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Monitoring high-shear granulation using sound and vibration measurements

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Abstract

Sound and vibration measurements were investigated as monitoring methods for high-shear granulation. Five microphones and one accelerometer were placed at different locations on a 10 and a 25 l granulator and compared to find the optimum location and the effect of scale. The granulation process could be monitored using the mean frequency and root mean square sound pressure levels from acoustic emissions measured using a microphone in the filtered air exhaust of the granulators. These acoustic monitoring methods were successful for both the 10 and the 25 l granulation scales. The granulation phases, however, were more clearly defined for the larger scale granulation. The root mean square acceleration level from vibration measurements was also able to monitor the granulation, but only for the larger 25 l granulator.

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Keywords: Granulation monitoring; Sound and vibration measurements; Signal analysis; Acoustic emissions; Granulator scale-up

1. Introduction

In granulation, particles are adhered together to form larger multi-particle units called granules. In the pharmaceutical industry, granulation is used to increase the drug uniformity in the product and to improve the flow rate and flow uniformity of a mixture before tabletting. It also prevents segregation, improves compaction characteristics and reduces dust.

The high-shear mixer is commonly used for producing wet granules. This machine exerts shearing and compaction forces on the particles with a large rotating impeller blade. A small side-mounted chopper blade breaks large pieces into smaller granules. Once powder components of the formulation are thoroughly mixed, a liquid solution of a binder is sprayed into the mixture. Liquid bridges are created between particles that, in combination with the shearing forces, result in agglomerate growth (Augsburger and Vuppala, 1997). Also, after liquid addition, further shearing will continue to change the granulation properties.

The high-shear granulation process must be stopped at the proper point to obtain the required granule characteristics. To determine this end-point, the granulation process must be monitored, and the measurements must be correlated to the granule properties. Improvements in this field have the potential to reduce the time required for scale-up of manufacturing new pharmaceutical products. Also, it will help to improve batch consistency to better meet product quality requirements.

Several granulation monitoring techniques for use in a process control scheme have been investigated, such as near-infrared reflectance spectroscopy (Frake et al., 1977; Han, 1998; Rantanen et al., 1998) and image analysis (Watano, 2001). These optical probe techniques require a clear line of sight into the granulator bowl; a hole must be drilled into the granulator bowl wall with a complex system to ensure the probe window is not obstructed by wet material sticking to it. Monitoring using a capacitance sensor has been able to detect increasing binder level during granulation (Corvari et al., 1992). Unfortunately, however, this technique also required a hole be drilled into the granulator lid.

During granulation, sound is produced as the particles and granules collide and impact upon the equipment and sound also comes from the working motor of the impeller and chopper. The sound can be expected to change as the particles become

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incorporated into granules and the size and number of granules change. The acoustics and the vibration of the motor will also change as the resistance of the wet-mass against the impeller increases as stronger bonds are formed and the cohesiveness of the mixture increases.

Sound monitoring during high-shear granulation has been investigated by Whitaker et al. (2000). Piezoelectric microphones were attached to the bottom of the granulator bowl of a Niro-Fielder PMA-10 high shear granulator and sound measurements recorded throughout the granulation of a 3 kg placebo formulation. The average signal level of the emissions corresponded to some changes in the granulation process, but an end-point could not be clearly determined.

Ohike et al. (1999) used a vibration probe to directly monitor the granulation of a 5 kg placebo formulation in a Niro-Fielder PMA-25 high shear granulator. A spherical probe was positioned inside the granulator bowl and attached to a strain gauge to measure particle impact on the probe. The magnitude of the peak at the impeller blade frequency obtained by fast Fourier transform (FFT) was found to increase as the median granule diameter increased. The probe was displaced more by the larger size particles than smaller ones and thus created larger vibration signal amplitudes. Also, motors powering the impeller and the chopper produced changing vibrations in the granulator. Previous work (Terashita et al., 1990a,b; Watano et al., 1992; Laicher et al., 1997; Betz et al., 2003) has also shown that the power consumption of the main impeller motor shows a characteristic profile during the granulation process. This is due to the change in resistance of the wet-mass as stronger bonds are formed and the cohesiveness of the mixture increases.

The general objective of the research presented in this article was to investigate sound and vibration monitoring to determine the end-point of granulation in a 10 l (PMA-10) and a 25 l (PMA-25) high-shear granulator. Results from the two granulators were compared to investigate scale effects. For each scale, the granulator was operated under typical processing conditions (impeller speed, water addition rates, and final moisture content); these conditions are usually not held constant during scale-up.

2. Materials and methods

2.1. Product formulation

A placebo formulation consisting of 87 wt.% (dry basis) of lactose monohydrate NF (Foremost Farms, grade 312), 10 wt.% corn starch NF (Roquette) and 3 wt.% polyvinylpyrrolidone USP (BASF) was used in the experiments. A dry mass of 2 kg was used for each batch experiment with the Niro-Fielder PMA-10 while a dry mass of 8 kg was used with the Niro-Fielder PMA-25 batches. For both scales, the main impeller was operated at 250 rpm and the chopper at 1500 rpm. USP water was injected through a nozzle into the granulator bowl using a pressure vessel and compressed dry air. A regulator was used to adjust the injection rate while an electronic balance placed beneath the pressure vessel was used to measure the amount of water added.

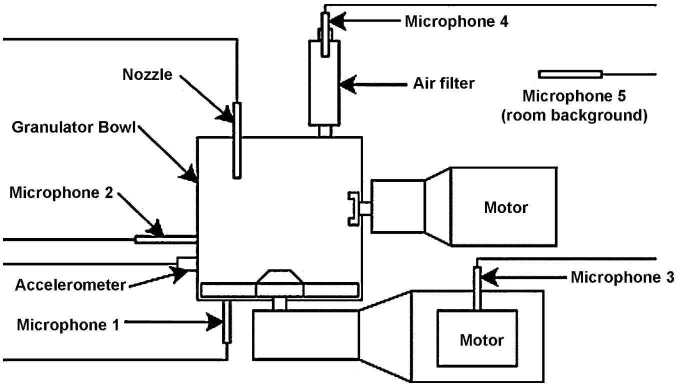

Fig. 1. The location of the microphones and the accelerometer.

2.2. Sensor measurements

Sound data was obtained using five PCB Piezotronics model 130D10 electret microphones and 130P10 preamplifiers. Vibration data was obtained using one PCB Piezotronics model 353B34 accelerometer. The sensors were temporarily but securely attached to the granulator at the locations indicated in Fig. 1. The accelerometer and microphones 1 and 2 were mounted on the granulator bowl with the microphone openings flush to the equipment surface. Microphone 3 was placed on the exterior of the motor casing and microphone 4 was centered in the air filter opening. Finally, microphone 5 was attached to the wall behind the granulator to record any significant background noise.

The data from all the sensors was acquired using a 16-bit National Instruments DAQCard-6036E. Since the granulation equipment produced sound changes detectable by human operators, the samples were recorded at a sampling rate to ensure no information is lost in the 0–20,000 Hz range. Therefore the signals were sampled at 40,000 Hz.

2.3. PMA-10 operation

The impeller and chopper were operated without water addition for the first 3 min to mix the dry powder. At 3 min, water addition was started and continued at a rate of approximately 42 g/min until 400 g of water was added. Mixing of the wet mass was continued for 2 min beyond water addition.

2.4. PMA-25 operation

The impeller and chopper were operated without water addition for the first 5 min to mix the dry powder. At 5 min, water addition was started and continued at a rate of either 180 or 140 g/min until 1480 g of water was added. Mixing of the wet mass was continued for 2 min beyond water addition.

2.5. Experimental procedure

For both granulators, the impeller and chopper were operated for the entire duration of the granulation. The amount of

Table 1
List of sensors used in each trial

	Granulator model/Water rate														
	PMA-10, 42 g/min							PMA-25							
								180 g/min						140 g/min	
Trial	A	B	C	D	E	F	G	A	B	C	D	E	F	G	H
Accelerometer	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Microphone 1	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Microphone 2	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Microphone 3				✓	✓	✓	✓			✓	✓	✓	✓	✓	✓
Microphone 4				✓	✓	✓	✓			✓	✓	✓	✓	✓	✓
Microphone 5				✓	✓	✓	✓			✓	✓	✓	✓	✓	✓
Samples				✓								✓	✓		

water added ensured that granulation continued beyond the endpoint in order to obtain signals from an over-granulated state. Signals were recorded without interruption for the entire granulation process except for trials when samples were withdrawn at intervals. Table 1 lists all the trials using both the PMA-10 and PMA-25 granulators.

Samples were obtained from some trials at regular intervals during the granulation process by stopping the impeller and chopper, and removing a small amount (approximately 10 g) of the mixture carefully to minimize interference with the ongoing granulation process. The particle size distributions of the wet granules were obtained using a Malvern Mastersizer 2000 with toluene as the dispersion agent.

2.6. Signal analysis

Fig. 2 shows examples of signals that were recorded during the granulation. Visually, the raw signal from the sensors did not provide much insight into the process. Therefore, more advanced analysis was performed off-line using MATLAB version 6.5. Calculations were done on each consecutive 10 s block of the sensor signals. These values were plotted against time to show the change in the statistic as the granulation proceeded. A wide range of analysis methods were investigated including statistical, frequency, wavelet and fractal techniques. Frequency analysis, however, was the most relevant since sound and vibration sensors record fluctuations in sound waves and vibration.

The standard deviation was used as an indication of the sound pressure level or vibration level. The frequency content of the signals was investigated using the power spectral density estimated using Welch's method with 2048 Hamming windows and 50% overlap (The Mathworks, 1999). The mean frequency was then calculated by the magnitude-weighted arithmetic mean. The one-third octave band sound pressure level was found by filtering the signals using standard one-third octave bands (Barron, 2003) then calculating the root-mean square sound pressure level (reference level 20 μdB) in each frequency range. The root-mean square acceleration level was calculated the same way, but with a 10 μm/s^2 reference level.

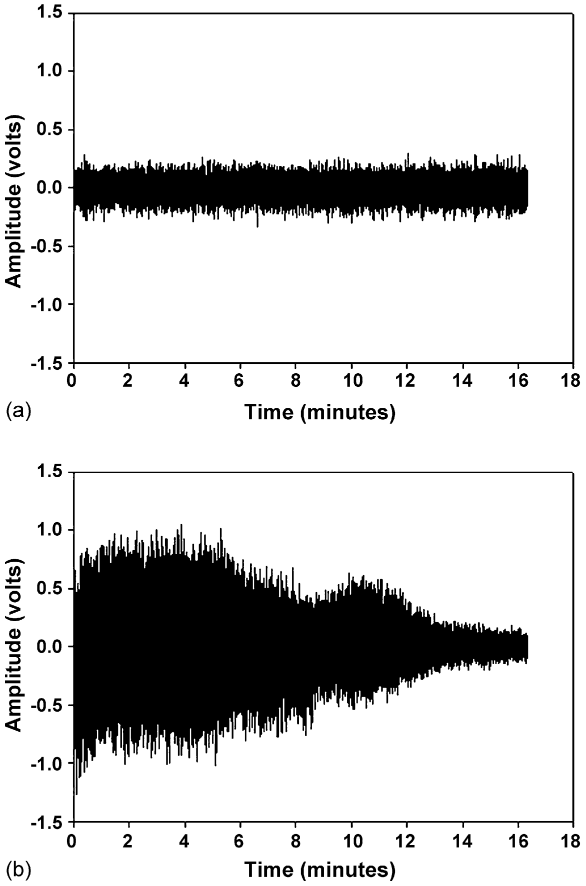

Fig. 2. The raw signal from (a) microphone 1 (bottom of granulator) and (b) microphone 4 (air filter outlet) measured during PMA25-C.

3. Results and discussion

3.1. Sampling

Fig. 3 shows the particle size distribution from the 180 g/min granulation in trial PMA25-F. The mean particle size quickly increased with time. At 11 min the samples contained a visible amount of fines. The sample at 12 min had a mean particle size distribution of 896 μm. Qualitative examination of this sample also revealed the granules did not break upon handling, and could

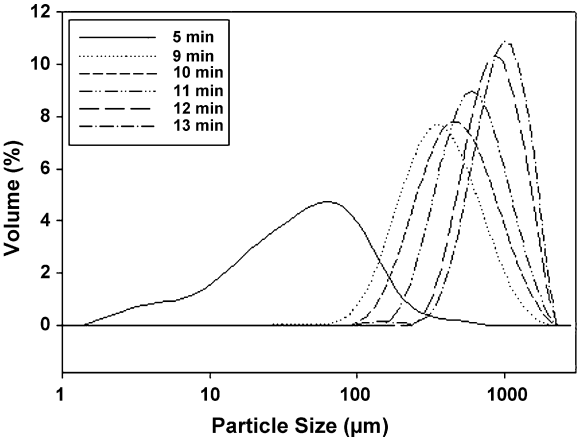

Fig. 3. Particle size distribution of the wet granules at various time intervals during the granulation process of PMA25-F.

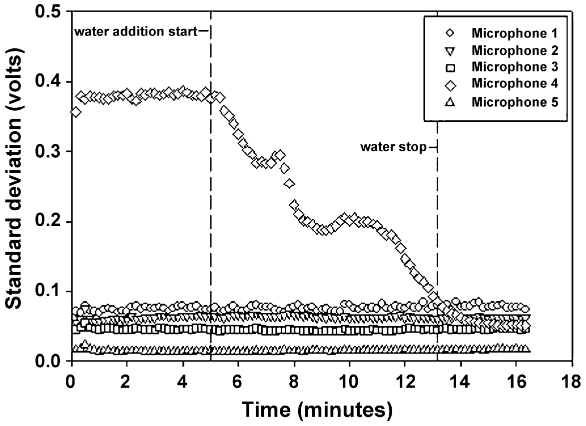

Fig. 4. Standard deviation of the microphone signals averaged over trials PMA25-C, PMA25-D and PMA25-E.

be compressed by hand into a ball. These properties are typical of a granulation that will make good tablets. Therefore, 12 min was identified as the optimum end-point of the 180 g/min granulation; this corresponded to a moisture content of 15.75% (on a dry basis). Large 1 cm diameter agglomerates were present in the 13 min sample. This was an indication that the batch was over-granulated. Further mixing resulted in the formation of a wet cake around the perimeter of the bowl. When this state occurs, the mixture is over-granulated and the batch is discarded.

Visual observations identified an optimum end-point at approximately 14 min for the PMA-25 granulations with a water addition rate of 140 g/min. This again corresponded to a moisture content of 15.75%.

Particle size distributions from PMA-10 granulations showed similar profiles to the PMA-25 with an optimum end-point at 10 min that corresponded to a moisture content of 14.7% (Daniher et al., in press).

3.2. Sound

The objective of this investigation was to compare the results of sound monitoring in two scales of granulation, the 10 l PMA-10 and the 25 l PMA-25. Using the PMA-10, it was discovered that the microphone located in the air filter outlet was more sensitive to changes occurring during granulation than microphones placed on the exterior of the bowl or on the motor housing (Daniher et al., in press). The air filter microphone was more sensitive because sound emissions from within the granulator were transmitted through an air opening rather than through the solid stainless steel granulator wall. This result was confirmed in the PMA-25 (Fig. 4).

In the PMA-25 sound monitoring, the mean frequency of the air filter microphone signal showed a varying profile during granulation (Fig. 5a). This suggests that different granulation mechanisms may be dominant during certain periods of the process. After a small initial period to start nucleation and the transition to nuclei growth, the increase in the mean frequency may indicate further granule growth in the ball growth phase (Aulton, 2002). The plateau may indicate a balance between granule growth and granule breakage. The end-point of the PMA-25 granulation at a water addition rate of 180 g/min was identified in preliminary tests to occur at 12 min. This corresponded to the point on the profile where the second increasing phase began and may indicate growth into oversized granules.

The mean frequency of the same microphone location from the PMA-10 granulations showed an increasing trend with the start of the water addition (Fig. 5b), but it did not show the same plateau that occurred between 8 and 11 min in the PMA-

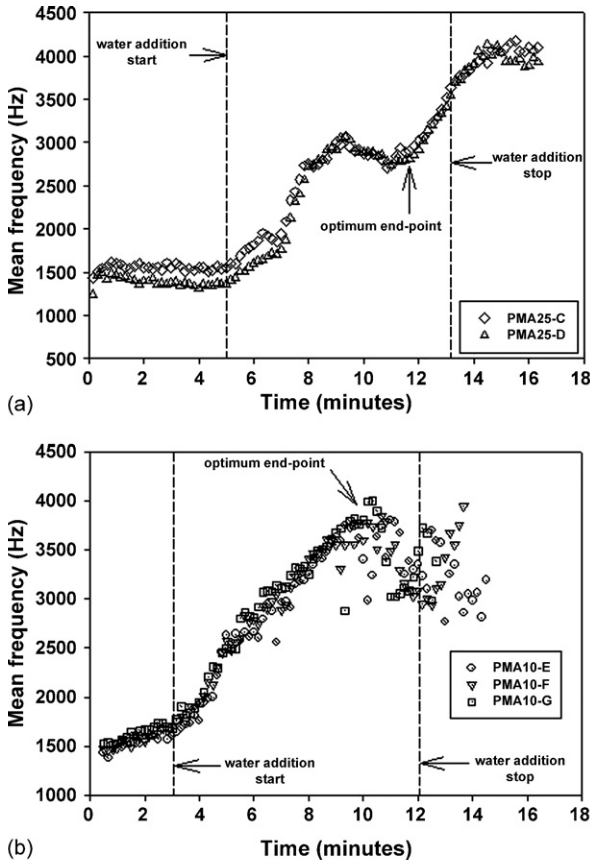

Fig. 5. Mean frequency of signals from microphone 4 (air filter outlet) for (a) PMA-25 and (b) PMA-10.

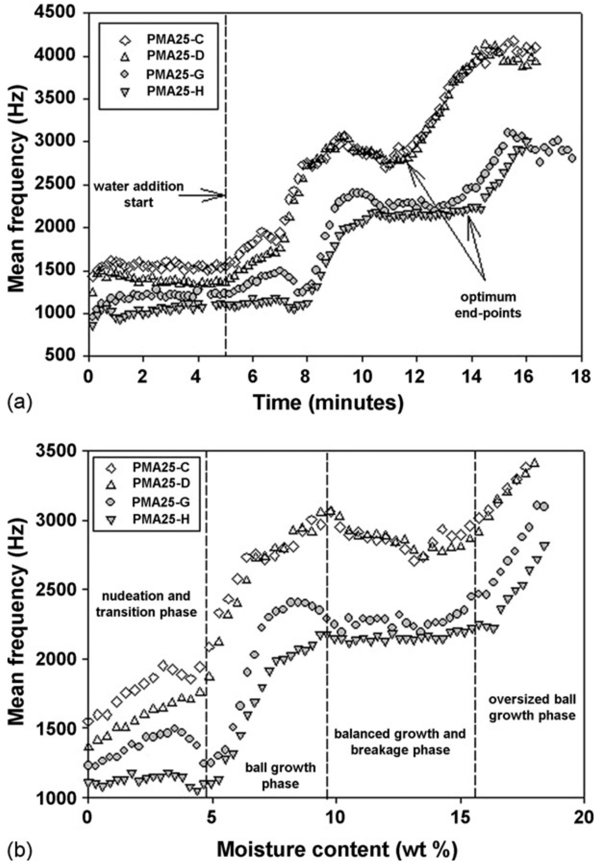

Fig. 6. Mean frequency of signals from microphone 4 (air filter outlet) for PMA-25 for water addition rates of 180 and 140 g/min plotted against (a) time and (b) moisture content.

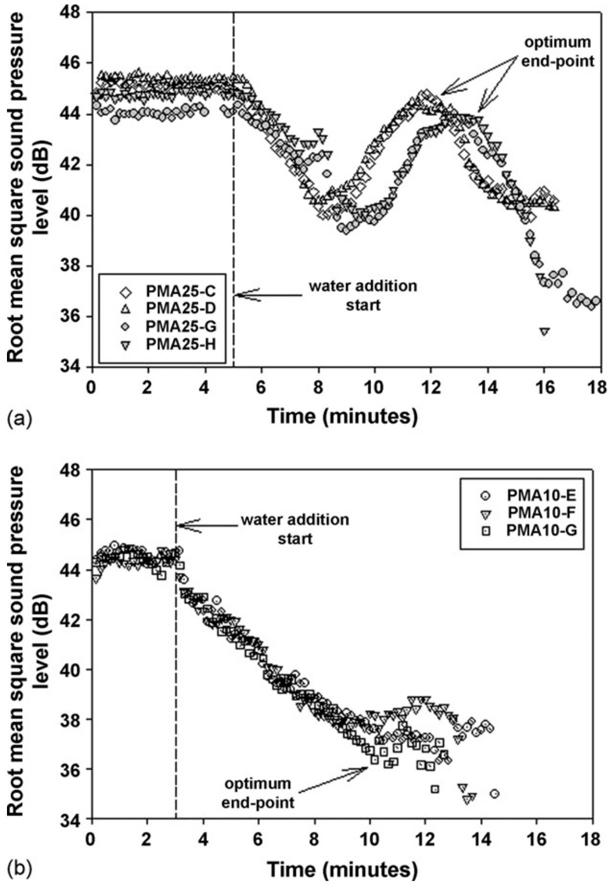

Fig. 7. Root mean square sound pressure level of the (a) 140–180 Hz frequency band from microphone 4 (air filter outlet) for the PMA-25 and (b) 112–140 Hz band for the PMA-10.

25. For the PMA-10, the optimum end-point corresponded to the maximum mean frequency. The difference in the mean frequency profiles could be due to the higher water addition rate and impeller tip speed in the PMA-25 that may influence the duration and dynamics of each phase of the granulation process.

Fig. 6a shows the effect of the water addition rate on the mean frequency profile for the PMA-25. The profile at a water addition rate of 140 g/min resulted in a similar profile to the 180 g/min water addition rate trials, but with a time delay. The second increasing phase, in both cases, corresponded to the previously determined end-points. Fig. 6b shows the mean frequency profile against moisture content. For both the water addition rate trials, the transitions between phases corresponded to the same moisture content with an end-point estimated at a moisture content of 15.75 wt.%. This suggests that this sound monitoring technique can identify four phases in the granulation with respect to moisture content: (1) nucleation and transition phase, (2) ball growth phase, (3) balanced growth and breakage phase and (4) oversized ball growth phase.

One-third octave band analysis is a standard acoustic technique for examining power in specific frequency ranges. The air filter microphone sound pressure level for the PMA-25 trials in the 140–180 Hz band showed a decreasing trend beginning at the start of water addition (Fig. 7a). The pressure level reached a minimum between 8 and 10 min then increased to a peak. Both the 180 and 140 g/min water rate trials had similar profiles with a time delay in the 140 g/min profile due to the lower moisture content at a given time. The peak in the profiles at 12 and 14 min or at 15.75 wt.% moisture content corresponded to the optimum granulation end-point.

For the PMA-10 granulations, the sound pressure level in the 112–140 Hz band showed the clearest trend during granulation (Fig. 7b). Although the pressure level began to decrease with water addition for both the PMA-10 and PMA-25, the PMA-10 profiles subsequently failed to show a peak in the sound pressure level. The optimum end-point instead corresponded to the time at which the root mean square sound pressure level became approximately constant. This again may be due to the much lower water addition rate and impeller tip speed that may have affected the granulation phases.

Different frequency bands were identified to be sensitive in the PMA-10 and PMA-25 granulators. This may be due to different sized motors and impellers. The motors would produce different dominant frequencies during operation. Also, since the impeller diameters were different, but were operated at the same rotational speed, the tip speeds of the impellers were not the same. A faster tip speed in the PMA-25 granulator may have increased the collision rate of particles, thus increasing the sensitive frequency band.

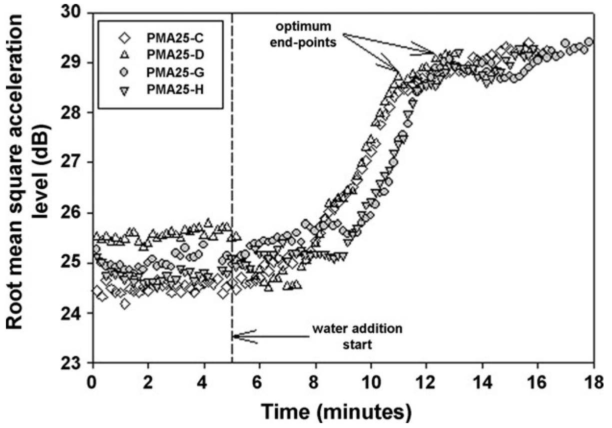

Fig. 8. Root mean square acceleration level of the vibration signal in the 140–180 Hz band for PMA-25 granulations.

The power spectral density was used to examine the one-third octave bands with high frequency resolution. For the PMA-10, it was found that within the 120–140 Hz band, the power at 127.5 Hz was significant (Daniher et al., in press). For the PMA-25, the 140–180 Hz band showed the clearest granulation profile. Power spectral density identified 150 Hz as the most significant component. The power spectra density profiles at 127.5 and 150 Hz were the same shape as the one-third octave band sound pressure level curves. Therefore, it is not necessary to identify individual frequencies within standard one-third octave bands.

3.3. Vibration

Vibration was measured during granulation with an accelerometer. For the PMA-25 granulations, the one-third octave-band analysis showed a trend in the 140–180 Hz band (Fig. 8). The root mean square acceleration level in this band increased after water addition and became constant near the optimum end-point of granulation. The time delay in the profiles seen in the 140 g/min compared to the 180 g/min water addition rate trials approximately corresponded to the moisture content differences.

For the PMA-10 granulations, the mean frequency of vibration varied during granulation and approximately indicated an end-point. The profiles, however, varied significantly between trials. Other signal analysis on the vibrations of the PMA-10 did not give profiles that could correspond to changes during the granulation process (Daniher et al., in press). The change in the physical properties of the granulation may have been too small to affect the vibrations of the PMA-10 granulator. However, for the PMA-25, the physical changes in the granulation mixture should have had a larger impact on the performance of the motor and on the vibration of the bowl and thus gave some indication of the process.

4. Conclusions

Acoustic and vibration measurements combined with advanced signal analysis successfully detected changes during wet high-shear granulation processes. Acoustic emissions from a microphone in the air filter outlet analyzed using mean frequency and one-third octave band techniques successfully monitored granulation in both the 10 l PMA-10 and the 25 l PMA-25 units and thus also allowed identification of the optimum end-point. The techniques could also detect a change in the rate of granulation caused by a slower water addition rate during some PMA-25 trials.

The vibration measurements of the PMA-25 granulator were found to be sensitive to the granulation process in the 140–180 Hz one-third octave band with the root mean square acceleration level clearly indicating a change from the powder mixture to the wet-granulated state. Vibrations of the PMA-10 granulator, however, could not consistently successfully monitor the granulation process.

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