AAPS PharmSciTech 2005; 6 (2) Article 29 (http://www.aapspharmscitech.org).

Monitoring the Fluidized Bed Granulation Process Based on *S*-Statistic Analysis of a Pressure Time Series

Submitted: July 16, 2004; Accepted: February 23, 2005; Published: September 30, 2005

Gareth Chaplin,[1] Todd Pugsley,[1] and Conrad Winters[2]

[1]Department of Chemical Engineering, The University of Saskatchewan, Saskatchewan, Saskatoon, Canada S7N 5C5
[2]Merck and Co, Inc, West Point, PA 19486-0004

ABSTRACT

Pressure fluctuation measurements collected during the fluidized bed granulation of pharmaceutical granule have been analyzed using the attractor comparison technique denoted as the *S*-statistic. Divergence of the bed state from the reference during granulation is followed by a return to a condition statistically similar to the original state of the dry fluidized ingredients on drying. This suggests insensitivity of the *S*-statistic technique to the changes in particle size distribution occurring during the granulation process. Consequently, the monitoring of pressure fluctuations alone may provide an easily implemented technique for the tracking of granule moisture and process end-point determination.

KEYWORDS: fluidized bed, granulation, *S*-statistic, hydrodynamics, chaos, pressure fluctuations

INTRODUCTION

A number of pharmaceutical dosage forms are prepared by fluid bed granulation. Fluid bed granulation offers a number of advantages, including product containment of potent materials, processing at ambient temperatures for thermosensitive materials, and generation of low-density, free-flowing granules. A drug substance can be added as a solid or by a solution. In this process, the addition of atomized liquid, containing a drug substance and/or a binder, directly into a bed of fluidized material causes the agglomeration of particles to form granules. The vigorous granule mixing provided by the fluidized bed allows both the even distribution of a drug substance and a binder and the uniform drying of the granule product. Process control is commonly accomplished by the monitoring of outlet air and product temperatures. The attainment of a limiting value of either of these quantities signifies the completion of the drying phase. Because the bed temperature only begins to increase once surface moisture is lost from the particles, this type of temperature monitoring only provides information about bed moisture content late in the drying process. Furthermore, temperature measurement provides no information about the fluidization behavior of the bed.

The direct on-line measurement of bed moisture during fluid-bed granulation has been performed by Kawai,[1] Watano et al,[2] Gore et al,[3] and Rantanen et al[4] using infrared spectroscopy. Rantanen et al[4] have shown that different drying times are required for different formulations. This highlights the importance of the quantification of changes in moisture. The moisture profiles in Gore et al[3] and Rantanen et al[4] show an increase in moisture to a maximum in the granulation phase followed by an immediate decrease during the drying phase to bed moisture content similar to the initial moisture of the dry ingredients. In Kawai[1] and Watano et al,[2] a period of constant moisture is maintained at the maximum moisture to allow for the growth of granules before the drying phase. Watano et al[2] have shown that infrared measurements can be used to control the rate of binder addition throughout the constant moisture phase to maintain the desired bed moisture content. Kawai[1] has indicated that moisture content is a major factor affecting granule size and bulk density. Therefore, the measurement and control of moisture is crucial to control product quality. Although moisture content is a key process parameter, its measurement gives no indication of the hydrodynamic changes taking place within the bed during granulation. Furthermore, the spectroscopic technique used for the on-line measurement of moisture in the above studies can be costly to implement and subject to measurement uncertainties caused by the presence of surface moisture.[1] The technique is also formulation-specific, which requires the generation of calibration sets for each product manufactured. The present work demonstrates an alternative method for the monitoring moisture content in a fluidized bed granulator through the use of pressure fluctuations.

Pressure fluctuations in a fluidized bed arise from a number of sources including bubble generation, bubble coalescence, and bulk bed oscillations.[5] Several analysis techniques have been applied to these fluctuations, including SD,[6] frequency[7,8] and chaos analysis.[8] The chaos analysis technique, denoted as the *S*-statistic, represents a statistical comparison between 2 bed states described by chaotic attractors reconstructed from separate time series of pressure

Corresponding Author: Todd Pugsley, University of Saskatchewan, 57 Campus Dr, Saskatoon, SK S7N 5A9 Canada. Tel: (306) 966-4761; Fax: (306) 966-4777; E-mail: todd.pugsley@usask.ca

fluctuations.[9] The *S*-statistic has been applied to pressure fluctuations collected in the drying of pharmaceuticals by Chaplin et al.[10,11] In the current study, we apply the *S*-statistic test to pressure fluctuations collected in a fluidized bed granulator used for the production of pharmaceuticals.

THEORY

The *S*-statistic represents a comparison of attractors reconstructed from 2 distinct sets of discretely sampled data denoted as the reference and evaluation time series. These data sets can be thought of as a sample of attractors describing the system behavior at 2 distinct system states. The algorithm makes a statistical comparison between these states and outputs a numerical value denoted as the *S*-statistic. A value of the *S*-statistic <3 indicates that no statistically significant change has taken place between the reference and evaluation states. Likewise, a value of $S > 3$ indicates that a statistically significant difference exists between the attractors reconstructed from the reference time series and those reconstructed from the evaluation time series. Details of the mathematical development of the *S*-statistic are given in Diks et al.[12] The application of the algorithm to fluidized systems is given in van Ommen[9] and van Ommen et al.[13]

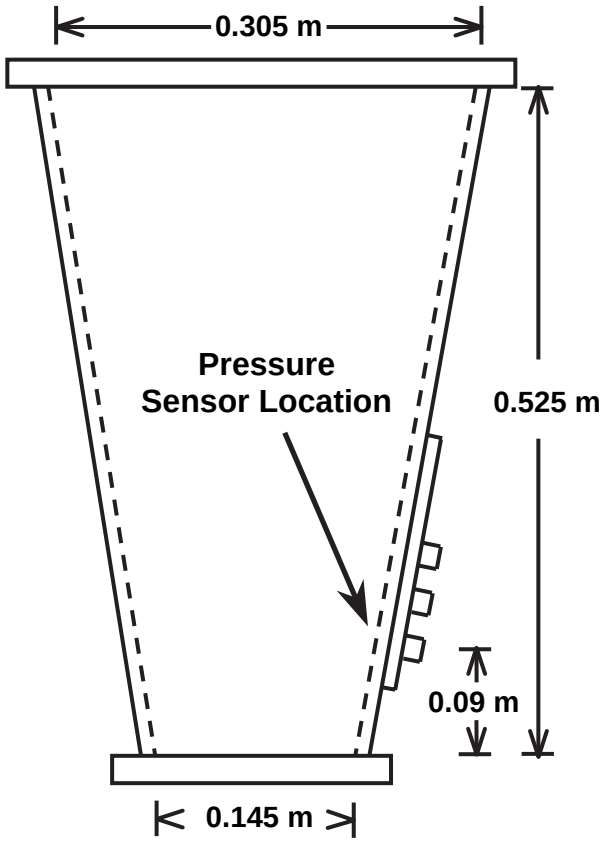

Figure 1. Schematic of the fluid bed granulator product bowl. Dimensions given in meters.

MATERIALS AND METHODS

The main dry granulation ingredient was Mannitol (Pearlitol SD200) from Roquette (Keokuk, IA). The aqueous binder solution consisted of 8% hydroxypropylcellulose (Klucel LF; Hercules Inc, Wilmington, DE).

Fluid Bed Granulation

A schematic of the product bowl for the batch-fluidized bed processor used in this study is shown in Figure 1. This unit, the GPCG1 (Glatt-Powder-Coater-Granulator) from Glatt Air Technologies Inc (Ramsey, NJ) allows for the manipulation of inlet air temperature and air velocity and is fitted with a top-spray granulation nozzle. The humidity of the fluidizing air was not controlled by the processor but was measured to be approximately 50% relative humidity at an ambient temperature of 20°C. Fitted with a 12% open-area wire mesh distributor, the conical product bowl fits into the air supply/conditioning module. For the granulation experiment, dry ingredients were placed in the product bowl. Subsequently, heated air was introduced into the bottom of the conical section to fluidize this material. Inlet air temperature was maintained at 30°C for all 3 phases of the granulation process. Superficial velocity was maintained at 2.9 m/s based on the average velocity across the inlet to the product bowl throughout the experiment. After an initial mixing phase, binder addition was performed over 27 min. The binder solution was introduced at a rate of 9.2 g/min. After the completion of binder addition, drying of the granule was performed over the following 12 min. The final dry mass of granules produced had an approximate average volume diameter of 250 μm.

Instrumentation

Product and outlet air temperature measurements were made using thermocouples placed directly within the bed and in the outlet air stream. The temperatures were read directly from a digital instrumentation panel at intervals of 5 min.

A high-frequency piezoelectric sensor (PCB-106B; Piezotronics, Depew, NY) was used in the measurement of pressure fluctuation data. The sensor diaphragm was flush-mounted to the inside wall of the fluidized bed at 90 mm above the distributor. A Keithly KPC-3101 12-bit data acquisition card was used for the acquisition of pressure data. Card control and data logging were made possible by the use of a graphical user interface developed in Labview. The raw data set was collected at a sampling rate of 400 Hz throughout the granulation and drying phases. Data were filtered offline using a type 1 Chebychev

band-pass filter design in Matlab between 0.5 and 170 Hz. Filtering was performed to fulfill the Nyquist criterion, as well as to eliminate low-frequency transitory effects associated with the piezoelectric sensor.

Data Analysis

Pressure fluctuation data were analyzed in Matlab using the *S*-statistic algorithm described in our earlier work.[10,11] This technique was calibrated for the optimum test parameters as described previously,[10,11] and the optimum parameters were found to be identical to those found for the drying of pharmaceutical granule in this fluidized bed unit. The pressure time series collected during the granulation process was broken into evaluation data sets lasting 1 min. These data sets were compared with a reference data set of 2 min in duration. Each evaluation data set was transformed into a single *S*-statistic value. Previously, an evaluation time series of 2 min was used for each *S*-statistic value.[10,11] The shorter evaluation time series of 1 min was selected to track the rapid changes observed in this process. It has been determined that the use of time segments of 1 min did not affect the performance of the test.

RESULTS AND DISCUSSION

Figure 2 shows the behavior of the outlet air and bed temperatures. From this plot, we can see that the temperatures of both the outlet air and bed begin to increase at 30 min. This increase occurs immediately after the completion of binder addition at 27 min. An increase in these temperatures at the end of drying is indicative of the loss of surface moisture from the particles. Completion of the drying process was identified at the attainment of a bed temperature of 30°C.

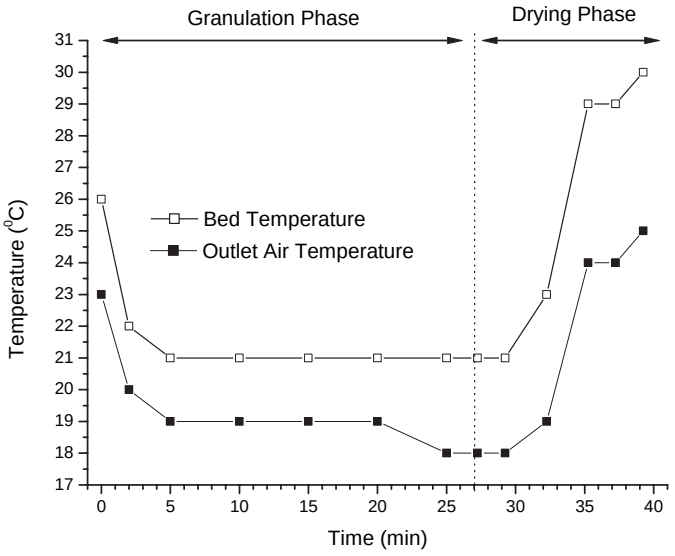

Figure 2. Outlet air and product temperature profiles during granulation along with the *S*-statistic when referenced to 35 min. An *S*-statistic value >3 indicates that a statistically significant change has taken place.

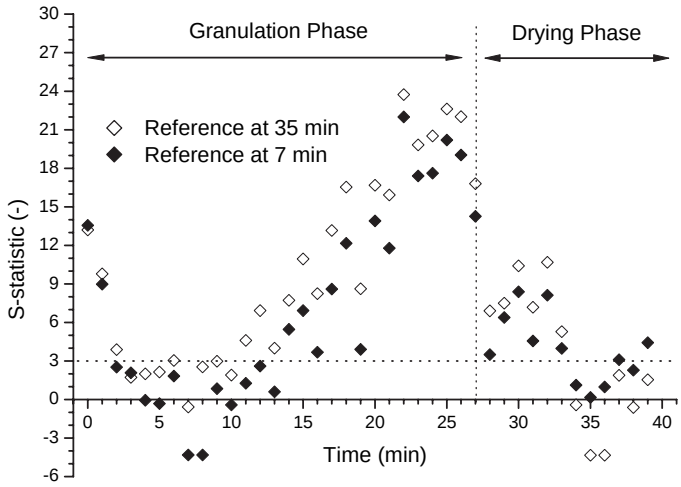

Figure 3. *S*-statistic referenced to times of 7 and 35 min. An *S*-statistic value >3 represents a statistically significant change.

The behavior of the *S*-statistic, when reference states were selected at 7 and 35 min from the start of the granulation phase, is given in Figure 3. When a reference state beginning at 35 min is chosen, the *S*-statistic identifies 2 periods of statistically similar hydrodynamic behavior (ie, an S value >3). The first consistent region occurs between 3 and 10 min, whereas the second lasts from 34 min to the completion of the drying phase. The *S*-statistic diverges from a state consistent with the reference state at 11 min, indicating a change in the hydrodynamic behavior of the bed at this time. Immediately after completion of binder addition at 27 min, the bed state begins to return to a state that is statistically similar to the initial state. A similar behavior of the *S*-statistic is seen when the reference state is chosen at 7 min. The resemblance of these hydrodynamic conditions can be verified using the second reference state. A second reference state was chosen within the initial period of consistent hydrodynamic behavior that was seen early in the granulation. Similarity in the shape of both of the *S*-statistic responses confirms the existence of the 2 consistent hydrodynamic states occurring in the early stages of granulation and the final stages of drying.

The shape of the *S*-statistic response given in Figure 3 is similar to the moisture profiles seen in both Gore et al[3] and Rantanen et al.[4] In these studies performed using pharmaceuticals, an increase in moisture content observed during the binder addition is followed by a decrease in moisture in the drying phase. The identical behavior is seen in the performance of the *S*-statistic with maximum divergence from the reference state occurring at 25 min. This is near the completion of the binder addition or a time when the bed has the highest moisture content. We conclude that the

S-statistic is responding to hydrodynamic changes arising from the introduction of moisture into the bed.

The fact that the second consistent hydrodynamic state is similar to that seen early in granulation when a small volume of the binder has been added indicates insensitivity of the *S*-statistic to the growth of granules in this granulation process. Insensitivity in the *S*-statistic to changes in particle size distribution was noted by Chaplin et al[10] where reduced sensitivity to changes in particle size distribution in the *S*-statistic at superficial gas velocities >2.8 m/s was observed in the same GPGC1 unit operated as a dryer. In Figure 3, it can also be noted that the *S*-statistic is initially >3 followed by an immediate drop to a consistent state within 2 min of the start of the experiment. This initial separation from the reference state may be characteristic of a differing hydrodynamic state in a very dry bed.

A similar separation is also seen at 39 min, where the particles have the lowest moisture near the end of drying. The initial separation of the *S*-statistic from the reference state over the first 2 min of the granulation experiment is of interest. Inspection of the pressure time series collected during this portion of the experiment indicates that it has a lower intensity to that seen in the subsequent region of consistent behavior between 2 and 14 min. The cause of this change in hydrodynamic behavior is not clear and requires additional investigation.

CONCLUSIONS

The *S*-statistic analysis of pressure fluctuations collected in the fluidized bed granulation process has identified 2 regions of consistent behavior existing in the initial stages of granulation and the final stages of drying. These regions of consistent behavior are separated by a divergence toward a dissimilar state. This divergence and return is similar to the rise and fall of bed moisture in the granulation process.[3,4] The fact that the 2 regions of consistent hydrodynamic behavior are statistically similar indicates that the increase in moisture, not the growth of granules, has the most significant impact on the hydrodynamic changes identified by the *S*-statistic. The use of this technique to determine the changes in moisture within the granulator may lead to better on-line monitoring and control of this process without the need for the direct measurement of moisture. Additional experimentation is needed to quantify this connection fully, but the potential use of this technique for process monitoring in the granulation process is clear.

ACKNOWLEDGMENTS

The authors would like to thank Merck Frosst Canada and Co (Montreal) and the Natural Sciences and Engineering Research Council of Canada for their financial support. We would also like to acknowledge the technical assistance in the running of the fluid bed granulator provided by Dr Hubert Dumont of Merck Frosst Canada and Co and consultation offered by Dr Ruud van Ommen, Delft University of Technology, regarding the implementation of the *S*-statistic.

REFERENCES

1. Kawai S. Granulation and drying of powdery or liquid materials by fluidized-bed technology. *Drying Tech.* 1993;11:719-731.

2. Watano S, Takashima H, Miyanami K. Control of moisture content in fluidized bed granulation by neural network. *J Chem Eng Japan.* 1997;30:223-229.

3. Gore AY, McFarland DW, Batuyios NH. Fluid-bed granulation: factors affecting the process in a laboratory development and production scale-up. *Pharm Tech.* 1985;9:114-122.

4. Rantanen J, Jørgensen A, Räsänen E, et al. Process analysis of fluidized bed granulation. *AAPS PharmsciTech.* 2001;2:E21.

5. van der Schaaf J, Schouten JC, van den Bleek CM. Origin, propagation and attenuation of pressure waves in gas-solid fluidized beds. *Powder Tech.* 1998;95:220-233.

6. Chong YO, O'Dea DP, White ET, Lee PL, Leung LS. Control of the quality of fluidization in a tall bed using the variance of pressure fluctuations. *Powder Tech.* 1987;53:237-246.

7. Kage H, Iwasaki N, Yamaguchi H, Matsuno Y. Frequency analysis of pressure fluctuation in fluidized bed plenum. *J Chem Eng Japan.* 1991;24:76-81.

8. Bai D, Bi HT, Grace JR. Chaotic behavior of fluidized beds based on pressure and voidage fluctuations. *AIChE J.* 1997;43:1357-1361.

9. van Ommen R. *Monitoring Fluidized Bed Hydrodynamics*. [PhD Thesis]. Delft, The Netherlands: Technical University of Delft; 2001.

10. Chaplin G, Pugsley T, Winters C. Application of chaos analysis to pressure fluctuation data from a fluidized bed dryer containing pharmaceutical granule. *Powder Tech.* 2004;142:110-120.

11. Chaplin G, Pugsley T, Winters C. Application of chaos analysis to fluidized bed drying of pharmaceutical granule. In: Arena U, Chirone R, Miccio M, Salatino P, eds. *Fluidization XI*, New York: Engineering Foundation; 2004;419-426.

12. Diks C, van Zwet WR, Takens F, DeGoede J. Detecting differences between delay vector distributions. *Phys Rev E.* 1996;53:2169-2176.

13. van Ommen JC, Coppens MC, van Den Bleek CM. Early warning of agglomeration in fluidized beds by attractor comparison. *AIChe J.* 2000;46:2183-2197.