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Research Article

Particle Size, Moisture, and Fluidization Variations Described by Indirect In-line Physical Measurements of Fluid Bed Granulation

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Abstract. The aim of this study was to evaluate an instrumentation system for a bench scale fluid bed granulator to determine the parameters expressing the changing conditions during the spraying phase of a fluid bed process. The study focused mainly on four in-line measurements (dependent variables): fluidization parameter (calculated by inlet air flow rate and rotor speed), pressure difference over the upper filters, pressure difference over the granules (lower filter), and temperature of the fluidizing mass. In-line particle size measured by the spatial filtering technique was an essential predictor variable. Other physical process measurements of the automated granulation system, 25 direct and 12 derived parameters, were also utilized for multivariate modeling. The correlation and partial least squares analyses revealed significant relationships between various process parameters highlighting the particle size, moisture, and fluidization effect. Fluidization parameter and pressure difference over upper filters were found to correlate with in-line particle size and therefore could be used as estimates of particle size during granulation. The pressure difference over the granules and the temperature of the fluidizing mass expressed the moisture conditions of wet granulation. The instrumentation system evaluated here is an invaluable aid to gaining more control for fluid bed processing to obtain repeatable granules for further processing.

KEY WORDS: fluid bed granulation; fluidization parameter; particle size; pressure difference; temperature.

INTRODUCTION

Fluid bed granulation is the established choice for improving the processing properties of pharmaceutical powders, e.g. flowing and tablet compression. The equipment, process, and product parameters influencing the quality of finished granules are identified quite detailed (1). Especially the spraying phase of fluid bed granulation is known to be multivariate and complex by nature. The granule growth stages are categorized as nucleation, transition, steady state, and ball growth (2,3), however, all these processes might also occur simultaneously (4). The fluidization process allows automatically controlled operations and fluid bed granulators are becoming increasingly instrumented including indirect physical measurements, e.g. temperatures, flow rates, and pressure differences (5–9). Until recently, these measurements have mainly been utilized for monitoring purposes and not for finding critical interactions or variation sources of the processes. In addition to various physical measurements, granule size can be measured during the process on-line and in-line from the process stream (10,11). There is clearly a need for methods to detect the changing granulation conditions in fluid bed chambers and thereby identify potential failure modes in a timely manner (12).

Homogeneously and smoothly fluidized beds are desired, but it is not clear how this target is defined and how deviations outside this objective are detected and controlled during the process. Whereas over fluidization may produce uneven or lumpy agglomerates and may also cause plugging of the upper filters, improper fluidization may stall the bed and ultimately lead to bed collapse (13). The material characteristics influencing fluidization were identified and deviating fluidization modes categorized (14,15). For example, spouted or slugging beds can result in uneven distributions of moisture and deviating particle size distributions. The correlation between fluidization mode and particle size during the spraying phase seems not to be clear. Nevertheless, one of the most important parameters contributing to proper fluidization is airflow rate. One indication of good fluidization is a free downward flow of the granulation at the window of a bowl, but such a limited observation can be misleading (13). If the outlet air temperature rises more rapidly than anticipated, it may be an indication that fluidization is incomplete (16). Räsänen *et al.* (17,18) found that the pressure difference over the granules as a function of velocity of the process air was a parameter expressing fluidization behavior. Low values of pressure difference over granules indicate loss of granules or dead zones, whereas the pressure

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difference over the upper filter bags is known to indicate blocking of filters (9). In recent studies (19) a parameter describing fluidization was calculated with inlet air flow rate and rotor fan speed. This fluidization parameter was clearly an indication of how the inlet airflow in the form of bubbles was carried through the moist mass; however, experience in using this parameter in practice is still limited. Recently, the effect of systematic granulation liquid feed pausing on the particle size of the finished granules was evaluated (20).

The various measurements indicating material behavior in a fluidized bed have not yet been thoroughly evaluated. Therefore, it is crucial that any parameters expressing these changing conditions be analyzed in an integrated manner. Our goal here was to specify how the changing conditions of wet granulation could be seen in the physical measurements of a fluid bed granulator. Correlation and multivariate analyses were utilized to determine the interactions between the variables. Measurement data of 16 experimental batches differing in granulation liquid feed and inlet air humidity were integrated and analyzed with partial least squares (PLS). The dependent variables in the PLS analyses were fluidization parameter (19), pressure difference over upper filters and pressure difference over granules. Other measurements were used as predictor variables. Temperature measurements were analyzed, focusing on the granulation liquid feed effect on temperature of the fluidizing mass.

MATERIALS AND METHODS

Materials

Each granulation batch consisted of 2.0 kg theophylline anhydrate 200 mesh (particle size under 75 μm; BASF Corporation, Ludwigshafen, Germany) and 2.0 kg α-lactose monohydrate 200 mesh (DMV International, Veghel, The Netherlands), granulated with 2 kg of 7.5% aqueous binder solution of polyvinylpyrrolidone Kollidon K-30 (BASF Corporation, Ludwigshafen, Germany).

Table I. Direct and Derived Measurements and Set Values of Glatt WSG 5

Factor (measurement or derived parameter)	Symbol	Unit
Direct		
Temperature of process room	T1	°C
Temperature after heater	T2	°C
Temperature of air before granulator	T3	°C
Temperature of air before granulator	T4	°C
Temperature of mass	T5	°C
Temperature of granulation chamber	T6	°C
Temperature of granulation liquid	T7	°C
Temperature after filters	T8	°C
Temperature after filters	T9	°C
Temperature on the chamber wall	T10	°C
Temperature in the outlet air duct	T11	°C
Pressure difference over upper filters	dP1	kPa
Pressure difference over granules	dP2	kPa
Relative humidity of inlet air	U1	RH%
Relative humidity of outlet air	U2	RH%
Flow rate of inlet air	Fin	g/s
Flow rate of outlet air	Fout	g/s
Fan speed, value of frequency converter	Paw292	Hz, 1/s
Control current of heating element	Paw294	mA
Atomization pressure	Paw288	bar
Control current of granulation liquid pump	Paw500	mA
Pump rotation speed of granulating liquid	N1	rpm
Amount of granulation liquid sprayed (scale)	M1	g
Set value of inlet air flow rate	W1	g/s
Set value of inlet air temperature	W2	°C
Derived		
Absolute humidity of inlet air	AH1	g/m^3
Absolute humidity of outlet air	AH2	g/m^3
Flow rate of inlet air	F1	l/s
Flow rate of outlet air	F2	l/s
Fluidization parameter, Fin/PAW292	FlowInd	g/rev
Median particle size measured by in-line SFT	d50med	μm
Specific enthalpy of water vapor in inlet air	Latent_heat	kJ/kg
Average flow of granulating liquid from start	AveM	g
Water content of inlet air	Water_in	g/s
Water content of outlet air	Water_out	g/s
Cumulative water amount of inlet air	Water_in_cum	g
Cumulative water amount of outlet air	Water_out_cum	g
Cumulative water balance (Water_in_cum-Water_out_cum)	Water_bal_cum	g

Manufacturing Process

The granules were produced in an automated and fully instrumented bench-scale fluid bed granulator (Glatt WSG 5; Glatt, Binzen, Germany). The inlet air humidity of the process air was modified with a humidifying system (Defensor Mk4; Brautek Oy, Espoo, Finland) (19). The parameters measured and derived are found in Table I and the instrumentation is described in further detail in Rantanen *et al.* (7). The atomization pressure of the granulating liquid was 0.1 MPa and nozzle height was set to 45 cm from the distributor plate. The inlet air temperature was 40°C during the mixing and spraying phases and was raised to 60°C during the drying phase. The inlet air flow rates were kept fixed by constant adjustment: 0.04 m^3/s during the preliminary mixing phase and then 0.08 m^3/s throughout the wet granulation and drying phases. The powder material was introduced in a repeatable manner into the chamber: first lactose and then theophylline followed by 2 min dry mixing.

Particle Size Measurements

An in-line spatial filtering technique (SFT) probe (Parsum® IPP 70; Gesellschaft für Partikel-, Strömungs- und Umweltmesstechnik, Chemnitz, Germany) was installed in the granulator at a height of 45 cm. The particles passed through an aperture (diameter 4 mm). Pressurized air was used to disperse the particles. The measured raw data were collected via A/D converter to a PC. During the fluid bed process, an average volume size distribution data at 10-s intervals were saved. Granules taken during the wet granulation by sampler were used for visual characterization and photographs of these samples were taken by an image system described in Laitinen *et al.* (21).

Experimental Design

A central composite face-centered design with three factors (inlet air humidity, granulation liquid feed rate, and systematic granulation liquid feed pausing) at three levels was used to attain variability in moisture conditions and particle size of the granules. The experimental design was the same as described in Närvänen *et al.* (20), except one central point repetition batch was omitted from the analysis due to an error in SFT data acquisition. The inlet air humidity levels were <6 g/m^3, 7–12 g/m^3, and >13 g/m^3. The granulation liquid was fed at three rates: 50, 70, and 90 g/min. Systematic granulation liquid feed pausing was initiated after half (1,000 g) of the total amount was sprayed. The granulation liquid feed was interrupted for 1 min every second minute, every third minute, or not at all.

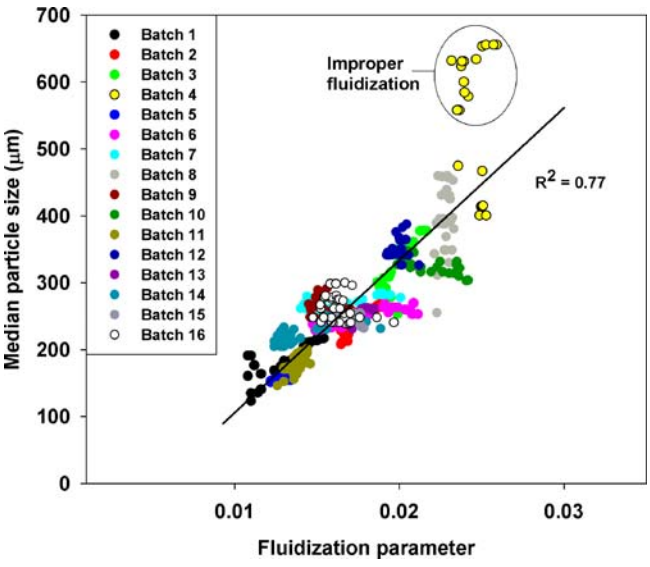

Fig. 1. Correlation of fluidization parameter and median particle size

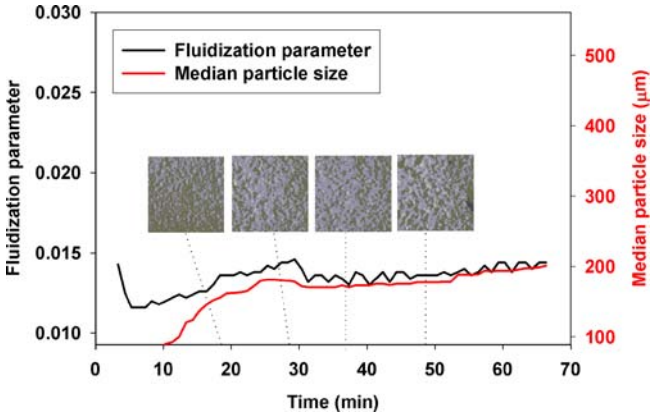

Fig. 2. Fluidization parameter and median particle size as a function of process time of the spraying phase in batch 11 (slow granulation liquid feed)

Modeling and Data Analysis

The measurement data of 16 experimental batches were pooled by data integration. Filter shakings caused periodic decreases in values and therefore measurement data just before the upper filter shakings were used. All direct and derived parameters described in Table I were obtained at 1 min intervals.

Simca-P+ 10.5 (Umetrics, Umeå, Sweden) was used for PLS modeling. These analyses were performed to determine

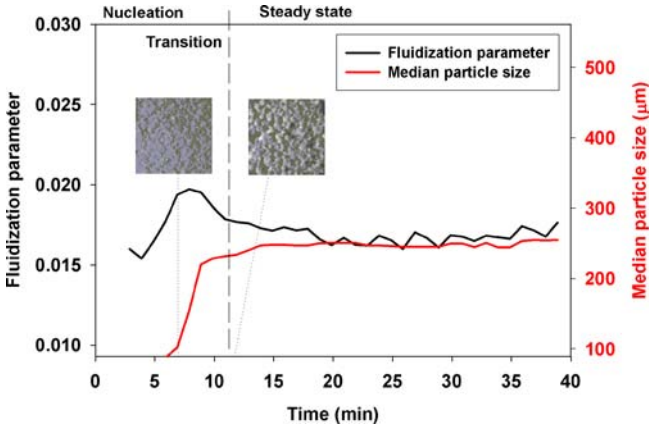

Fig. 3. Fluidization parameter and median particle size as a function of process time of the spraying phase in batch 15 (medium granulation liquid feed)

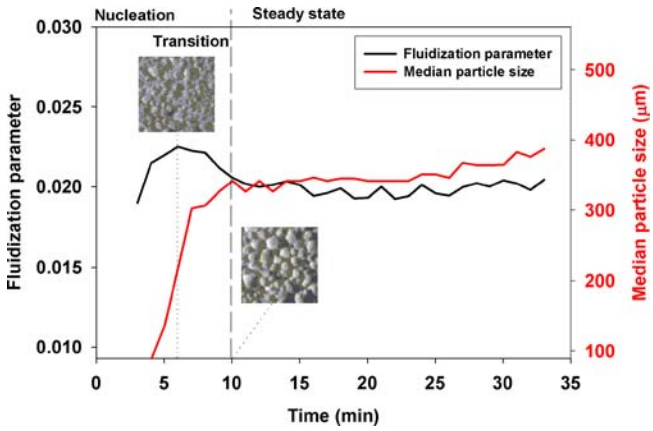

Fig. 4. Fluidization parameter and median particle size as a function of process time of the spraying phase in batch 12 (high granulation liquid feed)

the relationships between dependent variables (matrix Y) and predictor variables (matrix X). Fluidization parameter (symbol FlowInd in Table I, described earlier in (19)), pressure difference over upper filters (dP1) and pressure difference over granules (dP2) were chosen as dependent Y variables one at a time. All the rest measurements and derived parameters in the granulator (Table I) served as independent X variables in the model. Variable influence on projection (22), i.e. the VIP value, was used to summarize the importance of the X variables. Predictors with a VIP value larger than 1 are the most influential for the model. An intermediate phase of the PLS analysis included omitting variables with a VIP value under 0.7 (not significant for the model). Variables clearly reflecting the same phenomenon as another variable (such as flow rate in m/s and l/s) and measurements already included in the Y variable (Fin and Paw292 in fluidization parameter) were omitted from further analysis.

RESULTS AND DISCUSSION

Correlation Between Fluidization Parameter and In-line Particle Size

There was a correlation between fluidization parameter and median particle size for all the batches. The median particle size was drawn as a function of fluidization parameter values of all batches when an approximate steady state particle growth phase was achieved and 500–2,000 g granulation liquid sprayed (Fig. 1). The correlation was linear, except for the deviating extremely moist batch 4. High levels of air humidity and granulation liquid feed resulted in uncontrollable granule growth (coalescence, ball growth) in this batch and the mass was partly collapsed at the end of the wet granulation phase. Remarkably, the yellow points of batch 4 in the line are from the beginning of the spraying phase when the mass was still fluidizing properly, and a separated yellow group represents the measurements when the mass was partly collapsed.

A more detailed picture of this relationship was achieved when the correlation was obtained for each batch as a function of time. For example, three batches are presented in Figs. 2, 3, and 4, differing in the granulation liquid feed rate. As seen in these figures, correlation between fluidization parameter and median particle size was clearly observed after particle growth had diminished. A function fitting between fluidization parameter and particle size was constructed, using the data between 500 and 2,000 g granule liquid sprayed (Fig. 1):

$$d50med = 22788 \cdot FlowInd - 122 \quad (1)$$

in which

d50med = median particle size (µm)
FlowInd = Fluidization parameter (g/rev)

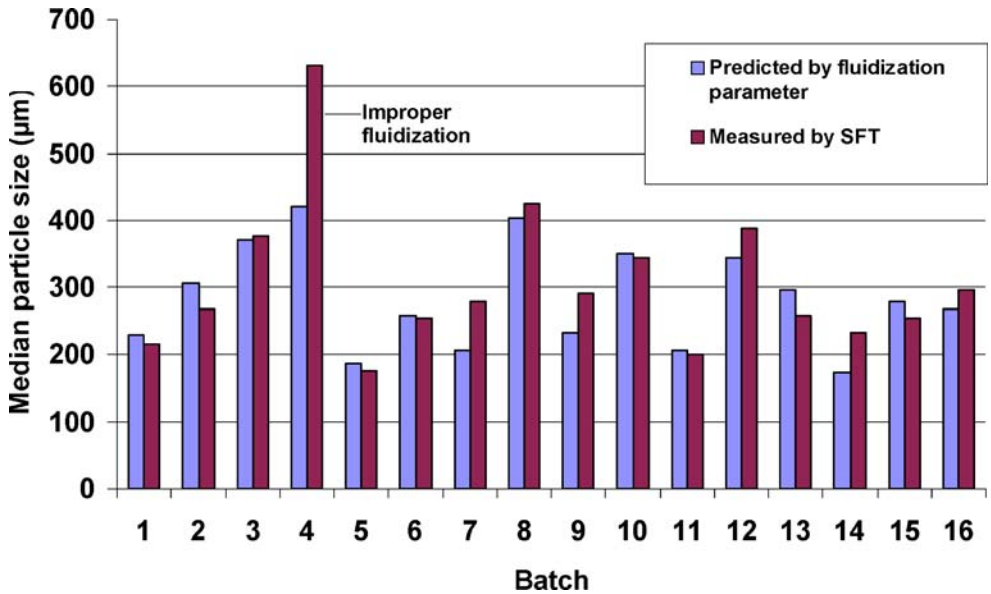

Fig. 5. Particle size at the end of the spraying phase measured by in-line SFT and predicted by fluidization parameter

Finally, using this formula (Eq. 1), the particle size was predicted at the end of the spraying phase by the last fluidization parameter values. As illustrated in Fig. 5, fluidization parameter values at the end of the spraying phase served as a quite good estimate of the median particle size except for batch 4 with deviating fluidization. The moisture of batch 4 was at least twice as high as in other batches (22% *w*/*w* in the end of the spraying phase). The bulk density of these very wet granules was about 0.6 g/ml compared to 0.4 g/ml in the dry state. The relatively high density of granules during the spraying phase contributed likely to the deviating fluidization behavior of batch 4.

PLS Analysis of Wet Granulation Stages

PLS analysis was performed to determine the parameters affecting the fluidization parameter at different stages of wet granulation. The fluidization parameter values of all batches operated as a Y-variable response and other factors (Table I) served as X-variable predictors. Three stages of wet granulation were analyzed representing approximately the nucleation, transition, and steady state stages. These selected stages were 0–250 g (I), 250–500 g (II), and 500–2,000 g (III) of granulation liquid sprayed. Table II presents the three most important factors affecting the fluidization parameter in these three stages. As already expected from Figs. 2, 3, 4, median particle size at the beginning of the spraying phase (stages I and II) did not operate among the factors most affecting the fluidization parameter. However, when the range 500–2,000 g (stage III) was analyzed, the significance of median particle size was revealed with a VIP value of 1.18. Thus, PLS analysis also confirmed that the longer the spraying phase had proceeded the more median particle size was correlated with fluidization parameter values. In the early stages of the spraying phase (I and II), pressure difference over filters (dP1) and flow rate of outlet air (F2) were especially important factors.

Pressure Difference Measurements

Pressure difference over filters (dP1) and pressure difference over granules (dP2) were also thought as potential describers of particle size and air flow through the granulating mass. The spraying stage 500–2,000 g (III) of these 16 batches was used for analyses as a uniform period. The same type of correlation with median particle size was tried to find for these parameters as previously for fluidization parameter values. Correlation was found with dP1 and median particle size, R^2 value was 0.75 when 500–2,000 g of granulation liquid

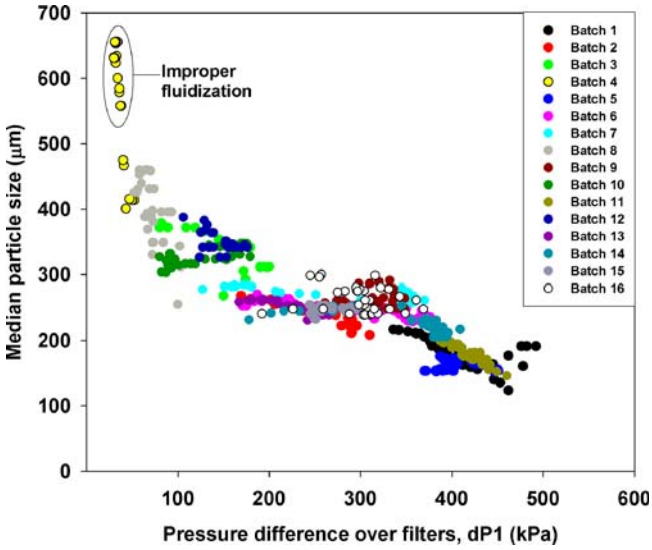

Fig. 6. Correlation of pressure difference over filters and median particle size

was sprayed (Fig. 6). As described earlier (Fig. 1), the corresponding value for fluidization parameter was R^2 0.77. The correlation for dP1 was, however, reversed compared with fluidization parameter: smaller pressure differences were observed with larger particles. This is a normal occurrence, considering that small particles become lodged in the upper filters and thereby elevate the pressure difference. When further stages (700–, 800–, 1,000–, 1,500–2,000 g) were compared, fluidization parameter had still higher correlation with median particle size than dP1. For example, in the stage 1,000–2,000 g, R^2 was 0.80 for fluidization parameter and median particle size compared with R^2 0.77 for dP1 and median particle size. Thereby fluidization parameter was considered to be somewhat better indication of particle size than dP1. Pressure difference over granules (dP2) was not correlated with median particle size. The PLS analyses revealed more specifically the factors affecting both these pressure difference measurements (Table III). The dP1 was mainly affected by air flow through the system (Paw292 and FlowInd) and particle size (d50med). The factors affecting dP2 were related to moisture in the system (M1 and Water_bal_cum) and pressure difference upstream (dP1).

Temperature Measurements

The particle size or fluidization behavior could not be observed in any of the several temperature measurements

Table II. The Most Important Factors Affecting Fluidization Parameter Values During Different Stages of Wet Granulation by PLS Analysis

I 0–250 g factor	VIP value	II 250–500 g factor	VIP value	III 500–2000 g factor	VIP value
Flow rate of outlet air (F2)	1.36	Pressure difference over filters (dP1)	1.32	Pressure difference over filters (dP1)	1.36
Pressure difference over filters (dP1)	1.27	Specific enthalpy of water vapor in inlet air (Latent_heat)	1.24	Median particle size (d50med)	1.18
Water content of outlet air (Water_out)	1.12	Flow rate of outlet air (F2)	1.24	Relative humidity of outlet air (U2)	1.07

Table III. The Most Important Factors Affecting Pressure Difference Over Filters (dP1) and Pressure Difference Over Granules (dP2) during Wet Granulation by PLS Analysis

dP1 500–2000 g factor	VIP value	dP2 500–2000 g factor	VIP value
Fan speed (Paw292)	1.28	Amount of granulation liquid sprayed (M1)	1.49
Fluidization parameter (FlowInd)	1.24	Cumulative water balance (Water_bal_cum)	1.43
Median particle size (d50med)	1.09	Pressure difference over filters (dP1)	1.18

points (T1–T11). However, the effect of granulation liquid pausing could be noticed clearly in the temperature of the fluidizing mass (T5). Low inlet air humidity, slow granulation liquid feed rate, and pausing granulation liquid feed every second minute resulted in very dry conditions for wet granulation and thus specific temperature changes. As soon as granulation liquid feed pausing began, the temperature of the mass began fluctuating (Fig. 7). This phenomenon was also seen in other batches involving liquid pulsing, although the moister the conditions the smaller was the temperature level change and fluctuation. The same type of temperature rise is seen at the end of a typical drying phase: as soon as particle surface water diminishes, the particulate material absorbs heat and a temperature rise is detected.

Comparison and Evaluation of Results

Correlation between fluidization parameter and median particle size was evident when about 25% of the total granulating liquid had been sprayed and the powder transformed into granules. Fluidization parameter as such could serve as an indicative particle size of the fluidizing granules. The effect of particle size on the fluidization parameter is clearly formulation dependent. In previous studies with an ibuprofen formulation (19) fluidization parameter values decreased as fluidization was impaired (the mass was partly or totally collapsed). This defluidization of sticky material was accompanied by partial blockage of the distributor plate and thereby insufficient inlet air flow rate. The over wetting of the mass caused increased particle size of the final granules. In the present study, the wet theophylline material did not cause blockage of the distributor plate during the spraying phase and the particle size could be monitored already during the wet granulation. The fluidization parameter was correlated with the median particle size directly. This indicated better flow of air through the moist mass as the particle size was increased. The primary cause was that the adjusted constant flow rate of inlet air (measured below the chamber) was achieved with slower rotor speed when the granules were moister and thus larger. The previous ibuprofen formulation as a hydrophobic material was more susceptible to moisture changes than this theophylline formulation. Excess moisture was prone to form layers on particle surfaces and promote defluidization with the ibuprofen formulation. Wettability and density changes of the present theophylline formulation may have contributed to latent channeling behavior, in which air flow through the system was apparently easier with moister material and larger particle size. Thus, how the optimum airflow is maintained for smooth fluidization and the factors affecting air flow are formulation and process dependent. Thereby interpretation of fluidization parameter is formulation dependent; here the parameter described the particle size and also likely the density changes more than the actual fluidization. Although moisture of granules during the spraying phase is one indication of density changes, in-line measurement of density changes during the spraying phase would be worthwhile in the future.

There are two ways how improper fluidization of material can become evident in fluid bed chambers: defluidization (collapse) and channeling. Channeling is indicated by varyingly large increases in outlet air temperature (16); however, these temperature changes were not observed here, although the instrumentation was complete. Here, deviation from the correlation curve (fluidization parameter *vs*. median

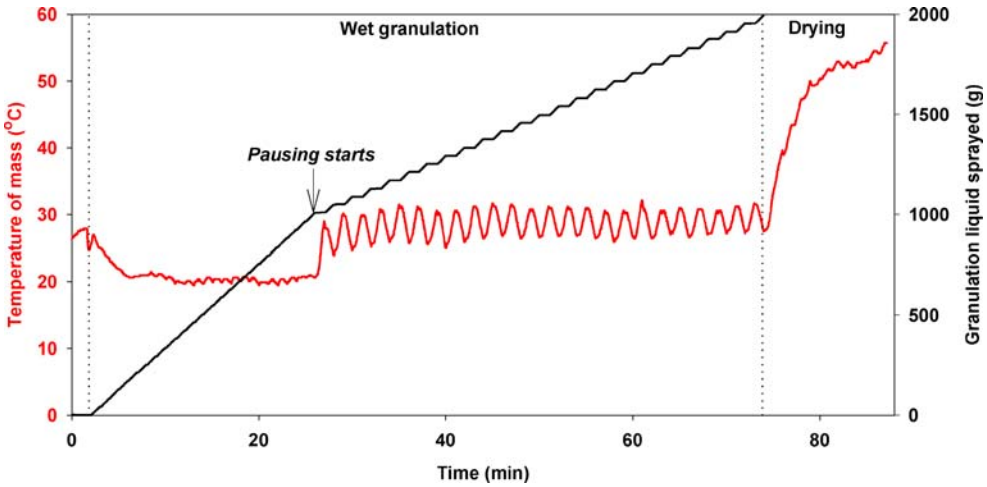

Fig. 7. Effect of pausing of granulation liquid on temperature of the granulation mass in batch 5

particle size) indicated deviating behavior of mass. In production scale manufacturing, repeating fluidization parameter values between different batches of the same composition can indicate similar fluidization conditions and thus uniform particle size, especially when moisture conditions are similar. On the other hand, deviating fluidization parameter values can mean processing variations and sliding out of the design space. Here, deviation from the direct correlation curve could be considered as an indication of wide variation in fluidization behavior. This concept of determining correlations and identifying sources of variation is consistent with recent guidelines for highlighting continuous improvement in manufacturing processes (23–25).

The pressure difference measurements over the granules and upper filters expressed diverse phenomena. We observed a correlation between pressure difference over filters and particle size. The dry conditions of wet granulation and the small particle size of the granules were seen as elevated values. Particle size did not affect pressure difference over granules. Instead, the moisture in the system (amount of granulation liquid sprayed and cumulative water balance) clearly affected this parameter.

The temperature measurements, especially of fluidizing mass, indicate the moisture conditions of wet granulation. Unexpected temperature rises in the chamber can mean improper fluidization (channeling) or interruption in granulation liquid feed. The effect of liquid feed pausing on the temperature of the granulating mass was shown in this study. When granulation liquid feed was stopped for a predetermined period, the temperature of mass began to rise, especially in batches with slow granulation liquid feed and low inlet air humidity. Unexpected interruption in granulation liquid feed, e.g. by blockage, can even influence the properties of the finished granules. This risk is more clear, if temperature of the mass rises and the particle surfaces dry too early. It is evident that pausing of granulation liquid can also confound the end-point indication based on temperature measurements, e.g. the ΔT criterion (26), because the temperature level changes. The effect of inlet air humidity on temperature measurements and thereby on end-point detection of drying was previously demonstrated (19,27). Thus, water in vapor and liquid form can be considered as a significant factor affecting temperature of the fluidizing mass.

Both fluidization parameter and pressure difference over filters expressed particle size when the granules had been formed. The moisture originating from granulation liquid and inlet air was seen in both pressure difference over granules and temperature of the mass. The various physical parameters evaluated here give valuable information on the behavior of the fluidizing moist mass. This type of instrumentation system is an invaluable aid to gaining more control for fluid bed processing to obtain repeatable granules for further processing.

CONCLUSION

Correlation with in-line particle size was found between both fluidization parameter and pressure difference over filters. These parameters can be used as indicative in-line estimates of particle size during granulation. Pressure difference over granules (lower filter) and temperature of fluidizing mass did not reveal particle size but these parameters did express the moisture conditions of wet granulation.

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REFERENCES

1. M. E. Aulton, and M. Banks. Fluidised bed granulation—factors influencing the quality of the product. *Int. J. Pharm. Technol. Prod. Manuf.* **2**:24–29 (1981).
2. M. Summers, and M. Aulton. Granulation. In M. Aulton (ed.), *Pharmaceutics, The science of dosage form design*, Churchill Livingstone, Spain, 2002, pp. 364–378.
3. O. Wørts. Wet granulation—fluidized bed and high shear techniques compared. *Pharm. Technol. Eur.* **10**:27–30 (1998).
4. S. M. Iveson, J. D. Litster, K. Hapgood, and B. J. Ennis. Nucleation, growth and breakage phenomena in agitated wet granulation processes: a review. *Powder Technol.* **117**:3–39 (2001).
5. T. Niskanen, J. Yliruusi, M. Niskanen, and O. Kontro. Granulation of potassium chloride in instrumented fluidized bed granulator—Part I: effect of flow rate. *Acta Pharm. Fennica*. **99**:13–22 (1990).
6. P. Merkku, A.-S. Lindqvist, K. Leiviskä, and J. Yliruusi. Influence of granulation and compression process variables on flow rate of granules and on tablet properties, with special reference to weight variation. *Int. J. Pharm.* **102**:117–125 (1993).
7. J. Rantanen, M. Känsäkoski, J. Suhonen, J. Tenhunen, S. Lehtonen, T. Rajalahti, J. P. Mannermaa, and J. Yliruusi. Next generation fluidized bed granulator automation. *AAPS PharmSciTech*. **1**(2):26–36 (2000).
8. J. Rantanen, A. Jørgensen, E. Räsänen, P. Luukkonen, S. Airaksinen, J. Raiman, K. Hänninen, O. Antikainen, and J. Yliruusi. Process analysis of fluidized bed granulation. *AAPS PharmSciTech*. **2**(4):13–20 (2001).
9. J. Rantanen, S. J. Laine, O. K. Antikainen, J.-P. Mannermaa, O. E. Simula, and J. Yliruusi. Visualization of fluid-bed granulation with self-organizing maps. *J. Pharm. Biomed. Anal.* **24**:343–352 (2001).
10. T. Närvänen, K. Seppälä, O. Antikainen, and J. Yliruusi. A new rapid on-line imaging method to determine particle size distribution of granules. *AAPS PharmSciTech* **9**(1):282–287 (2008).
11. T. Närvänen, T. Lipsanen, O. Antikainen, H. Räikkönen, J. Heinämäki, and J. Yliruusi. Gaining fluid bed process understanding by in-line particle size analysis. *J. Pharm. Sci.* (2008) doi:10.1002/jps.21486.
12. B. Scott, and A. Wilcock. Process analytical technology in the pharmaceutical industry: a toolkit for continuous improvement. *PDA J. Pharm. Sci. Technol.* **60**:17–53 (2006).
13. D. M. Parikh. Airflow in batch fluid-bed processing. *Pharm. Technol.* **15**:100–110 (1991).
14. D. Geldart. Types of gas fluidization. *Powder Technol.* **7**:285–292 (1973).
15. D. Kunii, and O. Levenspiel. Fluidization Engineering, 2nd ed., Butterworth-Heinemann, Newton, 1991.
16. J. Z. H. Gao, D. B. Gray, R. Motheram, and M. A. Hussain. Importance of inlet air velocity in fluid bed drying of a granulation prepared in a high shear granulator. *AAPS PharmSciTech*. **1**(4):1–3 (2000).
17. E. Räsänen, O. Antikainen, and J. Yliruusi. A new method to predict flowability using a microscale fluid bed. *AAPS PharmSciTech.* **4**:418–424 (2003).
18. E. Räsänen, J. Rantanen, J.-P. Mannermaa, and J. Yliruusi. The characterization of fluidization behavior using a novel multichamber microscale fluid bed. *J. Pharm. Sci.* **93**:780–791 (2004).

19. T. Lipsanen, O. Antikainen, H. Räikkönen, S. Airaksinen, and J. Yliruusi. Novel description of a design space for fluidised bed granulation. *Int. J. Pharm.* **345**:101–107 (2007).
20. T. Närvänen, T. Lipsanen, O. Antikainen, H. Räikkönen, and J. Yliruusi. Controlling granule size by granulation liquid feed pulsing. *Int. J. Pharm.* **357**:132–138 (2008).
21. N. Laitinen, O. Antikainen, J. Rantanen, and J. Yliruusi. New perspectives for visual characterization of pharmaceutical solids. *J. Pharm. Sci.* **93**:165–176 (2004).
22. S. Wold, E. Johansson, and M. Cocchi. PLS. In H. Kubinyi (ed.), *3D-QSAR in Drug Design, Theory, Methods, and Applications*, ESCOM Science, Ledien, 1993, pp. 523–550.
23. Food and Drug Administration FDA. Guidance for Industry; PAT—a framework for innovative pharmaceutical development, manufacturing and quality assurance (2004).
24. International Conference on Harmonisation. ICH harmonised tripartite guideline; Pharmaceutical Development Q8 (2005).
25. International Conference on Harmonisation. ICH harmonised tripartite guideline; Quality Risk Management Q9 (2005).
26. F. C. Harbert. Technical paper. Automatic control of dryers. *Metron Tech.* **4**:1–5 (1972).
27. T. Lipsanen, O. Antikainen, H. Räikkönen, S. Airaksinen, and J. Yliruusi. Effect of fluidisation activity on end-point detection of a fluid bed drying process. *Int. J. Pharm.* **357**:37–43 (2008).