Development of advanced control and optimization strategies for processes in the pharmaceutical industry integrating digital twin and machine learning concepts

Pharmaceutical manufacturing plants are composed of complex processes and they have to operate close to operational constraints having very strict specifications for the quality of the product. Moreover they deal with highly integrated and complex processes, process/model uncertainty, production targets that are usually varying and have variability in the raw material [1-4]. Traditionally, pharmaceutical manufacturing processes operate in batch, meaning that the final drug product is achieved by running a pre-determined amount of raw material through different unit operations. Quality control is performed in a quality-by-testing approach (QbT) meaning that the attributes of the drug product quality are tested at the final processing step of each batch.

Driven by the need for cost-effectiveness, improved sustainability, dependability, smart targeted solutions aiming at smaller patient population as well as due to modern manufacturing technology advancements, continuous manufacturing, a quicker, more effective process, has replaced batch pharmaceutical manufacturing in the pharmaceutical manufacturing industry [5-7]. This will also lead to a shift towards quality-by-control (QbC) which consists in designing and operating a robust system for manufacturing by using an active process control system based on the process design robustness, thus leading towards smart manufacturing [2].

This work lays the groundwork for cutting-edge Quality-by-Control (QbC) multi-parametric model based predictive control (mp-MPC) strategies for a tablet manufacturing process. First, a model of the process is determined which is validated and calibrated using real data from a Pilot Plant. The model is further used to design advanced mp-MPCs that are robust, especially when dealing with uncertainty, against variable time delay, good disturbance rejection and they can incorporate constraints explicitly. Explicit/multi-parametric model based predictive control (mp-MPC), uses multi- parametric programming to obtain offline the optimal solution of the problem. Therefore, the control inputs can be computed as a set of explicit linear functions based on the set-points, the states of the system, the disturbances, etc.[8, 9]. By using mp-MPC strategies, we can determine offline a map of all possible solutions helping us to determine the design space (DS) in closed-loop conditions [10]. Thus one of the important advantages that mp-MPC strategies are bringing to the pharmaceutical sector is that they are capable of offering a controllability map. As the full control law is available in a convenient map, the designers can easily identify uncontrollable operational regions and take action to remove the bottlenecks. This comes as a stark contrast to traditional MPC where there is no guarantee that the online controller will meet all the controllability objectives and/or satisfy all the operational constraints. This represents a great advantage for the pharmaceutical industries especially in dealing with the strict Food and Drug Administration (FDA) regulations. Another important advantage of using multi-parametric techniques (mp-MPC) is that through the use of offline optimization, the costly online computation of solving the optimisation problem at every sampling time is avoided, resulting in only the implementation of a straightforward lookup table and straightforward function evaluation.

The limits and performances of the developed control strategies are tested on the original high fidelity model for different targets of operation, sensor measurement noise as well as process disturbances. The developed techniques present good performances meaning no significant overshoot or undershoot as well as a fast settling time.

Process model

The lubricant/glidant feeder and the rotating tablet press represent some of the most important unit operations in pharmaceutical manufacturing. The lubricant/glidant feeder is used for the reduction of loses due to friction and it facilitates the flow of the powder during die filling as well as the formation of solid tablets through mechanical compression. Hence, to monitor and control the tensile strength as well as the porosity of the tablets the models of the glidant effects in die filling as well as compression processes are used. These mechanistic models are capable of capturing the mixing conditions as well as the effects of the glidant concentration [11].

To determine the convex tablet weight, W, which is formed utilizing Natoli D-type tooling having shallow cup depth, the following equation will be used:

$$W = \rho_b V_{fill} \left(1 - \xi_1 \frac{n_T}{n_F} + \xi_2 \frac{H_{fill}}{D}\right) \tag{1}$$

Where the variables ρ_b, V_{fill} , H_{fill}, n_T, n_F, and D represent the powder bulk density , the die cavity volume, the position of the dose, turret speed, the speed of the feed frame and the diameter of the die respectively. The model parameters ξ_1 and ξ_2 are estimated using data from experiments. The density of the bulk is dependent on the mixing conditions and the concentration of the glidant. The cavity volume for the Natoli D-type tooling is determined as follows:

$$V_{fill} = \frac{\pi D^2 H_{fill}}{4} + \frac{\pi h\left(\frac{3D^2}{4} + h^2\right)}{6} \tag{2}$$

where h represents the depth of the cup. The production rate of the tablet, $\dot{m}_{tablet}$ can be computed from:

$$\dot{m}_{tablet} = W n_T N_{station} \tag{3}$$

where $N_{station}$ represents the number of available turret stations. The pre-compression force (PCF) can be calculated from :

$$F_{pc} = \frac{\pi D^2}{4b}\left[\frac{\rho^{pc} - \rho_c}{\rho^{pc}(a-1) + \rho_c}\right] \tag{4}$$

Here, the *a* and *b* parameters (Kawakita constants [12]) are the maximum degree of compression respectively the reciprocal of the pressure that is applied in order to obtain this compression degree. ρ^{pc} is the relative density of the pre-compression and ρ_c represents the critical density. To compute the relative density of the pre-compression the following equations are used:

$$p^{pc} = \frac{W}{V^{pc}\rho_t} \tag{5}$$

and

$$V^{pc} = \frac{\pi D^2 H^{pc}}{4} + \frac{\pi h\left(\frac{3D^2}{4} + h^2\right)}{3} \tag{6}$$

where H^{pc} represents the powder true density and ρ_t represents the thickness pre-compression. Thus, F_{punch}, the main compression force is given by:

$$F_{punch} = \frac{\pi D^2}{4b} + \left[\frac{\rho^{in-die} - \rho_c}{\rho^{in-die}(a-1) + \rho_c} \right] \quad (7)$$

The in-die relative density $\rho^{in\text{-}die}$ is determined as follows:

$$\rho^{in-die} = \frac{W}{V^{in-die}\rho_t} \quad (8)$$

and

$$V^{in-die} = \frac{\pi D^2 H^{in-die}}{4} + \frac{\pi h\left(\frac{3D^2}{4} + h^2\right)}{3} \quad (9)$$

Where the main compression thickness is given by $H^{in\text{-}die}$. The density of the tablet, ρ^{tablet}, is determined using the elastic recovery, ε_ρ, of the tablet:

$$\rho^{tablet} = \left(1 - \varepsilon_\rho\right)\rho^{in-die} \quad (10)$$

The glidant mixing conditions doesn't have much influence on the elastic recovery model, and it is given by:

$$\varepsilon_\rho = \varepsilon_0 \frac{\rho^{in-die} - \rho_{c,\varepsilon}}{1 - \rho_{c,\varepsilon}} \quad (11)$$

where $\rho_{c,\varepsilon}$ represent the relative density where tablets do not present elastic recovery and ε_0 represents the in-die elastic recovery at full compaction [13].The tensile strength σ_t is dependent on glidant conditions and it is determined using the equation:

$$\sigma_t = \sigma_0\left(1 - \left(\frac{1-\rho^{tablet}}{1-\rho_{c,\sigma_t}}\right)e^{\left(\rho^{tablet} - \rho_{c,\sigma_t}\right)}\right) \quad (12)$$

where σ_0 represents the strength of the tensile when porosity is zero and $\sigma_{c,\,\sigma t}$ represents the relative critical density where tablets do not present any the tensile strength, meaning that it is the relative density needed for a tablet to start forming.

The glidant concentration, c_l depends on the bulk density and it can be included through:

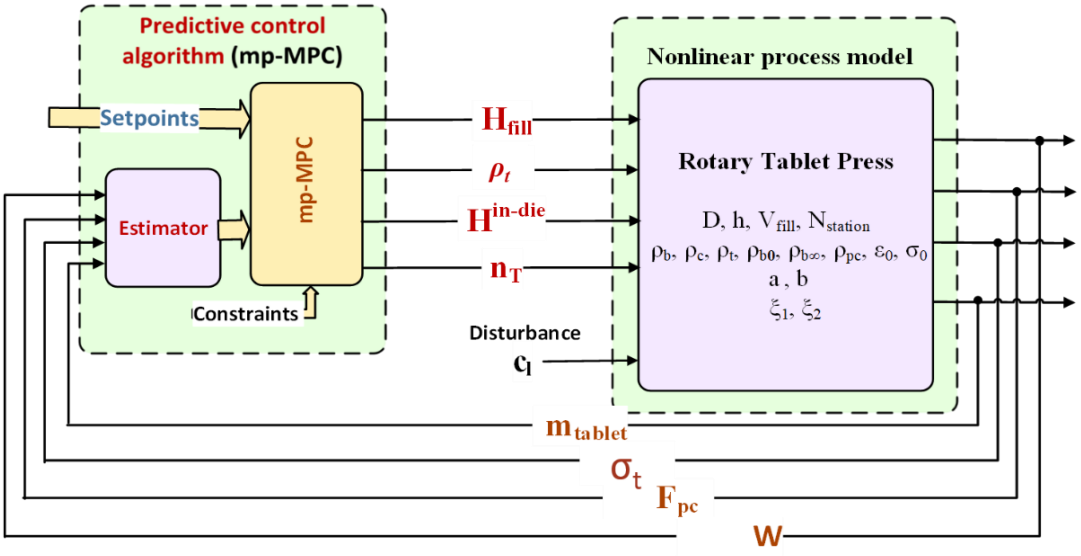
$$p_b = p_{b,\infty} - \frac{p_{b,\infty} - p_{b,0}}{1 + C_p} \quad (13)$$

Where $\rho_{b,0}$ defines the bulk density when the shear strain imparted is zero and $\rho_{b,\infty}$ defines the bulk density when the shear strain imparted is infinite. *Cp* represents the conditions of the glidant and it is a lumped parameter that can be determined as follows:

$$C_p = \frac{c_l^{r_1}\left(\gamma + \gamma_0\right)^{r_2}}{r_3} \quad (15)$$

where γ is the shear imparted to the powder while mixing and γ_0 is the initial shear strain that is imparted before mixing. r_1, r_2, and r_3 represent fitting parameters.

In this work a Natoli NP-400 tablet press and SOTAX AT4 tablet tester is used to manufacture the tablets and collect data from experiments performed at steady-state conditions. The data from experiments is further used to obtain the values of the parameters of the real model used for parameter fitting and to calibrate the model used for simulation.



Multi-parametric Model Predictive Control

Fig 1 presents a schematic representation of the developed hierarchical control system layers. To determine the mp-MPC control laws the mp-QP optimization problem presented below is solved by using the POP toolbox [14] and the controller is determined:

$$\begin{aligned}
&\min_u J = \hat{x}'_N P\hat{x}_N + \sum_{k=1}^{N-1} x'_k Q_k x_k + \sum_{k=1}^{N-1} (y_k - y_k^R)' Q R_k (y_k - y_k^R) \\
&\qquad + \sum_{k=0}^{N_u-1} (u_k - u^R)' R_k (u_k - u^R) + \sum_{k=0}^{N_u-1} \Delta u'_k R1_k \Delta u_k \\
&s.t. \quad x_{t+1} = Ax_t + Bu_t \\
&\qquad y_t = Cx_t \\
&\qquad y_{min} \le y \le y_{max} \\
&\qquad u_{min} \le u \le u_{max} \\
&\qquad x_t \in X \subseteq \Re^p, u_t \in U \subseteq \Re^s
\end{aligned} \tag{16}$$

where $\hat{x}$ are given by the state estimator and they represent the estimated states, y represents the outputs, u represents the control action and Δu represents the changes in control actions, $\Delta u(k) = u(k) - u(k-1)$. The output variables subsets that are being tracked have set points dependent on time y^R. N represents the prediction horizon and N_u the control horizon. The sets of the state constraints and input constraints are given by X and U and they include the origin within the interior. The states objective coefficient is given by Q, the states terminal weight matrix is given by P and the matrix for the controller outputs is given

by *R*. All of these matrixes are semi-positive definite (*Q>0, P>0, R>0*). Moreover, *QR* represents the quadratic matrix used for tracking the process outputs and *R1* is the weight matrix for the changes of the controller outputs(Δu)

A. Control Design

For the design the controller, the tuning parameters that are determined for this work are: the states objective coefficients (*x*), Q=0, the matrix used for the tracked process outputs (*y*), *QR* is the unit matrix, the matrix used for controller outputs (*u*), *R*=0, R1 is a diagonal matrix having the diagonal values [0.001, 0.01, 0.1, 0.01]. For the control horizon we have $N_u=1$ and for the prediction horizon we have $N=6$. The control and prediction horizons are chosen taking into account the process characteristics and the desired closed-loop performances. It is advised that *N* should be, at least *2n-1* but it shouldn't be larger than the process rise-time. When determining the value of N_u, for processes that have no unstable underdamped or unstable poles, such as the process at hand, $Nu=1$ is usually satisfactory. The sample time is of T_s=1 [sec] since measured data is available from the plant every 1 second. The constraints on the manipulated input (dosing position, main compression thickness, pre-compression thickness and turret speed) will be imposed. One of the benefits of model predictive controllers is that they can incorporate constraints. The constraints on the manipulated inputs are: the dosing position between 6mm and 14 mm, the pre-compression thickness between 0.5 mm and 14 mm, the main compression thickness between 0.5 mm and 6 mm and the turret speed between 0 rpm and 60 rpm.

Results

For this work, following the model of the process described in Section II.A, 4 inputs and 4 outputs are used to determine the MIMO linear model through the System Identification toolbox in MATLAB. The linear model will be further used for the design of the controller. The four controlled variables for this process are: the tablet weight, the pre-compression force, the production rate, and the tensile strength. The four manipulated variables are: the dosing position, the pre-compression thickness, the main compression thickness and the turret speed. It is presumed that sensor measurements of the tablet tensile strength are available every second. The model parameters used in this paper represent experimental data and are: $\xi_1 = 0.036$, $\xi_2 = 0.03$, ρ_b=0.365 [g/cm^3], ρ_c=0.265, $a = 0.8$, $1/b = 10.26$ [MPa], $\rho_t = 1.53$ [g/cm^3], , ε_0=0.08, $\rho_{c,\varepsilon,} = 0.57$, $\sigma_0 = 11.67$ [MPa], ρ_0=0.57, ρ_∞=0.61, $b_1 = 0.31$, $b_1 = 0.38$, $b_1 = 8.4$, $\rho_{b,\infty} = 0.45$ [g/cm^3], $\rho_{b,0} = 0.33$ [g/cm^3], $r_1 = 0.361$, $r_2 = 1.394$, $r_3 = 23.326$.

To determine the control laws and determine the controller, the optimization problem (16) is solved using the POP toolbox [15].

Setpoint Changes

To test how the designed control strategy performs, setpoint changes are given to the tablet weight from 225 mg to 255 mg at time t = 50 s, for the pre-compression force from 0.37 kN to 0.67 kN at time t = 100 s, for the production rate from 7.4 kg/h to 8.4 kg/h at time t = 150 s, and for the tensile strength from 5.6 MPa to 6.4 MPa at time t = 200 s, respectively.

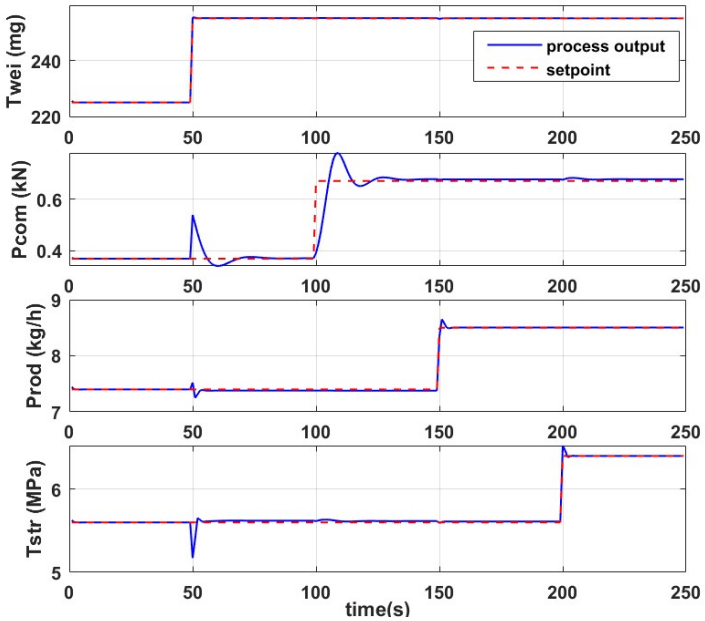


Fig. 2. mp-MPC, setpoint tracking – output variables (Twei - tablet weight, Pcom - pre-compression force, Prod - production rate, and Tstr tensile strength)

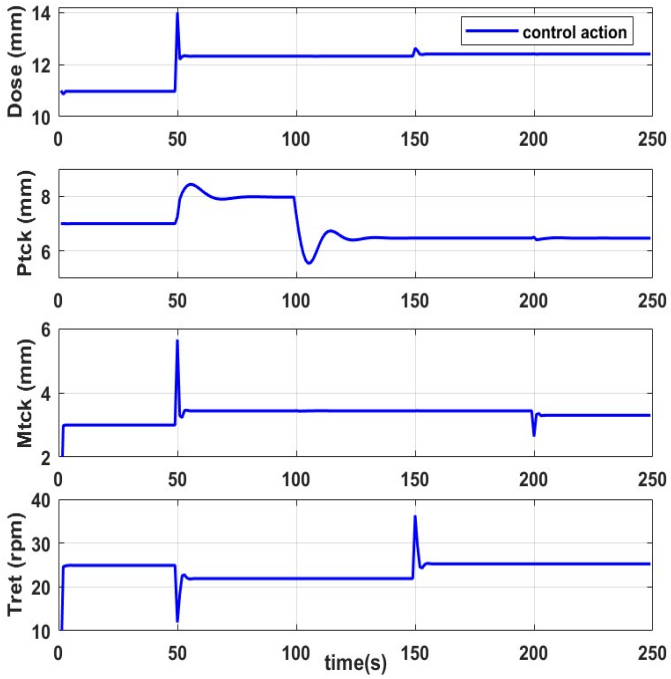


Fig. 3. mp-MPC, setpoint tracking - control action (Dose - dosing position, Ptck - pre-compression thickness, Mtck - main compression thickness and Tret - turret speed).

Fig. 2 and Fig. 3 presents the closed loop system response using the mp-MPC for different setpoint changes for the case where we have no noise on the measured outputs. Fig. 2 shows the setpoint step responses of the controlled variables and it can be observed

that the outputs are coupled meaning that a setpoint change on any of the outputs will affect the other ones. Fig. 3 presents the control action for the mp-MPC closed loop response. It can be observed that the setpoint change on the tablet weight (given at time t=50 seconds) has the strongest influence on all outputs.

The mp-MPC controller has good performances such as: fast settling time, small overshoot and undershoot and no setpoint offset for the successive changes in all references. The mp-MPC is multivariable, meaning that each control action is responsible for all 4 outputs. Thus, the control algorithm efficiently manages the input-output inter-influences, respectively minimizing the deviations of the other outputs from the reference values when the reference of one of the outputs changes. The evolution of the manipulated variables remains within the saturation limits. Moreover, every change of the manipulated variables shown in this work is realistic in nature and is feasible at normal operation of the tablet press.

Noise and Disturbance Rejection

To further evaluate the controller performances, sensor measurement noise is introduced. To simulate the noise the normally distributed error having zero mean and variance is added to the real sensor variability which is taken from the historical plant data. The closed loop response results for the controlled variables and the control actions are presented in Fig. 4 and 5, respectively. It can be seen that the mpMPC controller has good performances when dealing with sensor measurement noise, all dynamic and stationary parameters of the response are maintained as in the case without noise. By an appropriate choice of the design parameters, it is possible to achieve an attenuation of the measurement noise oscillations and a compromise between the response time and the propagation of these oscillations in the control loop. It can be observed in the evolution of the 4 outputs that the response time of the 2nd output (Pcom) is longer than for the other outputs and thus the oscillations on the second manipulated input are more attenuated. If a damping of these oscillations for all manipulated variables is desired, one can act by reducing the aggressiveness of the controller on the respective loops by choosing the appropriate design parameters.

Monitoring the powder bulk density is very important in the tablet press process, since it influences the tablet properties. Disturbances can occur throughout any of the upstream unit operations , e.g., during refill, within the feeder unit operations, when the feeder changes from gravimetric mode to volumetric mode, which will lead to either an increase in the bulk density because of compression or a decrease in bulk density given by aeration [16].

The disturbance on the bulk density is given by positive as well as negative changes in step on the silica concentration from the nominal value of 0.2% to 0.35% at time t=250 s and from 0.2% to 0.05% at time t=300 s, respectively. To determine how the direction of the disturbance impacts the performance of the controller, step changes are introduced in both directions.

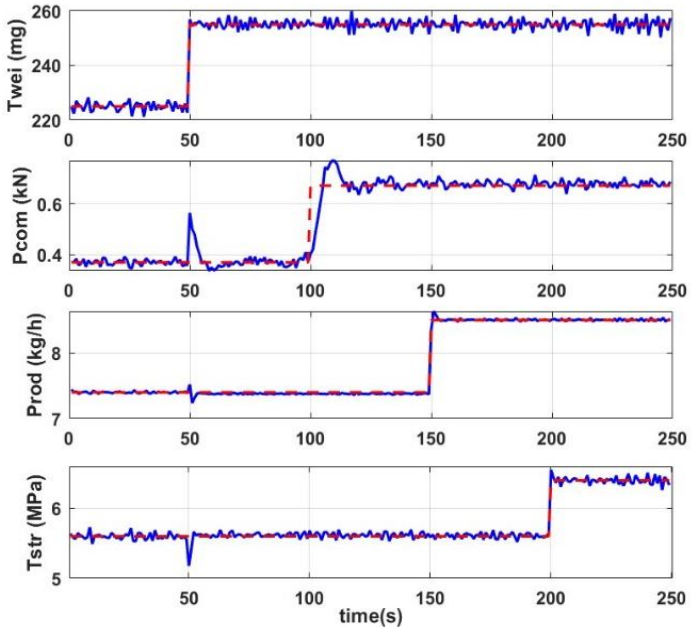


Fig. 4. mp-MPC, setpoint tracking – output variables with sensor measurement noise (Twei - tablet weight, Pcom - pre-compression force, Prod - production rate, and Tstr tensile strength)

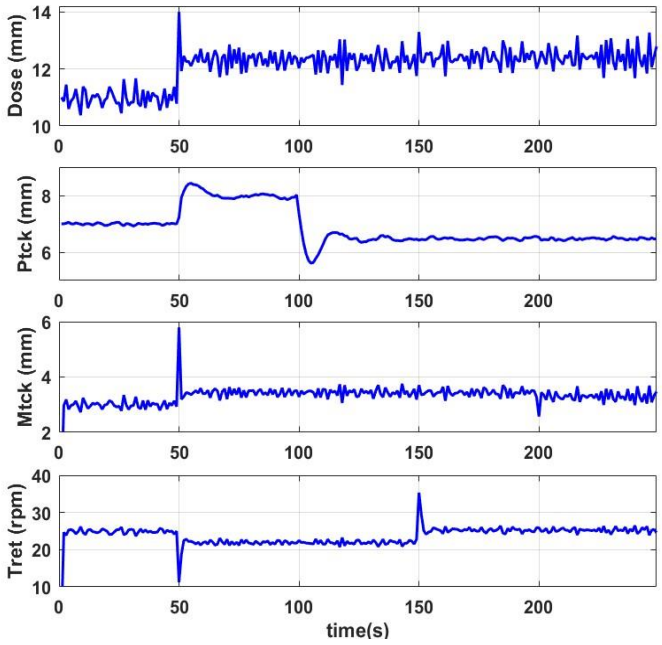


Fig. 5. mp-MPC, setpoint tracking - control action with sensor measurement noise (Dose - dosing position, Ptck - pre-compression thickness, Mtck - main compression thickness and Tret - turret speed)

Fig. 6 and Fig.7 presents the closed loop response of the outputs and the control action of the process under this disturbances. It can be observed that the controller presents good performances, it is capable of bringing the process back to the desired setpoint values even when dealing with process disturbances.

In all the cases presented, to improve the control performances different tuning parameters of the predictive controllers can be given. To change how fast and how aggressive the

controller responds, different prediction horizon can be given as well as different penalties on the different control actions.

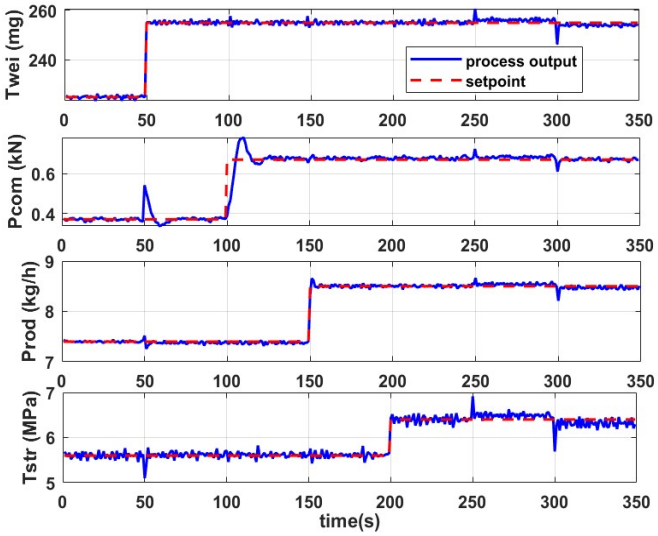


Fig. 6. mp-MPC, disturbance rejection - output variables with sensor measurement noise (Twei - tablet weight, Pcom - pre-compression force, Prod - production rate, and Tstr tensile strength)

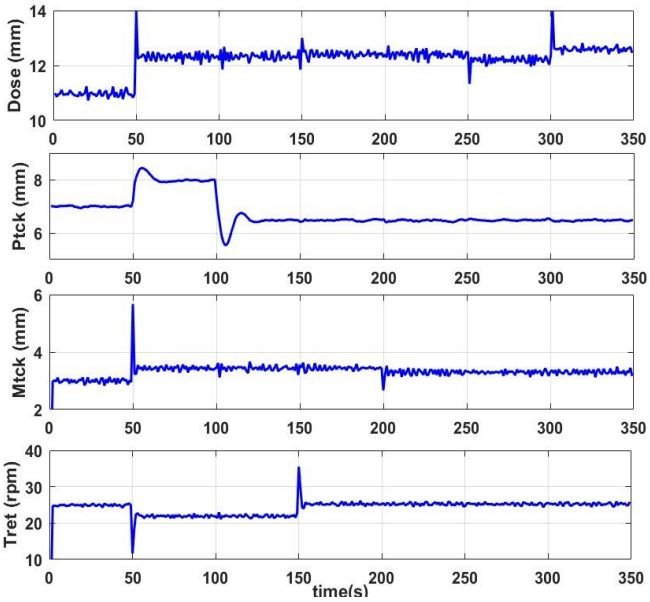


Fig. 7. mp-MPC, disturbance rejection - control action with sensor measurement noise (Dose - dosing position, Ptck - pre-compression thickness, Mtck - main compression thickness and Tret - turret speed)

1. Seborg, D.E., et al., *Process dynamics and control*. 2017.
2. Su, Q., et al., *A perspective on Quality-by-Control (QbC) in pharmaceutical continuous manufacturing.* Computers and Chemical Engineering, 2019. **125**: p. 216-231.

3. Su, Q., et al., *Resilience and risk analysis of fault-tolerant process control design in continuous pharmaceutical manufacturing.* Journal of Loss Prevention in the Process Industries, 2018. **55**: p. 411-422.
4. Ierapetritou, M., F. Muzzio, and G. Reklaitis, *Perspectives on the continuous manufacturing of powder-based pharmaceutical processes.* AIChE Journal, 2016. **62**(6): p. 1846-1862.
5. Nașcu, I., et al., *Advanced model predictive control strategies for evaporation processes in the pharmaceutical industries.* Computers & Chemical Engineering, 2023. **173**: p. 108212.
6. Destro, F. and M. Barolo, *A review on the modernization of pharmaceutical development and manufacturing – Trends, perspectives, and the role of mathematical modeling.* International Journal of Pharmaceutics, 2022. **620**: p. 121715.
7. Nascu, I., N.A. Diangelakis, and E. Pistikopoulos, *Multiparametric Model Predictive Control Strategies for Evaporation Processes in Pharmaceutical Industries.* 32nd European Symposium on Computer Aided Process Engineering; Elsevier, 2016;, Computer Aided Chemical Engineering, 2022.
8. Pistikopoulos, E.N., et al., *On-line optimization via off-line parametric optimization tools.* Computers and Chemical Engineering, 2002. **26**(2): p. 175-185.
9. Diangelakis, N.A., et al., *Process design and control optimization: A simultaneous approach by multi-parametric programming.* AIChE Journal, 2017. **63**(11): p. 4827-4846.
10. Pistikopoulos, E.N., et al., *PAROC - An integrated framework and software platform for the optimisation and advanced model-based control of process systems.* Chemical Engineering Science, 2015. **136**: p. 115-138.
11. de Meira, R.Z.C., et al., *In Vitro Dissolution Profile of Dapagliflozin: Development, Method Validation, and Analysis of Commercial Tablets.* International Journal of Analytical Chemistry, 2017. **2017**: p. 2951529.
12. Kawakita, K. and K.-H. Lüdde, *Some considerations on powder compression equations.* Powder Technology, 1971. **4**(2): p. 61-68.
13. Gonzalez, M., *Generalized loading-unloading contact laws for elasto-plastic spheres with bonding strength.* Journal of the Mechanics and Physics of Solids, 2019. **122**: p. 633-656.
14. !!! INVALID CITATION !!! [10, 14, 15].
15. Oberdieck, R., et al., *POP - Parametric Optimization Toolbox.* Industrial and Engineering Chemistry Research, 2016. **55**(33): p. 8979-8991.
16. Blackshields, C. and A. Crean, *Continuous Powder Feeding for Pharmaceutical Solid Dosage Form Manufacture: A Short Review.* Pharmaceutical Development and Technology, 2017. **23**: p. 1-19.