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Research Article

Monitoring Fluidized Bed Drying of Pharmaceutical Granules

Lauren Briens[1,2] and Megan Bojarra[1]

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Abstract. Placebo granules consisting of lactose monohydrate, corn starch, and polyvinylpyrrolidone were prepared using de-ionized water in a high-shear mixer and dried in a conical fluidized bed dryer at various superficial gas velocities. Acoustic, vibration, and pressure data obtained over the course of drying was analyzed using various statistical, frequency, fractal, and chaos techniques. Traditional monitoring methods were also used for reference. Analysis of the vibration data showed that the acceleration levels decreased during drying and reached a plateau once the granules had reached a final moisture content of 1–2 wt.%; this plateau did not differ significantly between superficial gas velocities, indicating a potential criterion to support drying endpoint identification. Acoustic emissions could not reliably identify the drying endpoint. However, high kurtosis values of acoustic emissions measured in the filtered air exhaust corresponded to high entrainment rates. This could be used for process control to adjust the fluidization gas velocity to allow drying to continue rapidly while minimizing entrainment and possible product losses.

KEY WORDS: acoustic monitoring; fluidized bed drying; granules; pharmaceuticals; vibration monitoring.

INTRODUCTION

In the manufacture of pharmaceutical tablets, wet granulation combines the active pharmaceutical ingredient and excipients with binder into multi-particle units. Granulation is important as it improves flowabilty, compressibilty for tableting, dispersability, and the uniformity of the particulate components (1,2). Wet granulation is usually accomplished in two stages: the granules are produced by agglomerating the various components with a binder solution in a high shear mixer and then the wet granules are dried to stabilize the granule structure (3).

Fluidized bed drying is often the method of choice to dry the wet granules. It offers several advantages, including rapid heat and mass transfer, large capacity, and relatively low capital cost (3,4). When drying pharmaceutical granules, care must be taken to avoid over-drying as this could result in significant attrition and entrainment, leading to product loss. In order to avoid losses and poor product quality, monitoring the drying process to determine suitable operation conditions and an optimal endpoint is necessary.

There are many methods described in the literature for monitoring fluidized bed drying. One method is to remove samples from the bed to determine the moisture content of the particulates within the sample. This method is limited, as the analysis is performed off-line, is time consuming, and can easily be affected by sampling difficulties or maldistribution within the bed (5,6).

Alternatively, temperature may be used to monitor fluidized bed drying. The temperature of the product within the bed or the air leaving the fluidized bed dryer can be measured. During drying, the air and product temperatures are cooled as a result of the evaporation of water from the granules. The drying end-point can therefore be estimated by an increase in the air or product temperatures (7–10). Alden *et al.* (11) describe the temperature-difference technique to indicate the drying end-point: the moisture content of the granules within the bed is estimated from the difference in temperature between the dry bulb temperature measured within the bed and the wet bulb temperature of the bed when the granules are very wet. Another temperature-based method for monitoring drying involves estimating the humidity of the air leaving the dryer by comparing the wet bulb and the dry bulb temperatures. Initially, the humidity of the air leaving the dryer is very high due to evaporation of water from the granules during drying. As the granules dry, the humidity of the outlet air decreases and the end-point of drying occurs when the humidity of the inlet and outlet air approach the same value. Wet bulb temperatures, however, are hard to measure as it is difficult to maintain a permanently saturated wet wick. Another disadvantage of temperature-based monitoring methods is limited accuracy due to poor fluidization conditions within the bed.

Near-infrared (NIR) spectroscopy has been used to monitor drying by measuring the moisture content of the air moving through the dryer and, more commonly, by measuring the moisture content of the granules within the bed (12). Morris *et al.* (7) used NIR monitoring of the granule moisture

[1] Department of Chemical and Biochemical Engineering, Faculty of Engineering, The University of Western Ontario, London, Ontario N6A 5B9, Canada.
[2] To whom correspondence should be addressed. (e-mail: lbriens@uwo.ca)

content by placing the NIR sensor externally at an inspection window. Frake *et al.* (13) and Räsänen *et al.* (3) used NIR monitoring of the granule moisture content by coupling the NIR sensor to a fiber optic probe and inserting the system into the fluidized bed. Both methods suffer from difficulties in keeping a clear path between the sensor tip and the granules to be measured as particulates can adhere to the inspection window and to the probe inserted into the bed. In addition, the monitoring method would be affected by maldistribution in the bed as the measured granules would not be representative of the overall granule moisture content within the bed (12).

Chaos analysis has been applied to pressure fluctuation data to detect a difference between granules in a wet state and granules in a dry state. By using the S-statistic, Chaplin *et al.* (8) were able to able to detect a difference between the two states. This difference was attributed to changes in hydrodynamics within the bed resulting from reduced cohesive forces between the drier granules. Chaplin *et al.* (9) also found that chaos analysis and the S-statistic could be used to predict entrainment from the fluidized bed. Disadvantages of this monitoring method include difficulties in implementing the S-statistic calculations and that the method appears to be affected by many operation parameters and would thus be difficult to implement and use reliably in industry.

The objective of the research presented in this paper was to investigate non-invasive vibration and passive acoustic emission measurements as techniques to supplement current methods to indicate drying endpoint and to provide additional information about the process that could be used to improve operation and process control.

MATERIALS AND METHODS

Fluidized Bed Dryer

The fluidized bed dryer is shown schematically in Fig. 1. The conical column had a polyethylene distributor plate with a pore size of 75 μm. A sampling thief was located at the base of the column. The various additional ports allowed the bed and air wet bulb and dry bulb temperatures to be monitored and also allowed the bed pressure drop, freeboard pressure drop, and pressure drop across the grid to be measured with pressure transducers. The top of the fluidized bed was fitted with four air outlets. Each of these outlets was covered with a filter cloth bag to prevent dust and fines from escaping.

Drying Experiments

Placebo granules consisting of 87 wt.% (on a dry basis) lactose monohydrate, 10 wt.% corn starch and 3 wt.% polyvinylpyrrolidone were granulated with 18 wt.% de-ionized water. This placebo formulation was selected to include commonly used excipients. The granules were made using a high-shear granulator. Approximately 2 kg of the wet granules were used for each trial.

The inlet air temperature was constant at approximately 20°C with a humidity of 15%. The superficial gas velocities tested were 0.8, 1.0, 1.2, 1.4, and 1.6 m/s.

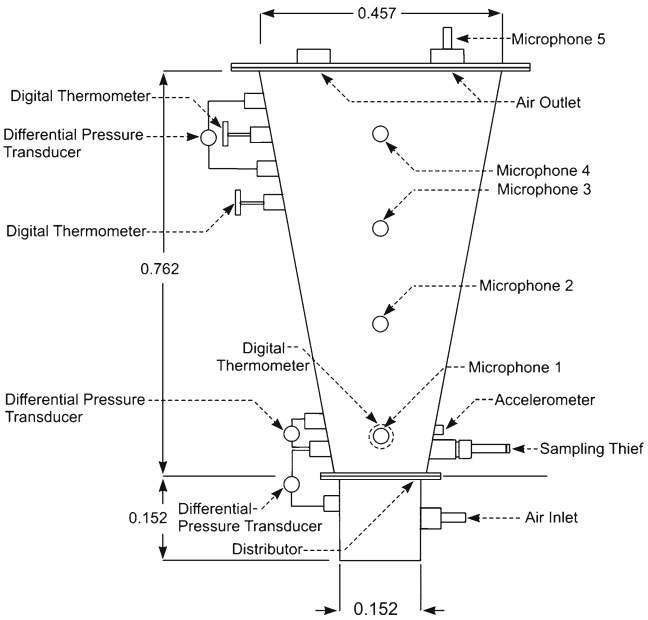

Fig. 1. Schematic diagram of fluidized bed dryer

Samples were taken at 5-min intervals throughout each trial. Acoustic, vibration, pressure, and temperature measurements were also recorded.

Sampling

Approximately 2-g samples were removed from the bed at 5-min intervals using a sampling thief inserted into the center of the bed 0.051 m above the grid. The samples were analyzed off-line for moisture content by loss-on-drying at 105°C using a Mettler–Toledo HG63 halogen moisture analyzer. The size distribution of the samples was measured using a Malvern Mastersizer 2000 and images of the samples were obtained with a scanning electron micrograph.

Data Acquisition

Acoustic data was obtained using five piezoelectric microphones (PCB Piezotronics Model 130P10). Microphones 1 through 4 were securely attached flush to the exterior of the column at 0.085, 0.285, 0.480, and 0.655 m above the grid allowing measurements within the bed region and at various freeboard levels (i.e., above the solids bed height). Microphone 5 was suspended in one of the filtered air outlets. Data from all microphones was recorded at a sampling rate of 40,000 Hz throughout the entire drying period.

Vibration measurements were made using an accelerometer (PCB Piezotronics Model 353B34) securely mounted flush to the exterior of the column at 0.045 m above the grid. The sampling rate was 40,000 Hz throughout the entire drying period.

Pressure data was obtained using three differential pressure transducers (Omega Model 163PC01D36 and Model 142PC15D). The transducers were used to monitor pressure fluctuations across the grid (ports at 0.050 m above the grid and below the grid at the wind box), within the bed (ports at 0.050 and 0.100 m above the grid), and within the upper

freeboard (ports at 0.560 and 0.685 m above the grid). Data from all pressure transducers was recorded at a sampling rate of 1,000 Hz throughout the entire drying period.

Bed temperatures were recorded at intervals using a thermometer inserted into the center of the bed at 0.071 m above the grid. Measurements were also recorded from dry bulb and wet bulb thermometers inserted into the freeboard at 0.497 and 0.626 m above the grid. Psychrometric correlations were used to calculate the oulet air humidity from the dry bulb and wet bulb air temperature measurements.

Data Analysis

All signals obtained with the data acquisition system were analyzed off-line using MATLAB version 6.5 in 10-s consecutive chunks. A wide range of analysis methods were investigated including statistical, frequency, fractal, and chaos techniques.

Entrainment Experiments

Additional experiments were conducted to monitor entrainment. Granules were prepared by the same procedure used for the drying experiments. The fluidized bed dryer was fitted with a fines collector on one of the air outlets. A filter bag attached to the collector was removed and weighed at 5-min intervals during drying. Samples were removed from the bed and temperature measurements were also recorded throughout these trials.

RESULTS

Figure 2 shows the granule moisture content as a function of time, determined through sampling and loss on drying measurements. The granule moisture content, initially just below 20 wt.%, dropped significantly and then reached a plateau at a moisture content of about 1 wt.%. A dry granule endpoint of less than 2 wt.% moisture content was specified. The drying time, based on this criterion, decreased with superficial gas velocity from 82 min at 0.8 m/s to 33 min at 1.6 m/s.

Figure 3 shows the measured bed temperature during drying. With very wet granules, the bed temperature was approximately 7–10°C. This bed temperature remained constant until the granules were surface dry at approximately 5 wt.% moisture content. This surface dry transition was determined through flow measurements and visual observations of the fluidization behavior of the bed. Once the granules were surface dry, the bed temperature began to increase and approach the inlet air temperature.

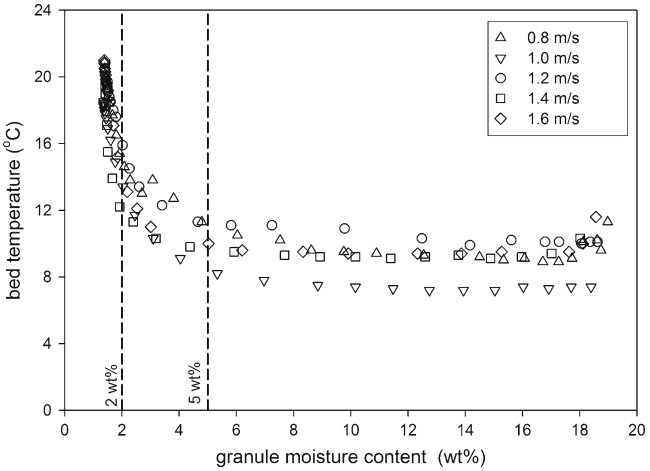

Fig. 3. Bed temperature *versus* granule moisture content

Figure 4 shows the air outlet temperature during drying. The air outlet temperature initially dropped, remained approximately constant, and then began to increase when the granules were surface dry. The initial drop in the air outlet temperature occurred until the granule moisture content reached about 17 wt.%.

As shown in Fig. 5, the air outlet humidity was initially high and then dropped after the granules became surface dry. There was significant initial scatter and lower measured humidity values during the 0.8 and 1.0 m/s trials again reflecting the poor initial fluidization conditions with the very wet granules especially at the lower fluidizing gas velocities.

Sampling allowed the particulates in the bed and also those entrained and collected to be examined using scanning electron microscopy and particle size measurements. Figure 6a–c shows images from scanning electron microscopy of the individual powders used in the formulation. Figure 6d and e then compares wet and dry granules for a trial at a superficial gas velocity of 1.2 m/s with Fig. 6f showing the

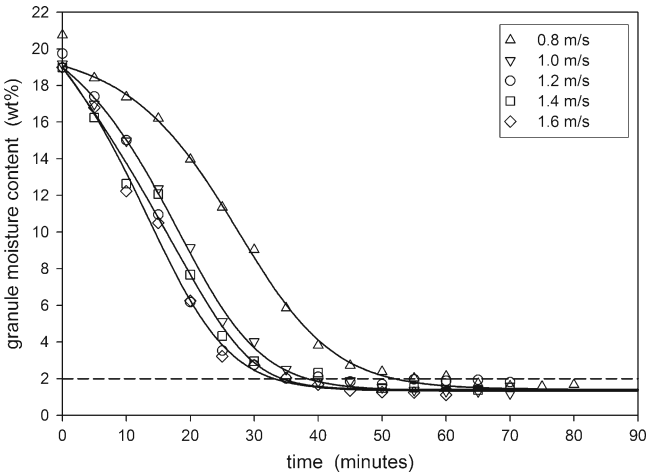

Fig. 2. Granule moisture content *versus* time

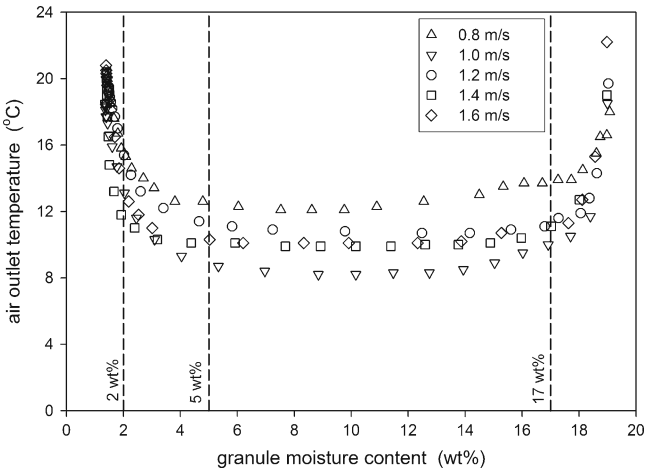

Fig. 4. Air outlet temperature *versus* granule moisture content

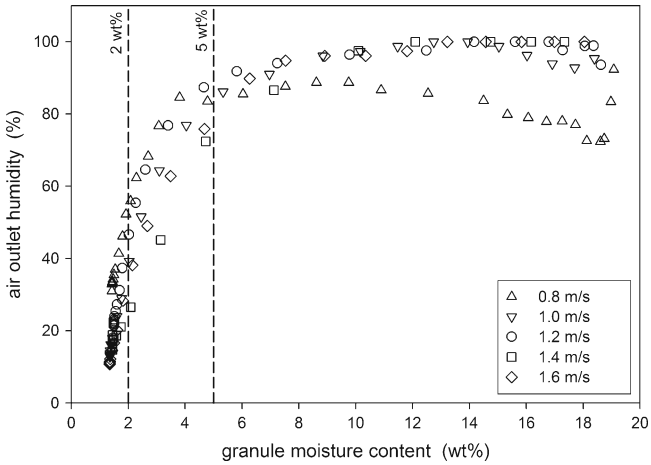

Fig. 5. Humidity of the outlet air *versus* granule moisture content

collected fines from this trial. The images show that the small amount of PVP in the formulation dissolved in the water binder, the corn starch particles were small with diameters of less than 40 μm, the lactose particles ranged in size from 40 to 400 μm and the granules were agglomerates of lactose and corn starch with diameters ranging from about 400–1,000 μm. The initial granulation mixture had a distribution of about 90 vol% granules with 10 vol% individual corn starch and lactose particles that had not been incorporated into the granules.

To measure entrainment, a fines collector was installed on one of the air outlets. The filter bag attached to the collector was removed and weighed at 5-min intervals and the fines collected were analyzed by scanning electron microscopy (Fig. 6f). Figure 7 shows that the entrainment of fines was minimal at low superficial gas velocities. Figure 8 shows that the entrainment of fines for the trial at a superficial gas velocity of 1.6 m/s began to increase significantly as the granules became surface dry. The entrained and collected fines were individual corn starch and lactose particles (Fig. 6f).

Examples of the average bed pressure drop are given in Fig. 9. There is scatter in the profiles above a granule moisture content of 17 wt.% when the granules were very cohesive. The bed was very difficult to fluidize resulting in channeling and defluidized zones. The bed pressure drop

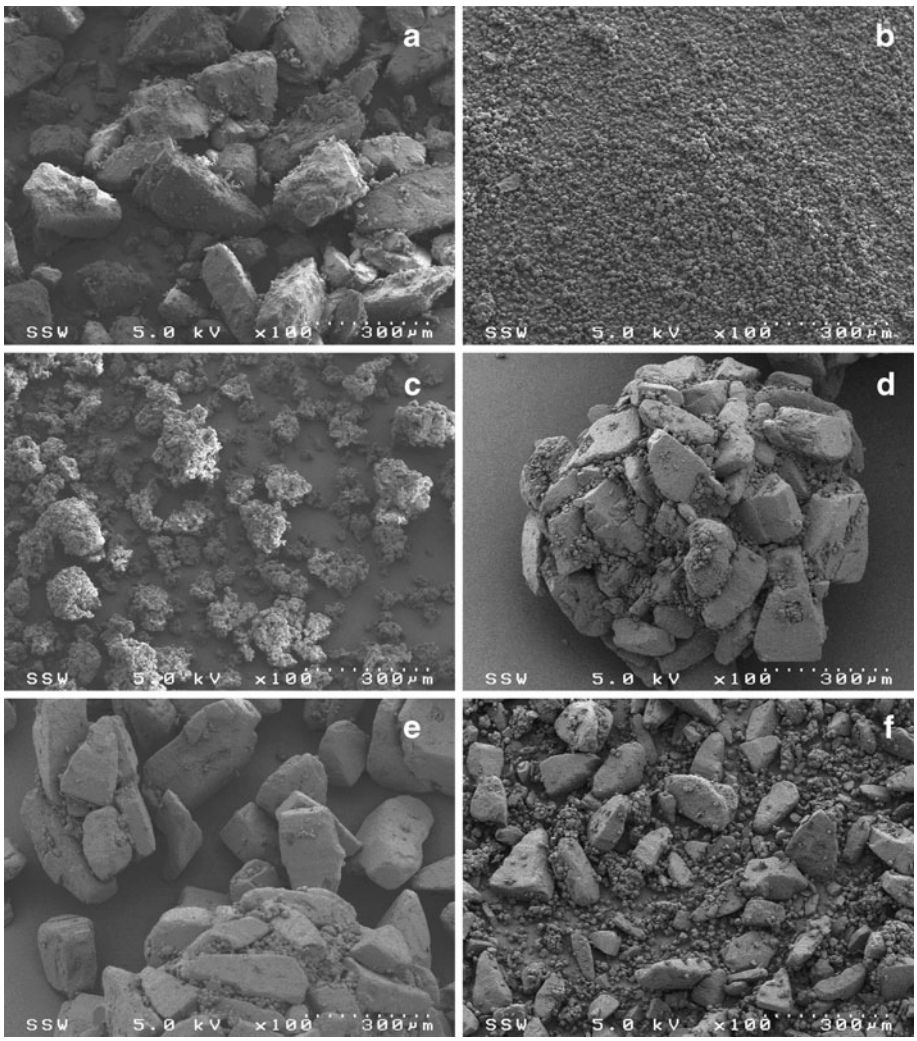

Fig. 6. Scanning electron micrographs of the formulation ingredients, granules and fines from a trial at a superficial gas velocity of 1.2 m/s. **a** Lactose monohydrate, **b** corn starch, **c** PVP, **d** wet, initial granules, **e** dry, final granules, and **f** fines collected during drying

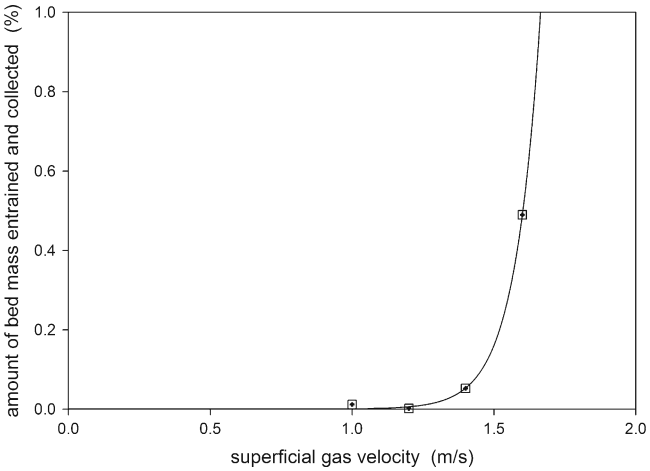

Fig. 7. Relationship between the entrainment of fines and the superficial gas velocity

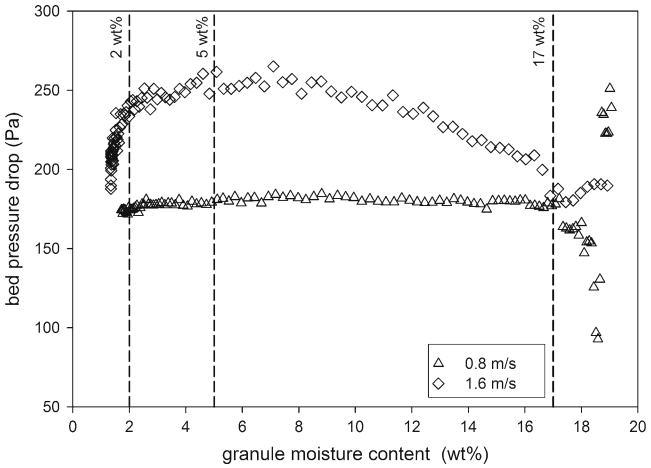

Fig. 9. Bed pressure drop

profile was almost constant for the trial at a superficial gas velocity of 0.8 m/s. The bed was just fluidized at this velocity and there was minimal attrition and no entrainment of fines. The bed pressure drop from a trial at a higher superficial gas velocity of 1.6 m/s was very different: the bed pressure drop profile showed a maximum near the granule moisture content corresponding to surface dry granules and then decreased sharply at 2 wt.%, the criterion for dry granules.

Examples of the freeboard pressure drop are given in Fig. 10. The profiles are scattered above a granule moisture content of 17 wt.% reflecting the difficulties in fluidizing these very wet granules. Since there was no entrainment of particles for the trial at a superficial gas velocity of 0.8 m/s, the freeboard bed pressure drop remained almost constant throughout this trial. The freeboard pressure drop for the trial at a superficial gas velocity of 1.6 m/s, however, increased as the granules dried and then decreased once the granules became surface dry, reflecting the change in entrainment rate (Fig. 8).

Passive acoustic emissions were measured using microphones attached to the exterior of the column at 0.085, 0.285, 0.480, and 0.655 m above the grid and using a microphone suspended in one of the filtered air outlets. The average acoustic emissions data showed scatter with no clear visible indication of hydrodynamic changes within the bed and the end point of drying.

Many signal analysis methods were applied to the measured passive acoustic emissions, but a technique that reliably indicated a drying endpoint for all tested gas velocities was not identified. Figure 11, however, shows that the kurtosis of the emissions measured in the air outlet indicated the entrainment of fines from the bed.

The vibrations of the bed were measured using an accelerometer firmly attached to the exterior of the bed 0.045 m above the grid (Fig. 1). Figure 12 shows the acceleration levels during drying.

DISCUSSION

Sampling with moisture content analysis allowed the drying profiles to be obtained. Sampling, however, is intrusive and time consuming. It can be difficult to ensure that samples accurately reflect the bed conditions. Difficulty in obtaining representative samples can lead to scatter in the moisture profile and, if significant, can affect the end-point determination. Sampling can also affect the calibration and therefore accuracy of on-line monitoring methods such as near-infrared spectrometry (14). In addition, sampling can

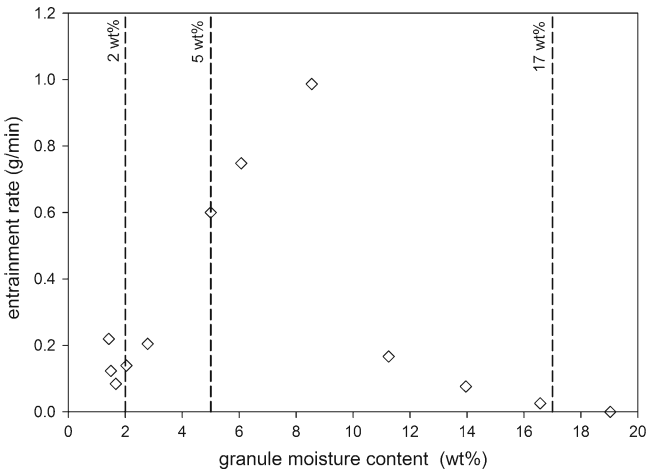

Fig. 8. Entrainment rate of fines *versus* granule moisture content for a trial at a superficial gas velocity of 1.6 m/s

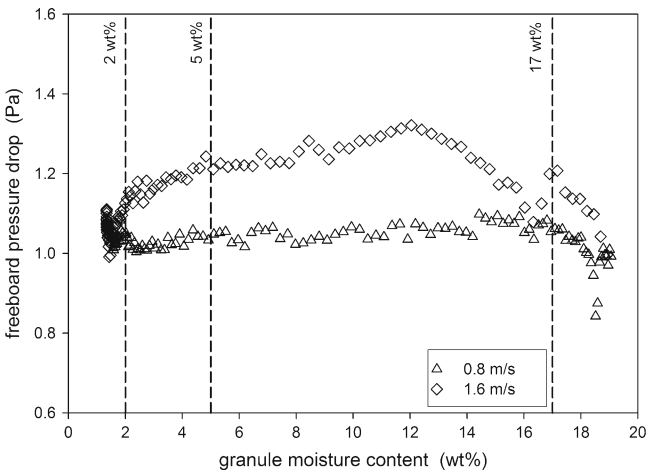

Fig. 10. Freeboard pressure drop

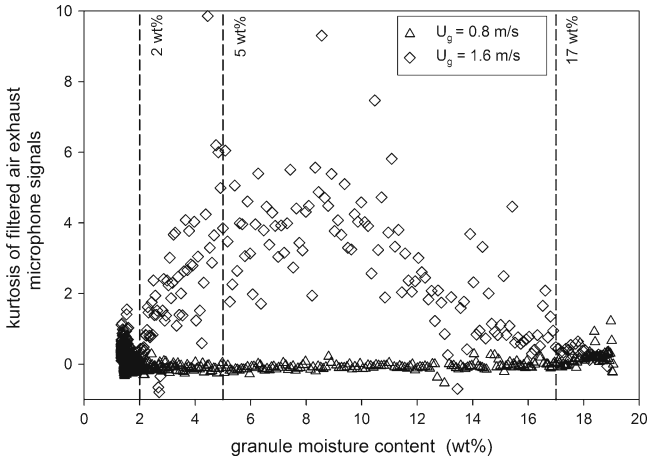

Fig. 11. Kurtosis of acoustic emissions measured in the filtered air exhaust

only easily be performed during product development. Stopping the process during commercial production for sampling is not recommended.

As shown in Fig. 2, the granule moisture content profile at a superficial gas velocity of 0.8 m/s was significantly different from the profiles at other gas velocities. At a superficial gas velocity of 0.8 m/s, the bed was not well fluidized. The solids did not mix efficiently with the air and therefore drying was slower. Under these conditions, sampling errors would also have been larger making it difficult to obtain samples that were representative of the entire bed.

The bed temperature, air outlet temperature, and air outlet humidity were all measured during drying. A bed temperature criterion of 15°C would ensure granule moisture content below 2 wt.%. Bed temperature is used during commercial operation as a monitoring method combined with minimum drying time information from moisture profiles obtained during the development stage. Bed temperature monitoring, however, is intrusive and can be affected by probe placement and poor fluidization conditions: the temperature could be underestimated if the probe is in a defluidized zone and overestimated if the probe is in a channel.

At high moisture levels, the granules were very cohesive which resulted in poor fluidization conditions of defluidized zones and channeling; the overall contact of the air with the

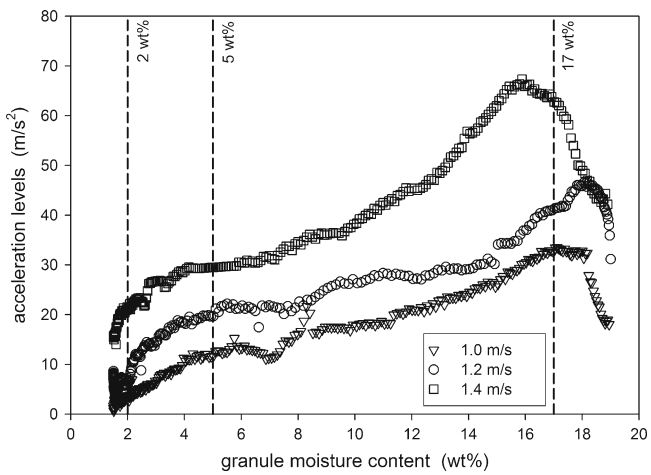

Fig. 12. Bed acceleration levels during drying

granules was decreased and therefore the air temperature was between the wet and dry bulb temperatures. Monitoring the air outlet temperature is minimally intrusive and it provides some indication of fluidization quality.

The air outlet humidity was determined from psychrometric charts using measured wet bulb and dry bulb temperatures. Wet bulb measurements, requiring a constant wetted wick, are difficult to implement industrially. Near-infrared spectrometry can be used to measure the humidity of the air, but this method requires an expensive sensor and extensive calibration which requires appropriate sampling (12,14). Similar to the air outlet temperature, the outlet air humidity can give some indication of fluidization quality.

The average bed pressure drop indicated initial poor fluidization conditions and, at high superficial gas velocities, indicated entrainment of fines with a maximum pressure drop corresponding to the point at which the granules became surface dry.

Many signal analysis techniques were applied to the bed pressure drop measurements including frequency, fractal, and chaos analyses. However, an analysis technique that reliably identified the drying end point for all gas velocities was not identified. The S-statistic used by Chaplin *et al.* (8,9) was applied. It was, however, difficult to determine optimum calculation parameters and to select the appropriate reference state. The drying profiles therefore varied and were difficult to use in identifying the drying endpoint.

The average passive acoustic emissions data did not clearly indicate changes within the bed and the end-point of drying, regardless of the sensor position. This is due to the dampening of the emissions as they were recorded after transmission through the column wall and the many sources and complex variability of the emissions throughout drying. Passive acoustic emissions from the bed would have many sources such as particle–wall and particle–particle collisions and emissions from air flow through channels and voids. The emissions would vary in a complex manner throughout the drying: as the granules dried and became lighter, the sound from their collisions would change, the flow pattern of the air would change as the bed became better fluidized with the dry granules, and a collision that results in attrition would have a different acoustic emission than a collision that preserves intact granules (15).

Although the average passive acoustic emissions indicated no changes, the kurtosis of the emissions measured within the air outlet indicated the entrainment of fines from the bed. Kurtosis indicates the relative peakedness of the distribution of values within a signal. Kurtosis is calculated by:

$$K = \frac{\sum \left(y - \overline{y}^4\right)}{\sigma^4 M} - 3$$

where y is the signal value, $\overline{y}$ is the signal mean, and M is the number of points in the signal (16).

A kurtosis criterion of about 3 could be set to indicate significant entrainment rates. As passive acoustic emission monitoring in the air outlet is a non-intrusive, this measurement and criterion could be used together as part of a control system to adjust the fluidizing gas velocity to minimize entrainment while still maximizing the drying rate.

The vibrations of the bed were measured using an accelerometer. The wet granules were heavy and their collisions with each other and the column wall resulted in

an initially high level of bed vibrational acceleration. As the granules became smaller through attrition and lighter due to the drying, the collisions had lower energies and the acceleration levels dropped. The flow of air alone through the column provided some vibration. The measured acceleration levels increased correspondingly with superficial gas velocity. With a suitable correction for gas velocity, the non-intrusive bed vibration measurements show potential as a supplemental method for indicating the drying endpoint.

Passive acoustic emission and vibration measurements offer potential to supplement current methods for monitoring fluidized bed drying of pharmaceutical granules. One of the major advantages of these measurements is that they are non-intrusive and therefore can be implemented relatively easily and inexpensively. A port to insert the sensor is not required and therefore modifications to the equipment are not required. The cost of an acoustic and vibration sensor used in this research was estimated to be about a quarter of the cost of commercially available NIR sensors.

Poor fluidization conditions during drying can lead to inaccurate moisture content and temperature measurements. As these measurements do not clearly indicate fluidization conditions, measurement inaccuracies from fluidization difficulties can be difficult to detect and evaluate during drying. Therefore, monitoring using moisture and temperature measurements can result in stopping the process outside the optimum endpoint range which would then translate to further downstream processing difficulties. Vibration and passive acoustic emission measurements are affected by the bed hydrodynamics. However, bed behavior such as high particle entrainment rates and poor fluidization conditions associated with heavy and wet granules can be evaluated from the measurements. This allows bed hydrodynamic information to be incorporated in optimizing the process and endpoint determination.

CONCLUSIONS

Fluidized bed drying experiments were carried out with placebo granules over a range of superficial gas velocities. Passive acoustic and vibration monitoring techniques were investigated for monitoring drying and compared to more traditional monitoring methods of granule moisture content, temperature, humidity, and pressure measurements.

The kurtosis of passive acoustic emissions obtained from a microphone suspended in the filtered air exhaust indicated particle entrainment from the bed and could provide a non-intrusive method to be incorporated into a control system to adjust the fluidizing gas velocity for optimum operation.

Bed vibration measurements showed potential as a non-intrusive supplemental monitoring method. These measurements indicated fluidization difficulties with the wet cohesive granules, followed the progression of drying with decreasing acceleration levels and showed potential for a calibrated criterion to indicate a drying endpoint.

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