Detection and Characterization of Acoustic Signals from a Granulation Process

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Abstract

This paper presents the development of an acoustic emission monitoring system and its application to the investigation of acoustic emissions from a high-shear granulation. The system utilizes two piezoelectric sensors which between them cover a frequency range of 0 Hz-300 kHz. Granulations were performed in a 10 Litre granulator at 400g and 1kg scales. The acoustic emissions monitoring was successful for both scale granulations. The results show a correlation between the mean granule size and average frequency emitted by the process.

1 Introduction

Granulation is the process of particle enlargement, where a formulation of powders is mixed together with a binder which is used to cause powder particles to adhere together to form larger multi particulate matter called granules [1]. It is a process of great practical importance in the pharmaceutical industry and is also widely used in food, agriculture and chemical industries [2].

The Process Analytical Technology (PAT) initiative was launched by the FDA to encourage the pharmaceutical industry to introduce and develop more on-line techniques for process monitoring and control. In the case of granulation, use of an in line monitoring technique could improve the product quality, avoid irregular shutdown and reduce the number of recycled or bad batches. In–line measurements correlated with granule properties could be used to determine the endpoint for the granulation [1]. The endpoint can be defined as the point at which the granule properties such as granule size distribution are optimal. The required analytical tools must be online and real time to achieve these goals.

Over the years, various PAT tools have been developed. These can be categorized as indirect or direct measurement techniques. For example, power consumption [3,4,5] and torque are indirect measurements while infra-red spectroscopy [6,7], image processing [2,8,9] and vibration analysis [10] are direct measurements. Acoustic emissions analysis is another direct measurement PAT tool for monitoring the granulation process. The use of acoustic emissions monitoring in the pharmaceutical industry has only picked up pace in the past decade whereas in other fields such as fracture mechanics, non-destructive testing and material science the technique has been used for almost 60 years [11].

Acoustics emissions techniques can be passive or active mode. In active mode, a known signal is transmitted into the process vessel, and the change in the returned signal is measured. In the case where the acoustic emissions from the process itself are measured, the technique is passive mode. In this study passive mode was used to monitor the granulation process. This technique has several advantages in comparison to others, for example, it is non-invasive hence the sensor can be on the outside wall of the vessel removing the requirement for a drill hole as required for near-infrared [6] and image processing [2] techniques. Another major advantage of monitoring high frequency acoustic emissions is that high frequency acoustic waves are attenuated easily and only travel short distances. This makes the high frequency acoustic emissions measurements more localised and reduces the interference from ambient environmental factors.

In this study the on-line acoustic monitoring system developed was used to investigate the acoustic emissions from a granulation process. This work focuses on analysing the acoustic emissions from the granulator, some of which are due to changes in granules properties and thus aid in endpoint determination.

2 Acoustic Emissions Monitoring System

The acoustic emissions monitoring system consists of three main components. The first and foremost component of an acoustic emissions system is the acoustic sensor. To cover the wide frequency range (0-300kHz) two sensors were used. One has a resonant frequency of 30 kHz and other has a resonant frequency of 150 kHz.

The amplitude of the signal emitted from the high shear granulation process is low; the raw signal is on the order of microvolts. Thus, the signals from the sensor require a pre-amplification stage to obtain a signal that is more usable. The amplifier must have minimal susceptibility to interference in a noisy pharmaceutical environment. Thus, to limit interference, sensors with in-built amplifiers were utilized.

The signal is often filtered after the amplification stage. This helps to remove any unwanted frequencies. In the system designed; the isolation circuit includes a high pass filter.

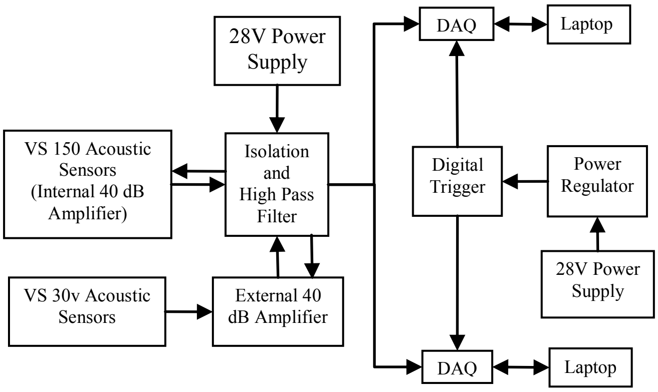

Figure 1. Block Diagram of measurement system

The isolation circuit uses a capacitive coupling technique to protect the data acquisition cards from high voltage. A block diagram of the system is shown in Figure 1.The high-pass filter designed has a cut-off frequency of 110 Hz with -5dB attenuation in the frequency range of interest. Figure 2 depicts the frequency response of the high-pass filter.

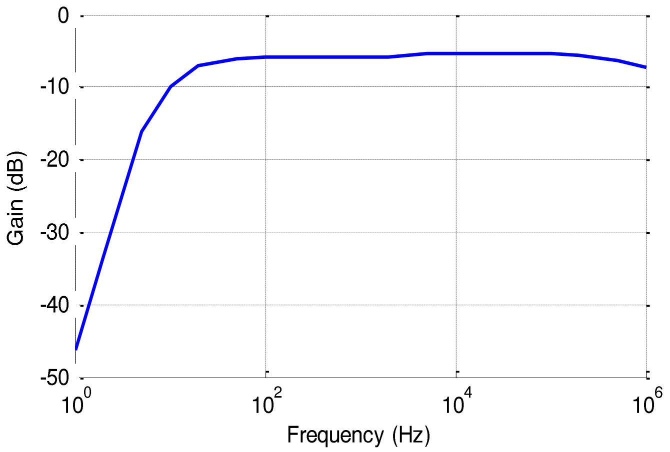

Figure 2. Frequency response of the high-pass filter

3 Materials and Method

3.1 Materials

In this study two batch scales have been used, a 400g and 1kg mixture. The material used for the formulation was a placebo mixture consisting of 91.7% w/w (Lactochem Pharmaceutical Lactose) crystalline lactose monohydrate and 8.33% w/w microcrystalline cellulose (Avicel PH101). An aqueous solution of 5% w/w of polyvinylpyrrolidone (Kollidon 30) was used to granulate the mixture. Table 1 summarizes the quantity of materials used for the 400g and 1 kg mixture.

3.2 Equipment

The granulations were performed in an Aeromatic Fielder GP1 high shear mixer using a 10 litre bowl. After the completion of the granulation, samples of the granules were dried in a vacuum oven. The particle size distribution of the granules was determined by using Malvern Mastersizer fitted with a Scirocco2000 dry powder dispersion unit.

Table 1.The composition of granulation for 400g and 1kg batches

Materials	Batch Size	
	400 g	1 kg
Crystalline Lactose Monohydrate (91.7% w/w)	366.8g	917g
Microcrystalline Cellulose(8.33% w/w)	33.3g	83.3g
Polyvinylpyrrolidone (5% w/w of aqueous solution)	44-88ml	170ml

The acoustic data was acquired using VS150 RI and VS 30 V sensors; the signal from the sensor was amplified using a 40 dB amplifier. The amplified signal was logged using a National Instrument 6251 M series data acquisition cards and the system was controlled using LabVIEW. The data was logged in binary file format for post-acquisition analysis.

3.3 Granulation Process

The placebo formulation was used in both batch sizes. For the 400g batches, the formulation was dry mixed for 2 minutes at an impeller speed of 200 rpm. This was followed by adding 44 ml of liquid binder over 34 seconds. The chopper was turned on after the binder addition, at a speed of 1000 rpm and left on until the end of granulation. The wet massing proceeded for 16 minutes and the final stage involved collection of the granule samples. To vary the granule size in this batch of granulations, the liquid to solid (L/S) ratio was varied i.e. the amount of binder added was changed to 60ml, 68ml, 80ml and 88ml. These five granulation runs made a set (See Table 2) and the set was repeated six times for the 400g batch.

Table 2. L/S ratio used for granulation runs in a set

Set 1	
Granulation Run	L/S Ratio
1	11%
2	15%
3	17%
4	20%
5	22%

The procedure was slightly different for a 1kg batch. The formulation was dry mixed for 2 minutes, followed by an addition of 170ml (i.e. a liquid to solid (L/S) ratio of 17%) of binder over 2 minutes. The wet massing was continued for 12 minutes and samples of granules were taken every 2 minutes. The impeller and chopper were kept at 200rpm and 1000 rpm respectively. The 1kg batch granulation was repeated three times. The granules samples from both the batches were dried overnight at 55º C.

This allowed study of the granule growth. The acoustic data was collected by placing the piezoelectric sensors on the outside wall under the vessel as shown in Figure 3. The sensors were mounted on to the granulator vessel by applying a coupling agent on the surface of the sensor.

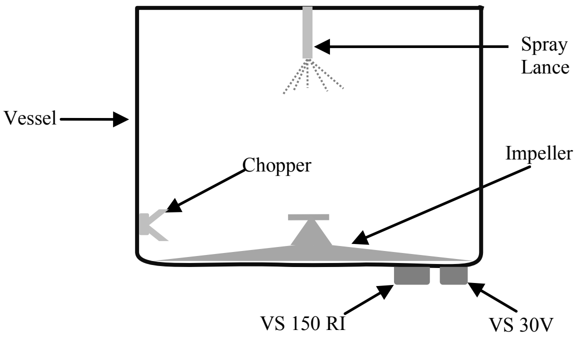

Figure 3. Placement of the sensors on the granulator vessel

The use of coupling agent ensures the maximum transfer of power of the acoustic signals. The setting used for data acquisition for the two batch runs is summarized in Table 3.

Table 3. The data acquisition setting for 400g and 1kg runs

	400 g		1kg	
	VS150 RI	VS30 V	VS150 RI	VS30 V
Sampling Frequency(kHz)	600	200	600	200
Amplification	40 dB			
Duration of Acquisition	20 Min		16 Min	

4 Data Analysis

4.1 Average signal level

The average signal level (ASL) is often referred to as the root mean square (RMS) value and is the simplest data analysis that can be preformed to examine changes in acoustic signals. Equation (1) is used to calculate the ASL for each time period of one second of acoustic emissions data acquired.Thus, with sampling frequency of N kHz, the ASL was calculated for each N sample values.

$$x_{RMS} = \sqrt{\frac{\sum_{i=1}^{n} x_i^{2}}{N}} \qquad (1)$$

x_i = the value of magnitude of the acoustic signal
N= length of x

The acoustic monitoring system developed is capable of generating the ASL profile online during the granulation. The changes in the ASL profile allow identifying stages of granulation, such as dry mixing, binder addition and wet massing. The profile obtained from our system was equivalent to what would be obtained from a high end system commercially available. Figure 4 is an example of ASL profile obtained from our system during a granulation run.

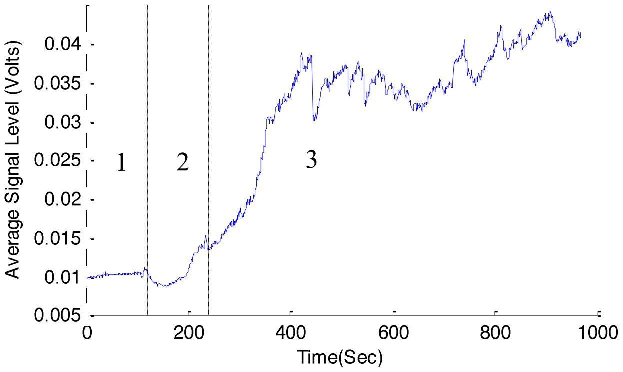

Figure 4. Average signal level (ASL) obtained from a granulation run using VS 150 RI sensor; (1) dry mixing,(2) binder addition, (3) wet massing

4.2 Frequency Analysis

The acoustic signals were sampled at 600 kHz and 200 kHz. Then the frequency representation of the signal was calculated using Fast Fourier Transform (FFT), which is given by:

$$x(k) = \sum_{n=0}^{N-1} x(\mathrm{n}) \mathrm{e}^{-\mathrm{j}(2\pi/\mathrm{N})\mathrm{kn}}$$

k = 0...N -1 (2)

Where x (n) is the discrete time domain sequence, x (k) is the computed frequency domain sequence and N is the size of the time sequence. The acoustic signal varies over time thus a static FFT would not be an accurate representation of the acoustic signal. Therefore, time dependent Fourier transform was used, where this signal is passed through a time window of defined length and the FFT is calculated. This method of averaging number of spectra over time is a commonly used technique to obtain a sufficient estimate of the signal FFT.

To investigate the relationship between the average frequency and granule size, the acoustic data was averaged and the FFT was calculated with 1024 points. Equation (3) was then used to calculate the average frequency (f).

$$\mathrm{f} = \frac{\sum_{\mathrm{i}=1}^{\mathrm{N}} \mathrm{f_i P_i}}{\sum_{\mathrm{i}+1}^{\mathrm{N}} \mathrm{P_i}} \qquad (3)$$

Where $\mathrm{P_i}$ = power of magnitude of the data sample i and $\mathrm{f_i}$ is the frequency of data sample i.

5 Results

The objective of this work was to investigate how the change in granule size during granulation may be determined by changes in the acoustic emissions detected from the process. The variables that have an impact on acoustic emissions, such as impeller speed and chopper speed were kept constant for all granulation runs. Also since granulation scales were small, samples were only taken at the end of the granulation for all 400g runs. This insured that the change detected in the acoustic emissions would be due to change in granule size. It was found that when the L/S ratio was over 20% for 400g mixture, it resulted in over granulation with a bimodal particle size distribution.

The overall average frequency of the acoustic data was calculated for 30 seconds of data at end of the granulation, when samples were taken. Figure 5 and Figure 7 depict the results from the VS 150 and VS 30 sensor respectively.

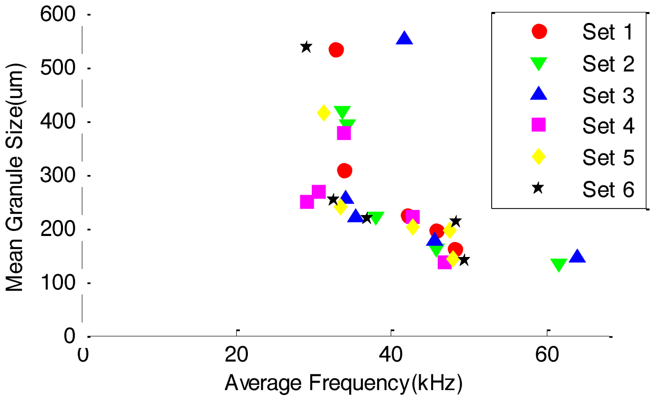

Figure 5. Average frequency versus mean granule size data for VS150 RI sensor

The measurement from VS 150 sensor depicts that as the granule size increases the average frequency decreases. However, the average frequency does not decrease after mean granule size was above 250 µm. The repeatability of measurement is shown in Figure 6, a good grouping was found for granules up to 200µm.

The variation in measurement may be due to slight change in the actual amount of binder added through the spray lance. During the granulation runs the binder is added through an air pressure controlled spray lance. It was found that since the air pressure was not constant at all times and the actual amount of binder added may vary slightly, even after the air pressure was adjusted to obtain the correct amount.

The measurement from the VS30 sensor did not show any trend between granule size and average frequency. Thus, it suggests that more information about granule size is found in high frequencies. The data from VS150 shows similar results for 1kg mixture as depicted in Figure 8.

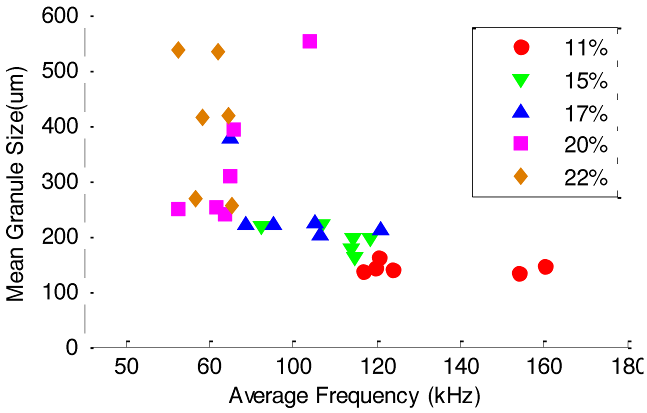

Figure 6. Repeatability of the measurement for VS150 RI

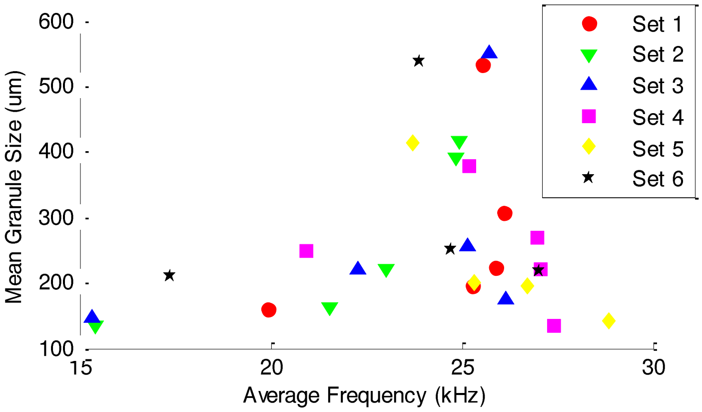

Figure 7. Average frequency versus mean granule size data for VS 30V sensor

This suggests that this may be a viable technique for granule size determination even when the batch size is scaled up. However, the average frequency emitted for 1Kg mixture is different than a 400g mixture for similar granule size. Thus, the scale of granulation may have an impact on the acoustic emission.

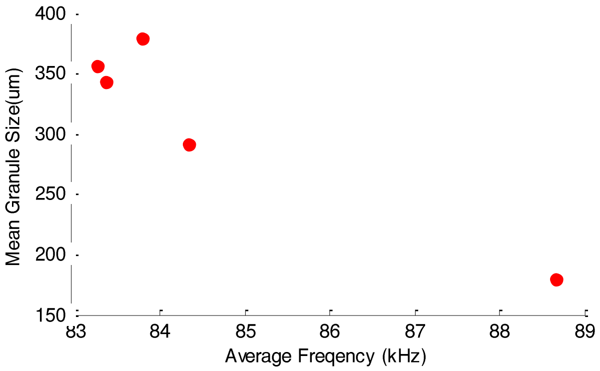

Figure 8. Average frequency versus granule size for a batch size of 1kg using VS150 sensor

6 Conclusion

In this work, a low cost acoustic monitoring system was developed. It was used to acquire acoustic data from a series of 400g and 1kg granulation runs. Sampling with wide acoustic bandwidth showed a strong relationship between the average acoustic frequency and the granule size. Initially during the granulation run the granules grow uniformly and the average acoustic frequency decreases too. The comparison of results from high frequency sensor and low frequency sensor also suggest higher frequencies contain more information about the granulation process. The lower frequency emissions may be dominated by machine and ambient environmental noise. It was also discovered that the scale of batch has an impact on the average frequency emitted from the process.

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References

[1] M. D. Parikh, *Handbook of pharmaceutical granulation technology*. New York: Marcel Dekker, 1997.

[2] S. Watano, "Direct control of wet granulation processes by image processing system," *Powder Technology*, vol. 117, pp. 163-172, 2001.

[3] H. Leuenberger, "Granulation,New Techniques," *Pharm. Acta Helv.*, vol. 57, no. 3, pp. 72-82, 1982.

[4] P. Holm, T. Schaefer, and H. G. Kristensen, "Granulation in High-Speed Mixers Part VI. Effects of Process Conditions on Power Consumption and Granule Growth," vol. 43, pp. 225-233, 1985.

[5] P. Holm, T. Schaefer, and H. G. Kristensen, "Granulation in High-Speed Mixers Part V. Power Consumption and Temperature Changes During Granulation," vol. 43, no. 3, pp. 213-223, 1985.

[6] P. Frake, I. Gill, C. N. Luscombe, D. R. Rudd, J. Waterhouse, and U. A. Jayasooriya, "Near-infrared mass median particle size determination of lactose monohydrate, evluating several chemometric approches," *The Analyst*, vol. 123, pp. 2043-2046, 1998.

[7] P. Frake, D. Greenhalgh, S. M. Grierson, J. M. Hempenstall, and D. R. Rudd, "Process control and end-point determination of a fluid bed granulation by application of near infra-red spectroscopy," *International Journal of Pharmaceutics*, vol. 151, pp. 75-80, 1997.

[8] S. Watano, T. Numa, K. Miyanami, and Y. Osako, "A fuzzy control system of high shear granulation using image processing," *Powder Technology*, vol. 115, pp. 124-130, 2001.

[9] Watano.K and Miyanami.K, "Image Processing for on-line monitoring of granule size distribution and shape in fluidized bed granulation," *Powder Technology*, vol. 83, pp. 55-60, 1995.

[10] D. Daniher, L. Briens, and A. Tallevi, "End-point detection in high-shear granulation using sound and vibration signal analysis," *Power technology*, vol. 181, pp. 130-136, 2008.

[11] M. K. Papp, C. P. Pujara, and P. Rodolfo, "Monitoring of High-shear Granulation using Acoustic Emission: Predicting Granule Properties," *J Pharm Innov*, vol. 3, pp. 113-122, 2008.