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Sensor Network for Continuous Tablet Manufacturing

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Abstract

The progress in the mechanistic understanding of the unit operations and the availability of multiple sensor technologies enable the inline implementation of data reconciliation and gross error detection methods in continuous pharmaceutical manufacturing. In this work, we demonstrate the benefits of accurate real-time monitoring of the process state in a continuous tableting process, with case studies representative of common situations in pilot-plant or manufacturing line implementation.

Keywords: Pharmaceutical Tableting, Continuous Manufacturing, Process Analytical Technology, Sensor Network, Data Reconciliation.

1. Introduction

Developing robust process operations for continuous production and real-time release testing in pharmaceutical manufacturing is progressing in earnest with the encouragement from regulatory agencies and prominent companies. The Process Analytical Technology (PAT) guidance set the foundation for modernizing pharmaceutical manufacturing by proposing an integration of subject matter expertise in pharmaceutics, powder technology and real-time process management. Accurate real-time measurements of Critical Quality Attributes (CQAs) and Critical Process Parameters (CPPs) are crucial. Some of these variables can be measured directly in real-time, while others require soft sensors, mainly using spectroscopic methods for inline measurements. Ierapetritou et al. (2016) discuss the process and technical challenges for continuous tableting.

In this work, we describe our progress in developing a reliable monitoring system for continuous pharmaceutical tableting**.** We limit this discussion to the application of data reconciliation (DR) and gross error detection (GED) for accurate inline measurements of the process state by using data from individual sensors. The paper illustrates the application of DR and GED in a subsystem of a continuous tableting line which uses dry granulation.

2. Continuous Tableting Process Description

Loss-in-weight (LIW) feeders are used for feeding the active pharmaceutical ingredient, excipients, inert additives, etc. into the continuous blenders. Then the blend is compacted into tablets. Depending on material properties, the blends may require granulation, milling, etc. before tableting. The sensor network is comprised of built-in equipment sensors for CPPs and external sensors for CQAs. The communication framework for connecting equipment and sensors to a distributed control system (DCS) is crucial to effective network utilization (Singh et al. 2015). Our pilot-plant (Fig. 1) includes an Alexanderwerk WP120 roller compaction unit, two Schenck Accurate AP-300 LIW feeders for metered feed of API (acetaminophen) and excipient (microcrystalline cellulose PH-102), and a Gericke GCM 250 continuous blender. The blend is granulated and blended with a lubricant (0.5 wt% Magnesium Stearate) or glidant (0.2% Silicon Dioxide) using a Schenck DP-4 LIW feeder in another Gericke blender. The final blend is compacted in a Natoli BLP-16 tablet press. As shown in Fig. 1, the sensor network consists of load cell measurements from all the LIW feeders, NIR sensors at locations 2, 3 and 5, microwave sensor (Gupta et al., 2015) at 3; an InnopharmaLabs Eyecon camera at 4, x-ray sensor (Ganesh et al., 2017a) at location 3 and a Sotax AT4 automatic tablet tester at location 6. Additional details of our system are available in Moreno et al. (2017).

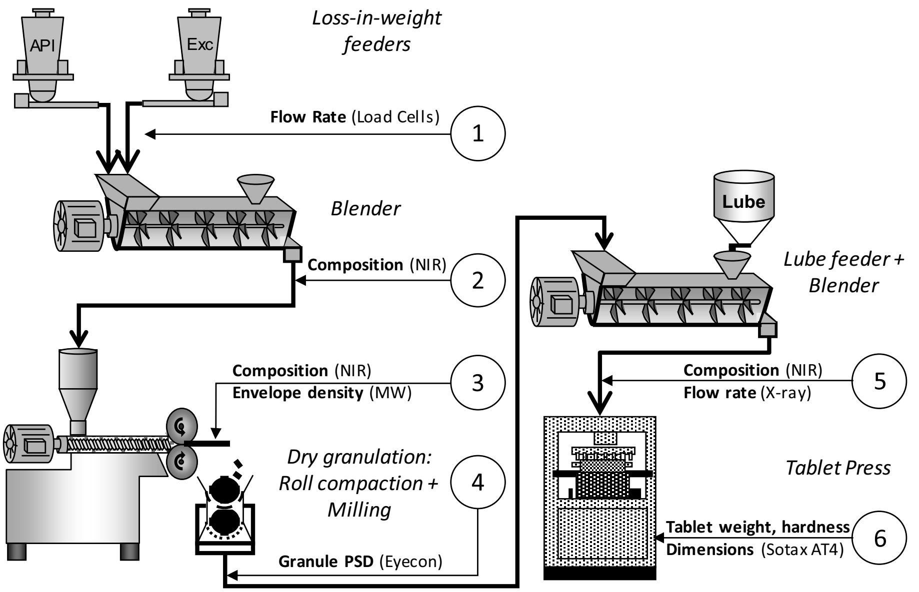

Figure 1. Schematic of pilot plant and available sensor network at Purdue University

3. Systematic approach to measurement accuracy

Real-time release testing in continuous tableting requires accurate and reliable inline measurements. However, there exist several operational challenges. Spectroscopic sensors, such as NIR and microwave, require data pre-processing and analysis before recording in the DCS. Calibration of such sensors is material and sensor location specific. Due to a lack of well-established communication protocols in the industry, tasks such as data acquisition, filtering and processing are performed in separate software. Software issues can result in possible communication failures, rendering the measurement unavailable for specific periods during the process. Handling particulate streams can be subject to frequent fouling of sensor interfaces, leading to biased measurements. Further, tablet properties such as hardness, weight and dimension are measured at set time intervals minutes apart by destructive testing of the samples drawn. Moreover, measurements are always subject to random errors arising from sources such as power supply fluctuations, network transmission delays, changes in ambient conditions, etc.

Data reconciliation (DR), gross error detection (GED) and sensor network design (SND) have been demonstrated to address such challenges for improved measurement accuracy (Narasimhan and Jordache, 1999). DR and GED require direct simultaneous measurement of a number of variables which is larger than the process degrees of freedom to permit the estimation of all variables in the sensor network. Multiple measurements of the same process variable can improve the reliability of that measured variable; however, it does not affect the observability of the unmeasured variables. Besides, sensors using the same technology can miss certain process features which can only be seen via measurements utilizing a palette of alternative technologies. Thus, though the blend uniformity is the primary concern for a continuous tableting process, integrating available mechanistic understanding with sufficient measurements to maintain network redundancy and observability of unmeasured variables is essential for reliable continuous operations.

4. Case Study

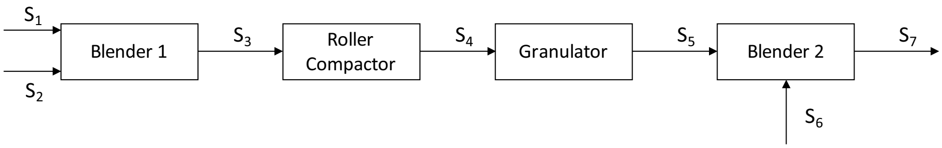

Figure 2. Block diagram for subsystem case study

In this study, the improvements in the accuracy of estimating the process state achieved using DR and GED for a subsystem of the continuous tableting line are demonstrated using three case studies representing situations commonly encountered in experimental implementation. We only consider the feeding, blending and granulating operations in the continuous manufacturing process, leading to the block diagram shown in Figure 2. There are seven material streams, and we assume there is no loss of material. The process variables are summarized in Table 1.

The measurement technologies, if applicable, are indicated in the 'Tool' column. The corresponding expected true values, and relative standard deviations ('RSD' column) of measurements obtained from experimental data under steady-state operations are as indicated. All the unit operations are represented using overall material balances and

Table 1**.** Process variables with measurements, NOC mean and standard deviations

Variable		Tool	True Value (units)	RSD
F_1	API Flow	Load Cell	1.00 kg/h	2%
F_2	Excipient Flow	Load Cell	9.00 kg/h	2%
F_3	Blender1 Flow	-	-	-
x_3	Blender1 CU	NIR	10.00 wt%	6%
F_4	Ribbon Flow	-	-	-
S	Roll Gap	RC equipment	1.960×10^{-3} m	3%
ρ_R	Ribbon Density	NIR	0.963 kg/m^3	6%
x_4	Ribbon CU	NIR	10.00 wt%	6%
F_5	Granule Flow	-	-	-
x_5	Granule CU	-	-	-
F_6	Lubricant/Glidant Flow	LIW Load Cell	0.055 kg/h	15%
F_7	TP Inlet Flow	X-ray	10.00 kg/h	3%
x_7	TP Inlet CU	NIR	10.00 wt%	6%

component balance for the API across each node. Thus, there are eight material balance equations. Further, the flow rate from the roller compactor can be calculated using measured values for ribbon density and roll gap as shown in the equation (1). Also, mechanistic understanding of the roll compaction as shown in Equation (2) can be integrated in to the framework. Details of the model, notations and parametric values can be referred to Ganesh et al. (2017b). The roll speed (N_R) and hydraulic pressure (P_H) are treated as fixed parameters, given the low standard deviations of their measurements.

$$F_4 = \pi \rho_R N_R W D S \tag{1}$$

$$\rho_R = \rho_0 P_0^{1/K} \tag{2}$$

Where $1/2\, P_0(1+\sin\delta_E)WDF = P_H * A$

and $F = \int_{\theta=0}^{\theta=\alpha}\left[1+\frac{1-f_0}{f_0}\left(\frac{\theta}{\alpha}\right)^n\right]^K\left[\frac{S/D}{(1+S/D-\cos\theta)\cos\theta}\right]^K \cos\theta\, d\theta$

The set of equations has 3 degrees of freedom for the process, which means the process has a minimum requirement of four gross error free measurements for data reconciliation. Table 1 shows the availability of nine inline measurements, leading to six degrees of redundancy (DoR) in the system for the GED tests. However, given the frequency of fouling, communication errors, requirement of feeder refilling, etc., consistent availability of gross error free measurements from these sensors is challenging. Moreover, LIW tuning parameters are material bulk density specific, which can vary for the raw materials. Also, calibration models for all the spectroscopic sensors are material, location and probe position specific. Hence, the redundancy is crucial to achieving robustness of this system.

The model based DR and GED problems are solved in MATLAB using the approach reported in Moreno et al. (2017). The GED involves solving the global test (GT) and measurement test (MT). MT requires linearization of constraints. The bilinear component balances and Equation (1) are linearized using Taylor series expansion. Equation (2) is highly nonlinear and is linearized as a linear function of roll gap at the corresponding operating conditions. A total of 1000 random normal measurements using the mean and standard deviations given in Table 1 are simulated. Average values of these noisy measurements are compared with the corresponding reconciled values to demonstrate the improvement in measurement accuracy and are presented in Table 2, with units same as those given in Table 1.

Table 2**.** Measured variable estimates after data reconciliation and gross error detection

Var	NOC		Case 1		Case 2		Case 3	
	Mean	RSD	Mean	RSD	Mean	RSD	Mean	RSD
F_1	1.000	1.79	1.001	1.92	1.003	1.87	1.001	1.80
F_2	8.997	1.57	9.005	1.55	8.997	1.95	9.004	1.55
x_3	10.002	2.04	10.003	2.13	10.032	2.38	10.004	2.03
S	1.929	1.68	1.931	1.66	1.929	2.06	1.930	1.66
ρ_R	0.955	0.24	0.955	0.24	0.955	0.30	0.955	0.24
x_4	10.002	2.04	10.003	2.13	10.032	2.38	10.004	2.03
F_6	0.055	15.20	0.055	15.04	0.055	15.14	0.055	14.77
F_7	10.051	1.43	10.060	1.41	10.056	1.76	10.060	1.42
x_7	9.948	2.04	9.949	2.12	9.977	2.38	9.949	2.03

4.1 Normal operating conditions (NOC)

At NOC, all the nine measurements are expected to be active with true values and RSD as shown in Table 1. DR and GED for the system of equations result in improved accuracy for most process variables, particularly for the CU at all locations, as shown in Table 2 ('NOC' column), while ensuring material balance closure across all units and the process.

4.2 Case 1: Biased measurement from the NIR sensor

Suppose the NIR sensor reports the CU for x_3 as 15 wt%, while the measurements from the rest of the sensors are normal. In such situation, a bias resulting from fouling might be expected. By performing GED and DR, this faulty measurement can be rectified. The reconciled estimate for the CU at Location 3 is closer to the NOC conditions. The reconciled measurement for a shorter duration of gross errors in x_3 is shown in Fig.3 (left). The results of the case study are in Table 2 ('Case 1' column).

4.3 Case 2: Biased measurement from X-ray sensor

During steady-state plant operations, the X-ray sensor at Location 3 (F_7) reports a reduced flow rate of 8 kg/h. With a granulation process, material losses or ratholing in hoppers are always a possibility. However, if both cases are dismissed, the measurement must simply be biased. For the X-ray sensor, faulty measurements arising from communication failure or calibration error resulting from corrective actions for mitigating fouling are possible. In this case, the GED and DR use the existing redundancy in the sensor network to confirm that the process state remains within bounds and thus, a shutdown of the process is avoided. The reconciled measurement for a shorter duration of gross errors in F_7 is shown in Fig. 3 (right) and the results are presented in Table 2 ('Case 2' column).

4.4 Case 3: Unavailability of ribbon density sensor

Calibration of sensors for providing inline measurements of physical properties such as ribbon density is challenging. Moreover, installation of such sensors within the compactor at the ribbon location may require modifications to the equipment and plant setup. The decision to avoid these complexities will result in the unavailability of a direct density measurement. In this case study, we assume ρ_R is an unmeasured variable, reducing the DoR to five. However, an estimate of the ribbon density is important for downstream tableting. DR can accommodate sensor unavailability for estimation of CQAs using process models and measurement redundancy. DR can provide accurate state estimates as shown in Table 2 ('Case 3' column), confirming that the process is within bounds.

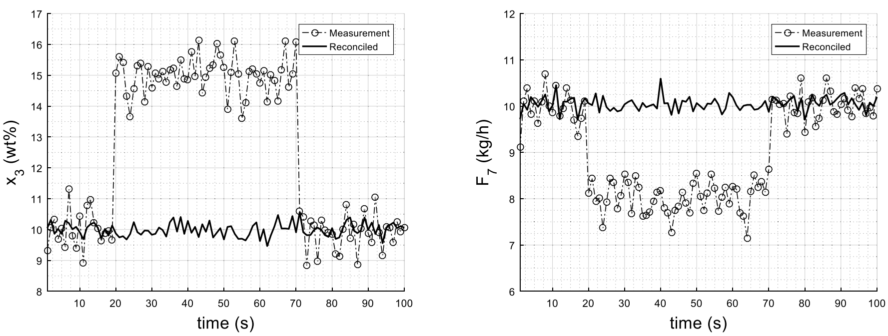

Figure 3. The reconciled values for measurements with gross errors. Bias in x_3 (Case 1, Left figure) and F_7 (Case 2, Right figure)

5. Discussion

For pharmaceutical processes, a measurement of the blend CU inline after every unit operation is essential and is typically achieved using NIR. The measurement RSD for the sensor depends on the material, location, spectra averaging, smoothing, etc. The challenge is to maintain the RSD within regulatory limits. Newer technologies for direct measurement of process variables with simplified calibration are very much desired. However, maintenance action to correct fouling of a sensor could result in bias for the measured variable which is beyond acceptable limits. It would be infeasible to pause a continuous process frequently to check for such errors. Also, ensuring material balance closure is crucial to maintain robust and profitable operations.

6. Conclusions

The case studies in this paper illustrate some of the practical challenges in the implementation of robust inline sensing in continuous pharmaceutical tableting. Specifically, we demonstrate the application of DR and GED to the system of unit operations and sensors using mechanistic models and material balance to obtain reliable and accurate estimates of the process state. Expanding this framework to add the models of other unit operations and measurement technologies is a part of our current research. Moreover, in ongoing work, we show that the application of a DR framework facilitates effective implementation of process control systems (Su et al., 2017). Robust process operations using systematic sensing and control systems are essential for reliable function of a material-tracking framework, leading to real-time release testing in pharmaceutical manufacturing.

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