From batch to continuous tablet manufacturing: a control perspective

Diego Malevez[1] **and Dana Copot***[1,2]

[1] *Research group of Dynamical Systems and Control, Ghent University, Tech Lane Science Park 125, 9052, Ghent, Belgium*
[2] *EEDT—Core Lab on Decision and Control, Flanders Make Consortium, Tech Lane Science Park 131, 9052, Ghent, Belgium*
Corresponding author: dana.copot@ugent.be

Abstract: Despite manufacturing innovations and the technologies on the rise, solid oral dosage in the pharmaceutical industry is still mass production. Although this is efficient and cost-effective, it is typically based on a 'one-size-fits-all' product concept and lacks the flexibility and agility required to fully meet the needs of the individual patient. Nowadays pharmaceutical industry is experiencing a paradigm shift from batch to continuous manufacturing. This will lead to increased flexibility to target diverse populations as well as more consistent product quality to ensure best efficacy. Continuous processing integrated with online/inline monitoring tools coupled with an efficient automatic feedback control system is highly desired by the pharmaceutical industry. To facilitate the transition from the batch wise production to continuous manufacturing in the pharma industry engineering tools are needed. Hence, the aim of this paper is to enhance the advantage of modeling and control techniques in the field of pharmaceutical applications.

Keywords: continuous manufacturing, process control, advanced manufacturing, personalized medicine

1. INTRODUCTION

In the domain of healthcare, understanding disease mechanisms and developing successful treatments are enormous societal challenges. Moreover, the pandemic crisis during the past year posed unprecedented challenges to the continuity of drug production and highlighted that pharmaceutical manufacturing capacity needs to be flexible and adaptive to ensure that it remains proportional to actual needs. In short, there is evidence to indicate that classical state of art drug manufacturing is failing to cope with the fast-changing demand and specifications of the product in the context of personalized medicine Samad (2017); Vanhoorne and Vervaet (2020); Allison et al. (2015).

Globalization and the increased need for more personalized drug therapies require a paradigm change in pharma manufacturing. Continuous manufacturing will replace traditional batch production processes leading to a greater flexibility to target diverse populations but also more consistent product quality to ensure efficacy Nepveux et al. (2015); Byrn et al. (2015); Vanhoorne and Vervaet (2020). Continuous manufacturing enables up- and down scaling of production on demand which will allow a dramatic increase in supply during crisis situations but will also avoid unnecessary stock piling of medicines (which are then discarded on expiration). The tangible benefits of continuous production will result in: 50% reduction in product variations; 50-70% reduction in time required for quality control; up to 40% reduction in power consumption; lower the risk of stock-out; an economically viable route for personalized medicine, of which citizens will want more and more; 50-60% smaller physical footprint of the equipment.

In this context the application of predictive tools and the development of advanced control strategies will be crucial to ensure that the production process is optimized and resulting product quality is guaranteed at all times. Recent reviews have promoted timely applications of advanced control to optimize productivity and increase economic efficiency of manufacturing processes, while emphasizing the role of systems and control theory as enabling Industry 4.0 goals Lamnabhi-Lagarrigue et al. (2017); Schenkendorf et al. (2020). The scope of control makes it the quintessential multidisciplinary field Astrom and Kumar (2014). As highly relevant tools for industry application, PID (proportional-integral-derivative) control, identification methods and model based predictive control made the top three in industry Samad (2017); Lamnabhi-Lagarrigue et al. (2017); Lee et al. (2015).

To facilitate the transition from the batch wise production to continuous manufacturing in the pharma industry engineering tools are needed. Hence, the aim of this paper is to enhance the advantage of modelling and control techniques in the field of pharmaceutical applications. Section 2 is presenting the current state of the art and challenges in the field of pharmaceutical manufacturing. The equations governing the complex process of tablet manufacturing are briefly introduced in Section 3. A control feasibility study

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for continuous manufacturing of tablets is presented in Section 4. Preliminary results and and their interpretation are given in Section 5. Conclusions of this study and the future perspectives are provided in Section 6.

2. CONTINUOUS TABLET MANUFACTURING PROCESS: CHALLENGES AND OPPORTUNITIES

The entire process consists of a series of separate unit operations (e.g. dispensing, blending, granulation, drying, tableting). In continuous manufacturing, all unit operations are integrated into a single production train without interruptions. Consequently, to ensure that the final product complies with the approved certification for the specific drug, continuous monitoring of the parameters is ensured using the process analytical technology (PAT) (Xie and Schenkendorf, 2019).

The transition from batch to continuous represents a new landscape of opportunities and benefits such as: i) reduction in production costs: this can be achieved by design and implementation of event based control strategies and this without the necessity of new certification, ii) reduce manpower and consequently reduce human error; iii) reduce the production time (i.e. from raw material dispatch to finished product release) which will reduce the risk of drug shortages; iv) reduction in product deviations; v) reduce the time needed for quality control. There is a increased interest in both modelling and control of pharmaceutical processes as it can be seen from figure 1.

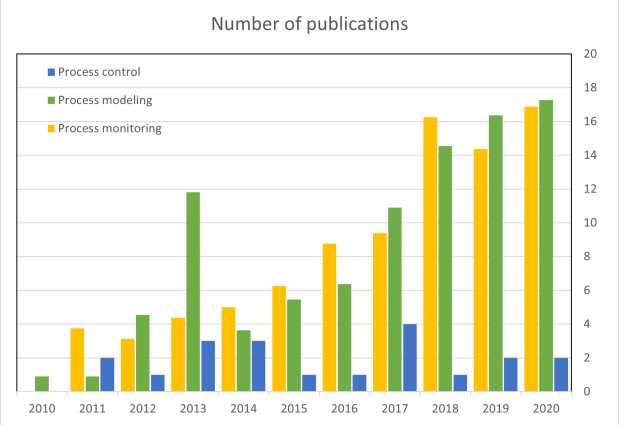

Fig. 1. Evolution of publications on process monitoring, modeling and control of pharmaceutical processes.

Continuous manufacturing does not require any space for storing in-process material as once the batch is initiated, the finished product will be the output of the process. Additionally, continuous manufacturing prevents the segregation of material, which occurs with different batch manufacturing processes during in-process material transfer from one process area to another process area. In continuous manufacturing lab scale equipment's can be used for production scale (Nicolaï, 2019). In conventional batch manufacturing, any discrepancies during the process may lead to rejection of the entire batch (Xie and Schenkendorf, 2019). However, because a specific amount of product is processed at each step in continuous manufacturing, any discrepancies may lead to the rejection of only limited product, thereby saving the unaffected material. The development of advanced inline monitoring techniques tracks the product at each individual stage of manufacturing and eventually saves additional analysis time, thereby enabling the direct release of the continuously manufactured batch into the market without delay.

Current bottlenecks in tablet manufacturing operations include:

- Fluctuations in tablet weight, usually caused by uneven powder flow into the die due to poor powder flow properties.
- Fluctuations in dosage of the active pharmaceutical ingredient, caused by uneven distribution of the API in the tableting blend (either due to poor mixing or separation in process).
- Sticking of the powder blend to the tablet tooling, due to inadequate lubrication, worn or dirty tooling, or a sticky powder formulation.
- Capping, lamination or chipping. This is caused by air being compressed with the tablet formulation and then expanding when the punch is released: if this breaks the tablet apart, it can be due to incorrect machine settings, or due to incorrect formulation (either because is too brittle or not adhesive enough, either it has too low bulk density).

3. PROCESS DESCRIPTION

A model library to describe the dynamics of the different process units in a tableting manufacturing line was developed. In the tablet-pressing process, it is important that all ingredients be fairly dry, powdered or granular, somewhat uniform in particle size, and freely flowing. Mixed particle sized powders segregate during manufacturing operations due to different densities, which can result in tablets with poor drug or active pharmaceutical ingredient content uniformity, but granulation sub-unit process should prevent this. To optimize tablet production, essential properties of the material need to be used and follow up during the various process stages. The process of tablet manufacturing considered in this paper is a multivariable system with interacting sub-systems as shown in figure 2.

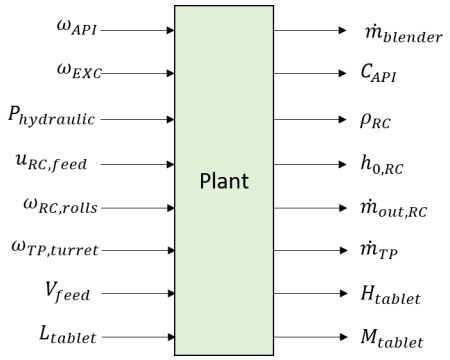

Fig. 2. Input-output representation of the tablet manufacturing process.

The feeders are used to feed the API, excipients and lubricants into the blender. The dynamics of the feeder can be characterized by Heckel's equation:

$$\rho_{apparent}(P) = \rho_{true} - (\rho_{true} - \rho_{bulk})e^{-kP} \quad (1)$$

where $\rho_{apparent}$ is the apparent material density after compression takes place, ρ_{true} is the true density of the material, ρ_{bulk} is the bulk density of the material, P is the pressure exerted on the material and k is a certain constant of the material that relates the compression pressure to changes in the apparent density.

A population balance modelling approach has been used to model the blending process as described by equation (2).

$$\frac{\partial m_{ij}}{\partial t} = F_f[m_{i-1,j} - m_{i,j}] + F_b[m_{i+1,j} - m_{i,j}] + F_r[m_{i,j+1} + m_{i,j-1} - m_{i,j}] \quad (2)$$

The above equation shows the powder holdup of both the API and the excipient in each compartment. The fluxes in the equations above can be obtained using:

$$\begin{aligned} F_f &= a\omega_{blender} + b \\ F_b &= c\omega_{blender} + d \\ F_r &= e \end{aligned} \quad (3)$$

where $\omega_{blender}$ represents the speed of the blender and the rest are constant parameters estimated from experimental data.

The hopper model is quite simple and the change in volume in the hopper can be described by the following equation when $h < H_1$:

$$\frac{dV}{dt} = \frac{1}{3}\pi\left[\left(\frac{R_2}{H_1}h\right)^2 + R_1\left(\frac{R_2}{H_1}h\right) + R_1^2\right]\frac{dh}{dt} \quad (4)$$

or when $h > H_1$

$$\frac{dV}{dt} = \pi R_2^2 \frac{dh}{dt} \quad (5)$$

Mass balance equation governing the system dynamics is given by:

$$\rho_b \frac{dV}{dt} = \dot{m}_{in} - \dot{m}_{out} \quad (6)$$

$\dot{m}_{in}$ in equation (6) represents the inlet mass flow rate that is coming from the blender. $\dot{m}_{out}$ is the outlet mass flow rate which is assumed to be equal to $\dot{m}_{out} = b\sqrt{h}$.

Weight of the tablet can be calculated as $M = V_0\rho_{bulk}$. Feed volume for the tablet is $V_0 = L_{depth}A_{tablet}$ with the area of the tablet $A_{tablet} = \frac{\pi d_{tablet}^2}{4}$. The pre-compression and main compression pressures are derived from the Kawakita compression equations, given by equations (7) and (8). These equations give the peak compression pressure and use a Kawakita parameter b which is a material dependent parameter.

$$C\_P_{pre} = \frac{V_0 - V_{pre}}{b_{pre}(V_0(\epsilon_0 - 1) + V_{pre})} \quad (7)$$

$$C\_P_{main} = \frac{V_{pre} - V_{tablet}}{b_{main}(V_{pre}(\epsilon_{main} - 1) + V_{tablet})} \quad (8)$$

If the true densities of the API and excipient are known, the initial porosity can be calculated using the following equations:

$$\epsilon_0 = 1 - \left(\frac{\rho_{true}}{\rho_{bulk}}\right) \quad (9)$$

$$\rho_{true}^{mix} = \rho_{true}^{A}\left(\frac{w_A}{w_A + w_B}\right) + \rho_{true}^{B}\left(\frac{w_B}{w_A + w_B}\right) \quad (10)$$

where w_A and w_B represent the weight of the API and the excipient in the blend.

After the pre-compression, there is a change in the porosity of the tablet which is called the main porosity or the porosity before the main compression in the model.

$$\epsilon_{main} = 1 - \frac{(1 - \epsilon_0)V_0}{V_{pre}} \quad (11)$$

The equations (7) and (8) also need the volume of the tablet V_{tablet} and the pre-compression volume V_{pre}:

$$\begin{aligned} V_{tablet} &= L_{tablet}A_{tablet} \\ V_{pre} &= L_{pre}A_{tablet} \end{aligned} \quad (12)$$

where L_{pre} is the pre-compression length which is the height of the powder after the compression in the die.
The pre- and main-compression force involve a multiplication by 10^6 and are given by:

$$\begin{aligned} C\_F_{pre} &= 10^6 C\_P_{pre}A_{tablet} \\ C\_F_{main} &= 10^6 C\_P_{main}A_{tablet} \end{aligned} \quad (13)$$

The hardness of a tablet is computed as follows:

$$H_{tablet} = H_{max}(1 - e^{\rho_r - \rho_{rc} + \lambda_{hard}}) \quad (14)$$

where the relative density ρ_r and the intermediate term λ_H can be calculated using the equations down below:

$$\begin{aligned} \rho_r &= \frac{V_{solid}}{V_{tablet}} \\ \lambda_H &= log\left(\frac{1 - \rho_r}{14 - \rho_{rc}}\right) \end{aligned} \quad (15)$$

where the solid volume V_{solid} of the powder is determined by $V_{solid} = (1 - \epsilon_0)V_0$.

The input/output operation ranges are given in tables. 1-2

Table 1. Operating ranges for input variables

Input variable	Nominal	LB	UB	unit
Screw speed Exc (ω_{Exc})	207.6	0	240	rpm
Screw speed API (ω_{API})	37.4	0	240	rpm
Velocity rolls ($\omega_{RC,rolls}$)	5	1	10	rpm
Feed speed (u_d)	2.017	1	5	cm/s
Hydraulic pressure ($P_{hydraulic}$)	1	1	10	MPa
Height tablet (L_{tablet})	4	3.8	5	mm
Feed volume (V_{feed})	0.96	0.9	1.1	cm^3
Turret speed ($\omega_{TP,turret}$)	45	40	50	rpm

Table 2. Operating ranges for output variables

Output variable	Nominal	LB	UB	unit
Mass flowrate ($\dot{m}_{blender}$)	20	17	23	kg/h
Concentration API (C_{API})	0.15	0.10	0.20	-
Density outlet RC (ρ_{RC})	1.057	0.8	1.2	g/cm^3
Throughput ($\dot{m}_{out,RC}$)	20	17	23	kg/h
Roller gap ($h_{0,RC}$)	1.6	1	5	mm
Hardness (H_{tablet})	5.433	4	6	MPa
Mass tablet (M_{tablet})	0.4566	0.44	0.47	g
Tablet rate ($\dot{m}_{TP}$)	20	17	23	kg/h

4. CONTROL DESIGN: A FEASIBILITY STUDY

Despite the increased process knowledge and measurement techniques, control of the intermediate and final quality attributes in the pharmaceutical industry is still mainly based on a fixed recipe approach, where parameters are optimized once for a theoretical steady-state output, combined with acceptance sampling strategies Matero et al. (2013). However, in reality the appearance of changes in raw material properties, equipment status with respect to physical wear and varying ambient conditions contribute to disturbances which vary in time and demand for continuous corrective actions during production. In fact, changes in material throughput related to market demand can also be seen as a disturbance which needs to be compensated for to assure product quality. The traditional manufacturing approach which generally adopts automatic regulatory process control in combination with manual supervision, does not compensate in real-time for such critical quality attribute variations. Therefore, the concept of continuous pharmaceutical manufacturing does still not completely align with the design, analysis, and control framework proposed in the process analytic technology guidance.

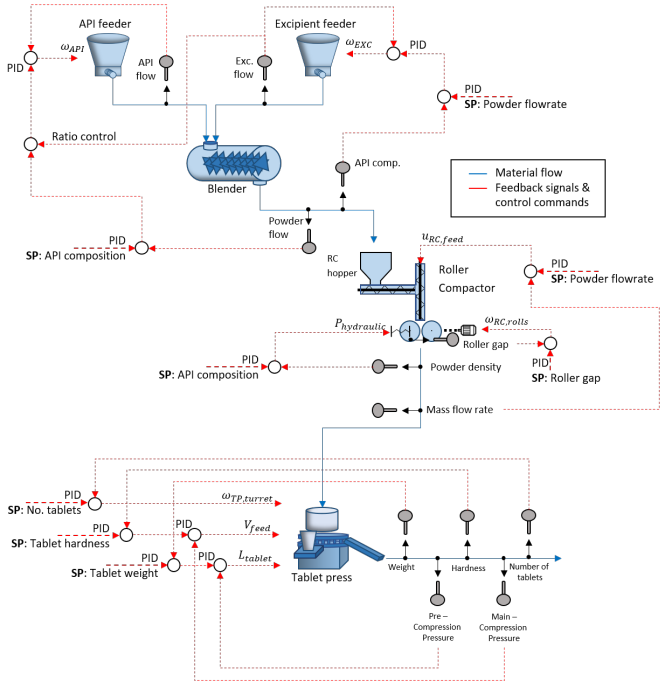

Fig. 3. Overview of the process units implemented in Matlab/Simulink benchmark platform.

To tackle these challenges, academia and industry both make attempts to include automated supervisory process control in the manufacturing process. The aim is to automatically assure that critical quality attributes are consistently in agreement with the acceptance criteria in real-time (Singh et al., 2015). A schematic representation of the process units implemented in the simulator are depicted in figure 3. Some of the commonly encountered subunit processes in real life production of tablets are: direct compaction, dry granulation wet granulation, extrusion, granule lubrication, tablet pressing, coating, splitting, etc.

As a closed-loop optimal control based method with explicit use of a process model, model predictive control (MPC) has proven to be a very effective control strategy over the last 20 years and has been widely used in process industries such as oil refining and bulk chemical production. It has the advantage of being rather operator friendly for non-precision processes and tested successfully in a wide range of simulation processes and experimental setups, ranging from multivariable systems, to time delay systems and open loop unstable systems (Ionescu and Copot, 2019; Maxim et al., 2018, 2019). However, because of different level of complexities involved (e.g., solid handling, irregular flow) in addition to the unavailability of a suitable process model, the design and implementation of MPC in pharmaceutical manufacturing involving solid dosage forms is still an open area of research.

MPC has established itself in industry as an important advanced process control strategy, because of its advantages over conventional regulatory controllers, and it continues to be the technology of choice for constrained multivariable control applications in the process industry (Maxim et al., 2019; Samad, 2017). MPC refers to a family of control algorithms that employ an explicit model to predict the future behavior of the process over an extended prediction horizon. These algorithms are formulated as a performance objective function, which is defined as a combination of set point tracking performance and control effort. This objective function is minimized by computing a profile of controller output moves over a control horizon (Maxim et al., 2019, 2018; Nicolai et al., 2018). However, in this paper a PID control approach is designed and tested on the developed simulator. Ongoing research is focused on the development of plant-wide control design for performance improvement.

5. RESULTS AND DISCUSSION

Tablets represent the most used and most conveniently applied route of drug administration. A tablet comprises a mixture of active substances and excipients, usually in powder form, pressed or compacted from a powder into a solid dose. The excipients can include diluents, binders or granulating agents, flow aids and lubricants to ensure efficient tableting. It may also have dis-integrants to promote tablet break-up in the digestive tract, sweeteners or flavors to enhance taste and pigments to make the tablets visually attractive or aid in visual identification of an unknown tablet. A polymer coating is often applied to make the tablet smoother and easier to swallow, to control the release rate of the active ingredient, to make it more resistant to the environment (extending its shelf life), or to enhance the tablet's appearance.

The production thereof is a complex multivariable process and modifications to any of the mentioned components can have important implications on the efficiency of the production process (eg. changes in powder stickiness or mixture viscosity). Therefore, optimal control of production efficiency and product properties are essential to guarantee a manufacturing process that is adaptive while maintaining quality at all time. In this paper a comprehensive simulator has been developed including the processes involved in the manufacturing of tablets. This resulted in a complex 8x8 multivariable system.

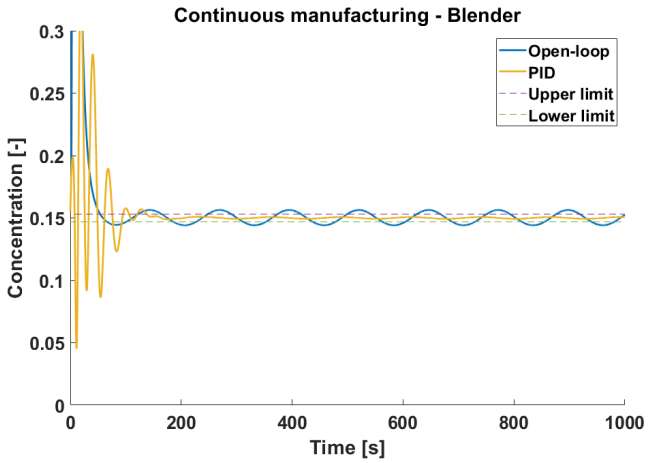

Fig. 4. PID performance for the concentration of API.

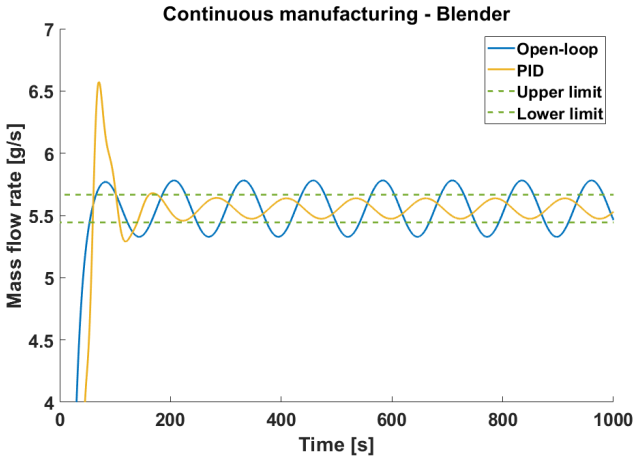

Fig. 5. PID performance for mass flow rate.

A preliminary control implementation has been performed and the first-hand results are given in figures 4-8. These incentive results have been obtained with classical PID control algorithm. For each unit a PID control has been designed and it can be noticed that for most of the controlled variables the results are within the recommended intervals. However, there is much room for improvement specially if we discuss from the perspective of continuous manufacturing. Hence, more advanced control strategies such as MPC need to be considered. Depending on the process dynamics and given that MPC requires a detailed process model and the optimization procedure is computationally expensive, a less exhaustive control scheme might be necessary. In this case, the optimal solution will be a hybrid control strategy integrating the advantages of both classical and advanced control. This will result in a optimal system-wide control of a process exhibiting both fast and delayed dynamics.

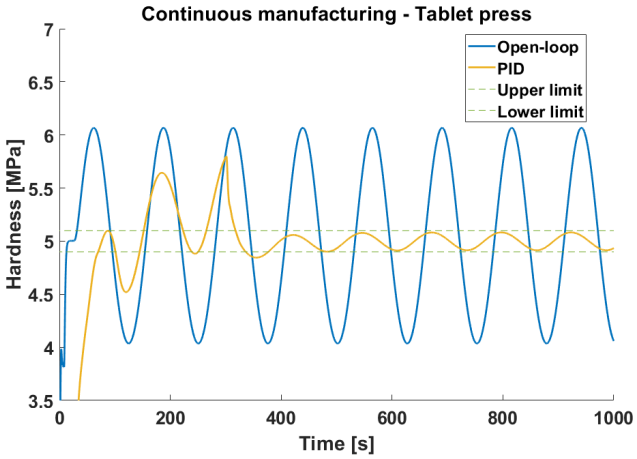

Fig. 6. PID performance for tablet hardness.

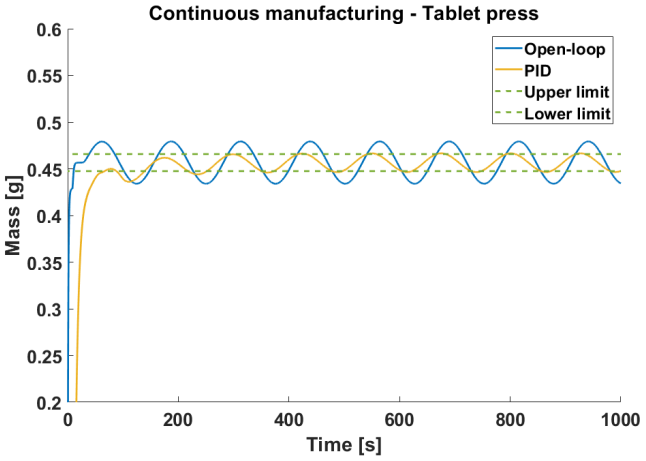

Fig. 7. PID performance for the mass of the tablet.

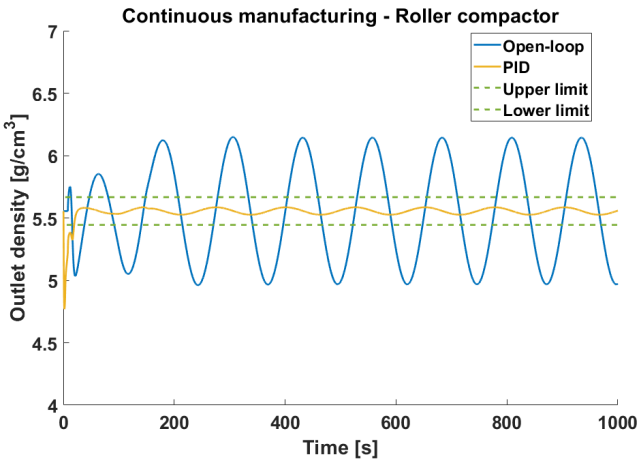

Fig. 8. PID performance for the density of the tablet.

The ability of the PID control strategy to track step changes in set point as well as to reject the disturbances has been analyzed. The performance for the blender is

shown in figure 4. A sinusoidal disturbance has been added to the controlled variable. As also shown in the figure, in the case of open-loop control the control variable violates the operational ranges. In the case of closed loop control it can be observed that PID suppress the disturbance and maintains the variable within the specified limits. Similarly, for the other outputs the same performance is obtained.

The preliminary results presented in this paper suggest that classical PID control strategies are suitable for individual control of the process units. However, from a plant-wide perspective a hybrid control strategy where MPC acts as the supervisory controller and generates the set point for the slave PID controller would result in better performance. Hence, there is still room for improvement in terms of optimal control of continuous manufacturing of tablets.

6. CONCLUSIONS AND FUTURE PERSPECTIVES

In this paper a PID based control strategy for controlling the process of tablet manufacturing has been presented. The performance of the control algorithm is satisfactory and was able to track the set point and also to reject disturbances. However, there is still room for improvements and ongoing research focuses on development of hybrid control strategies where PID is implemented as slave controller and MPC as supervisory. This will result in an efficient and optimal control strategy for the pharmaceutical processes often consisting of fast and delayed mixed dynamics responses.

REFERENCES

Allison, G., Cain, Y., Cooney, C., Garcia, T., Bizjak, T., Holte, O., Jagota, N., Komas, B., Korakianiti, E., Kourti, D., Madurawe, R., Morefield, E., Montgomery, F., Nasr, M., Randolph, W., Robert, J., Rudd, D., and Zezza, D. (2015). Regulatory and quality considerations for continuous manufacturing. *Journal of Pharmaceutical Sciences*, 104, 803–812.

Astrom, K.J. and Kumar, P. (2014). Control: A perspective. *Automatica*, 50(1), 3–43.

Byrn, S., Futran, M., Thomas, H., Jayjock, E., Maron, N., Meyer, R., Myerson, A., Thien, M., and Trout, B. (2015). Achieving continuous manufacturing for final dosage formation: challenges and how to meet them. *Journal of Pharmaceutical Sciences*, 104, 792–802.

Ionescu, C.M. and Copot, D. (2019). Hands-on MPC tuning for industrial applications. *Bulletin of the Polish Academy os Science: Technical Sciences*, 67(5), 925–945. doi:10.24425/bpasts.2019.130877.

Lamnabhi-Lagarrigue, F., Annaswamy, A., Engell, S., Isaksson, A., Khargonekar, P., Murray, R.M., Nijmeijer, H., Samad, T., Tilbury, D., and Van den Hof, P. (2017). Systems and control for the future of humanity, research agenda: Current and future roles, impact and grand challenges. *Annual Reviews in Control*, 43, 1–64.

Lee, L., O'Connor, T.F., Yang, X., Cruz, C., Chatterjee, S., Madurawe, R., Moore, C., Yu, L., and Woodcock, J. (2015). Modernizing pharmaceutical manufacturing: from batch to continuous production. *Journal of Pharmaceutical Innovation*, 10, 191–199.

Matero, S., van Den Berg, F., Poutiainen, S., Rantanen, J., and Pajander, J. (2013). Towards better process understanding: chemometrics and multivariate measurements in manufacturing of solid dosage forms. *Journal of Pharmaceutical Sciences*, 102(5), 1385–1403.

Maxim, A., Copot, D., Copot, C., and Ionescu, C. (2019). The 5W's for control as part of Industry 4.0: Why, what, where, who and when – a PID and MPC control perspective. *Inventions*, 4(10), 10.3390/inventions4010010.

Maxim, A., Copot, D., De Keyser, R., and Ionescu, C. (2018). An industrially relevant formulation of a distributed model predictive control algorithm based on minimal process information. *Journal of Process Control*, 68, 240–253.

Nepveux, K., Sherlock, J., Futran, M., Thien, M., and Krumme, M. (2015). How development and manufacturing will need to be structured-heads of development/manufacturing. *Journal of Pharmaceutical Sciences*, 104, 850–864.

Nicolai, N., De Leersnyder, F., Copot, D., Stock, M., Ionescu, C., Gernaey, K., Noppens, I., and Beer, T.D. (2018). Liquid-to-solid ratio control as an advanced process control solution for continuous twin-screw wet granulation. *AIChE Journal*, 64(7), 2500–2514.

Nicolaï, N. (2019). *Supervisory process monitoring, identification and control for continuous pharmaceutical wet granulation.* Ph.D. thesis, Ghent University, Belgium, Department of Data Analysis and Mathematical Modelling.

Samad, T. (2017). A survey on industry impact and challenges thereof. *IEEE Control Systems Magazine*, 37(1), 17–18.

Schenkendorf, R., Gerogiorgis, D., Mansouri, S., and Gernaey, K. (2020). Model-based tools for pharmaceutical manufacturing processes. *Processes*, 8(49), 1–4. doi: 10.3390/pr8010049.

Singh, R., Roman-Ospino, A., R.Romanach, Ierapetritou, M., and Ramachandran, R. (2015). Real time monitoring of powder blend bulk density for coupled feed-forward/feed-back control of a continuous direct compaction tablet manufacturing process. *International Journal of Pharmaceutics*, 495(1), 612–625.

Vanhoorne, V. and Vervaet, C. (2020). Recent progress in continuous manufacturing of oral solid dosage forms. *International Journal of Pharmaceutics*, 579, 119194.

Xie, X. and Schenkendorf, R. (2019). Robust process design in pharmaceutical manufacturing under batch-to-batch variation. *Processes*, 7(509), 131–144. doi: 10.3390/pr7080509.