J Pharm Innov (2010) 5:58–68
DOI 10.1007/s12247-010-9079-x

RESEARCH ARTICLE

A PAT Approach to Enhance Process Understanding of Fluid Bed Granulation Using In-line Particle Size Characterization and Multivariate Analysis

Jun Huang · Chimanlall Goolcharran · Julia Utz · Pedro Hernandez-Abad · Krishnendu Ghosh · Arwinder Nagi

Published online: 18 June 2010

Abstract The purpose of this study was to achieve improved process understanding of fluid bed granulation using in-line particle size analyzer in conjunction with multivariate methods. The combined use of process analyzers and multivariate tools provides a useful means to drug development within the framework of quality by design utilizing process analytical technology. The evaluation of in-line monitoring manufacturability quality attributes, particle size, and particle size distribution, was conducted using the Parsum probe which is based on spatial filtering technique. Several granulation batches were manufactured and monitored using a commercial-scale fluid bed granulator. Reference measurements by offline Malvern MasterSizer showed good agreement with those by Parsum at end-of-spray phase. Multivariate/batch statistical process control methods were used to evaluate batch process performance, batch-to-batch variation and develop potential control strategy. The results indicated that the Parsum analyzer is a viable tool for in-line particle size characterization and improved process understanding in combination with multivariate tools.

J. Huang (✉) · C. Goolcharran · P. Hernandez-Abad · K. Ghosh · A. Nagi
Pfizer Inc,
401 N Middletown Rd,
Pearl River, NY 10965, USA
e-mail: jun.huang1@pfizer.com

J. Utz
Excella GmbH,
Nürnberger Strasse 12,
90537 Feucht, Germany

Keywords Parsum · Fluid bed granulation · Particle size distribution (PSD) · Quality by design (QbD) · Process analytical technology (PAT) · Multivariate statistical process control (MSPC)

Introduction

Quality risk assessment, performed in accordance with ICH Q9 guidance, identified fluid bed granulation as one of critical unit operations for this product. In particular, granulation attributes—particle size and particle size distribution were identified as intermediate quality attributes that impact product manufacturability (flow and compressibility) and final product performance (dissolution profile). Therefore, it is crucial to monitor and control granule particle growth and particle-size distribution during fluid bed granulation.

Few techniques are commercially available for in-line particle size measurement during wet granulation [1, 2]. Near-infrared (NIR) spectroscopy has been shown to be promising in measuring particle size due to its cross-sensitivity. Particle size information can be extracted from baseline offset and slope change in the NIR spectra through chemometric modeling [3–8]. Other techniques reported in the literatures are the usage of in situ image processing system [9, 10] and passive acoustic emission technique to monitor particle size during fluid bed granulation [11–13].

Focused beam reflectance measurement (FBRM) and Parsum spatial filtering technique (SFT) are becoming more recognized in the pharmaceutical industry, but the reported applications to fluid bed granulation at manufacturing scale are comparatively few [14–18]. Both techniques are designed to directly characterize particle size and tracking

real-time change of particle size and distribution in the process. Although both techniques are laser based, the measurement principles are different, which leads to differences in sampling mechanism, measurement range, sample state/conditions, and thus application areas. FBRM probe requires that particles flow in front of the probe window while a rotating laser beam is focused on particles. The probe detects backscattered light and records measured chord lengths. With Parsum probe, laser light obscuration signal from individual particles can be translated into size information for analysis by extended spatial filter as particles pass through an aperture on the probe tip. In wet granulation, probe fouling could be one of most significant obstacles that hinder representative and accurate measurement. Pressurized air is used to disperse particles in the Parsum probe and minimize fouling, whereas the newly developed FBRM C35 utilizes a mechanical scraper to prevent probe from fouling. More information about these two techniques can be found elsewhere [1, 14–18]. A detailed comparison of these two techniques is beyond the scope of this paper, but may be investigated in the future.

In recent years, especially after FDA's Process Analytical Technology initiative, the pharmaceutical industry has seen more and more applications of multivariate tools such as multivariate/batch statistical process control (MSPC/BSPC) [19–25]. Multivariate tools are becoming increasingly essential to extract useful information from complex data generated by process analyzers. The study reported here utilized combination of Parsum probe and multivariate batch modeling to evaluate the feasibility of in-line monitoring of the particle size and distribution at a commercial-scale fluid bed granulator and evaluate batch-to-batch variation or consistency. The ultimate goal is to monitor and control batch evolution (process trajectory) and determine granulation endpoint using Parsum, in combination with other approaches, such as NIR and process parameters.

Materials and Methods

Material

Each batch consists of 40% (*w*/*w*) BCS class 4 compound granulated with 10% (*w*/*w*) aqueous solution of povidone (Kollidon K25; BASF Corporation, Ludwigshafen, Germany).

Granulation Process

The Aeromatic S3 (GEA Pharma System AG, Bubendorf, Switzerland) fluid bed granulator was utilized for the top spray granulation and drying of the granules. The Aeromatic S3 was equipped with a 155 L bowl and capable of manufacturing 35 kg of granulation. The fluid bed granulator was operated with the process parameters indicated in Table 1 for the batches manufactured. Immediately after charging the fluid bed, the material was dried for 5 min prior to granulation. The granulating solution was top sprayed at 200 g/min for 120-150 min with an inlet air temperature of 80°C and inlet air volume of 300-350 m^3/h. As part of the operation of the fluid bed, the filter located at the top of the unit was purged at regular interval to dislodge any adhered material. During these filter purges, the inlet air and the granulating solution spray rate are shut down. For the initial 15 min of spraying, the filter purges occurred at 50-s interval. The purge intervals were subsequently increased to 100 s for the remainder of the process. The granules were subsequently dried to a moisture content of 1.5–2.5% with an inlet air temperature of 65°C and inlet air volume of 350 m^3/h.

All clinical batches were run under the same process conditions, and no design of experiments (DOE) was used to vary process parameters to study their impact on particle size and distribution at this stage. The purpose of the Parsum analyzer was to in-line monitor the particle size growth of granulation batches and evaluates batch-to-batch variation with respect to particle size using multivariate batch modeling.

Parsum Analyzer

The measurement principle of Parsum is based on SFT [2, 15]. An extended spatial filter can convert light obscuration signals from individual particles into size information for analysis. Measurement range spans from 50 μm up to 6 mm at velocities up to 50 m/s. Particle size calculations are based on statistical evaluation of a specified quantity of individual particles. The chord length of an individual particle is measured, which is the link between two points on the perimeter of the measured particle's projection face.

Table 1 Granulation process parameters for HKI-272

Parameter	Initial drying	Spraying	Drying	Unit
Inlet air volume	300	350	350	m^3/h
Inlet air temperature	70	80	65	°C
Shaking pause	50	100[a]	100[a]	S
Shaking time	15	15	15	S
Spray air	–	3.0	–	Bar
Time	5	120-150	–	Min

[a] For the initial 15 min of spraying, the shaking pause was set at 50 s

The measurement's statistical reliability increases with a larger number of individual particles measured. This sample population forms the basis to calculate particle size distributions such as number/volume distribution density q0(x)/q3(x) and cumulative number/volume distribution Q0(x) over chord length x. Particle size characteristics can subsequently be computed from the distributions, e.g., the mean, X50, X10, and X90, etc. It should be noted that not only does the Parsum measure particle size and distribution profiles but also other useful parameters such as particle velocities for all size classes, signal strength, loading (percentage of particles filled in the measurement volume), and particle rate, etc. These parameters can also be good indicators of process change, e.g., fluidization behavior and can be included in multivariate batch modeling.

The Parsum analyzer, Inline Particle Probe IPP 70-S with Eductor D23 was evaluated. The system consists of a probe, air supply box, and a computer running the data acquisition software ParsumView®. The computer was installed in the air-lock cabinet and connected to the probe with a 25-m cable. The air supply box was placed next to the fluid bed granulator and connected to the probe with two flexible pipes (DN 4 mm). The air supply box was provided with an input pressure of approximately four to five bars.

Installation of the Parsum Probe

It is critically important that the Parsum probe be installed at a proper position in the Aeromatic S3 fluid bed to achieve representative sampling and accurate measurement. Parsum IPP 70 was mounted with a DN50 Tri-clamp through an existing sight window to introduce minimum modification to the equipment (see Fig. 1). The probe tip was positioned about 30 mm below the spraying nozzle outside the spray cone. No clogging of the probe occurred during the process. It should be noted that the probe position may not be necessarily optimal at this stage and yet there is restriction to study different probe positions. Further investigation of probe position will be conducted in the near future.

Data Acquisition

Data acquisition and analysis was performed using ParsumView software, which can display real-time graphs of particle size and distribution. The data acquisition parameters need to be optimized to obtain high quality and representative data, dependent on the dynamics of the process. One of the critical parameters, the ring buffer sets the number of particles to be measured as the basic population to calculate a particle size distribution at each time point. After optimization, the ring buffer length was set to 150,000 particles, which allows for detection of particle size change and discounting the influence of possible single big agglomerates or lumps causing spikes in the data trend. For this granulation, it was sufficient to measure particle size distribution every 30 s as we would not expect any drastic change in particle size within such a time interval based on prior knowledge and experience.

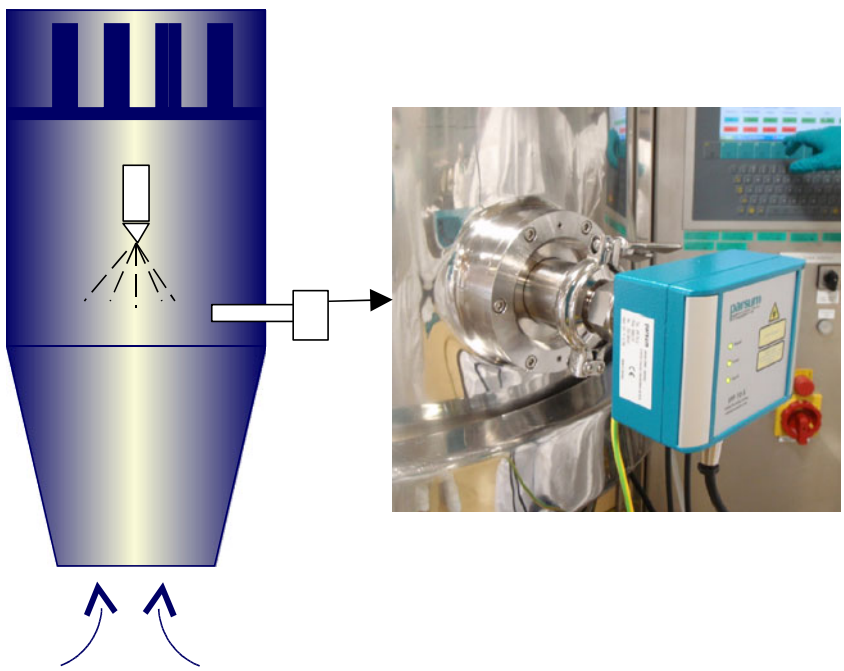

Fig. 1 Positioning of the Parsum analyzer on the aeromatic S3 fluid bed

A reference method (offline) by laser diffraction, MasterSizer (Malvern, UK), was used to determine granules sizes at end of spray and during drying. It was, however, not possible to collect samples during spray phase. MasterSizer measurements were obtained using dry dispersion with dispersing pressure of 0 bar.

Multivariate Data Analysis

Besides univariate data trending, the methodology of MSPC/BSPC was adopted to analyze the wellness of the granulation process/product by modeling simultaneously multiple variables, e.g., particle size distribution, loading, particle rate, and velocity, etc., collected by Parsum probe in real time. The MSPC models monitor and diagnose process performance, operating on top of the controllers. MSPC is capable of detecting process upsets due to unforeseen disturbances and provide information to the controllers that will actively adjust process parameters.

Theory of multivariate batch statistical process modeling has been widely discussed in literature, and is still evolving [25–30]. There are two common batch modeling approaches, depending on how batch data is organized prior to principal component analysis (PCA) or partial least squares (PLS). With batch processes, J variables are measured on K batches at regular time intervals, resulting in an $I \times J$ matrix for each batch (I time points times J variables). Stacking K batches on top of each other consequently leads to a three-way matrix of dimension ($I \times J \times K$). It should be noted that batches may have different length in time and in this case special alignment algorithms may be needed [26].

These two approaches will be used to diagnose evolving batches and evaluate overall batch performance in this study. Figure 2 depicts the first approach, observation-level modeling, nomenclature by Umetrics [26, 31], based on variable wise unfolding of a three-way matrix ($I \times J \times K$) into a two-way matrix ($(I \times K) \times J$). A dummy y variable is constructed, representing batch time or maturity index. A PLS model is then developed between X and Y [26, 31].

$$X = \mathrm{TP}' + E \tag{1}$$

$$Y = \mathrm{UC}' + F \tag{2}$$

where

T	is a matrix of scores that summarizes the X variables
P	is a matrix of loadings showing the influence of the X variables
U	is a matrix of scores that summarizes the Y variables
C	is a matrix of weights expressing the correlation between Y and T (X)
E, F	is a matrix of residuals; the deviations between the original values and the projections.

Score vectors for each batch can be derived to represent evaluation traces or process trajectories. MSPC calculates standard deviations (SD) at each time point, then typically uses ±3 SD as tolerance intervals based on score traces of multiple batches used in training. This approach preserves the direction of the variables, allowing for monitoring batch evolution.

Another approach, described in Fig. 3, unfolds a three-way matrix ($I \times J \times K$) into a two-way matrix ($K \times (I \times J)$). Original variables or scores can be arranged so as to preserve the directions of the batches, allowing for evaluation of overall batch performance using PCA (Eq. 1) and prediction of Y (quality attributes) using PLS from evaluation traces at batch completion, as well as

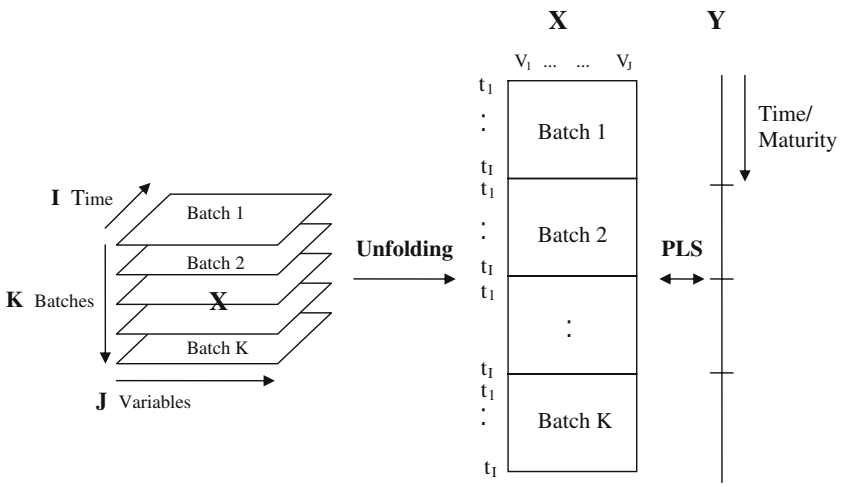

Fig. 2 Variable-wise unfolding of a three-way matrix ($I \times J \times K$) into a two-way matrix ($(I \times K) \times J$)

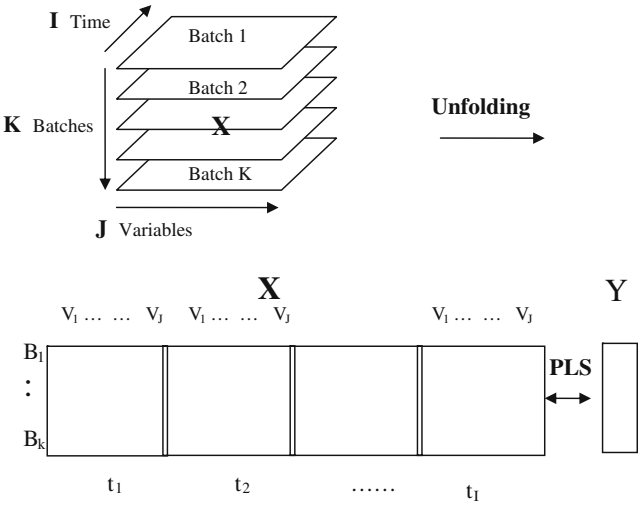

Fig. 3 Batch-wise unfolding of a three-way matrix ($I \times J \times K$) into a two-way matrix ($K \times (I \times J)$). Y may be quality attributes

during batch evolution where partial prediction can be made as data is being collected. This can be advantageous in facilitating feed-back/feed-forward control, and ultimately real-time release, in the pharmaceutical industry. Intermediate/final product quality attributes, e.g., granulation flow, tap/bulk density, and dissolution, can be predicted in process instead of end product testing. In this study, this approach will only be used to evaluate overall batch performance using PCA.

More details on MSPC/BSPC can be found in Ref [19–22, 26–31].

Multivariate batch modeling was performed in SIMCA-P+ 12.0 (Umeterics Inc, NJ, USA) [31].

Results and Discussion

Univariate Data Trending

Figure 4 displays the traces of chordlength X10, X50, X90 (volume based) and particle rate during the evolution of one batch using Parsum IPP70. After charging and preheating, spray begins around 8:25am. Particle size grows rapidly between 8:58am and 9:30am with X50 from 80 to 170 um, and further particle growth occurred at a slower rate until the end of spray at 10:40am. At the end of spray, X50 reaches 220 um, X90 at 500 um and X10 at 90 um. The particle rate represents number of particles passing through the optical path or measurement volume of the probe per second. Particle rate grows rapidly between 8:25am and 9:00am, indicating more particles reaching the probe as the powder bed gets fluidized. At around 9:00am, it begins dropping quickly as more particles are wetted/nucleated and growing larger, and at a slower rate after 9:30am as nucleation/agglomeration slows down. After drying starts at 10:40am, particle size decreases quickly indicating sample population measured by the probe appears to change drastically towards increasing finer particles.

Figure 5 shows volume-based particle size distribution profiles, q3 density distribution and Q3 sum distribution, at the beginning, end of spray and end of drying. As can be seen, the particle size distribution profile shifts from left at 8:30am to right at 10:41am, then back to left at 11:19am. The derived X50 starts with 83 um, and increases to 228 um, then decreases to 106 um. X10 and X90 follows the same trend. Clear differentiations in particle size

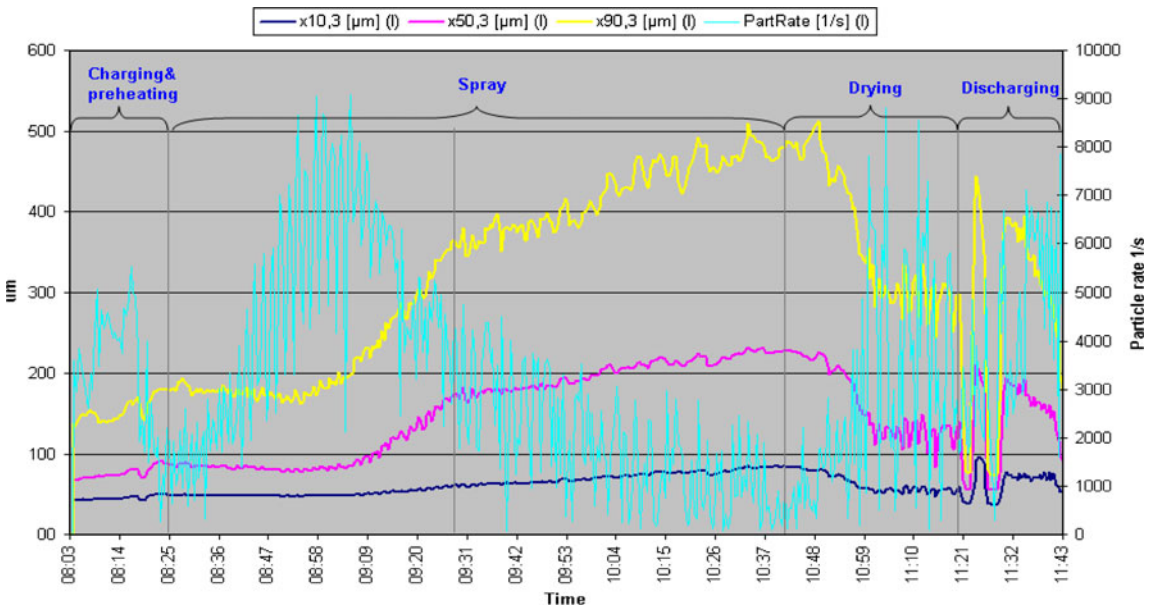

Fig. 4 Particle growth and particle rate during the granulation

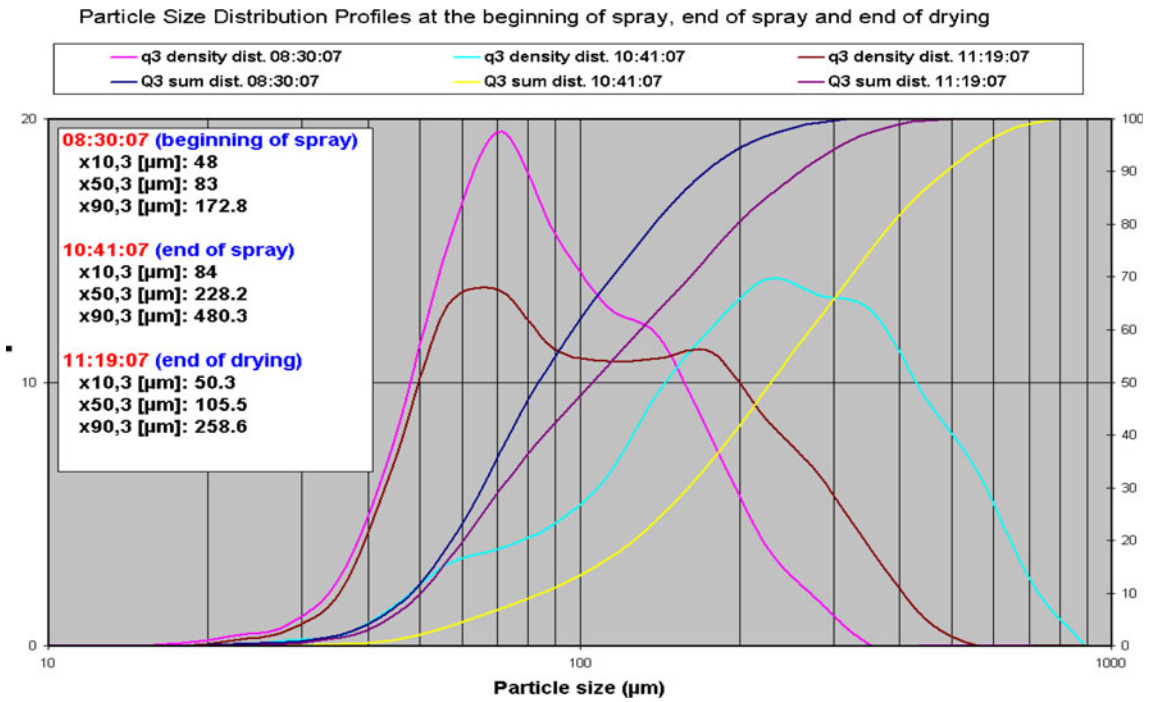

Fig. 5 Particle size distribution profiles at the different phases of granulation/drying

distribution indicate that Parsum is capable of characterizing in-process particle size and potentially determining granulation endpoint based on a target particle size distribution. A target particle size distribution, however, needs to be specified or defined by studying its impact on the quality attributes of the downstream unit operations.

As in-process quality attribute, particle size and distribution is directly linked to process parameters such as inlet air volume, temperature, dew point, relative humidity, spray rate, and differential pressure, etc. Univariate charting of process parameters during batch evolution is shown in, Fig. 6. For instance, after 20 min elapsed during spraying, differential pressure reaches a peak and then drops, resulting in a similar trend in particle rate. Particle size growth then becomes more prominent, and slows down after 1 h. This is likely in part due to an increase in inlet air volume around 9:30am. As inlet air volume increases, moisture evaporates faster, and wetting and agglomeration slows down.

Multivariate/Batch Statistical Process Control

A total of five batches were compared side-by-side in terms of median size, X50, Fig. 7. Although overall trajectories appeared similar, a certain degree of variation can be observed. Trajectories of Batches 1 and 2 that were more similar show smaller X50 (approximately 200 µm) at end of spray, compared to those of the other three batches that resulted in greater X50, approximately 250 µm.

A MasterSizer (Malvern UK), based on laser diffraction technique, was used to compare with Parsum measurement. Six samples were withdrawn from sampling port located at lower part of granulator bowl for MasterSizer measurements during drying phase, whilst this was not possible prior to end of spray. It can be seen that Parsum measurements matched MasterSizer results rather well at end of spray, but differ as drying proceeded. Although MasterSizer results also showed some decline in X50, they were not as significant as Parsum measurements. The difference observed between Parsum and MasterSizer measurement may be due largely to sampling positions. Parsum probe samples in the upper part of granulator bowl, while MasterSize

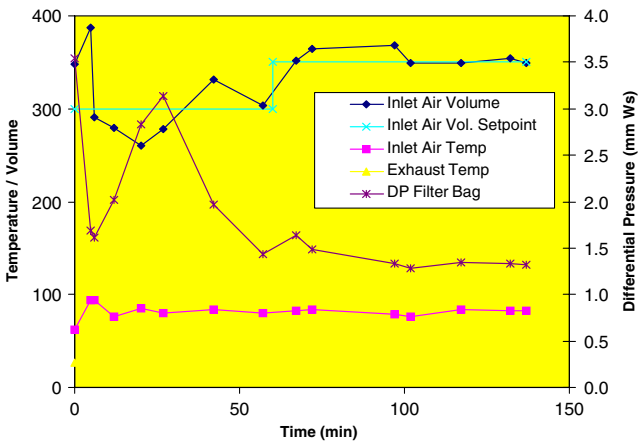

Fig. 6 Univariate process trajectories of individual parameters during granulation

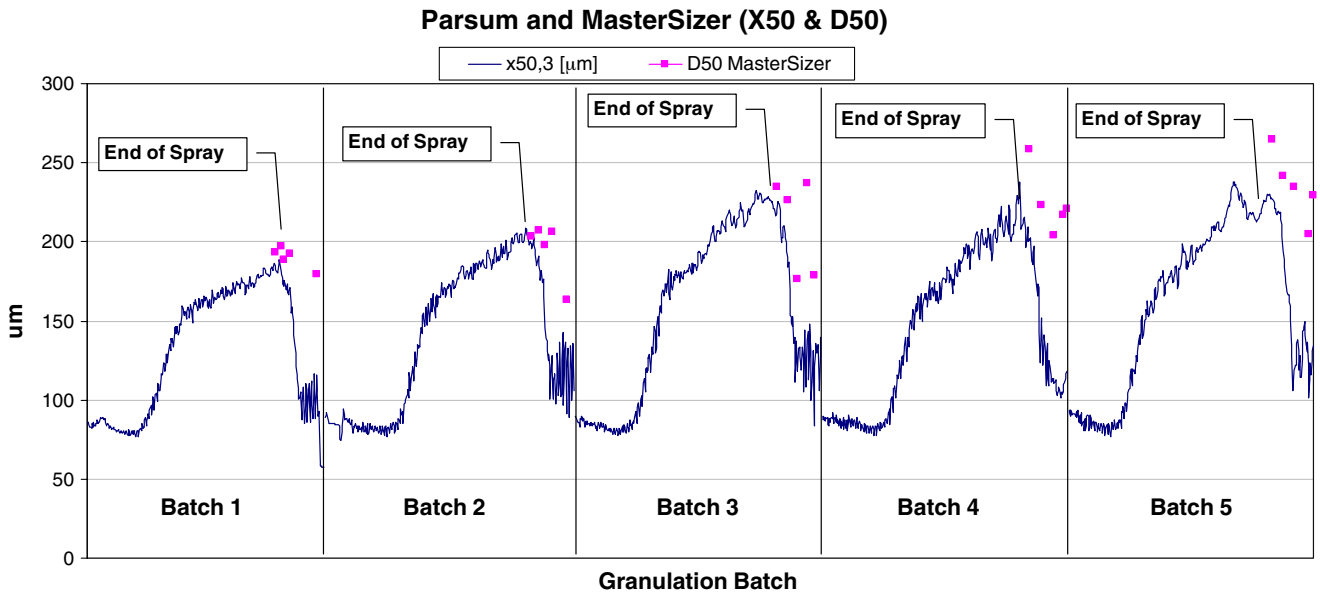

Fig. 7 Parsum and MasterSizer data of five batches during spray and drying

samples were obtained from the sampling port at the lower part of bowl. Sampling is influenced by size segregation during the fluidization which is a common phenomenon that has been extensively studied previously [32–34]. More finer particles travel to upper part of the chamber, resulting higher concentration of fines, whereas more larger particles stay at lower part of the chamber. This is especially true once spray has ended and drying started. The differences between Parsum and other techniques were also discussed in Ref [1]. The comparison may suggest that Parsum probe detect more fines during drying and probe positioning during drying phase be further investigated and optimized. It is however important to recognize that particle size characterization during spray phase, especially around end of spray, is critical as the ultimate goal of Parsum is to determine granulation endpoint with respect to particle size and distribution. End of spray is related to quality attributes at end of drying. On this aspect, Parsum has proven to be a useful technique for in-line particle size characterization. Further investigation on probe positioning will be carried out to achieve more representative sampling and measurement.

As seen in Fig. 7, in terms of X50 alone, batches 3, 4, and 5 appeared coarser at the end of spray. However, it is not sufficient, sometimes misleading, to just study X50 alone to examine how coarse or fine the samples are. Additional X10, X90 or the entire particle size distribution if available should be used and can be analyzed through multivariate techniques. As mentioned in "Parsum Analyzer" section, Parsum probe generates detailed particle size distribution profiles along with other related measurements. With multiple batches and variables available, one can use (MSPC/BSPC) methodology to analyze batch-to-batch variation, monitor, and diagnose process performance. Two critical steps in MSPC/BSPC are as follows:

Training based on historical data

1. Study batch-to-batch variation
2. Select good batches (demonstrated to ensure final product quality)
3. Establish control limits

Prediction using the trained model. Monitor new batches against good operations

1. Detect and diagnose process events/faults as batch evolves;
2. Evaluate overall batch performance

First, observation level batch models based on unfold PLS technique, as illustrated in Fig. 2, was used to study batch-to-batch variations among five batches, A dummy y variable was used, representing batch time/maturity. One hundred thirty-nine X variables from Parsum measurement are included in the model, e.g., cumulative/non-cumulative particle size distribution, particle velocities at different size classes, loadings, and particle rates. These variables are centered and scaled to unit variance so all variable have equal weights on the model, i.e., the base weight is computed as $1/\text{std}_j$, which is standard deviation of variable j computed around the mean..The first PLS component explains 74.1% variation, and the second component accounts for 4.6% variation.

Batch scores plot derived from the model, Fig. 8, displays batch-to-batch variation at observation level where each point represents an observation or time point which is a combination of original variables including mostly

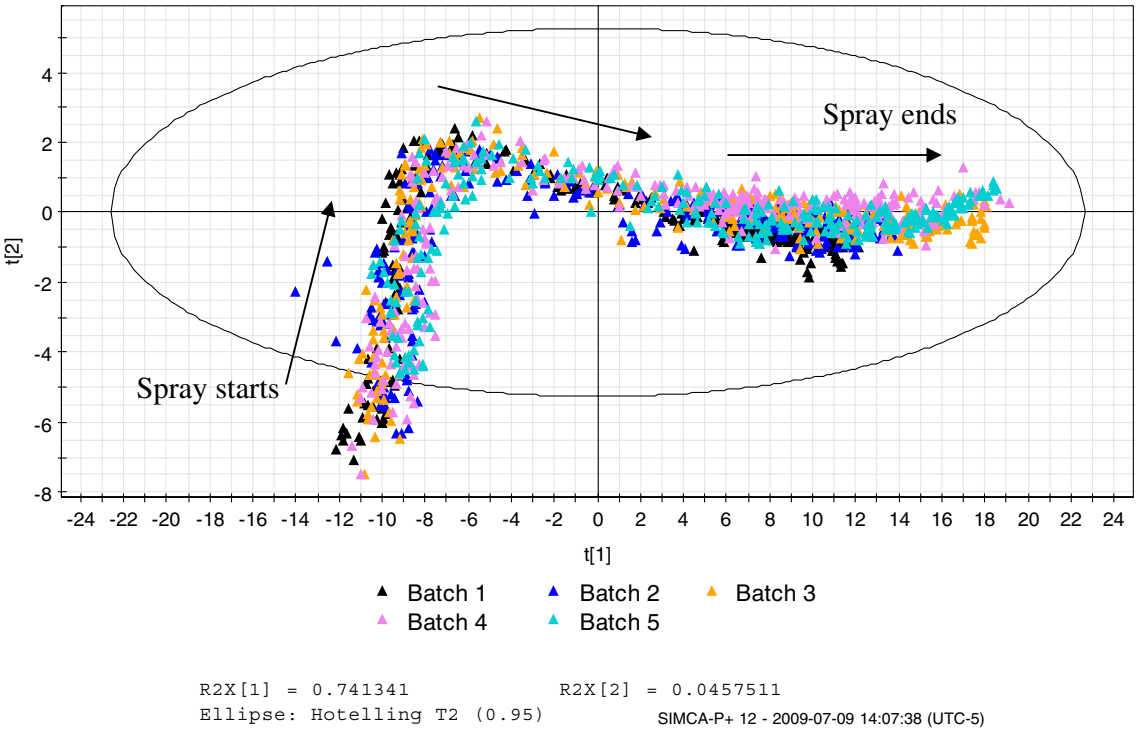

Fig. 8 Batch scores plot (t1-t2) of five batches displaying process trajectories (Spray phase) at observation level

particle size and related measurements. Each trace or trajectory can be viewed as a process signature that depicts a particular batch evolution. It is clear that all five batches follow similar trajectories with a certain degree of variations. Batches 3, 4, and 5 appear more similar than batches 1 and 2. A closer look towards end of spray indicates that batches 1 and 2 reached about the same endpoint while the other three (batches 3, 4, and 5) evolved further and arrived at a similar endpoint.

As shown in loading plot (p1), variables with higher positive values and lower negative values are highly correlated with batch time/maturity (Fig. 9). Variations from these variables likely result from process change and can be linked or traced back to the influencing process parameters.

Scores (*t*1 through *t*4) of each batch derived from the previous observation level model were unfolded and included in a batch level model using unfold PCA, as illustrated in Fig. 3. The batch level model was used to study batch-to-batch variation more efficiently as each point represents a batch shown in the batch-level score plot, Fig. 10. All five batches are well within 95% confidence interval (ellipse) calculated using Hotelling's T2. Batches 1 and 2 can be seen separated from the other

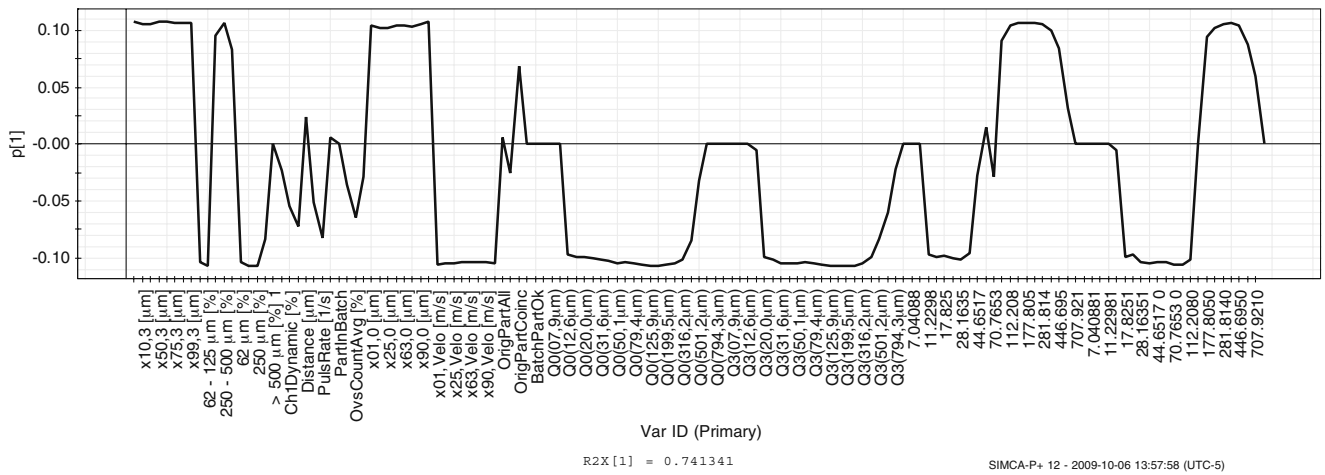

Fig. 9 Loading plot (p1) showing important variables with regard to batch time maturity (not all variable names are shown due to space limit)

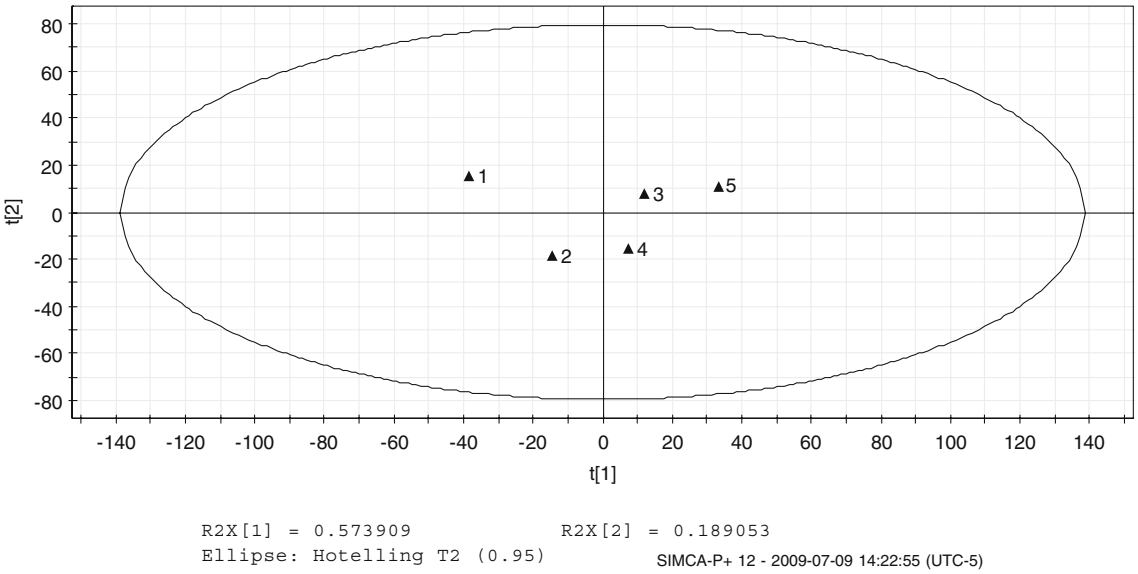

Fig. 10 Batch level score plot (t1-t2) of five batches displaying batch-to-batch variation based on spray phase

three batches by *Y*-axis along score t1, indicating some degree of difference between two groups (Batches 1 and 2 vs. Batches 3, 4, and 5). This is consistent with the results shown in Fig. 8.

Now that batch-to-batch variations have been studied, good batches (demonstrated to ensure final product quality) can be selected to train a BSPC model and establish control limits to monitor future batches. In practice, the more batches are used to train the model, the more robust the model would be. The current study, unfortunately, did not provide a larger number of batches. However, the BSPC approach can still be demonstrated with the five batches used for modeling. Assume that batches 1, 2, and 3 are desired target batches that ensure product quality. We can build a model based on these three batches and establish control limits. The batch scores control chart in Fig. 11, displays the score *t*1 over granulation (both spray and dry phases) for the three good

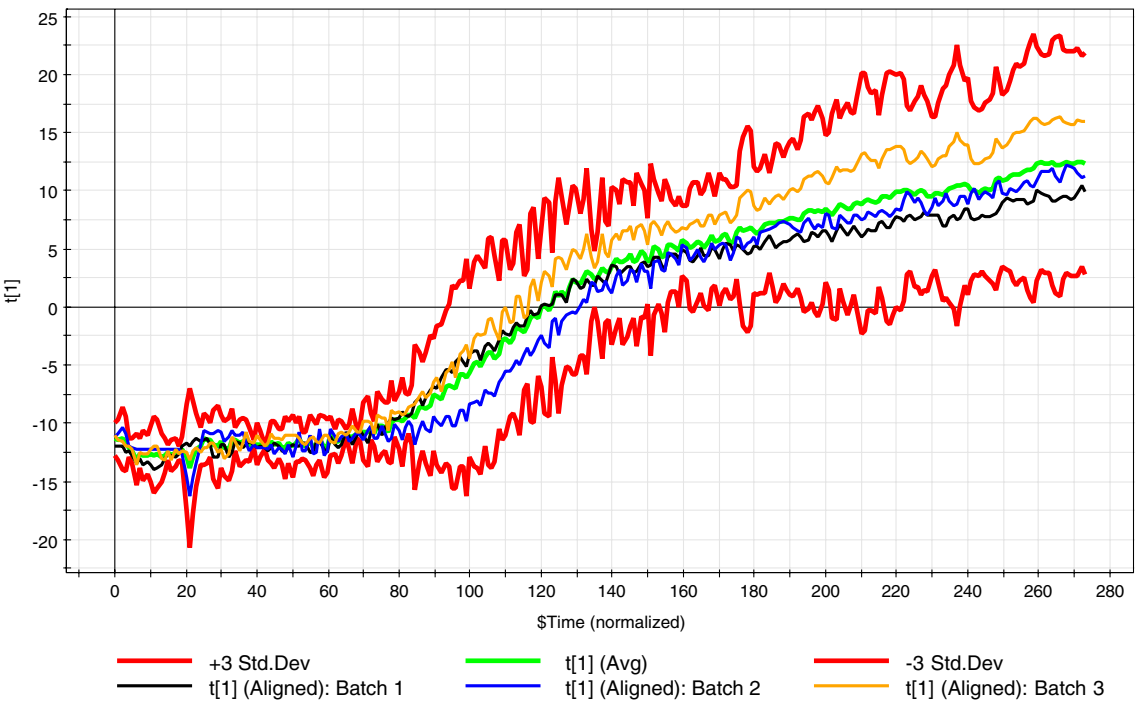

Fig. 11 Batch score control chart (t1) based on batches 1, 2, and 3 during spray phase with control limits (±3 SD) in red, and average trace marked in green

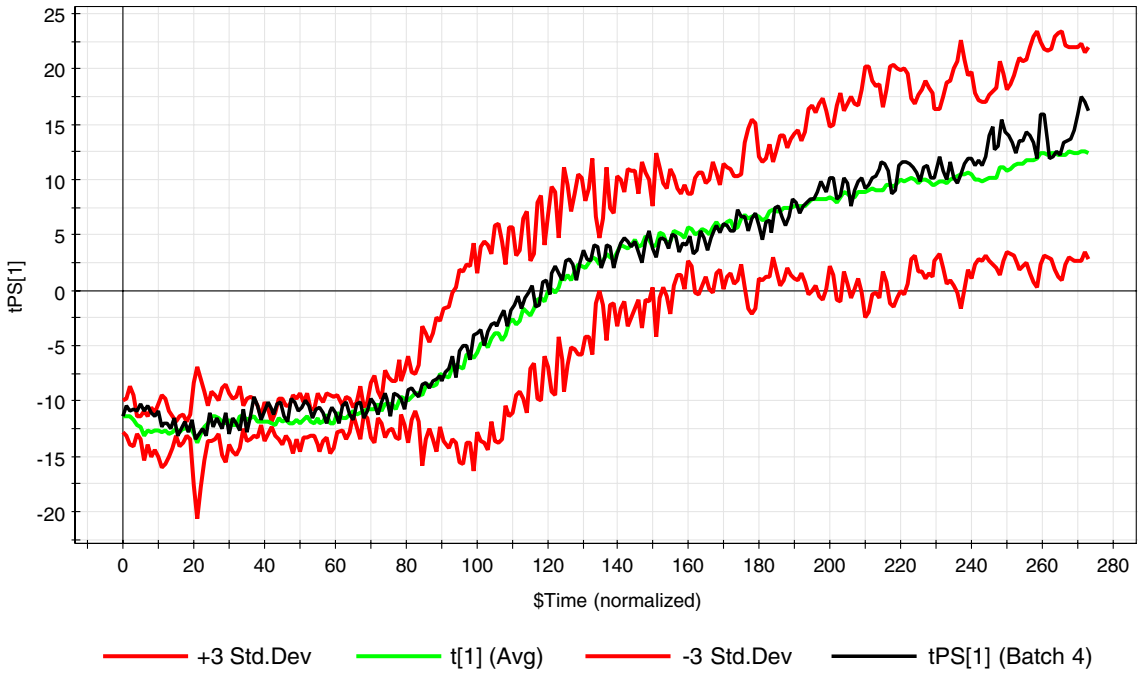

Fig. 12 Predicted batch score control chart (tPS1) for batch 4 during spray phase

batches. Each point represents a combination of multiple variables at a particular time point. The green trace represents average batch, and the red traces 3 sigma control limits. The batch scores control chart can then be used to predict or monitor new batches against the target operations.

Once an observation level batch model based on unfold PLS (Eqs. 1 and 2), as shown in Fig. 2, has been built, it can be used to predict batch maturity, scores, distance-to-model, and Hotelling T2, etc., for each observation from the prediction set (new data collected as batch evolves). The predicted scores tPS, one vector for each model component, are scores (new variables) computed from the model for each observation, summarizing the *X*-variables as they are collected during batch evolution.

Prediction of a new batch (batch 4) using the model in Fig. 11 is shown in the predicted batch score control chart (tPS1: predicted score 1; Fig. 12). It can be seen that batch 4 evolves right along the average batch (green), staying well inside the control limits throughout the entire granulation. It can therefore be concluded that the batch 4 is a well-behaved batch. The batch scores control chart, in combination with the contribution plot (not shown here), is useful in diagnosing process upsets if any and find out which variables are contributing to the problems. Other commonly used batch control charts include Hotelling's T2Range which displays the distance from the origin in the model plane (score space) for each selected observation, and the distance-to-model which estimates how far the observation is from the model plane, in the *X* or *Y* space. For more information, see Ref [31].

Conclusions

The study has demonstrated that Parsum is a useful tool for in-line particle size characterization during fluid bed granulation for this drug product. All data generated by Parsum probe during production can be utilized by multivariate statistical methodology to study batch-to-batch variation and evaluate overall batch performance. When implemented, MSPC/BSPC can be used to analyze and diagnose batch process performance as it evolves or at batch completion, and potentially predict downstream quality attributes. The methodology proposed here will contribute to not only improving process performance, but also assurance of acceptable end product quality.

Further work shall include investigation of probe positioning to achieve optimal sampling and accurate measurement representative of process; apply Parsum in process DOE/optimization and study impact of raw material variation, process, and environmental disturbance on particle measurement; Develop correlations between fluid bed granulation process parameters and particle size distribution, allowing for adjusting process parameters based on Parsum measurement.

Acknowledgment The authors gratefully acknowledge Norbert Straub at Excella, Thirunellai Venkateshwaran, Chun Cai, Victor

Wong, and Saly Romero-Torres at Wyeth for constructive discussions and strong support.

References

1. Närvänen T, Lipsanen T, Antikainen O, Räikkönen H, Heinämäki J, Yliruusi J. Gaining fluid bed process understanding by in-line particle size analysis. J Pharm Sci. 2009;98:1110–17.
2. Schmidt-Lehr S, Moritz H, Jürgens KC. Online control of particle size during fluidised bed granulation. Pharm Ind. 2007;69:478–84.
3. Rantanen J, Wikström H, Turner R, Taylor LS. Use of in-line near-infrared spectroscopy in combination with chemometrics for improved understanding of pharmaceutical processes. Anal Chem. 2005;77:556–63.
4. Frake P, Greenhalgh D, Grierson SM, Hempenstall JM, Rudd DR. Process control and end-point determination of a fluid bed granulation by application of near infra-red spectroscopy. Int J Pharm. 1997;151:75–80.
5. Goebel SG, Steffens KJ. Online-measurement of moisture and particle size in the fluidized-bed processing with the near-infrared-spectroscopy. Pharm Ind. 1998;60:889–95.
6. Nieuwmeyer FJS, Damen M, Gerich A, Rusmini F, Maarchalk KV, Vromans H. Granule characterization during fluid bed drying by development of a near-infrared method to determine water content and median granule size. Pharm Res. 2007;24:1854–61.
7. Rantanen J, Räsänen E, Tenhunen J, Känsäkoski M, Mannermaa JP, Yliruusi J. In-line moisture measurement during granulation with a four-wavelength near infrared sensor: an evaluation of particle size and binder effects. Eur J Pharm Biopharm. 2000;50:271–6.
8. Findlay WP, Peck GR, Morris KR. Determination of fluidized bed granulation end point using near-infrared spectroscopy and phenomenological analysis. J Pharm Sci. 2005;94:604–12.
9. Watano S, Miyanami K. Image processing for on-line monitoring of granule size distribution and shape in fluidized bed granulation. Powder Technol. 1995;83:55–60.
10. Watano S. Direct control of wet granulation processes by image processing system. Powder Technol. 2001;117:163–72.
11. Halstensen M, de Bakker P, Esbensen KH. Acoustic chemometric monitoring of fluidized bed granulation: part I. Powder Handl Proc. 2005;17:206–11.
12. Halstensen M, de Bakker P, Esbensen KH. Acoustic chemometric monitoring of an industrial granulation production process—aPAT feasibility study. Chemometr Intell Lab Syst. 2006;84:88–97.
13. Huang J, Ose S, de Silva S, Esbensen KH. Non-invasive monitoring of powder breakage during pneumatic transportation using acoustic chemometrics. Powder Technol. 2003;129:130–8.
14. Ruf A, Worlitschek J, Mazzotti M. Modeling and experimental analysis of PSD measurements through FBRM. Part Part Syst Char. 2000;17:167–79.
15. Petrak D. Simultaneous measurement of particle size and particle velocity by the spatial filtering technique. Part Part Syst Char. 2002;19:391–400.
16. Kougoulos E, Jones AG, Jennings KH, Wood-Kaczmar MW. Use of focused beam reflectance measurement (FBRM) and process video imaging (PVI) in a modified mixed suspension mixed product removal (MSMPR) cooling crystallizer. J Cryst Growth. 2005;273:529–34.
17. Barrett P, Smith B, Worlitschek J, Bracken V, O'Sullivan B, O'Grady D. A review of the use of process analytical technology for the understanding and optimization of production batch crystallization processes. Org Process Res Dev. 2005;9:348–55.
18. Hu X, Cunningham JC, Winstead D. Study growth kinetics in fluidised bed granulation with at-line FBRM. Int J Pharm. 2008;347:54–61.
19. Kourti T. Process analytical technology and multivariate statistical process control. Wellness index of process and product-Part 1. J Proc Anal Techn. 2004;1:13–9.
20. Kourti T. Process analytical technology and multivariate statistical process control. Index of wellness of product and process-Part 2. J Proc Anal Techn. 2005;2:24–8.
21. Kourti T. Process analytical technology and multivariate statistical process control. Index of wellness of product and process-Part 2. J Proc Anal Techn. 2006;3:18–24.
22. Kourti T. Multivariate dynamic data modelling for analysis and statistical process control of batch processes, start-ups and grade transitions. J Chemometr. 2003;17:93–109.
23. FDA. PAT—A framework for innovative pharmaceutical development, manufacturing and quality assurance; 2004
24. ICH harmonised tripartite guideline, pharmaceutical development q8, 2005
25. Mattila M, Saloheimo K, Koskinen K. Improving the robustness of particle size analysis by multivariate statistical process control. Part Part Syst Char. 2007;24:173–83.
26. Wold S, Kettaneh N, Friden H, Holmberg A. Modelling and diagnostics of batch processes and analogous kinetic experiments. Chemometr Intell Lab Syst. 1998;44:331–40.
27. Wold S, Geladi P, Esbensen K, Ohman J. Multi-way principal components and PLS analysis. J Chemometr. 1987;1:41–56.
28. Kresta JV, MacGregor JF, Marlin TE. Multivariate statistical monitoring of process operating performance. Can J Chem Eng. 1991;69:35–47.
29. Nomikos P, MacGregor JF. Multivariate SPC charts for monitoring batch processes. Technometrics. 1995;37:41–59.
30. Nomikos P, MacGregor JF. Multi-way partial least squares in monitoring batch processes. Chemometr Intell Lab. 1995;30:97–108.
31. Simca-P+. Multivariate data analysis software, Umetrics AB, NJ. 2008 v 12.0
32. Hoffmann AC, Romp EJ. Segregation in a fluidized powder of a continuous size distribution. Powder Technol. 1991;66:119–26.
33. Huilin L, Yurong H, Gidaspow D, Lidan Y, Yukun Q. Size segregation of binary mixture of solids in bubbling fluidized beds. Powder Technol. 2003;134:86–97.
34. Wormsbecker M, Adams A, Pugsley T, Winters C. Segregation by size difference in a conical fluidized bed of pharmaceutical granulate. Powder Technol. 2005;153:72–80.