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The variability of pharmaceutical granulation

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ABSTRACT

High shear wet granulation is traditionally considered a highly unrepeatable solids processing step, with the considerable domination of art over science. In the United States, the Food and Drug Administration, a major regulator of pharmaceutical processes is encouraging pharmaceutical companies to understand the science and engineering aspects of their process, and move from the current qualitative understanding to a quantitative and mechanistic understanding of their processes.

In order to examine the intrinsic variability of granulation, many carefully controlled repeat granulations were performed in a high shear mixer and the size distributions of the resulting granules were analysed, along with traditional on-line process data surrounding current consumption of the mixer, and temperature of the granulating mass. The raw experimental results were combined and analysed with the use of multivariate techniques to examine the causes of variability. It is seen that none of the measured variables fully explain the variability observed and that despite the care taken to repeat exact conditions, the granules still produced were variable.

Final analysis of the data shows that batches can be separated into two different sets, distinguished by different operators showing that minute unrecorded changes to the experimentation process, affect the numerical outcome of the procedures. The current study shows the power of multivariate techniques to analyse data, and provide insight into the variability of the underlying process.

1. Introduction

In high shear wet granulation, powder is combined with liquid in a high shear mixer to produce powder agglomerates where individual powder particles are still distinguishable. This is a common step within the pharmaceutical industry where powders are mixed together and agglomerated to enhance dissolution profiles, flowability and reduce process driven segregation. It is commonly acknowledged that this granulation step is the most variable step with the pharmaceutical processing chain. Little academic research is available in the open literature to compare the variability of granulation, and to provide a measure of the variability that one might expect from the manufacturing process itself.

Lately, driven by the United States, Food and Drug Administration (FDA) quality by design initiative [1], much research has been conducted to look for changing conditions, and characteristic signatures of the granulation process, that are ideally powder and granulator independent. Some success has been reported using power curves [2–4] and torque data to express the variability in the process, and enhance knowledge of what is happening in the mixer bowl from a bulk level. And work progresses [5–9] to examine and explain the stepwise evolution of granules over time.

From a pharmaceutical perspective, the bulk understanding of granulation is an intensely cost driven process, as a wasted batch equates to many thousands of pounds, providing lost earnings and missed targets. Control and monitoring schema for the process are slowly becoming apparent and the burgeoning field of multivariate analysis (or chemometrics), is being used to increase the understanding gained from the huge amounts of multivariate time series process data now being generated from today's modern on and off line process measurement instruments [10–16].

Indeed, the interaction of the control schema and the bulk process is the subject of the current draft process validation guidance from the FDA [17]. This guidance renews the FDA's call for well understood and quality by design approaches to pharmaceutical manufacturing, with high degrees of assurance that the process is operating within specified limits of safety, hence producing on specification drug products, and that, crucially; the variability of the process is explainable and quantified. This emphasizes the use of multivariate analysis within the process development framework, to examine this variation, and to try and pin point batch–batch deviations from the on specification, in order for the continued life cycle approach to be applied to the products in question.

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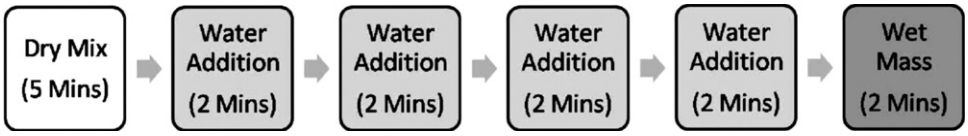

Fig. 1. Experimental timeline, blocks show processing, and intervals represent stops for sampling from the powder bed.

Attempts to use multivariate methods capable of visualising these deviations and subtle changes, such as partial least squares (PLS) [13,18], principal component analysis (PCA) [2], self-organizing maps (SOM) [19], and other mathematical techniques to enable the visualisation and understanding of multidimensional sets from process measurement techniques (e.g. near-infrared, chemical imaging), process parameters (e.g. temperatures and pressure sensors) or product attributes (e.g. tablet dissolution, granule density) are slowly becoming commonplace in industrial experimental design, analysis and in the future, control [20–22].

In the context of this study, the primary goal of multivariate analysis is to allow for enhanced understanding and appreciation of variability with granulation data sets and allow for a method to isolate the individual parameters responsible for the variability seen, in an attempt to move granulation technology towards the desired six-sigma goal.

2. Materials and methods

As these experiments are designed to assess variability of the granulation unit operation it is vital to remove as much variability from the process and setup conditions as possible. Thus these experiments were performed using the same granulator with a repeatedly calibrated and checked experimental setup, under the guise of good manufacturing practice (GMP), in the same temperature and humidity controlled room, designed to maintain constant conditions throughout the experiments. Two operators performed the experiments, both following the same carefully documented procedure summarised below.

2.1. Materials

A common set of pharmaceutical excipients were used in these placebo trials, 73.5% (w/w) lactose monohydrate (Pharmatose 200 M, DMV, The Netherlands), 20% (w/w) microcrystalline cellulose (Avicel Ph101, FMC BioPloymer, USA), 5% (w/w) hydroxypropyl-methyl-cellulose (Methocel E5, Dow Chemicals USA), and 1.5% (w/w) Cross carmellose Sodium (Ac-Di-Sol, FMC BioPloymer, USA).

2.2. Granulation equipment

A PMA65L Fielder granulator, with a bottom driven, three bladed impeller rotating at 200 rpm with blades inclined at 30° to the horizontal. A horizontal chopper is fitted and rotated at 1500 rpm during the water addition and wet massing phase of granulation. Water was added at a constant rate from a loss in weight feed reservoir via a spray nozzle and peristaltic pump, (Watson-Marlow, 502U).

2.3. Data collection and analysis

Proprietary data collection software was used to collect on-line data regarding the temperature and humidity of the process room and data surrounding the granulator, (current draw, temperature, impeller and chopper speed). Impeller current was measured directly from the motor drive of the granulator, while temperature is measured using a temperature sensor fitted to the edge of the bowl.

Size distributions were measured by sampling 5 g of the granules via an automated image analysis system (Qicpic, Sympatec, Germany). This sampling was not a major source of error ($X_{50} \pm 30\ \mu m$) as confirmed by repeat sampling of the same granulation samples. 100 logarithmic size classes were chosen between 20 and 7000 μm.

Data were collated within Microsoft Excel, and further analysed using scripts written using built in matlab routines. Cross correlation analysis and principal component analysis was performed using matlab 7.5 (R2007b).

2.4. Experimental procedure

In total 11 kg (±2 g) of placebo material was loaded into the granulator, on-line data collection was started, and then pre-blended at 100 rpm for 5 min, until fully mixed. The granulator

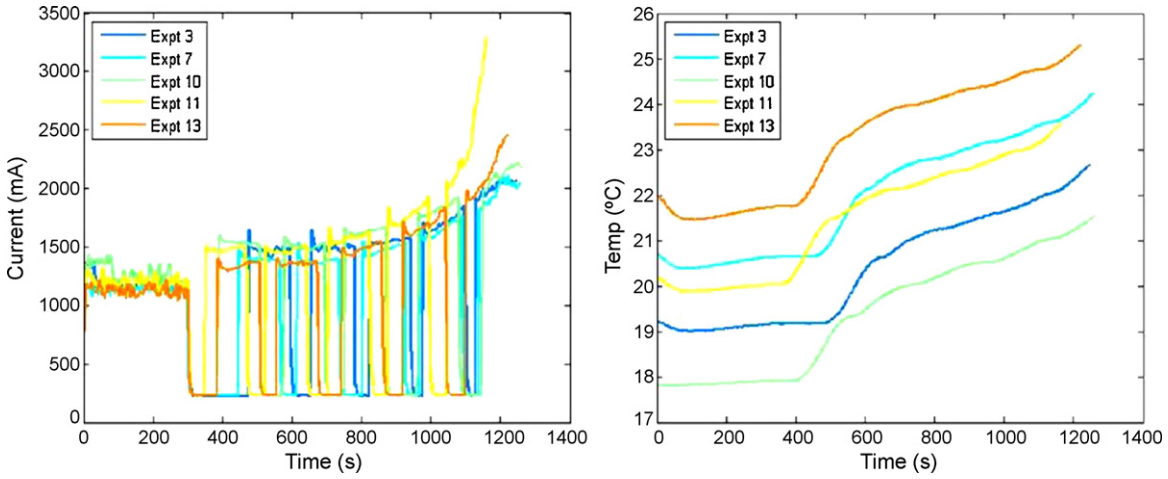

Fig. 2. Impeller current and temperature for 5 sample batches from the data.

was stopped. The water nozzle inserted, and the impeller speed set to 200 rpm, a chopper speed of 1500 rpm was set. When the impeller and chopper were up to speed, water addition was started at 220 g/min from the pump (pre-calibrated). This continued for 2 min, when the water was stopped, and the granulator opened to sample and remove approximately 50 g of granules onto an aluminium tray and sealed into a plastic bag. The granulator and water addition system were immediately re-started, with repeated samples at 4, 6, and 8 min. For the last 2 min no water was added, and the powder mix was just agitated with the chopper and impeller. The process was deemed complete at 10 min of granulation. Particle size for the samples was measured at the end of the batch approximately 30 min after the experiment had completed (Fig. 1).

3. Results

3.1. Granulator impeller current and temperature data

Using the data collection software, it is possible to collate data for the following batches, and provide this for plotting. Fig. 2 show 5

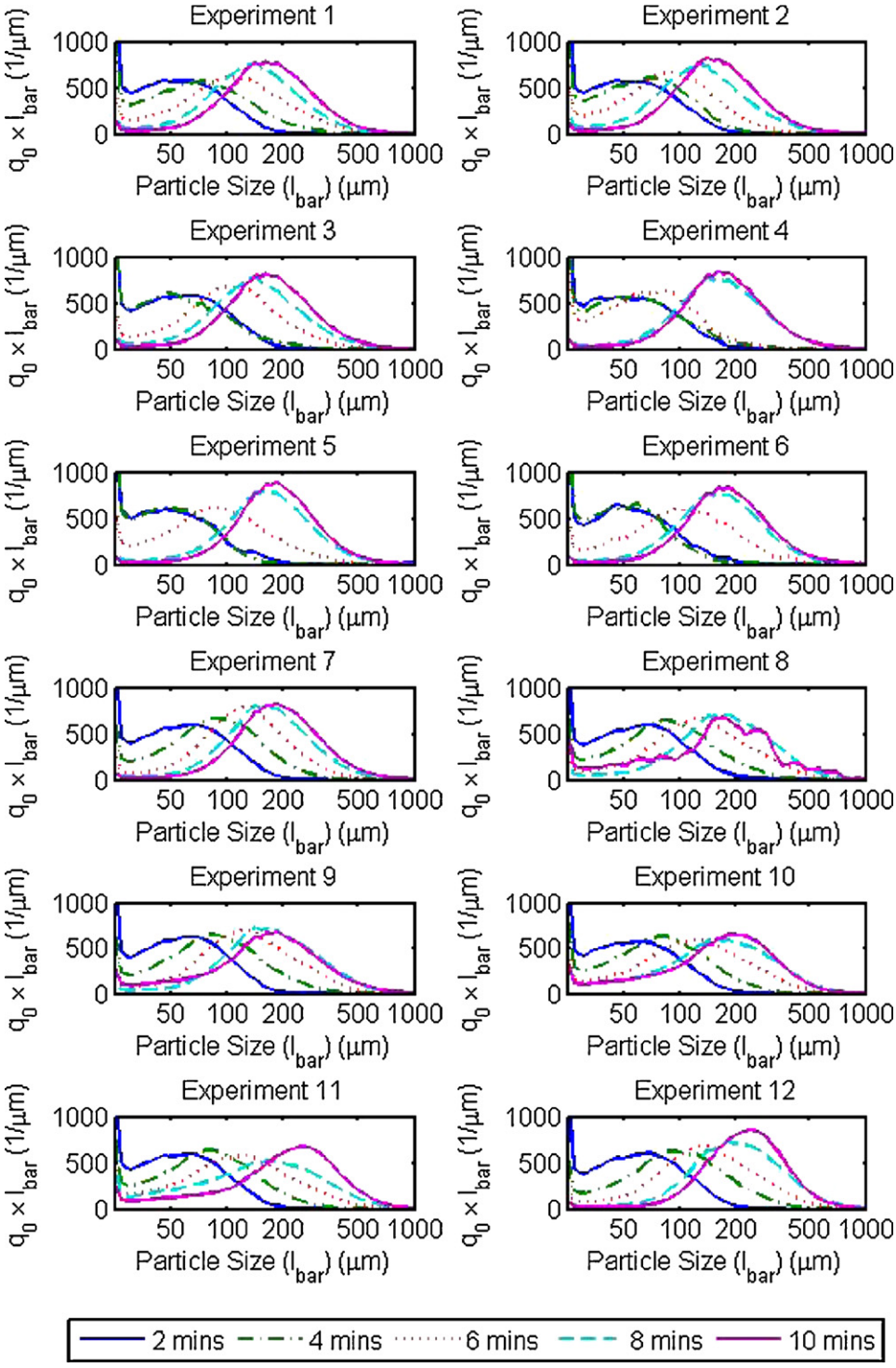

Fig. 3. Example size distributions (l_{bar}, mean particle size of bin) q_0 (number weighted density).

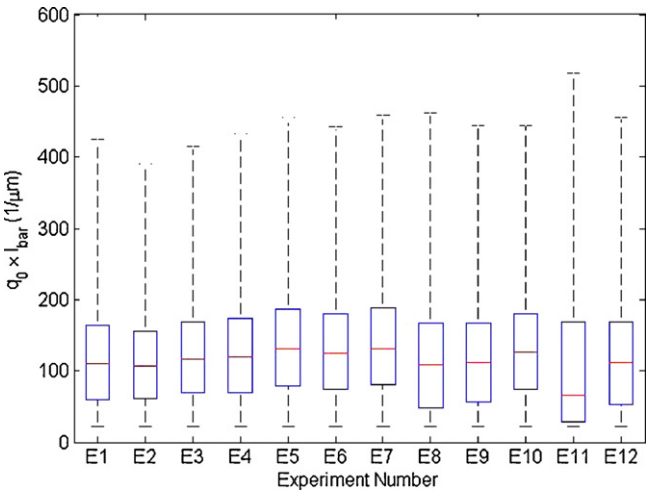

Fig. 4. A box plot of the data showing the variability in final granule size.

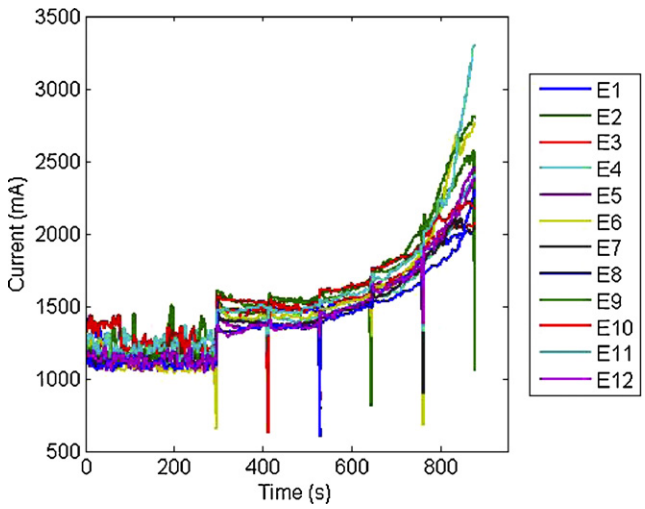

Fig. 5. Showing the alignment process for impeller current and the corresponding trends.

samples of the temperature and power variations recorded during the granulations.

It is seen that the granulations are repeatable with both the current draw and temperature increasing throughout the batch. The sampling points for the granulations can clearly be seen as the current draw drops quickly to a lower level as the granulator the impeller is turned off. The sampling times recorded at ±2 s from their desired values, the sampling stage creates a bigger variation in overall process time. This is symptomatic of human controlled experimentation, and is a major uncontrolled factor in this experimental system. The temperature of the granulator bowl is shown to vary by 4 °C during the experimental set, this is accounted for by successive experimentations as they warm the bowl, and is again something uncontrolled in the experiments due the huge mass of granulator and its housing.

3.2. Granule size distributions

The number size distributions as generated by the QicPic platform are shown in Fig. 3. It is seen that there are a very large number of fines within the system. The consistency of the methods can be seen, which show, very similar distributions.

The granules seem to grow steadily with the first 8 min of processing and then slightly within the wet massing stage. The number distributions are consistent to within ±50 μm of the mean for all the data sets, this is a reproducible measure, as sample to sample variation of similar batches was recorded at approximately ±30 μm for different samples from within the same batch. To show the variability in the final distributions, a box plot of the granules sampled data from the end of the granulation is shown in Fig. 4. This figure shows the variability recorded in the batches, and how this is consistent across batches. The box represents the inter-quartile range of the batches, while the mean is shown by the line across the width box.

4. Analysis and discussion

4.1. Impeller current and temperature data

An often quoted control method within industry is the use of power, torque or impeller current curves [3,4,23–27] to provide a more sophisticated control method than simply granulating for a set period of time. Thus, due to the consistent method of these granulations, it was often accepted that the power curve would be able to explain some of the variability noticed within the size distributions. Fig. 5 shows the impeller current curves over time after stretching and aligning the impeller current curves to provide a constant basis for further analysis, and removing the slight timing inaccuracies (±2 s) caused by the human operated nature of the experiments. This stretching and aligning procedure is achieved, by interpolating to create a fixed number of data points, between the two key steps of off and on for each sampling interval. The removal of the power consumption data for the sampling interval periods causes the *x* axes to contract, in Fig. 5 when compared with Fig. 2 that shows the total process time.

The curves show repeatability, and a certain characteristic shape, limited by measurement noise within the granulator measurement system during the dry mix phase and subsequently slowly increasing with time as more water is added. During the wet massing phase there is still significant increase in observed current as the granulator works harder moving the moist cohesive granular mass around within the bowl. Despite the repeated conditions the variability in measured current increases as the process is continued. At the end of the process after 15 min of processing the measured current lies between approximately 2000 and 3300 mA, a large and significant variation in data output.

4.2. Principal component analysis

PCA is a widespread multivariate technique that is used to summarise main trends, e.g. groups of similar batches, outliers, characteristic variables, in large multidimensional datasets. The procedure extracts from the original variables a small subset of new variables (principal components) that geometrically correspond to the direction of main variability in the multidimensional space, and can be used to generate scatter plots representing the relative similarity of the objects analysed. The procedure is particularly effective when data are highly correlated, as is apparent from Fig. 5.

In this case PCA is applied on both impeller current and temperature data after alignment, with results summarised in the scatter plot in Fig. 6. Two principal components are used to represent the relative similarity of batches, representing approximately half (37% + 14% = 51%) of the overall variability in the profiles.

4.3. Assessment of repeatability

The proposed way of quantifying repeatability on the basis of impeller current profiles is that of measuring an index that directly relates to the amount of correlation in each 2 min sampling interval.

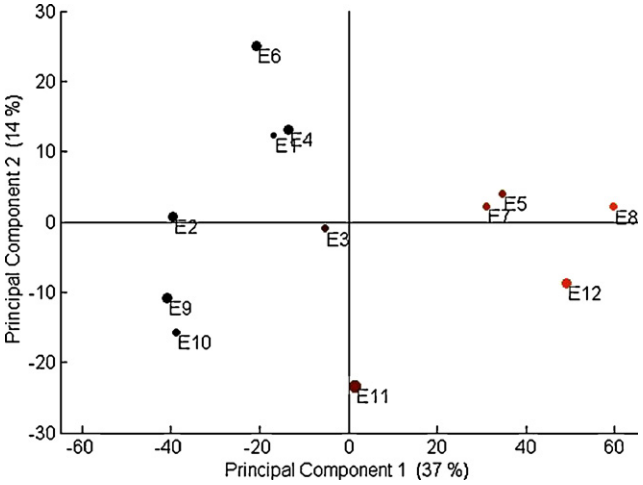

Fig. 6. Showing principal component analysis of aligned granulator current and temperature data (lighter colours show higher final temperatures, bigger points show higher final impeller currents).

The closer (more correlated) the current curves, the more repeatable the process is thought to be. The procedure relies again on PCA: the principle is that highly correlated data can be represented efficiently by few components that will span a larger percentage variability of the original dataset. The index to measure repeatability is calculated as [28]:

$$K = \frac{\sum_{m=1}^{p} \left| EV_m - (1/p) \right|}{2(p-1)/p} \times 100 \quad \text{with} \quad 0 \le K \le 100 \quad \text{with} \quad EV_m = \frac{\lambda_m}{\sum_{m=1}^{p} \lambda_m} \tag{1}$$

where p is the number of principal components selected to describe the dataset and λ_m is the eigenvalue of the m-th component.

This index is sensitive to noise and trajectory divergence, but it insensitive to trajectory offset, as caused by differing start-up conditions. It is described using one value for all trajectories under consideration, showing the total repeatability per sampling interval of the data.

If the data is broken into 6 segments (dry mix, 4 sample points, and then final wet massing, as shown in Fig. 2) and then analysed from Fig. 7 it is shown that the K-index slowly increases over time, up to 8 min, were the score is higher, so that it is shown that granulator current is a repeatable measure of granulation, even

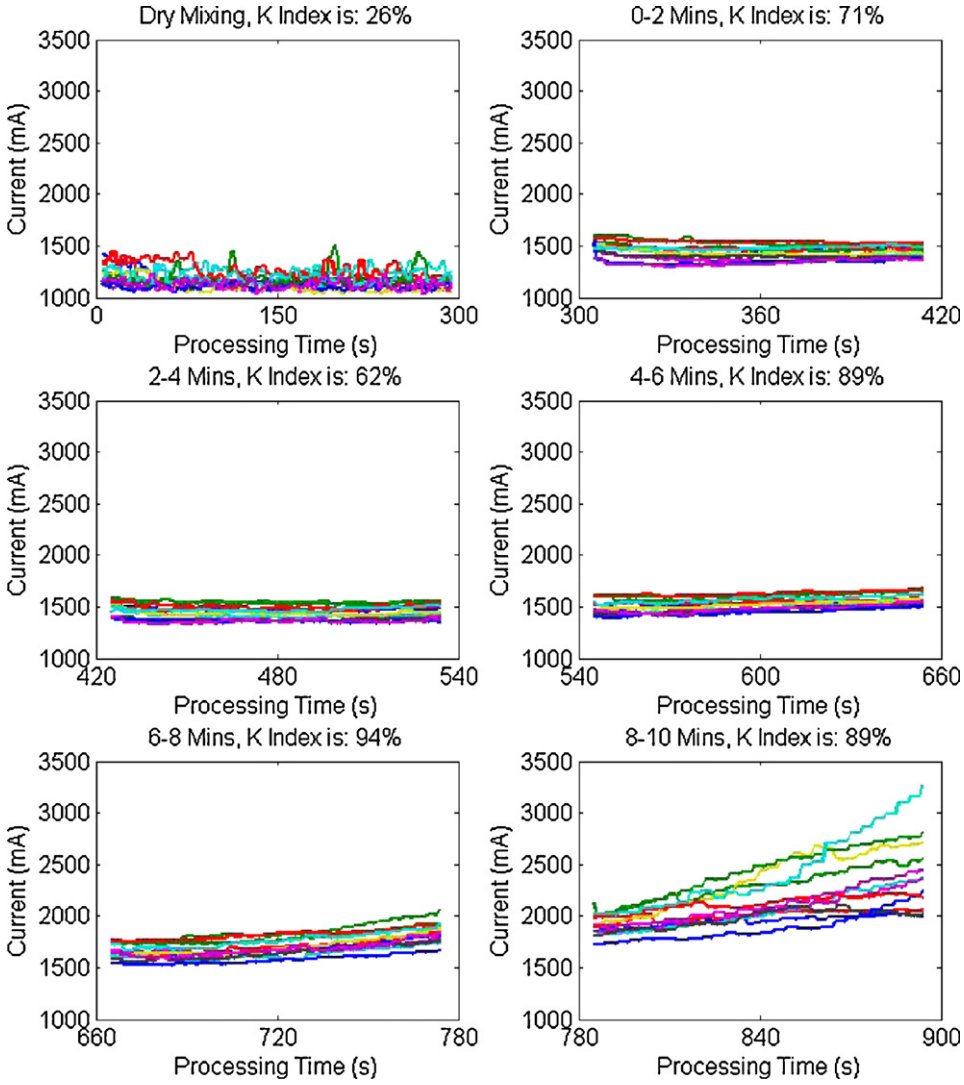

Fig. 7. K-Index of the granulation runs (plot colours same as Fig. 5).

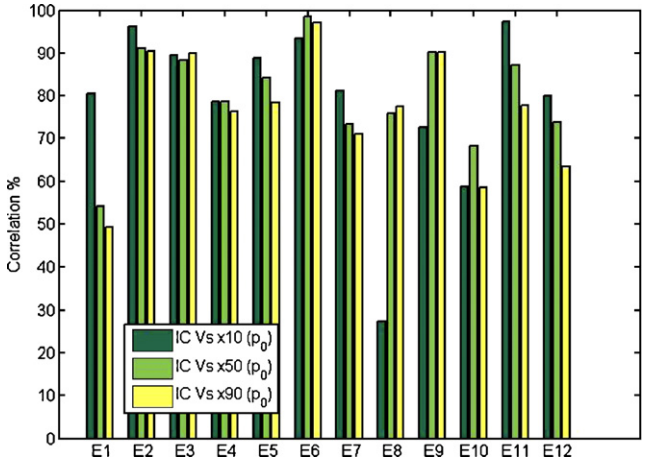

Fig. 8. Correlation of 10×, 50× and 90× to impeller current change (one value for each experiemtnal set, realting change in impleler current to change in particle size for each experiment for all times).

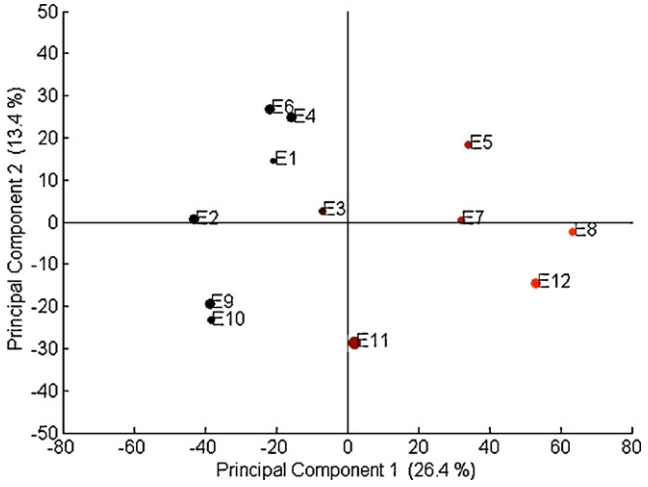

Fig. 9. Combined PCA on experiments with a complete data set (lighter colours show higher final temperatures, bigger points show higher final impeller currents).

if not by "absolute" value, where raw numerical values can be used.

It is interesting to note two things from Fig. 7. Firstly the nature of the graph, the *K*-index is seen to increase during the progress of water addition 0–8 min, indicating that adding water, leads to a better consistency to the impeller current data. The *K*-index then decreases during wet massing (8–10 min), showing that the process becomes less well controlled during this time as the granules grow from the wet mass.

4.4. Size distributions correlation of ×10, ×50 and ×90 to impeller current

To see if the differences in impeller current draw were correlated to the size distributions measured, to this end, 3 percentiles of the size distributions (×10, ×50, ×90) at each sampling time were taken as descriptors of the granulation process and cross-correlated to the impeller current change over each sampling time, calculated between the relative increases in each sample time of 2 min of the impeller Current and the relative increases in ×10, ×50, ×90 percentiles for each batch. The equation below shows the correlation as estimated between the vector of impeller current change over each sampling time ($\Delta IFLC$) and the vector of median difference over each sampling time ($\Delta x50$), where over-line indicates the average of the two vectors, s their standard deviation and n the number of elements:

$$c(\Delta IFLC, \Delta x50) = \frac{(\Delta IFLC_i - \overline{\Delta IFLC})(\Delta x50_i - \overline{\Delta x50})}{(n-1)s(\Delta IFLC)s(\Delta x50)} \quad (2)$$

If impeller current is a "good" predictor of granulation and granule size, then it would be expected that the results would be highly correlated, i.e. a change in impeller current is related to a change in particle size. This would then correlate to a 100% value in Fig. 8.

Fig. 8 shows this correlation. It is shown that there is indeed a distinct association between granulator current and granule size for the number distribution. There is reasonable correlation between the impellor current measure and the granule size for each subinterval. However there is also great variation in the magnitude of this association, showing that the impeller current is not fully able to correlate to size within the granulator, and that if used as a control scheme would cause some on target batches (such as E8) to be scrapped causing great loss of material and investment. This would translate that such simple correlations, are not useful as predictors of the process output, and that more performance criteria would achieve extra clarity in the results.

4.5. Principal component analysis on combined data

Combining the whole data set and then performing principal component analysis on the data collected (impeller current, product temperature, and particle size (p_0)) allows for an appreciation of clustering within the data, and to see if any overall trend can be identified.

The principal components distinguish between the data well, with the first component (*x* axes) corresponding to final product temperature, with the hotter batches are towards the right, while the second component (*y* axes), while not attributable to anything directly in the data, (impeller current or temperature) partitions the data into two seemingly separate groups, using a positive second component to distinguish one group (E1–E7) and a negative second component to differentiate the other (E8–E12). These experiments are separated by two different operators, showing the power of PCA to demonstrate that even minor, seemingly insignificant changes to procedure, can affect the results of the process (Fig. 9).

5. Conclusions

The results from this paper show that despite the best efforts, (temperature and humidity controlled room, same material batches, clearly defined experimental procedure, same equipment) to keep the conditions of the granulator, materials, and processing steps the same, the output from the granulation process is still highly variable with respect to the recorded variables, or impeller current draw, powder temperature, and recorded particle size.

The significance of this result for a pharmaceutical manufacturing environment, is that, as detected here, the second most significant feature giving rise to variability in the process was that of operator, this has considerable implications, in that, product variability may be explained by the slight differences recorded for experimental operators, and their own intrinsic human variability in ways of working, despite the closely controlled method description.

There is a need to examine this further, if essentially the same operating conditions and process setup as reported here, produce different granules, this the shows the complicated, multidimensional nature of granulation. Obviously the variables measured are not enough to explain the process fully so any control schema based on such measurements can be used as a guide only. Work to reduce errors further by means of developing fully automated granulation systems, is ongoing.

Acknowledgements

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References

[1] FDA, Guidance for Industry, PAT—A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance, 2004.
[2] I. Niklasson Björn, et al., Empirical to mechanistic modelling in high shear granulation, Chemical Engineering Science 60 (14) (2005) 3795–3803.
[3] M. Bardin, P.C. Knight, J.P.K. Seville, On control of particle size distribution in granulation using high-shear mixers, Powder Technology 140 (3) (2004) 169–175.
[4] A. Faure, P. York, R.C. Rowe, Process control and scale-up of pharmaceutical wet granulation processes: a review, European Journal of Pharmaceutics and Biopharmaceutics 52 (3) (2001) 269–277.
[5] P.K. Le, et al., The kinetics of the granulation process: right from the early stages, Powder Technology 189 (2) (2009) 149–157.
[6] C.A. Biggs, et al., Coupling granule properties and granulation rates in high-shear granulation, Powder Technology 130 (1–3) (2003) 162–168.
[7] L.X. Liu, R. Smith, J.D. Litster, Wet granule breakage in a breakage only high-hear mixer: effect of formulation properties on breakage behaviour, Powder Technology 189 (2) (2009) 158–164.
[8] J.M.H. Poon, et al., Experimental validation studies on a multi-dimensional and multi-scale population balance model of batch granulation, Chemical Engineering Science 64 (4) (2009) 775–786.
[9] R. Ramachandran, et al., A mechanistic model for breakage in population balances of granulation: theoretical kernel development and experimental validation, Chemical Engineering Research and Design 87 (4) (2009) 598–614.
[10] J. Aaltonen, et al., Perspectives in the use of spectroscopy to characterise pharmaceutical solids, International Journal of Pharmaceutics 364 (2) (2008) 159–169.
[11] B. Campisi, et al., Melt granulation in a high shear mixer: optimization of mixture and process variables using a combined experimental design, Chemometrics and Intelligent Laboratory Systems 48 (1) (1999) 59–70.
[12] S. Matero, et al., The feasibility of using acoustic emissions for monitoring of fluidized bed granulation, Chemometrics and Intelligent Laboratory Systems 97 (1) (2009) 75–81.
[13] Y. Roggo, et al., A review of near infrared spectroscopy and chemometrics in pharmaceutical technologies, Journal of Pharmaceutical and Biomedical Analysis 44 (3) (2007) 683–700.
[14] N.E. Sever, et al., Process analytical technology in solid dosage development and manufacturing, in: Developing Solid Oral Dosage Forms, Academic Press, San Diego, 2009, pp. 827–841.
[15] D. Vojnovic, D. Chicco, H. El Zenary, Doehlert experimental design applied to optimization and quality control of a granulation process in a high shear mixer, International Journal of Pharmaceutics 145 (1–2) (1996) 203–213.
[16] G.M. Walker, et al., Influence of process parameters on fluidised hot-melt granulation and tablet pressing of pharmaceutical powders, Chemical Engineering Science 60 (14) (2005) 3867–3877.
[17] FDA, Draft Guidance for Industry Process Validation: General Principles and Practices, 2008.
[18] S. Matero, et al., Monitoring the wetting phase of fluidized bed granulation process using multi-way methods: The separation of successful from unsuccessful batches, Chemometrics and Intelligent Laboratory Systems 96 (1) (2009) 88–93.
[19] N. Laitinen, et al., Visualization of particle size and shape distributions using self-organizing maps, Chemometrics and Intelligent Laboratory Systems 62 (1) (2002) 47–60.
[20] M. Fransson, S. Folestad, Real-time alignment of batch process data using COW for on-line process monitoring, Chemometrics and Intelligent Laboratory Systems 84 (1–2) (2006) 56–61.
[21] T. Glaser, et al., Model predictive control of continuous drum granulation, Journal of Process Control 19 (4) (2009) 615–622.
[22] C.F.W. Sanders, M.J. Hounslow, F.J. Doyle Iii, Identification of models for control of wet granulation, Powder Technology 188 (3) (2009) 255–263.
[23] G. Betz, P.J. Bürgin, H. Leuenberger, Power consumption profile analysis and tensile strength measurements during moist agglomeration, International Journal of Pharmaceutics 252 (1–2) (2003) 11–25.
[24] G. Betz, P.J. Bürgin, H. Leuenberger, Power consumption measurement and temperature recording during granulation, International Journal of Pharmaceutics 272 (1–2) (2004) 137–149.
[25] I.T. Cameron, et al., Process systems modelling and applications in granulation: a review, Chemical Engineering Science 60 (14) (2005) 3723–3750.
[26] H. Leuenberger, et al., Chapter 15 Granulation process control—production of pharmaceutical granules: the classical batch concept and the problem of scale-up, in: Handbook of Powder Technology, Elsevier Science B.V., 2007, pp. 705–733.
[27] H. Leuenberger, et al., Manufacturing pharmaceutical granules: is the granulation end-point a myth? Powder Technology 189 (2) (2009) 141–148.
[28] R. Todeschini, Data correlation, number of significant principal components and shape of molecules. The K correlation index, Analytica Chimica Acta 348 (1–3) (1997) 419–430.