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Research Article

Investigation of the Variability of NIR In-line Monitoring of Roller Compaction Process by Using Fast Fourier Transform (FFT) Analysis

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Abstract. The purpose of this research was to investigate the variability of the roller compaction process while monitoring in-line with near-infrared (NIR) spectroscopy. In this paper, a pragmatic method in determining this variability of in-line NIR monitoring roller compaction process was developed and the variability limits were established. Fast Fourier Transform (FFT) analysis was used to study the source of the systematic fluctuations of the NIR spectra. An off-line variability analysis method was developed as well to simulate the in-line monitoring process in order to determine the variability limits of the roller compaction process. For this study, a binary formulation was prepared composed of acetaminophen and microcrystalline cellulose. Different roller compaction parameters such as roll speed and feeding rates were investigated to understand the variability of the process. The best-fit line slope of NIR spectra exhibited frequency dependence only on the roll speed regardless of the feeding rates. The eccentricity of the rolling motion of rollers was identified as the major source of variability and correlated with the fluctuations of the slopes of NIR spectra. The off-line static and dynamic analyses of the compacts defined two different variability of the roller compaction; the variability limits were established. These findings were proved critical in the optimization of the experimental setup of the roller compaction process by minimizing the variability of NIR in-line monitoring.

KEY WORDS: FFT; NIR; roller compaction; variability.

INTRODUCTION

Roller compaction (RC) process is commonly used in pharmaceutical industry as an alternative to wet granulation to avoid heat and moisture during the drying step of the materials. RC can improve the flow of materials and prevent segregation of the final blends (1–3). The roller compaction process involves the use of two counter-rotating rolls to compress the powders that are flowing between them. The resulting surface can be smooth, or rugged depending on different purposes. The compacts produced by this process are then milled into granules. The roller compaction process has its own advantages for some pharmaceutical products. It involves less unit operations, thus it imposes less risk to disturb the integrity of the materials subject to the processing. In addition, roller compaction has the potential for continuous processing of pharmaceutical materials. Due to those advantages, roller compaction has been increasingly utilized to improve the flow and compression properties of materials in the pharmaceutical industry. Several authors have attempted to understand the roller compaction process by mathematically modeling the densification process (4–6). The fundamental mechanism of roller compaction is still poorly understood due to the complexity of the materials properties and the process variables. The raw materials properties include flow characteristics, compressibility, and elasticity. In addition, the process variables include roll surface, roll dimension, roll gap, roll pressure, roll speed and feeding speed, etc. Impacted by all these factors, roller compaction could be subjected to large variability. As a result, the current process development of roller compaction still largely depends on experience and design of experiment.

In the last decade, near-infrared (NIR) spectroscopy has been increasingly used as an in-line analytical technique for process control purposes in the pharmaceutical industry (7–9). The recent Process Analytical Technology (PAT) initiative of the US Food and Drug Administration (FDA) also encourages the application of NIR sensors or similar analytical techniques to reduce production cycle times by implementing on-, in-, and/or at-line measurements. Through timely measurements of critical quality and performance attributes of raw and in-process materials, the quality of the final product could be controlled within the specifications (10). The relatively long wavelength of NIR, ranging from 780 to 2500 nm, makes it possible to nondestructively and simultaneously analyze multiple constituents present in relevant pharmaceutical matrices. This eliminates the waiting period for laboratory results at the end of each unit operation. It also provides the continuous real-time quality

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assurance as suggested by the FDA in the PAT initiative. Gupta *et al.* reported the use of NIR spectroscopy as a non-destructive technique to in-line monitoring roller compaction process (11,12). The study has shown that with an appropriate design of experiments and calibration model, the tensile strength and content uniformity of the compacts could precisely predict in-line by a Partial Least Square (PLS) model. The PLS model was constructed based on NIR spectra collected from the training set of the simulated ribbons.

Although NIR spectroscopy has proved to be successful in monitoring the process of roller compaction, the variability of real-time collected NIR spectra was still significant. This could seriously affect the precision and robustness of the prediction model built based on the NIR spectra. The inconsistency of NIR spectra during in-line monitoring can lead to different variability extents, especially in the case of reflectance mode NIR spectroscopy. The reasons for variability discarding the changes in material include the dusty, hostile environment of the roller compaction process, the sensitivity of NIR signal to the light travel pathway, the light stray variation, etc. It is apparent that an understanding of the fundamental mechanisms dominating the variability of the process and determining the variability limits will be crucially important for the development of a robust in-line monitoring technique.

The present investigation presents a new method based on Fast Fourier Transform (FFT) to determine the source of variability of NIR spectra during in-line monitoring of the roller compaction process. The variability limits were established and the underlying causes of the variability were investigated such that a better understanding of the process could be achieved. Based on the findings, new experimental setup was implemented and resulted in significant reduction of variability.

MATERIALS AND METHODS

Materials

Acetaminophen (Ruger Chemical Co. Inc., Irvington, NJ, USA) and microcrystalline cellulose (Avicel PH200, FMC International, Wallingstown, MD, USA), were used to prepare a binary formulation for this study.

Experimental Methods

Raw Materials Preparation

For in-line NIR monitoring of the roller compaction process, binary powder blends containing acetaminophen and microcrystalline cellulose (10:90% *w*/*w*) were mixed at 15 RPM for 20 min using a 1-ft^3 TOTE customer made bin blender (Burleson, TX, USA). For the NIR measurement of the variability limits of roller compaction process, pure microcrystalline cellulose was used such that the chemical contents would be consistent. This ensures that the variability measured would only represent variability of the roller compaction process itself. The powder was sieved through number 30-sieve prior to use (ASTM standard test sieve, W. S. Tyler, Mentor, OH, USA). The sieved powder was equilibrated overnight under different relative humidity (RH) conditions (15–75%). All experiments were performed under controlled environmental conditions of temperature (20–26°C) and RH (20±2%).

Roller Compaction

Compacts were prepared from the equilibrated powder using a Chilsonator IR220 (The Fitzpatrick Co., Elmhurst, IL) fitted with 20 cm diameter and 2 cm thick smooth rolls under 6,560±20 lb/in roll force at different RH. The feeding rate of the powder was kept constant by fixing the horizontal feed screw (HFS) speed and vertical feed screw (VFS) speed at 200 or 240 rpm and 30 or 36 rpm respectively. Compacts were prepared at roll speed of 4–10 rpm. Each roll speed compaction was carried out for four minutes and a single strip of compact ribbon, at least 65 cm in length (about the circumference of the roll), was collected at the end of the third minute and stored at controlled temperature and humidity conditions for further analysis.

Near-Infrared Spectroscopy

A Near-infrared Spectrometer (Control Development, Inc., South Bend, IN) was fitted with a 256 diode array InGaAs detector covering wavelength range from 1100 to 2200 nm with resolution of 4.4 nm. A 35 KW tungsten–halogen lamp was used as the light source. Spectra were collected using Spec32® software, supplied with the instrument, at an integration time of 20 ms. Individual spectra were collected at 1 s interval without averaging for real-time monitoring of the roller compaction, while 16 scans of spectra were averaged for off-line measurements. Spectra were collected by focusing the detector lens on the center-point of the face of the ribbon.

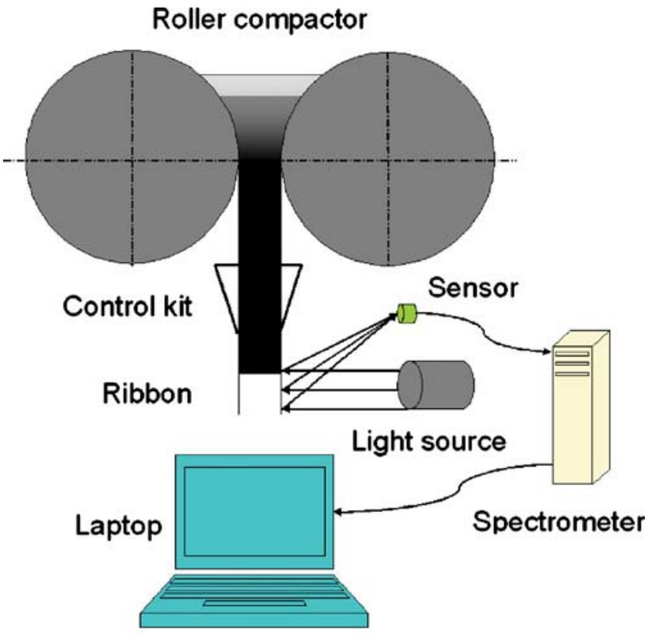

Fig. 1. Schematic of NIR in-line setup for monitoring roller compaction process

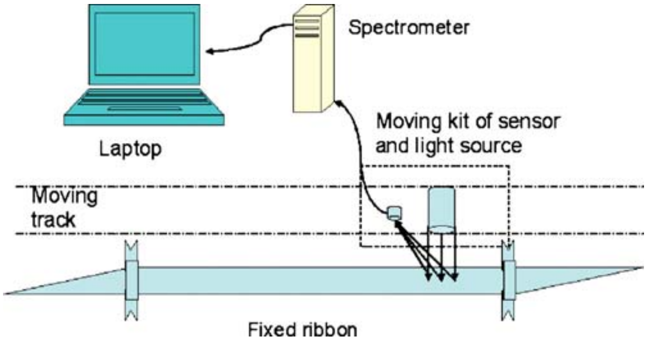

Fig. 2. Schematic of NIR off-line setup for measuring the compact variability

In-line NIR Monitoring Setup

The light source and probe were positioned right below the exit of the ribbon and perpendicular to the face of the ribbon such that the sensor could receive the reflected beams without any stray effects. The light source and probe were also well fitted with an acrylic cover to prevent any powder from depositing on the light source or probe. The signal received by the probe was transferred to the spectrometer by an optical fiber for analysis and then outputted on a laptop using Spec32® software. The flowing motion of the compact ribbons was well controlled using a funnel shaped aluminum restriction kit with adjustable gap and width the detector always focused on the middle point of the face of the ribbons. Figure 1 shows the schematic of the in-line setup.

Off-line Simulated NIR Monitoring Variability Measurement

The long strips of the compacted ribbon were collected from the roller compaction process for off-line variability analysis. The purpose of a motor-driven moving rack was made for this simulated NIR monitoring variability measurement. The dynamic NIR spectra can be collected by moving the sensor at a constant velocity over the fixed ribbon to simulate the situation during NIR in-line monitoring roller compaction process. The static NIR spectra were collected by positioning the sensor over equally divided small ribbon segments to get the minimum variability limit. Figure 2 shows the schematic setup of this off-line variability measurement.

Data Analysis Methods

Best-fit line slope. A straight line was fitted through every individual NIR spectrum collected from the sample. *The best-fit line slope* was obtained by minimizing the sum of square error between the data points and the fitted line. A C++ program was developed for real-time transformation of spectra data so that the *best-fit line slope* can be obtained.

Fast Fourier Transform (FFT) analysis. The best-fit line slope was used as a parameter to monitor the roller compaction process. Previous reports have explained that the slope is related to the physical properties of the compact, such as relative density, tensile strength (11,12). The time dependence of this slope was analyzed by FFT method to detect any dominant frequency during the roller compaction process. The FFT analysis was performed by implementing an algorithm developed under MATLAB software.

RESULTS AND DISCUSSION

NIR In-line Monitoring

The roller compaction process was monitored by using best-fit line slopes derived from the NIR in-line spectra. Figure 3 shows the NIR in-line trace of the ribbons obtained from the roller compaction containing 10% (*w*/*w*) acetaminophen and 90% (*w*/*w*) microcrystalline cellulose. The roll speed is controlled at 6 rpm, with VFS speed of 30 rpm and HFS speed of 200 rpm at the temperature of 25°C and RH of 20%.

The average slope of 0~20 min was about 0.286 Au/μm with a coefficient of variance of 5.34, while for 1~20 min the coefficient of variance was only 4.86. The initial high variability was due to the equilibrium phase at the beginning of the roller compaction process. By scrutinizing the data, it is not difficult to identify the periodicity nature of the oscillating signals. By magnifying the signal between 3 and 5 min (Fig. 3b), the periodicity could be identified. The periodicity of the NIR signals suggested that the in-line variability of

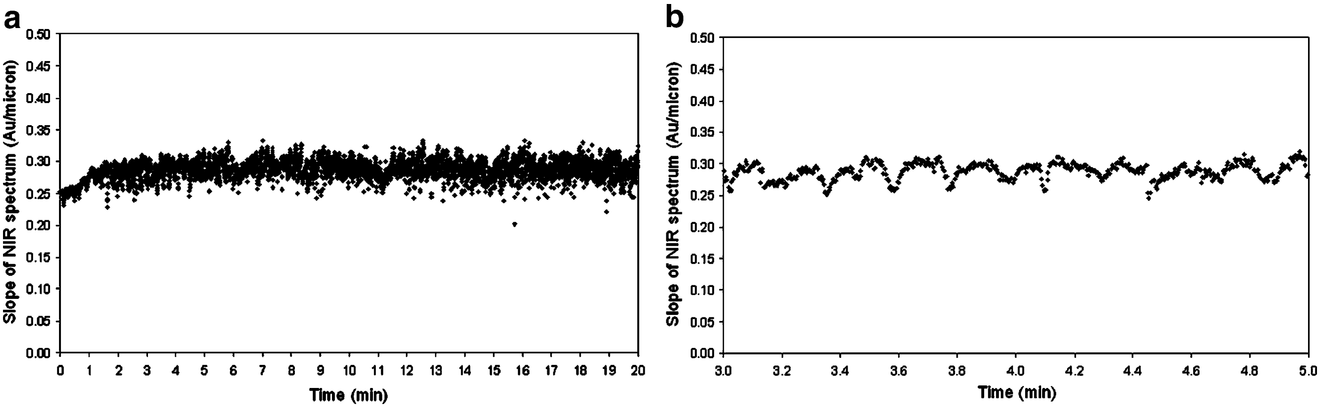

Fig. 3. NIR in-line track of roller compaction process. **a** Whole process 0~20 min. **b** Magnification of time 3~5 min

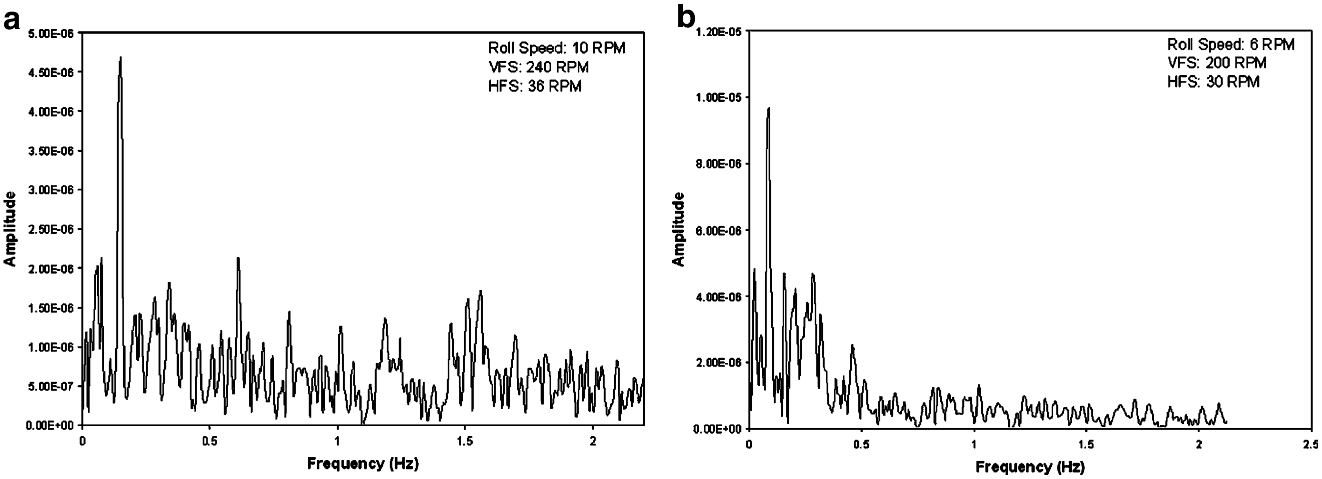

Fig. 4. FFT analysis of variability in roller compaction process **a** with roll speed of 10 rpm, VFS 240 rpm, and HFS 36 rpm **b** with roll speed of 6 RPM, VFS 200 rpm, and HFS 30 rpm

roller compaction process was not from random noise, but from some systematic fluctuation source.

FFT Analysis

The best-fit line slope of the NIR spectra collected in-line was plotted against time. FFT analysis was used to investigate any dominant frequency in the variable slopes of the NIR spectra. A variety of different factors including roll speed, VFS, HFS were investigated to determine if any correlation exists between the dominant frequency and these variables. Figure 4a and b indicate that 10 rpm and 6 rpm roll speeds correspond a frequency of 10/60=0.167 Hz and 6/60=0.1 Hz respectively, both represented by the highest peak in the spectrum. It was found that the dominant frequency had a strong correlation with the roll speed. This translates to the FFT analysis of a variety of different experimental parameters suggesting a strong correlation between the frequency of NIR signals and the roll speed.

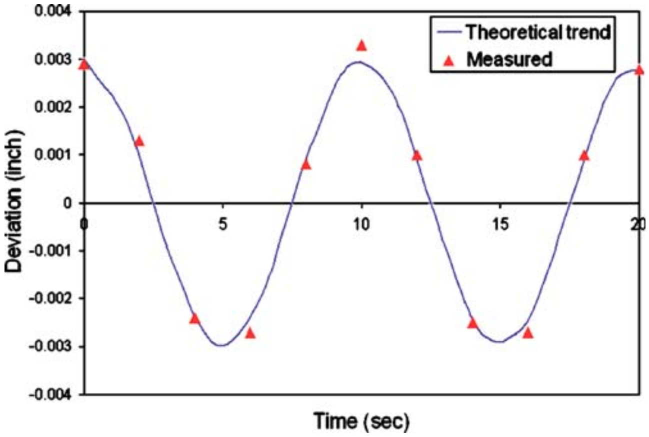

Fig. 5. Deviation distances predicted theoretically based on the eccentricity model and data measured by dial indicator. *Solid line* represents theoretical trend and *triangle points* are data measured experimentally

Eccentricity Measurement

With the observation of the strong correlation between frequency and roll speed, the eccentricity of the rolls was considered as an immediate cause. A dial indicator was used to measure the eccentricity of the two rolls used for roller compaction. The measurements showed no eccentricity detected for the two rolls to the precision of 0.001 in. However, when the rolls were mounted on the shaft and in operation, the dial indicator measurements suggested significant eccentricity of the rolling motion. The left roll was fixed and no appreciable eccentricity was detected, while the right roll had significant eccentricity. Figure 5 shows the deviation profile for the mounted right roll with time. Figure 6 is a

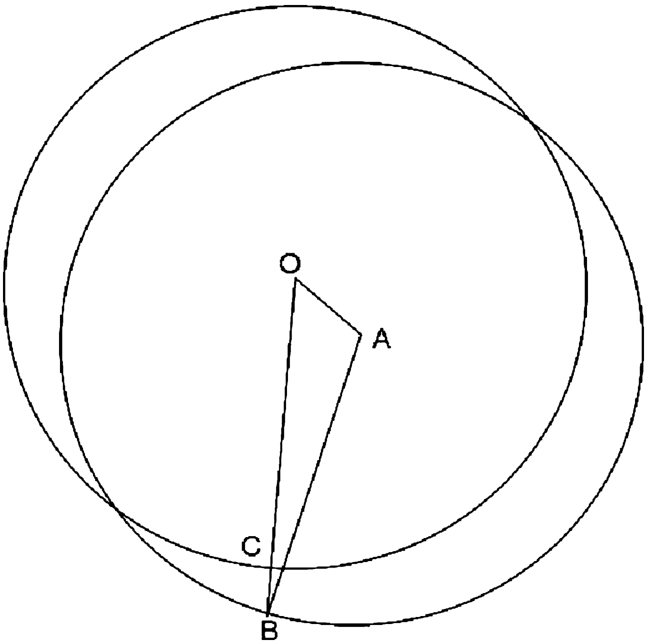

Fig. 6. Schematic of the eccentricity effects on the deviation. The circle with center *O* is the ideal rolling trace with no eccentricity, while the circle with center *A* is the real rolling trace with certain eccentricity

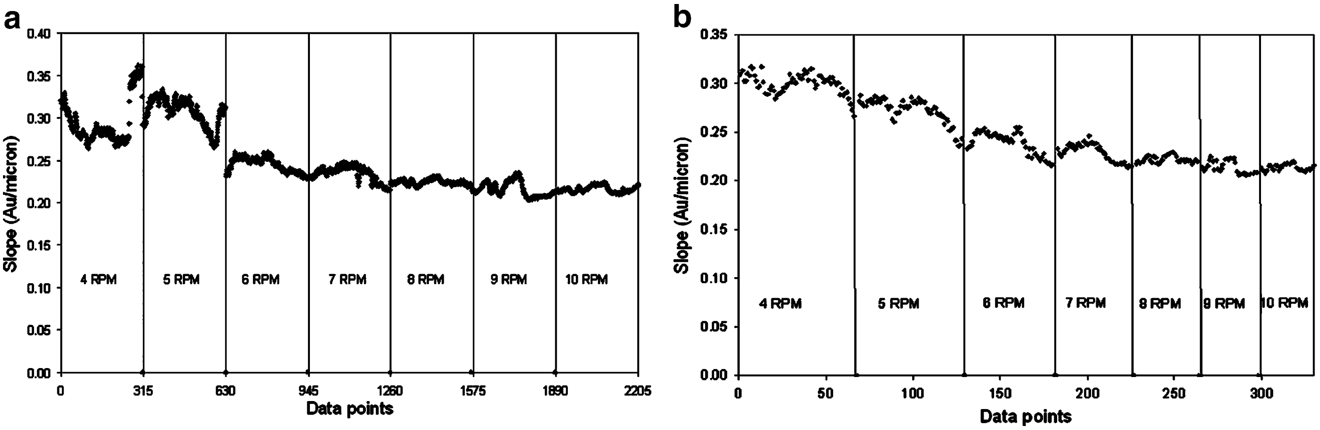

Fig. 7. Off-line NIR spectra slope profile. **a** Dynamic measurements. **b** Static measurements. Each figure is divided into different columns corresponding to different roll speed: 4, 5, 6, 7, 8, 9, 10 rpm

schematic to describe the theoretical deviation of the rolling motion due to the eccentricity effects. There are two circles in Fig. 6, with the center of *O* and *A*. The circle with center *O* represents the ideal rolling trace with no eccentricity, while the circle with center A represents the real rolling trace with certain eccentricity. The dial indicator actually measures the deviation of the real rolling trace from the ideal one with no eccentricity. The deviation is denoted as *x* (marked as *BC* in the figure) in the derivation, the radius of the circle is denoted as *r* (marked as *OC* or *AB* in the figure), and the eccentricity is $\Delta r/r$ (marked as *OA*/*OC* or *OA*/*AB* in the figure). By using the following equation, the dependence of deviation on the eccentricity can be described.

$$r^2 = (r+x)^2 + \Delta r^2 - 2\Delta r(r+x)\cos\theta \qquad (1)$$

$$x = \sqrt{r^2 - \Delta r^2 \sin^2\theta} - (r - \Delta r\cos\theta) \qquad (2)$$

Eq. 2 illustrates the dependence of deviation measured by dial indicator on the arbitrary angle θ. Assuming reasonable value of $\Delta r/r$=0.001, the deviation profile obtained is also plotted in Fig. 5. As suggested in Fig. 5, the experimental measurements of the eccentricity by the dial indicator follow the theoretical profile very well. It meant that the systematic deviation of the rolling motion was caused by the eccentricity of the floating roll. This is confirmed by the strong correlation of the frequency of NIR signal and the roll speed rooted from the eccentricity of the floating roll.

Off-line Variability Measurement

The off-line variability was also measured for the pure MCC compacts produced by roller compaction process. Figure 7 shows the off-line NIR spectra slope against different roll speeds for both measurements, dynamic and static.

Both of the two plots showed the same trend that the best-fit line slope decreased with the increasing roll speed, which agreed with the results reported by Gupta *et al.* 2005. The offline variability profile also showed some fluctuation patterns with time, which implies that the systematic fluctuation due to the roll eccentricity transmitted into the density variability of the compacts produced from that specific process. The variability of the dynamic and static measurements was plotted in Fig. 8 to be compared with the in-line variability. Comparing the difference of variability profile for three different situations (in-line, off-line dynamic and off-line static), the variability can be classified into two different categories: *reducible and non-reducible or inherent variability.* Reducible variability is defined by the difference between in-line and off-line static. It can be reduced by design and optimization of NIR monitoring set-up. Non-reducible variability is defined by the off-line static variability. It is related with the process itself and material properties such as flowability, compressibility, segregation propensity, etc. These properties can not be easily changed given a specific formulation.

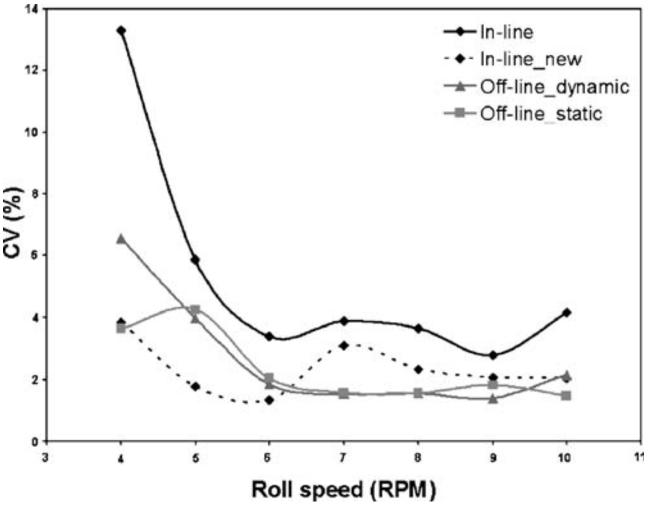

Fig. 8. Variability assessment of the roller compaction process: *solid line with diamonds* represents in-line measurements with the old NIR monitoring setup; *dashed line with diamonds* represents in-line measurements with the new control kit. *Solid line with triangles* represents off-line dynamic measurements, and *solid line with squares* represents off-line static measurements

Validation of New In-line Control Kit

Based on the analysis of variability limit in NIR monitoring roller compaction process, a new in-line control kit was developed and installed on the original roller compactor. It had the following advantages over the previous design:

- Powder reduction floating around the ribbon during compaction, which could effectively reduce the light stray effects of the NIR source.
- The position and motion of the ribbon could be strictly controlled such that consistent and optimized NIR spectra could be collected during the compaction process.
- Control compact fracture and external disturbance to minimize the influences on process variability.

The same measurements were made for the roller compactor equipped with the implemented new control kit. The variability of the roller compaction process with the new control kit was also plotted in Fig. 8 for comparison. All these features potentially contribute to the minimization of the variability of NIR monitoring during the roller compaction process.

By comparing the in-line variability of the new kit and the old one, it clearly suggested that the in-line variability was reduced substantially. The overall reduction of variability for this new setup suggested that the variability analysis performed based on the offline measurement was valid and could be used to reduce the variability of the process. At high roll speed, a general increase of variability with increasing roll speed occurs. The dwelling time for the powders within the compression region would decrease, resulting in significant density fluctuation or breakage of the ribbons, which could jeopardize the variability of the NIR spectra. At low roll speed, the variability was significantly reduced compared with the old in-line data. This was mainly due to the fact that with the new control kit the movement of ribbon was strictly controlled after it was released from the compression region. The waving or swaying motion of the ribbon was avoided such that consistent and optimized NIR spectra could be collected during the real-time monitoring of roller compaction process. The strict control of the ribbon movement can drastically reduce the NIR light stray fluctuations and disturbances caused by deformation and relaxation of the compacts, which contribute to robust and consistent NIR spectra. It was also noticed that at low roll speed, the in-line variability was even smaller than the off-line variability. The reason was not apparent. The authors attributed this to the relaxation effect. In real-time monitoring, the NIR signal captured the instant properties of the compacts right after compression, while the off-line NIR signal collected spectra of the compacts after several hours of relaxation. Typically the elastic relaxation of compact happens within very short time. After several hours of relaxation, it is reasonable to observe some differences on the spectra. Another possible reason is the temperature effect. During roller compaction, the compacts immediately compressed were heated by the frictional forces involved and temperature momentarily rose, which definitely had some effects on the NIR spectra. While during off-line measurements, the temperature of the compacts already equilibrated with the room temperature. It is expected, the spectra to be different from the ones collected during in-line monitoring due to precisely the temperature differences.

CONCLUSIONS

FFT analysis of NIR spectra of in-line monitoring of the roller compaction process on the systematic variability of NIR spectra was due to the eccentricity of the rolling motion of the rollers. Two sets of off-line variability measurements were developed, the NIR in-line monitoring was divided into two categories: reducible and non-reducible variability. Based on this classification, a new in-line control kit was designed and implemented on the original roller compactor. The new control kit reduced the variability due to the motion of the rolls. FFT on NIR in-line monitoring of the RC process offered a methodology to determine the source of variability, materials or roll motion.

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