

## Acoustic monitoring of a fluidized bed coating process

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Received 29 March 2006; received in revised form 11 September 2006; accepted 21 September 2006

Available online 29 September 2006

### Abstract

The aim of the study was to investigate the potential of acoustic monitoring of a production scale fluidized bed coating process. The correlation between sensor signals and the estimated amount of film applied and percentage release, respectively, were investigated in coating potassium chloride (KCl) crystals with ethylcellulose (EC). Vibrations were measured with two different types of accelerometers. Different positions for placing the accelerometers and two different product containers were included in the study. Top spray coating of KCl was chosen as a ‘worst case’ scenario from a coating point perspective. The acoustic monitoring has the potential of summarising the commonly used means to monitor the coating process. The best partial least squares (PLS) regressions, obtained by the high frequency accelerometer, showed for the release a correlation coefficient of 0.92 and a root mean square error of prediction (RMSEP) of 5.84% (31–82.8%), and for the estimated amount of film applied a correlation coefficient of 0.95 and RMSEP of 0.52% (0.6–6%). The results of the preliminary investigation are considered promising. There is however a need for further investigations on sampling procedures and product characterisation before a final conclusion on the applicability of acoustic monitoring can be made.

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**Keywords:** Process monitoring; Passive acoustic emission; Top spray coating; Ethylcellulose

### 1. Introduction

Cost-effectiveness of pharmaceutical manufacturing has become an important factor for the success of a drug product. While the costs in most other industries have been significantly reduced in recent years, there are strong indications that costs in pharmaceutical manufacturing have increased for a variety of reasons. FDA’s PAT initiative and the new ICH guidelines Q8 and Q9 are associated with the design of robust manufacturing processes being built on a mechanistic understanding of the processes and aiming at real-time release. Such efforts are likely to contribute to an improved cost-effectiveness because of reduced waste and need for re-working. A range of process analytical techniques have been proposed for process monitoring. Spec-

troscopic methods such as NIR and Raman spectroscopy have in particular been implemented. A disadvantage of new monitoring techniques is that the resulting models for the correlation between sensor signals and quality parameters generally are case specific and must be developed for each application (Boyd and Varley, 2001).

Acoustic emission (AE) monitoring techniques in the form of either active or passive acoustic emission (PAE) are used intensively by material scientists (Tönshoff et al., 2000), in the oil and gas industry (Folkestad and Mylvaganam, 1990) and in monitoring chemical reactions (Betteridge et al., 1981; Belchamber et al., 1986; Wentzell and Wade, 1989). The fact that temporal and spatial changes are sources of AE opens up a plethora of possibilities for in-line monitoring of processes by the use of PAE signals. Recent publications on the application of AE show that they lead to reliable quantitative results and do not function just as qualitative indicators. In powder processing AE sensing techniques have been applied to the monitoring

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of powder compaction processes (Hakanen and Laine, 1993, 1995; Salonen et al., 1997), for monitoring changes in physical properties of powder material during granulation (Whitaker et al., 2000). Correlation between the degree of powder comminution and acoustic signals during pneumatic transportation has been reported by Huang et al. (2003). Tsujimoto et al. (2000) applied an AE sensor to monitor the fluidisation conditions in a fluidised bed granulator and concluded that the AE measuring technique presented was highly feasible as a practical method for monitoring particle fluidisation in a gas–solid fluidised bed.

The sounds generated by the friction, collisions and fluid turbulence in powder processing include audible sounds detectable via air by a microphone as well as high frequency sounds in the non-audible range – elastic waves – detectable by AE sensors that incorporate piezoelectric transducers. Particle behaviour can be monitored and characterised by assessing the sounds, once the correlation between particular sounds and particle motion is established (Tsujimoto et al., 2000). Tsujimoto et al. (2000) describes three basic sources of PAE's in fluidised beds: (i) particle–particle or particle–chamber collision (impact sounds), (ii) particle–particle or particle–chamber friction (friction sound) and (iii) air turbulence in particle bed (aerodynamic sound).

The advantage of acoustic monitoring techniques compared to other techniques is the non-invasive and non-destructive character. It is inexpensive, safe intrinsically and no window is required, which should give an advantage over NIR, which has been used for in-process and at-line monitoring of the film coating process (Kirsch and Drennen, 1996; Andersson et al., 1999, 2000). However, to the best of our knowledge no studies have been published on the use of acoustics to control a pharmaceutically relevant fluid bed-based coating process.

The commonly used means to monitor and control pharmaceutical coating processes are records of liquid addition rate and atomizer air pressure as an indirect control of the air to liquid mass ratio, inlet air temperature and humidity and outlet air temperature and humidity. These variables are monitored by sensors placed outside the product container and may possibly form the basis for an automated control loop (Larsen et al., 2003). However, these instrumentations cannot directly monitor spray drying and agglomeration, which are crucial for the quality of microencapsulated products.

Of the different coating techniques available the top spray coating process is often considered as being the most difficult to control when the objective is the achievement of a modi-

fied release control (Jones, 1994). Several authors (Mehta and Jones, 1985; Mehta et al., 1986; Holm et al., 1991; Bertelsen et al., 1994) have reported that top spray results in lower degree of release retardation than bottom spraying. Mehta and Jones (1985) and Bertelsen et al. (1994) ascribed this difference primarily to a difference in porosity of the membrane. In the top spray-based process the product flow in the apparatus is somewhat arbitrary because of the bubbling fluidization what means that the coating zone is not fully controlled and this is causing relatively high variability. Therefore, the need of a method for monitoring the quality of the applied coat is most needed for the top spray-based coating process.

The present study was conducted to assess the potential of PAE for additional control of a fluidized bed coating process to achieve a controlled release product. Potassium chloride crystals were coated in a top spray production scale coater with EC using an organic-based coating solution. Along with the establishment of an acoustic-based in-line process it was attempted to correlate the processed signals to the essential product attributes, the amount of film applied and its uniformity and barrier properties as mirrored by release of potassium chloride. The estimated amount of film applied and the 6 h value for the release of potassium chloride were employed in the analysis.

## 2. Materials and methods

### 2.1. Materials

KCl crystals (Klinge Chemicals Ltd., UK) with a mean particle diameter less than 1000  $\mu\text{m}$  were used for the microencapsulation process. The organic-based coating solution was composed of EC (Dow Chemical, USA), isopropyl alcohol (Shell Chemicals, Belgium), acetyltributyl citrate (Croda, UK), hard paraffin (Schümann Sasol, Germany) and colloidal anhydrous silica (Degussa, Germany).

### 2.2. Methods

#### 2.2.1. Fluid bed coater

The coating of potassium chloride crystals with EC was performed in a production scale fluidised bed coater, Glatt WSG 200 (Glatt GmbH, Germany), equipped with top spray. Batch size 300 kg. Two different product containers were used, length of the product container wall was 65 cm and the height of the load 34 cm.

Table 1  
Overview of different product containers, sensor types and their position

Sensor	Type	Position	Batches A1 and A2 (cm)	Batches B1 and B2
1	High frequency <sup>a</sup>	Product container	44	43
2	Standard <sup>b</sup>	Product container	49	12
3	Standard	Product container	52.5	53
4	High frequency	Expansion chamber	15.5	15.5

Sensors 1–3, positions in cm from the bottom of product container. Sensor 4, position in cm from the bottom of the expansion chamber.

<sup>a</sup> Endeveco 7240C, sensitivity of 0.2647 pC/ms<sup>-2</sup> and upper frequency at 50 kHz.

<sup>b</sup> Brüel and Kjær 4393, sensitivity of 0.2922 pC/ms<sup>-2</sup> and upper frequency at 16.5 kHz.

### 2.2.2. Set-up of trials

Four batches were produced by use of two different product containers, A and B (Table 1). Each new batch was loaded into a product container outside the fluidised bed. Thereafter it replaced the container from the previous batch process. Duration of one batch process was 10 h. Samples for in vitro dissolution tests were drawn from the fluid bed coater each hour, resulting in 10 samples per batch, each consisting of approximately 500 g coated potassium chloride with different amounts of coating applied.

### 2.2.3. Accelerometers

Two different types of accelerometers were used to measure the vibrations from the process equipment in this study: Endevco 7240C which is a high frequency accelerometer with sensitivity of  $0.2647 \text{ pC/ms}^{-2}$  and with an upper frequency at 50 kHz, and Brüel and Kjær 4393 which is a standard accelerometer with sensitivity of  $0.2922 \text{ pC/ms}^{-2}$  and with an upper frequency at 16.5 kHz. Table 1 shows the accelerometer types and their position on the equipment. The accelerometers were attached to the equipment by gluing studs that were glued onto the coater. The accelerometers were screwed on the gluing studs. Sensors 1–3 were removed from the product container at the end of each coating process to allow the change of product container. For sensor 2, two different positions were investigated. For sensor 4, which was the only sensor placed on the expansion chamber and hence not demounted between batches, the distance is measured from the bottom of the expansion chamber.

### 2.2.4. Dissolution

Six samples each of 750 mg coated KCl crystals were subjected to dissolution testing in an USP/Ph.Eur. basket apparatus (AT-7, Sotax, Switzerland) using 100 rpm, 900 ml of deionised water (Milli-Q water) at  $37^\circ\text{C}$ . The removed amount of dissolution medium, 10 ml, was corrected for in the calculations. Thirteen hour dissolution profile was measured at 0.5, 1, 3, 6, 8, 10, 12 and 13 h. The amount of dissolved potassium chloride was analysed by Flame Atomic Absorption Spectrophotometer (FAAS 3300, Perkin-Elmer, USA) using a potassium selective electrode.

### 2.2.5. Theoretical amount of film applied

The amount of film applied was estimated by the loss of weight of the coating solution tank and the concentration of the coating solution.

### 2.2.6. Data analysis

The signals from the accelerometers were preamplified by a Brüel and Kjaer 2647 charge to Deltatron converter, thereafter conditioned using a Brüel and Kjaer NEXUS Conditioning Amplifier before being digitised by an ADC (National Instruments DAQ Pad 6070E). Data from the accelerometers was converted from analogue to digital signal. The acceleration (arbitrary scale) was then converted from the time domain into the frequency domain by means of the fast Fourier transform (FFT) algorithm giving power spectrum density (PSD) spectra in the range from 50 Hz to 25 kHz. Applying a Welch window (512

points) PSD was calculated using 20 segments with 50% overlap. Each channel was digitised into 12 bit with a successive approximation ADC at 50 ksamples/s. Because the PCA/PLS methods are used to analyse the PSD one does not require the same sensitivity throughout the spectrum. Hence, it is safe to use the full PSD spectrum, also outside the range specified by the manufacturer. This preliminary data treatment was performed with Data Interpretation and Model Management System (DIMMS) from The Danish Technological Institute. Multivariate data analysis was performed on the frequency spectra and the reference analysis using the software The Unscrambler Version 8.0 from Camo.

### 2.2.7. Multivariate data analysis

Principal component analysis (PCA) was developed based on the PAE data for each sensor. Variables 6–512 (300 Hz–25 kHz) were used, whereas variables 1–5 (50–250 Hz) incorporated background noise generated by mechanical vibrations such as blowers and compressors used in fluidised beds and from electricity. These variables were excluded from the models. For the PCA the PSD spectra was pre-processed by means of moving average in the time direction, average of 11 spectra (corresponding to 5 min), to reduce the effect of noise inside the data and to ease the interpretation of models.

The PLS regressions, using multivariate PLS calibration, were established to describe the relationship between the PAE data and the physical reference data on applied coat and release. Pre-processing of data was performed according to the same conditions as used for conducting the PCA. For the *X*-space, frequency spectra from an interval of 10 min close to the reference sample, and for the *Y*-space, the percentage dissolved at the 6th hour, from the 13 h dissolution profile or the estimated amount of EC film applied were used.

A good model fit does not necessarily mean that the model will be optimal for the future predictions. To assure this, the model needs to be validated with new data from new batch processes and the model which gives the highest correlation coefficient and lowest RMSEP value is considered to have the best prediction capability. The optimal validation is an independent test set, but this is very difficult with limited number of data. The most used validation in that situation is segmented cross-validation. The data are split into a number of segments. Each segment is validated as an independent test set based on a calibration developed on the rest of the segments. The calibration is validated based on all the segments acting as independent test set. The general cross-validation used in the data analysis was 20 segments having all measurements referring to one sample in the same segment. Furthermore, all four batches were represented in each segment. The best calibrations were tested for stability in general and for batch-to-batch stability particularly with a cross-validation with only four segments, one for each batch.

## 3. Results

### 3.1. Physical reference data

Table 2 summarises the reference data, i.e. the average percentage of potassium chloride released after 6 h, and the

Table 2  
Physical reference data

Sample	Batch A1		Batch A2		Batch B1		Batch B2	
	Release at 6 h (%)	Film amount (%)	Release at 6 h (%)	Film amount (%)	Release at 6 h (%)	Film amount (%)	Release at 6 h (%)	Film amount (%)
1	78.6	0.6	79.5	0.6	80.5	0.6	82.8	0.6
2	67.8	1.3	76.3	1.3	72.6	1.3	66.7	1.1
3	58.6	1.9	72.4	1.9	66.5	1.9	65.7	1.8
4	62.7	2.6	62.9	2.5	60.3	2.5	66.1	2.4
5	58.4	3.2	54.8	3.1	49.8	3.1	52.6	3.1
6	44.0	3.8	53.6	3.6	42.6	3.8	52.2	3.7
7	46.0	4.4	49.6	4.3	38.2	4.4	50.0	4.3
8	39.2	5.0	41.4	5.0	54.5	5.0	38.7	5.0
9	34.6	5.6	37.6	5.5	35.8	5.6	36.0	5.6
10	31.0	6.0	37.6	6.0	37.0	6.0	33.4	6.0

Percentage release of potassium chloride at 6 h and the estimated amount of film applied in terms of (w/w%) of potassium chloride.

estimated amount of film applied, here expressed as the percentage of the amount of the potassium chloride.

### 3.2. Acoustic data

The PLS regression method was chosen as a more appropriate technique for evaluation of the acquired raw PAE data than the principal component regression (PCR) method, to investigate the ability of variables to act as predictors of the responses given in Table 2. PLS focuses on extracting the part of information from the  $X$ -matrix that is relevant to  $Y$ , maximising covariance between the  $X$  and  $Y$ , whereas in case of PCR nothing guarantees that the extracted information from the  $X$ -matrix is relevant to  $Y$ . Tables and graphical plots with values for PLS models are presented in Tables 3 and 4 and in Figs. 1 and 2. Characteristics of acoustic calibration models are presented in Table 5.

Fig. 3 shows score plots for principal component 1 (PC1) and PC2 based on smoothed data obtained by sensors 1 and 4. Scores line plots of PC1 derived from sensors 1 and 4 for the four batches from the start to the end of the process are shown in Fig. 4.

Raw PAE data from sensor 1 throughout the four microencapsulation processes are shown in Fig. 5, one plot for each batch.

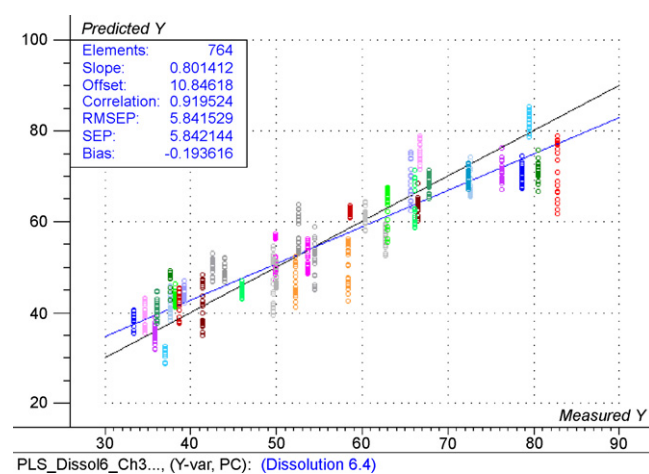


Fig. 1. PLS model, for release of KCl, developed for sensor 4 (ideal and best fitted line).

## 4. Discussion

### 4.1. Models for release

The data in Table 2 show that the release of potassium chloride did not follow the expected order when compared to the

Table 3  
PLS models and cross-validated PLS models for release

Model	Sensor	Correlation coefficient	RMSEP	PC
PLS-model 1, 20 segments	1	0.90	6.70	6
	2	0.82	8.67	5
	3	0.81	9.03	7
	4	0.90	6.34	4
PLS-model 2, 20 segments	1	0.91	6.40	6
	2	0.82	8.66	5
	3	0.83	8.63	7
	4	0.92	5.84	4
PLS-model 1, cross-validated, 4 segments	1	0.20	16.45	1
	2	0.69	11.09	9
	3	0.71	10.75	5
	4	0.89	6.83	4

Table 4  
PLS models and cross-validated PLS models for the amount of film applied

Model	Sensor	Correlation coefficient	RMSEP	PC
PLS-model 1, 20 segments	1	0.93	0.64	6
	2	0.87	0.88	5
	3	0.87	0.87	9
	4	0.92	0.68	4
PLS-model 2, 20 segments	3	0.88	0.84	6
	4	0.95	0.52	4
PLS-model 1, cross-validated 4 segments	1	0.27	1.86	1
	2	0.70	1.25	9
	3	0.77	1.13	4
	4	0.90	0.77	3

Table 5  
Characteristics of acoustic calibration models

Reference data	Range (%)	RMSEP	
		Percentage	Percentage of range
Release of potassium chloride	31.0–82.8	5.84	11.3
Estimated amount of film applied	0.6–6.0	0.52	9.6

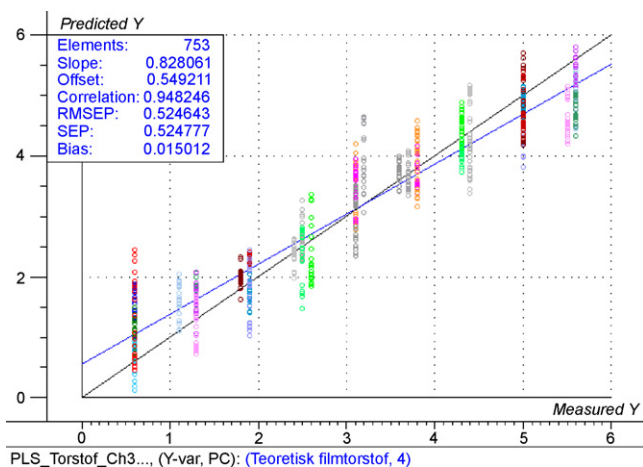


Fig. 2. PLS model, for the estimated amounts of film applied, developed for sensor 4 (ideal and best fitted line).

applied amount of film. The disorganised fluidization pattern in a top spray coater combined with the difficulty in drawing samples being representative for the entire batch is the most likely reason. Indeed the top spray coater was chosen for the present investigation as it was realised that this situation might occur and hence be a challenge to the capability of the PAE-based monitoring.

Table 3 presents the PLS models for prediction of the 6 h release and the cross-validated PLS model for the release. It was possible to establish a PLS regression model for the potassium chloride release having a correlation coefficient of approximately 0.9 and a RMSEP value of 6% (31–82.8%) from the data generated by sensors 1 and 4. The calibration models for sensor 4 provide the best correlations and the lowest RMSEP, 0.92 and 5.84% (31–82.8%) respectively. A plot of the predicted dissolution rate by PLS model 2 for sensor 4 against the actual (measured) values is presented in Fig. 1.

Also the data generated by sensors 2 and 3 gave RMSEP of reasonable value, around 9% (31–82.8%), the correlation

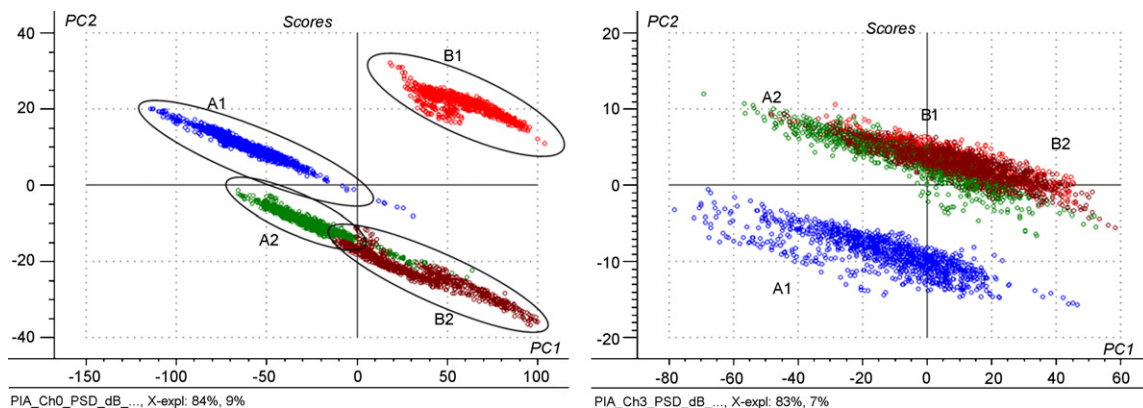


Fig. 3. Scores plot for PC1 and PC2, based on smoothed AE data from sensor 1 (left hand) and sensor 4 (right hand).

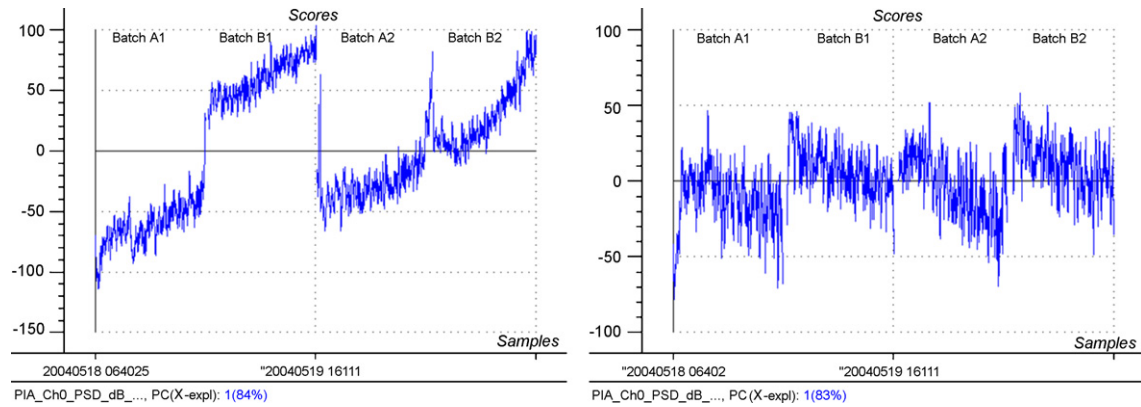


Fig. 4. Scores line plot for PC1 for four batch processes from the start to the end of the process, data from sensor 1 (left hand) and sensor 4 (right hand).

coefficient obtained was not of satisfactory level, only around 0.8, as may be seen from Table 3, indicating that sensors 2 and 3 having an upper frequency of 16.5 kHz did not suffice for monitoring the coating process, whereas sensors with upper frequency at 50 kHz were applicable.

Table 3 includes the cross-validated PLS models that were tested for stability in general and for batch to batch stability using only four segments, one for each batch. The four segment cross-validation of data generated by sensor 1 showed poor correlation indicating that the model is unstable because of batch to batch variation. Probably because the accelerometers were mounted on the product container and demounted between the batches.

Although the PCA indicated that signals from sensor 4 contain more noise, it resulted in the most stable cross-validated regression. PLS model 1 tested for batch to batch stability had a

correlation coefficient of 0.89 and a cross-validated RMSEP of 6.83% (31–82.8%) (Table 3).

#### 4.2. Models for the amount of film applied

Table 4 gives the results for the PLS calibration models and for cross-validated PLS models. Good linear correlations with acceptable RMSEP values were obtained. It was possible to develop PLS regression models with correlation coefficients of approximately 0.9 and RMSEP values of 0.6% (0.6–6%) based on data from sensors 1 and 4. As seen in Table 4, the data generated by sensor 4 again gave the best PLS regression model with an correlation coefficient of 0.95 and RMSEP of 0.52% (0.6–6%) for model 2. Fig. 2 shows the correlation between measured and predicted data, based on PLS model 2 for sen-

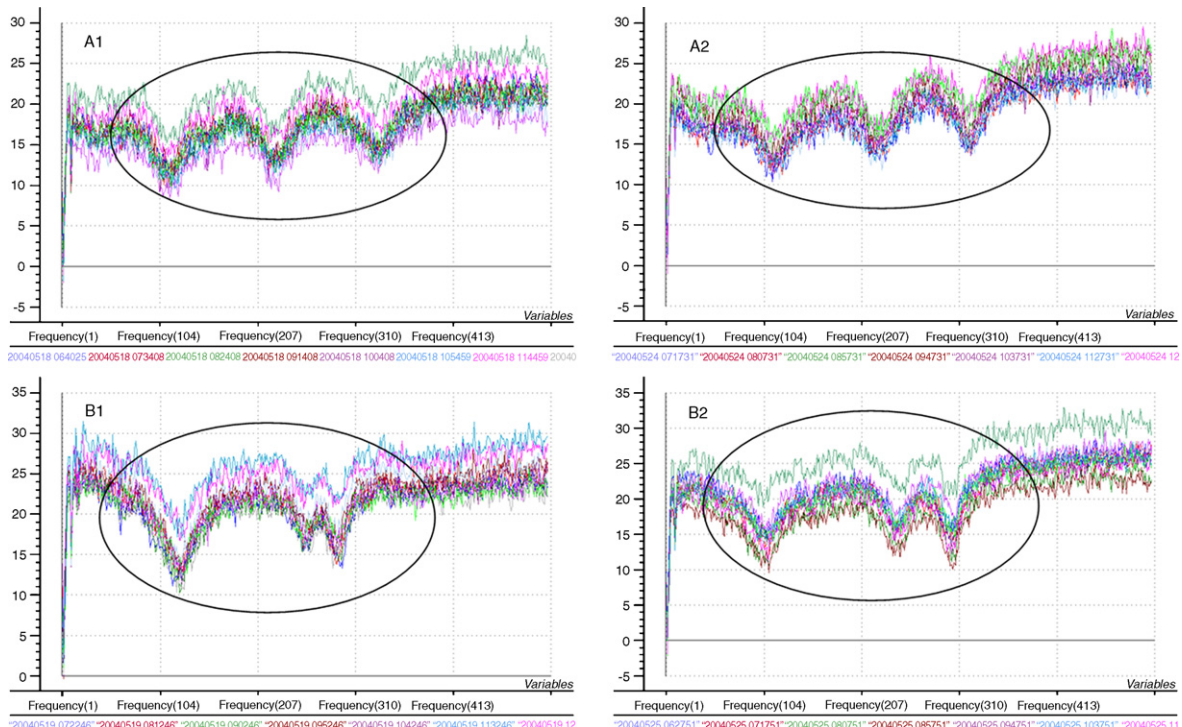


Fig. 5. Raw passive acoustic emission (PAE) data obtained by sensor 1 for the four batches.

sensor 4. The correlation coefficient was 0.95 and RMSEP 0.52% (0.6–6%).

The models were tested for batch to batch stability using the same cross-validation method as for PLS regressions on dissolution. The results showed the same tendency. Data from sensor 4 gave the most stable model with lowest values for batch to batch variation, 0.9, and highest prediction power, 0.77% (0.6–6%). Data from sensor 1 showed a high inter-batch variation.

#### 4.3. Positioning of sensors

Cross-validated PLS models resulted in low predictive power for sensor 1, even though the calibrated models gave satisfactorily high correlation coefficient and acceptable RMSEP for sensors 1 and 4. A closer look at the PCA data revealed the most likely causes for that.

PC1 was found to explain most of the variance inside the data for all sensors; data are not reported. Fig. 3 presents score plots of PC1 and PC2 for sensors 1 and 4 derived from PCA based on moving average in the time direction. The development in the scores value for PC1 and PC2 from the start to the end of the batch process is clearly seen. The graph shows clustering of the score values according to the actual batch for sensor 1. Scores plot for sensor 4 does not reveal distinct grouping of different batches.

Fig. 4 shows a development in the scores value for PC1 from the start to the end of the batch processes for all four batches, for sensors 1 and 4. The shift in data from batch to batch can be seen, what is more pronounced for sensor 1 than for sensor 4. The offset of the scores value from batch to batch were minor for sensor 4, probably because it was kept in the same position for all four batches in contrast to sensor 1 what was reattached between the batch processes.

Sensor 4 generated weaker signals and the impact of noise was therefore higher. This was likely due to its placement on the expansion chamber where fewer crystals hit the chamber wall and it is separated from the product container by a silicone membrane. Still trends in development of AE data could be recognized.

Halstensen and Esbensen (2005) referred to the problem of positioning the sensors to be able to gain most of the information out of the process. During this preliminary study it was seen that the positioning of sensors was not as important as considered previously but the run repeatability was affected by variability of accelerometers attachment. In production scenario a welded stud would be preferred.

Inter-batch variation is mainly explained by PC2, dealing with around 7–9% of variation inside the data. This variance may be due to the two different product containers used. Plots of PAE (Fig. 5) gave comparable features for each product container, for batches A1 and A2 and for batches B1 and B2 that corresponds to the different product containers, c.f. Table 1. This indicates that in next step, when more data from supplementary batch processes will be available, at least two models has to be built up, one for each product container. This is necessary for avoiding the batch to batch variation caused by using different product containers.

## 5. Conclusions

Despite the fact that the best PLS models achieved in the study do not fully suffice for a reliable prediction of the two reference product characteristics investigated, there are reasons to consider monitoring of passive acoustic emission as a promising technique for the control of the coating process. The experimental data sets given in Table 2 on percentage release at 6 h and the amount of film applied indicate that the sampling procedure was not optimal with regard to obtaining samples representative of the entire batch. Furthermore, the amount of film applied was estimated from the amount provided by the atomizer, not the amount of film really deposited on the solid surfaces. Moreover, the production scale top spray coater was chosen for the investigation because it represents a kind of ‘worst case’ situation due to the less controlled coating zone. Thus, there is room for improvement of the models by implementing better techniques for product characterisation, by inclusion of the entire release profile and by inclusion of a higher number of batch processes than done in the present preliminary study. In future work, different methods for pre-processing of PAE data should also be investigated.

The investigation gave information on sensor types and their positioning on the coater. The best regressions were derived from data generated by sensors 1 and 4, both of which were high frequency and sensitivity accelerometers, with an upper frequency of 50 kHz. Sensor 1, placed on the product container, revealed that the shift in data from batch to batch was high due to the replacement of sensor 1 between the batch processes. This results in unstable predictive models for the reference characteristics. The inter-batch variation for sensor 1 was caused by different product containers used. The data obtained by sensor 4 were not affected by the demounting between the batch processes and by the change of product container. That lead to the most stable regressions although the sensor generated weaker signals as it was mounted above the product and separated from the product container by a silicone membrane.

Further development of using acoustics for process monitoring requires development in the sensor technology in the meaning of wireless sensors and better signal interpretation.

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