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Variation and Risk Analysis in Tablet Press Control for Continuous Manufacturing of Solid Dosage via Direct Compaction

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Abstract

A continuous rotary tablet press is a multi-stage process with many punch stations running in parallel, in which each punch undergoes the following steps: die filling and metering, pre-compaction, main-compaction, tablet ejection, and tablet take-off from lower punch. Process uncertainties or disturbances within a punch station or among stations in the tablet press are a major source of variation in final product quality attributes, e.g., hardness, weight, etc., which in turn imposes challenges for the real-time release in pharmaceutical continuous manufacturing of solid dosage. In this study, the direct compression line at Purdue University was investigated and a Natoli BLP-16 tablet press was used to characterize powder compressibility, system dynamics and variation, as well as the interaction effects on process control development. The compressibility of tablets made from a blend of Acetaminophen (API), Avicel Microcrystalline Cellulose PH-200 (excipient), and SiO_2 (lubricant) was found to be largely independent of tableting speed. By contrast, filling depth or dosing level, turret speed, feed-frame speed, and compression force were interacting and significantly affected the die-filling process and the final product quality attributes. Thus, the design of the process control structure plays an important role in reducing process and product quality variations. A hierarchical three-level control design was proposed and evaluated, consisting of Level 0 Natoli built-in control, Level 1 decoupled Proportional Integral Derivative (PID) cascaded control loops for tablet weight and production rate control, and Level 2 advanced model predictive control. Process variations, e.g., in powder bulk density changes, during continuous steady-state operation were also investigated. Finally, a risk analysis of the effects of the process dynamics on variation on the product quality control was briefly discussed and summarized.

Keywords

continuous manufacturing; tablet press; process control; risk analysis

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1. Introduction

A real-time release strategy is essential to the pharmaceutical manufacturing industry as it shifts from batch to continuous processing. Such a strategy requires effective on-line process monitoring and control of pharmaceutical critical process parameters (CPPs) and critical quality attributes (CQAs) so as to achieve steady-state and consistent production of pharmaceutical ingredients, intermediates, or final products. Systematic frameworks for the development and implementation of process monitoring and control strategies in pharmaceutical continuous manufacturing have been extensively discussed in the past decade (Singh et al., 2014); however, reports of practical and thorough studies of the implementation and evaluation of monitoring and control systems in a physical pilot plant or manufacturing facility are still limited in the open literature. Specifically, the dynamic performance and risk analysis of the continuous manufacturing process in a control closed-loop operation are rarely reported (Bhaskar et al., 2017). In this study, our particular interest was focused on the control performance of a continuous rotary tablet press in the Purdue University pharmaceutical continuous manufacturing pilot plant. The continuous rotary tablet press is a multi-stage process, in which each station undergoes the following major steps: die filling and metering, pre-compaction, main-compaction, tablet ejection, and tablet take-off from lower punch. Process uncertainties or disturbances within a punch station or among stations in the tablet press are a major source of variation in final product quality attributes, e.g., hardness, weight, etc., which in turn challenges the real-time release decisions in continuous manufacturing of solid dosage. The Natoli BLP-16 tablet press was investigated within the direct compression line to characterize powder compressibility, system dynamics and variation, as well as their effects on process control development.

2. Process variation and characterization

The challenges of maintaining consistent product quality in the output of a tablet press are to identify the appropriate CQA and CPP variables, and to understand the effect of their variations on the target product profiles (TPPs). These critical-to-quality variables for the given system were identified as tablet weight, relative density, strength (hardness) and compaction force. For example, the weight of the tablet ultimately determines the API potency within a dose. Further, it also determines the main compression force at the set punch displacement and thus the relative density and tensile strength of the tablet, which in turn affect the final product attributes such as dissolution rate. Inline process characterization of the output of the tablet press was conducted using the Sotax AT4 automatic tablet testing system for a powder formulation of 10% Acetaminophen (API), 89.8% Avicel Microcrystalline Cellulose PH-200 (excipient) and 0.2% of SiO_2 (lubricant) by mass.

Tablet weight is the desired outcome of the die filling station, whose variation could be due to the changes in powder flowability and die filling time. It was found that powder bulk density is responsive to the variations in blend composition, moisture content, and temperature, which also result in variation in its flowability. Hence, the tablet weight variation was characterized by the following equation,

$$W_t = \tilde{\rho}_b \frac{\pi D^2}{4} DP(1 - cTS) \tag{1}$$

where W_t is the tablet weight, $\tilde{\rho}_b$ is the powder bulk density, D is the diameter of the die, DP is the dosing position, TS is the turret speed, and c is an efficiency parameter of powder flowing into the dies from the feed-frame.

Tablet relative density is the ratio of tablet bulk density to the powder true density, which can be calculated from tablet weight, as shown below and verified in Figure 1(a),

$$\rho_r = \frac{4W_t}{\pi D^2 t \rho_t} = \frac{\tilde{\rho}_b DP(1 - cTS)}{t\rho_t} \tag{2}$$

where ρ_r is the tablet relative density and t is the in-die tablet thickness and ρ_t is the known powder true density.

Tensile strength is a measure of tablet hardness which is independent of tablet dimensions. It can either be measured using a destructive test which fractures the tablets in between two platens (e.g., Brazilian test) or it can be estimated using the Leunberger equation (Kuentz and Leunberger, 2000), as described below,

$$\sigma_{t,m} = \frac{2F}{\pi D \bar{t}} \tag{3}$$

$$\sigma_{t,p} = \sigma_{max} \left[1 - \left(\frac{1 - \rho_r}{1 - \rho_{c,\sigma}} \right) e^{(\rho_r - \rho_{c,\sigma})} \right] \tag{4}$$

where $\sigma_{t,m}$ is the tensile strength measured from the Brazilian test, $\bar{t}$ is the out-of-die tablet thickness, and F is the breaking force. $\sigma_{t,p}$ is the predicted tensile strength from the tablet relative density as in Eq. (2), $\rho_{c,\sigma}$ is the critical density of strength, and σ_{max} is the tensile strength at full density, i.e., at $\rho_r = 1$.

Powder compressibility is characterized by the relationship between main compression force CF during compaction and the resulting tablet relative density ρ_r. It is one of the critical material attributes (CMAs) that affect consistent tablet manufacturing. There are many models characterizing the compressibility of a powder at various degrees of compression. In this study, the Heckel relationship was employed to characterize the main compression force at high tablet relative density, as given below and verified in Figure 1(b),

$$\frac{CF}{1 - \frac{\rho_c}{\rho_r}} = \frac{CF}{a} + \frac{\pi \frac{D^2}{4}}{ab} \tag{5}$$

where ρ_C is the critical density during compaction, parameters a and b are interpreted as the maximum degree of compression and the reciprocal of the pressure applied to attain the maximum degree of compression, respectively.

3. A hierarchical control development

A hierarchical three-level controller design was implemented on the Natoli tablet press following to the previously proposed systematic framework for process control design and risk analysis in continuous pharmaceutical solid-dosage manufacturing (Su et al., 2017). The framework consists of a series of steps involving system identification, control design and analysis, hierarchical three-level control, risk mapping, accessing and planning, performance evaluation, etc. The Natoli BLP-16 tablet press has a built-in programmable logic control (PLC) system to manipulate the process parameters of fill depth, turret speed, and feeder speed, which are regarded as providing Level 0 control in this context. In light of the above process variation characterization, the system identification step using state-space model and the control design and analysis step using classical control metrics, e.g., Condition number, Relative Gain Array (RGA) analysis, etc., suggested a Level 1 control with decoupled PID control loops for a cascaded control of tablet weight, production rate, and main compression force by manipulating the set points of fill depth and turret speed at the Level 0 control. The identified state-space model was further employed to develop the Level 2 linear model predictive control (MPC) scheme for the tablet press, in which the main compression force was constrained and monitored as it is closely related to the tablet CQAs of hardness, tensile strength, and dissolution rate. The Emerson DeltaV Control Studio and DeltaV Predict toolbox were utilized for Level 1 and 2 control implementations. Details of control loops and operating panels can be found in Figure 2.

4. Results and discussion

With the Level 0 Natoli built-in control of turret speed and dosing level (feeder speed was set constant and punch displacement was adjusted manually only), step changes in both turret speed and dosing level were conducted, as shown in Figure 3(a). It was observed that the measured tablet weight, as understood in process variation and characterization, strongly depended on dosing level after reaching steady-state. Step changes in turret speed, as highlighted with rectangles, showed only slight changes in tablet weight and main compression force due to changes in die filling time and flow dynamics, as described by Eq. (1). This is also consistent with the research findings of favourable compressibility of the powder formulation investigated (Tye et al., 2005), as described by Eq. (5). This variation was further studied when the tablet press was under closed-loop control operation, as shown in Figure 3(b). The Level 1 PID control for tablet production rate was deliberately set to be open, while a step change in turret speed was introduced. It was demonstrated that the cascaded control loop for tablet weight was capable of bringing the measured tablet weight to the set point of the master loop, as well as the main compression force of the slave loop. The variation of turret speed, viz., the die filling time, was compensated for by relatively minor adjustments of dosing level. Furthermore, this variation contributed insignificantly to the interaction of the decoupled control loops for tablet weight and production rate, as shown in Figure 4(a), when set point changes were made in tablet weight and production

rate. It is worth noting that the turret speed was first increased then reduced in response to the first increase in production rate then the following increase in tablet weight, during which both the tablet weight and main compression force reached their set points rapidly and steadily, thus achieving the desired critical quality attributes in relative density, tensile strength, as discussed previously. Due to the moderate nonlinearity and relatively modest interaction of the studied tablet press and specific powder blend, comparable promising performances were achieved for both Level 1 PID control and Level 2 linear MPC control (with sampling time of 1 second) in terms of process set point changes and under the risk of powder bulk density disturbances (see Su et al., 2017, for disturbances due to changes in API mass fraction set point in a feeding and blending system).

5. Conclusions and future work

The system variation and its effect on the development of control strategies for a tablet press were investigated. It was found that the monitoring and control of the tablet weight and main compression force, two of the critical-to-quality variables, were important to achieving the consistent product properties under the process variations of turret speed and the risk of uncertainty in powder bulk density. In ongoing work, we are investigating additional powder formulations with different compressibility properties and implementing the control framework on an industrial scale tablet press.

Acknowledgement

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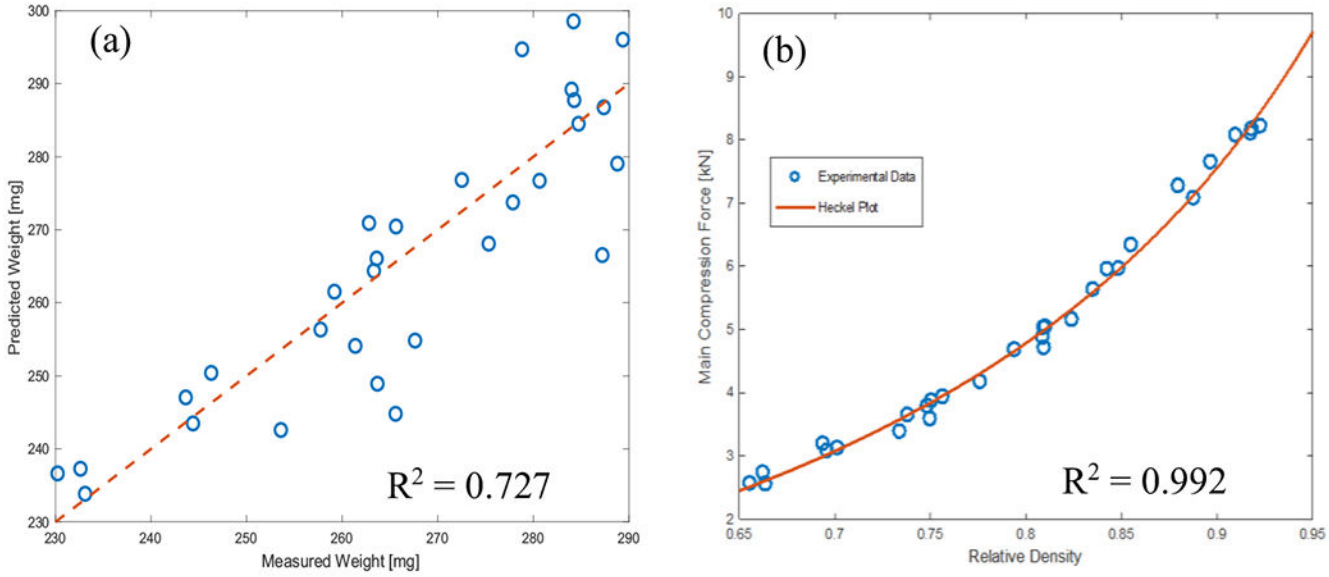

Figure 1.
Comparisons between predicted and measured tablet weight (left) and main compression force (right).

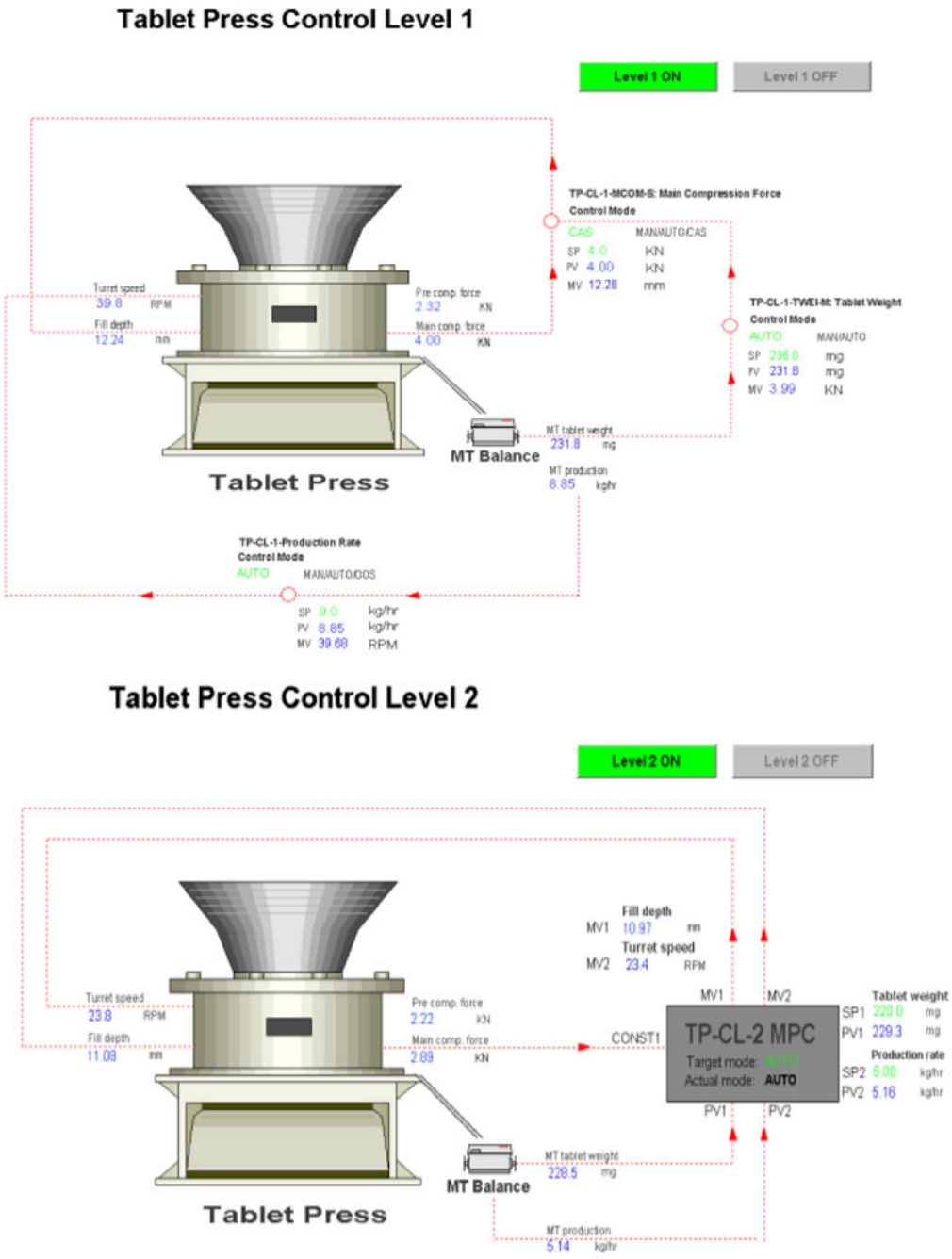

Figure 2.
The hierarchical Level 1 (top) and Level 2 (bottom) control for tablet press.

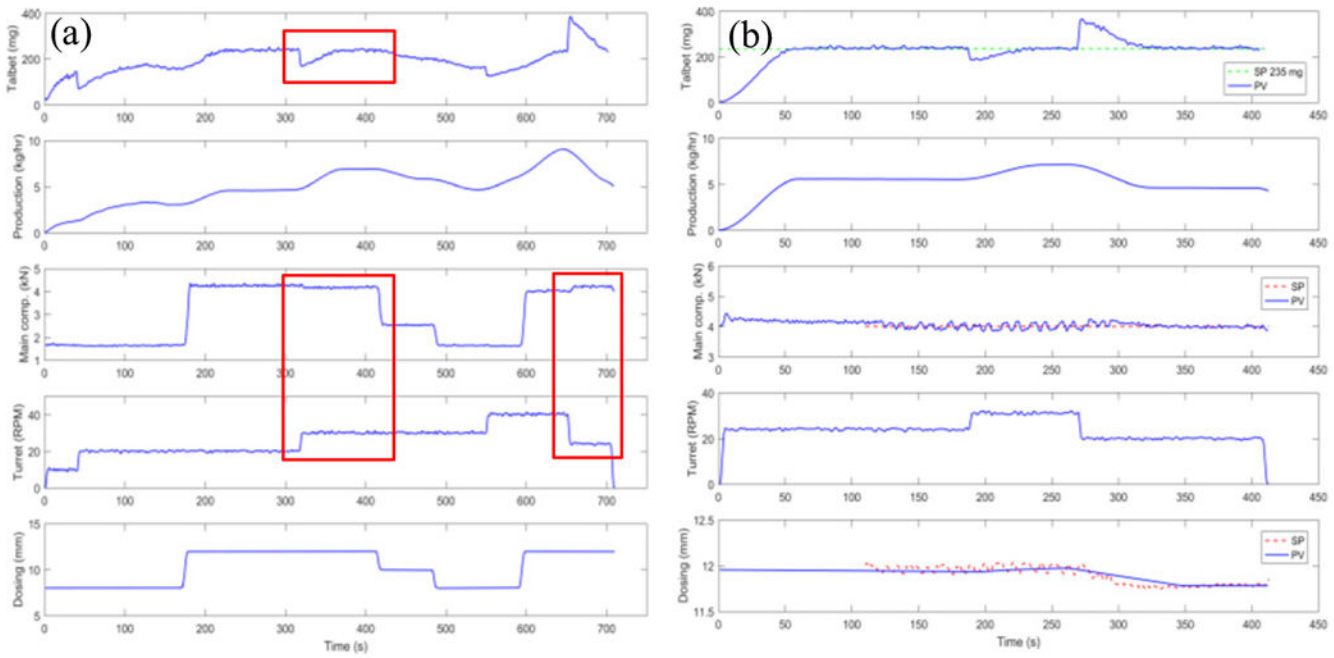

Figure 3.

(a) Step changes in turret speed and dosing level under Level 0 control; (b) variation of the turret speed on tablet weight and main compression force control under Level 1 control when production rate control loop was deliberately set to be open.

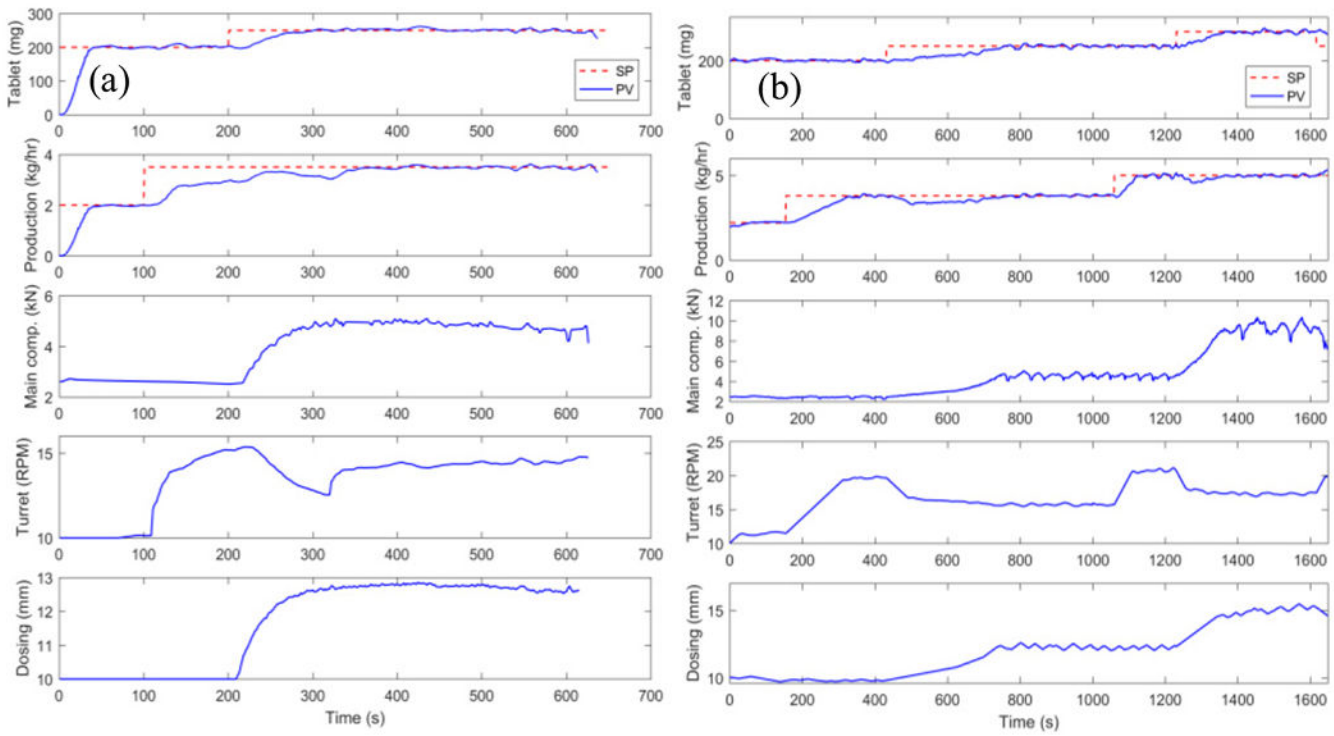

Figure 4.
Control performance of Level 1 PID (a) & Level 2 MPC (b) control loop for set point changes.