1. INTRODUCTION

Traditional pharmaceutical processes comprise of a series of batch-wise operations. Nowadays, a transition is being made from these batch processes to continuous manufacturing, to cope with the inefficiencies and high cost involved in process development[1]. Twin-screw wet granulation is an up-and-coming continuous granulation process that is being assessed for its performance in the solid dosage manufacturing[2]. However, since these continuous processes are fairly new in the pharmaceutical industry, detailed process knowledge and understanding is still lacking. Application of mechanistic models can help in bridging this gap by assessing the experimental data and uncovering the underlying mechanisms. In this work, a Population Balance Model (PBM) is developed for predicting the granule size distribution inside the granulator starting from the pre-blend, up until the wet granules at the end of the process.

In PBM, physical processes such as aggregation and breakage of granules are represented by kernels which are often empirical in nature with fitting parameters. Model equations have been solved using the Cell Averaging Technique (CAT)[3] which is able to deal with

aggregation and breakage. Different aggregation and breakage mechanisms can be implemented using different kernels. However, models are only useful when calibrated/validated using experimental data. Calibration of a PBM presents unique challenges in various intermediate steps.

First, the model grid needs to be defined (i.e. number and location of size classes). Different measurement techniques (laser diffraction, image analysis, sieve analysis) use different grids. As each measurement technique has its own peculiarities, it is difficult to compare measurements performed with different techniques. Second, an objective function needs to be defined quantifying the "deviation" between the model prediction and measured data. The current practice to calibrate PBM is similar to how this was done for time series and using deterministic models. Sum of Squared Errors (SSE) and Root Mean Squared Error (RMSE) are thus typical gold standards. Similarly, the information of a whole particle size distribution can be condensed into some characteristic numbers, such as mode, mean, span, and the Sauter diameter. Proper evaluation is needed to confirm whether this is indeed the way to go to obtain a good modelling practice for PBM. A lot of freedom is available when dealing with particle size distribution, but the question is how to deal with this kind of freedom and how it is best coupled to the modelling objective. Third, a technique to find the minimal value of the objective function has to be selected. In this study, predictions of a selected PBM formulation are generated using a global parameter space exploration by means of a large set of Monte Carlo simulations. Changing the aggregation and breakage kernel parameters yields different size distributions. Different objective functions are evaluated to determine the objective function whose optimum yields the optimal agreement between the simulated and measured particles bearing in mind the objective. This optimal agreement, within a predefined error range, is called the calibrated model for that process setting. This study is repeated for different process settings of the twin-screw granulator. By comparing the calibrated results for different process settings, the aggregation and breakage mechanisms can be identified, and the most dominant regimes can be found. Guidance on the different choices to be made during the calibration process will be provided.

2. EXPERIMENTAL METHOD

The ConsiGma^{TM} 25 continuous from-powder-to-tablet line from GEA was used to obtain granules. In this work, the focus is on the twin screw wet granulation process. A hydrophobic pharmaceutical formulation is granulated with water as liquid binder. A three level full factorial design of experiments was performed: the process parameters screw speed (between 450 and 900 rpm), powder throughput (between 5 and 25 Kg/h), and liquid to solid (L/S) ratio (between 0.3 and 0.6) were changed[4]. Off-line measurements were performed on dried granules with image analysis (QICPIC). This device uses image analysis to obtain a granule size distribution. Distributions of number and volume fraction are obtained. The granules inside the barrel are measured at four locations: location 0 is the preblend of the compound, location 1 is after the wetting zone, location 3 is after the first kneading element, and location 6 is at the end of the barrel, after the second kneading element and the size exclusion element. An example of measured data for low and high L/S ratio can be found in figures 1 and 2. It can be observed that for both L/S ratios, the size range of the granules is more or less equal. But for low L/S ratio, the distribution is more bimodal, an attribute which is already present after the wetting zone, and is retained in the final GSD at the end of the barrel. Further, some oversized granules are created after the wetting zone, but through kneading, they are reshaped to smaller granules in zones three and six.

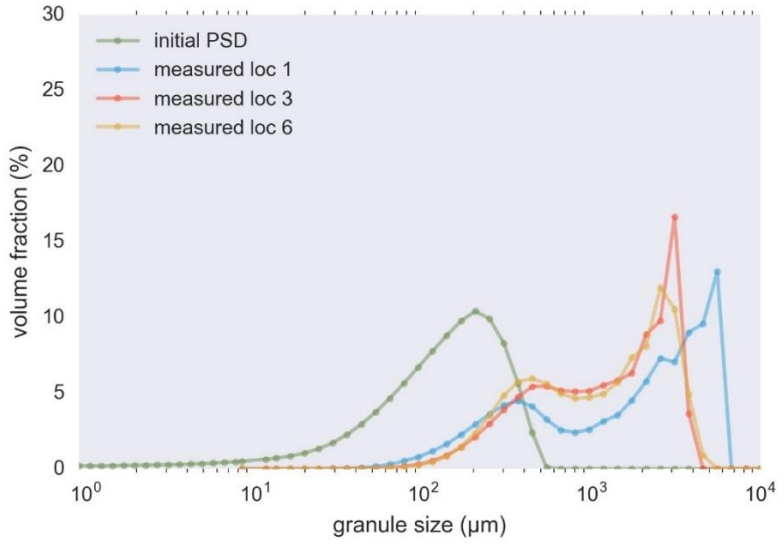

Figure 1: Measured GSD data at different locations in the barrel for a low L/S ratio of 0.3

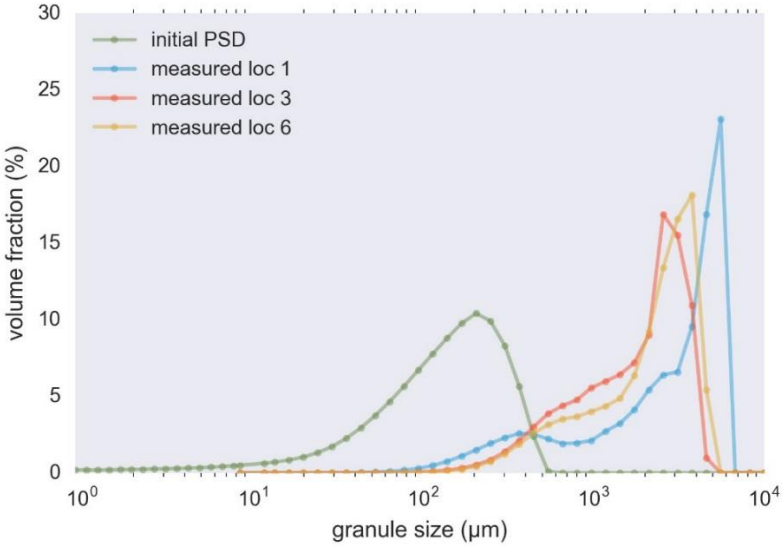

Figure 2: Measured GSD data at different locations in the barrel for a high L/S ratio of 0.6

3. MODEL DESCRIPTION

In this work, a population balance modelling (PBM) was used to predict the distribution of particle sizes inside the granulator. In this process setup we assume that the two main occurring processes are aggregation and breakage. In the former process, two particles combine to form a new particle, larger in size. The latter process describes the formation of two or more fragments from one mother particle. The mathematical description of spatially homogeneous system undergoing aggregation and breakage can be described by the following population balance equation (PBE) [5]:

$$\frac{\delta n(t,x)}{\delta t} = \frac{1}{2}\int_0^x \beta(t,x-\varepsilon,\varepsilon)n(t,x-\varepsilon)n(t,\varepsilon)d\varepsilon - n(t,x)\int_0^\infty \beta(t,x,\varepsilon)n(t,\varepsilon)d\varepsilon + \int_x^\infty b(t,x,\varepsilon)S(t,\varepsilon)n(t,\varepsilon)d\varepsilon - S(t,x)n(t,x)$$

To solve this integro-differential equation numerically, we need a discretisation method. Several methods are available in literature: fixed pivot, moving pivot, or the cell averaging technique [3]. Based on the comparison by Kumar [6], the cell averaging technique was chosen for this aggregation and breakage problem as this scheme is very accurate and efficient, even for coarse grids.

Since none of the traditional kernels worked, novel kernels were developed based on observations in the data. When granulating our compound, the main differences are observed in the granule size distribution (GSD) when the liquid to solid (L/S) ratio changes, see figures 1 and 2. At low L/S ratio, the GSD exhibits bimodality, whereas at high L/S ratio the GSD looks more unimodal.

With this model, a prediction of both the unimodal and the bimodal behaviour with one single aggregation kernel structure is the ultimate goal. This kernel exists of a convolution of a continuously increasing part (to drive the GSD to higher granule sizes) and a smooth stepping function to exhibit the bimodal behaviour. This stepping function can be lowered or switched-off in case of unimodal behaviour, and can be more emphasised when more bimodality occurs. The breakage kernel is a combination of attrition and uniform breakage.

The hypothesis for this aggregation kernel is that aggregation is the source of bimodality, whereas in literature it is often stated to be caused by breakage. However, the measured GSDs in fig. 1&2 clearly show that bimodality is induced in the wetting zone where breakage is highly unlikely. With changing L/S ratio, the amount of available liquid changes. When low amounts are available in the system (low L/S ratio), particles are held up in a certain size range because there is not sufficient liquid available to allow granulation to larger size. Particles of a larger size should therefore aggregate at a higher rate. In this way, mechanistic knowledge is built into the mathematical model. If breakage would be the source of bimodality, there is no reason why there are differences at different L/S ratios, as the observed friability is similar in both cases.

The full model is in fact a combination of three PBM models in series: a PBM compartmental model. For each zone for which data is gathered, a compartment is made: the wetting zone (preblend to after the addition of the liquid binder), kneading zone 1 (from after the wetting zone to after the first kneading elements), kneading zone 2 (just before the second kneading elements up until the end of the granulator barrel.

To calibrate the model, an objective function using a combination of moments of the distribution is used. Different moments give different information: from zero to four, they give information on the amount of particles, the size, the surface area, the volume, and the skewness of the distribution. If these moments are combined into an objective function, it assures that the larger particles are correctly predicted (third and fourth moment), but also that the fines are not neglected (moment zero, one, and two) which is a desired feature.

4. RESULTS AND DISCUSSION

By using the methodology from section three, we can predict GSDs with unimodal and bimodal behaviour. The results of the calibration exercise for an experiment with a low L/S ratio and one with a high L/S ratio are given in figures 3 and 4. Here, the measured GSD is

compared with the calibrated model at different locations inside the granulator. It can be noticed that, although unimodal behaviour can be simulated with more accuracy than bimodal behaviour, the bimodal distribution can be captured reasonably using the same kernel. The results show that both the GSD at the end of the granulator as well as at intermediate locations (wetting or first kneading zone) are predicted reasonably well.

The results in figures 3 and 4 show that a aggregation function is essential to tackle the issue of GSD prediction for low and high L/S ratios. However, these results also show that a very accurate fit is not yet achieved. The issue lies in the prediction of the wetting zone, if this zone is not predicted sufficiently accurate, the errors propagate through the kneading zones, until the end of the granulator. Though room for improvement exists in further refining the kernel, this approach seems to be very promising.

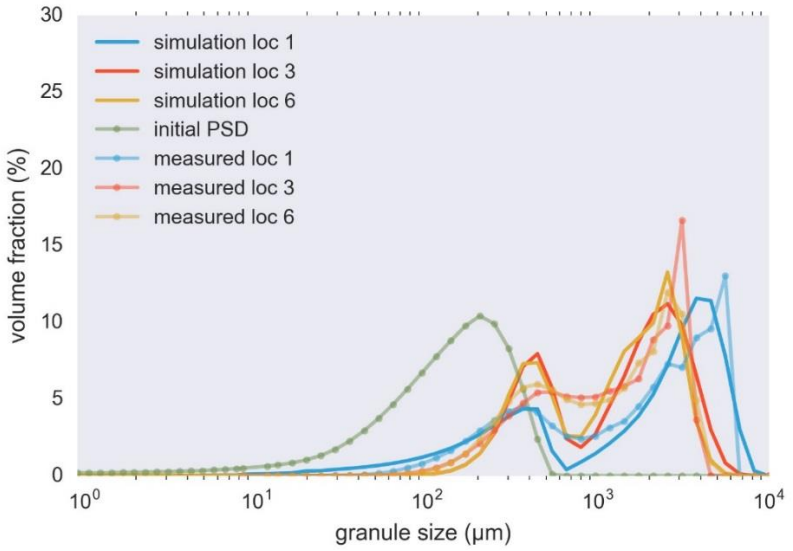

Figure 3: Simulated and measured GSD for a low L/S ratio

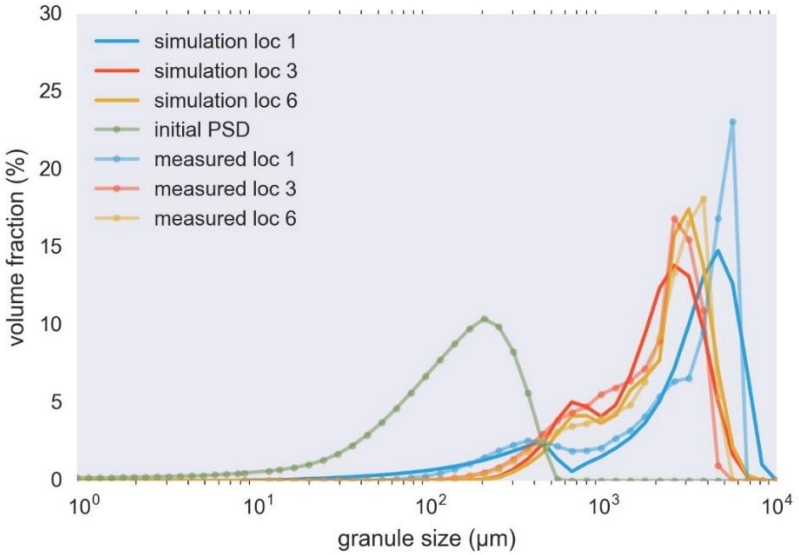

Figure 4: Simulated and measured GSD for a high L/S ratio

5. CONCLUSION

The model structure proposed for the aggregation kernel works for both low and high L/S ratios. Although some improvements can still be made regarding the prediction of granules for a low L/S setting, the use of one single kernel is a major step forward.

The objective function using the moments of the distribution is an good improvement. As it contains information on both the fines and the larger particles, it is possible to get a very good fit on the measured data, hereby using information of the entire GSD. Further improvements could be incorporating the non-parametric χ^2-homogenity test[7].

The model can be further improved by one or more of these measures: applying sensitivity analysis on the model parameters, further calibration (i.e. looking for another set of parameters that yields a better fit to the data), or changing the model structure.

This model will be used in future research to get a relation between preblend parameters (hydrophobicity, density, etc.), operating conditions (mass flow rate, screw speed, LS ratio), and desired GSD. The future goal is to obtain a model that can predict GSD and the operating conditions to get there for new preblends. Furthermore, an optimal experimental design protocol will be set up to select the experiments which yield the most information while using as little costly API as possible.

6. REFERENCES

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