Model Predictive Control Strategies for Continuous Manufacturing Processes

Ioana Nascua,d,\*, Nikolaos A. Diangelakisb, Mircea Șușcăa, Vlad Mihalya and Zoltan Nagy c

a Department of Automation Technical University of Cluj Napoca, Romania

b School of Chemical and Environmental Engineering Technical University of Crete

c Davidson School of Chemical Engineering, Purdue University, West Lafayette, USA

d Academy of Romanian Scientists, Romania

Ioana.Nascu@aut.utcluj.ro

Abstract

Under the influence of Pharma 4.0, the pharmaceutical manufacturing industry is experiencing a paradigm change from traditional batch manufacturing to continuous manufacturing, a faster and more efficient approach. This work paves the way towards state-of-the-art Quality-by-Control advanced model based predictive control (MPC) strategies for a continuous manufacturing process. Model based predictive control strategies are a great fit for assuring a Quality-by-Control approach and facilitate the transition towards Industry 4.0. An advanced model-based predictive control strategy is designed for the control of a continuous manufacturing process in the pharmaceutical industry, specifically for solid dosage forms. The model employed for the development of the advanced controlled strategies is first validated and calibrated with real data from a pilot plant. The results show enhanced process performance, characterized by increased process efficiency and flexibility, and reduced environmental impact, even in the presence of process uncertainties and measurement noise.

**Keywords**: pharmaceuticals, process control, rotary tablet press, model based predictive control, Quality by Control.

* 1. Introduction

The pharmaceutical industry involves complex processes that have to operate close to operational and regulatory constraints with strict quality specifications for its products. It deals with highly integrated and intricate processes, process/model uncertainty, varying production targets, and raw material variability (Su et al, 2019, Chen et al, 2022, Huang et al, 2022). Traditionally, pharmaceutical manufacturing follows a batch processing approach, where the quality control is implemented using quality-by-testing where the drug product quality is assessed in the final processing step of each batch.

Motivated by the need for cost-effectiveness enhanced sustainability, reliability, and the pursuit of targeted solutions for smaller patient populations, coupled with advancements in modern manufacturing technology, continuous manufacturing has started to replace batch manufacturing in the pharmaceutical industry (Nașcu et al, 2023, Destro and Barolo 2022, Nascu et al, 2022). This transition will also result in a shift towards quality-by-control (QbC). QbC involves designing and operating robust manufacturing systems that employs an active process control system, relying on the robustness of process design. This shift represents an important step towards smart manufacturing (Su et al, 2019, Nascu et al, 2023, Diangelakis et al, 2023, Pistikopoulos et al, 2021).

This work establishes the foundation for state-of-the-art Quality-by-Control model based predictive control (MPC) strategies for a tablet manufacturing process. Initially, a process model is developed, validated, and calibrated using actual data obtained from a pilot plant. Subsequently, this model is employed to design advanced MPCs with a focus on robustness, particularly in handling uncertainties, variable time delays, effective disturbance rejection, and explicit incorporation of constraints. This is a great advantage for the pharmaceutical manufacturing industries particularly when dealing with the exigent Food and Drug Administration (FDA) regulations.

* 1. Theoretical Background
     1. Process Model

The lubricant/glidant feeder and the rotating tablet press represent key unit operations in pharmaceutical manufacturing. Mechanistic models of the glidant's impact on die filling and compression processes are employed to monitor and control the tensile strength and porosity of the tablets (de Meira et al, 2017). To determine the weight (W) of the convex tablet formed using Natoli D-type tooling with a shallow cup depth, Eq (1) is used.

(1)

The variables *ρb, Vfill , Hfill, nT, nF*, and *D* denote the powder bulk density, die cavity volume, position of the dose, turret speed, speed of the feed frame, and the diameter of the die, respectively. The model parameters ξ1 and ξ2 are estimated using experimental data. The tablet's production rate,  is calculated using :

, (2)

where *Nstation* represents the number of available turret stations.The pre-compression force (PCF) can be computed using:

. (3)

*a* and *b* represents the Kawakita constants, *ρc* represents the critical density and *ρpc*, the relative density of the pre-compression involves the use of the following equations:

 . (4)

*Hpc* denotes the true density of the powder, and *ρt* represents the pre-compression thickness. Therefore, the main compression force, *Fpunch*, is determined using:

 (5)

The in-die relative density *ρin-die* is determined as follows:

and . (6)

The main compression thickness is represented by *Hin-die*. The density of the tablet, *ρtablet*, is determined using the elastic recovery*, ερ*:

. (7)

The tensile strength (*σt*) is influenced by glidant conditions and is calculated using the following equation:

. (8)

*σ0* represents the tensile strength when porosity is zero, while *σc, σt* denotes the relative critical density, where tablets do not exhibit any tensile strength.

In this study, a Natoli NP-400 tablet press and SOTAX AT4 tablet tester are used to produce tablets and collect data from experiments at steady-state conditions. The data obtained from experiments is utilized to determine the parameters for the real model. These parameters are then used to fit and calibrate the model used for simulations.

* + 1. Extended Prediction Self-Adaptive Control

Fig. 1 presents a schematic representation of the developed hierarchical control system layers. For the implementation of the MPC we have used the Extended Prediction Self-Adaptive Controller (EPSAC) approach, described in detail in De Keyser 2003) with four inputs and four outputs. To obtain the EPSAC control laws the following cost function is minimized:

Where *ri* are the reference trajectories for the controlled outputs, *ui* the process inputs and *yi* the measured process outputs.



Fig 1. Schematic representation of the rotary tablet press control diagram

* + 1. Control Design

To design the controller, the tuning parameters that are determined for this work are: the control horizons for the four inputs we have *Nui=1* and for the prediction horizons we have *N1=5, N2= N3= N4=10*. The selection of control and prediction horizons considers the characteristics of the process and the desired closed-loop performances. For processes without unstable underdamped or unstable poles, as in the current process, a value of *Nu=1* is generally sufficient when determining *Nu*. The sample time is set at Ts=1 s since measured data is available from the plant every 1 second. Constraints will be applied to all the manipulated inputs. Model predictive controllers offer the advantage of seamlessly integrating constraints. The specific constraints on the manipulated inputs are as follows: dosing position between 6mm and 20mm, pre-compression thickness between 0.5mm and 14mm, main compression thickness between 0.5mm and 6mm, and turret speed between 0 rpm and 60 rpm.

* 1. Results

In this work, based on the process model outlined in Section II.A, a total of 4 inputs and 4 outputs are employed to determine the multiple input multiple output (MIMO) linear model using the System Identification toolbox in MATLAB. This linear model will be subsequently utilized in the controller design. The four controlled variables in this process encompass the tablet weight, pre-compression force, production rate, and tensile strength. The corresponding manipulated variables are: dosing position, pre-compression thickness, main compression thickness, and turret speed. Sensor measurements for tablet tensile strength are available every second. The model parameters employed in this paper are derived from experimental data and include: ξ1 = 0.036, ξ2 = 0.03, *ρb*=0.365 g/cm3, *ρc*=0.265, *a* = 0.8, 1/*b*= 10.26 MPa, *ρt* = 1.53 g/cm3, *, ε0*=0.08, *ρc,ε,* = 0.57, *σ0* = 11.67 MPa, *ρ0=*0.57, *ρ∞*=0.61, *b1* = 0.31, *b1* = 0.38, *b1* = 8.4, *ρb,∞* = 0.45 g/cm3, *ρb,0* = 0.33 g/cm3, *r1* = 0.361*, r2* = 1.394*, r3* =23.326.

* + 1. Setpoint Changes

To test the performance of the implemented control strategy, setpoint changes are given for the tablet weight, from 225 mg to 255 mg at time t = 60 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 = 20 s, and for the tensile strength, from 5.6 MPa to 6.4 MPa at time t=140 s.



Fig. 2. MPC, setpoint (red line) tracking – output variables (blue line) (left side) (Twei - tablet weight, Pcom - pre-compression force, Prod - production rate, and Tstr tensile strength) and control variables (right side) (Dose - dosing position, Ptck - pre-compression thickness, Mtck - main compression thickness and Tret - turret speed).

Fig. 2 illustrates the closed loop system response for setpoint changes using the EPSAC assuming no noise on the measured outputs. On the left side we have the response for the controlled variables. It can be discerned that the outputs are coupled. This means that a setpoint change in any output affects the others. On the right side we have the close-loop response control action, highlighting that the setpoint change in tablet weight (introduced at time t=60 s) has the most significant impact on all outputs.

The EPSAC controller exhibits good performance characteristics, including rapid settling time, small overshoot and undershoot, and no setpoint offset for consecutive changes in all references. Being multivariable, the control algorithm efficiently manages the interdependencies between inputs and outputs, effectively minimizing deviations of other outputs from reference values when the reference of one output changes. The manipulated variables evolve within saturation limits, and every change illustrated in this study is realistic and feasible under normal operation conditions of the tablet press.

* + 1. Noise and Disturbance Rejection

To conduct a more comprehensive assessment of controller performance, sensor measurement noise is incorporated. To simulate this noise, a normally distributed error with zero mean and variance is introduced to the real sensor variability, sourced from historical plant data. The results of the closed-loop response for both controlled variables and control actions are depicted in Fig. 3. The EPSAC controller shows good performers in the presence of sensor measurement noise, with all dynamic and stationary parameters of the response maintained. Through an appropriate selection of design parameters, it becomes feasible to attenuate oscillations arising from measurement noise while maintaining a balance between response time and the propagation of these oscillations in the control loop. Should a damping of these oscillations be desired for all manipulated variables, one can achieve this by reducing the controller's aggressiveness on the respective loops through the selection of appropriate design parameters.



Fig. 2. MPC, setpoint (red line) tracking with sensor measurement noise– output variables (blue line) (left side) (Twei - tablet weight, Pcom - pre-compression force, Prod - production rate, and Tstr tensile strength) and control variables (right side) (Dose - dosing position, Ptck - pre-compression thickness, Mtck - main compression thickness and Tret - turret speed).

* 1. Conclusions

For the pharmaceutical manufacturing industry to advance into smart manufacturing and align with the Industry 4.0 revolution, a transition towards Quality-by-Control is imperative. The principal objective of this study is to develop advanced model-based predictive control techniques for a continuous pharmaceutical manufacturing process involving a rotary tablet press, following the Quality-by-Control paradigm. To assess the performances of the developed model predictive controller, it is implemented on a simulation platform utilizing the developed high fidelity model, validated and calibrated with real data obtained from a pilot plant. The controller performances are tested for: (i) tracking of reference changes, involving step changes in dosing position, pre-compression thickness, main compression thickness, and turret speed inputs; (ii) rejection of measurement noise

The developed control strategies exhibit promising performances, characterized by fast settling times, absence of offset errors, and negligible undershoot or overshoot, even in the presence of sensor measurement noise. These outcomes imply enhanced process efficiency, heightened process flexibility, and decreased environmental impact, even in the presence of process model uncertainties and measurement noise.

Acknowledgments

Financial support from Ministry of Research, Innovation and Digitization, CCCDI - UEFISCDI, project number PN-III-P2-2.1-PED-2021-1147, within PNCDI III

References

Chen, Y., Bhalode, P., Ou, Y. and Ierapetritou, M. (2022) 'PSE Tools and Challenges in the Development of Advanced Pharmaceutical Manufacturing' in *Computer Aided Chemical Engineering*,21-24.

De Keyser, R. (2003) *Model Based Predictive Control,* *Invited Chapter, in UNESCO Encyclopedia of Life Support Systems (EoLSS),* Eolss Publishers Co Ltd, Oxford, 2003,.

de Meira, R. Z. C., Maciel, A. B., Murakami, F. S., de Oliveira, P. R. and Bernardi, L. S. (2017) 'In Vitro Dissolution Profile of Dapagliflozin: Development, Method Validation, and Analysis of Commercial Tablets', *International Journal of Analytical Chemistry,* 2017, 2951529.

Destro, F. and Barolo, M. (2022) 'A review on the modernization of pharmaceutical development and manufacturing – Trends, perspectives, and the role of mathematical modeling', *International Journal of Pharmaceutics,* 620, 121715.

Diangelakis, N. A., Pappas, I. and Pistikopoulos, E. N. (2023) 'Robust (explicit) optimization and control via Mixed Integer Programming' in *Computer Aided Chemical Engineering*,1711-1716.

Huang, Y. S., Sheriff, M. Z., Bachawala, S., Gonzalez, M., Nagy, Z. K. and Reklaitis, G. V. (2022) 'Application of MHE-based NMPC on a Rotary Tablet Press under Plant-Model Mismatch' in *Computer Aided Chemical Engineering*,2149-2154.

Nascu, I., Diangelakis, N. A., Huang, Y.-S., Nagy, Z. K., Birs, I. and Nascu, I. (2023) 'Multi-parametric Model Predictive Control Strategies for a Rotary Tablet Press in Pharmaceutical Industry', *IEEE INTERNATIONAL CONFERENCE ON SYSTEMS, MAN, AND CYBERNETICS*

Nașcu, I., Diangelakis, N. A., Muñoz, S. G. and Pistikopoulos, E. N. (2023) 'Advanced model predictive control strategies for evaporation processes in the pharmaceutical industries', *Computers & Chemical Engineering,* 173, 108212.

Nascu, I., Diangelakis, N. A. and Pistikopoulos, E. (2022) '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*.

Pistikopoulos, E. N., Barbosa-Povoa, A., Lee, J. H., Misener, R., Mitsos, A., Reklaitis, G. V., Venkatasubramanian, V., You, F. Q. and Gani, R. (2021) 'Process systems engineering - The generation next?', *Computers & Chemical Engineering,* 147.

Su, Q., Ganesh, S., Moreno, M., Bommireddy, Y., Gonzalez, M., Reklaitis, G. V. and Nagy, Z. K. (2019) 'A perspective on Quality-by-Control (QbC) in pharmaceutical continuous manufacturing', *Computers and Chemical Engineering,* 125, 216-231.