International Journal of Pharmaceutics 510 (2016) 100–115

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Optimized continuous pharmaceutical manufacturing via model-predictive control

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ARTICLE INFO

Article history:
Received 29 February 2016
Received in revised form 25 May 2016
Accepted 7 June 2016
Available online 16 June 2016

Keywords:
Model-predictive control
Continuous pharmaceutical manufacturing
Model-based control
Feeding blending unit

ABSTRACT

This paper demonstrates the application of model-predictive control to a feeding blending unit used in continuous pharmaceutical manufacturing. The goal of this contribution is, on the one hand, to highlight the advantages of the proposed concept compared to conventional PI-controllers, and, on the other hand, to present a step-by-step guide for controller synthesis. The derivation of the required mathematical plant model is given in detail and all the steps required to develop a model-predictive controller are shown. Compared to conventional concepts, the proposed approach allows to conveniently consider constraints (e.g. mass hold-up in the blender) and offers a straightforward, easy to tune controller setup. The concept is implemented in a simulation environment. In order to realize it on a real system, additional aspects (e.g., state estimation, measurement equipment) will have to be investigated.

1. Introduction

During the last years, several pharmaceutical companies have started to implement a change from a batch-based production to a continuously operated production, see e.g. Plumb (2005) and Lee et al. (2015). Continuous manufacturing is advantageous in many aspects: in-line monitoring of critical quality attributes (CQA) is a prerequisite, leading to reduced product variability and consequently a reduction in product waste. Furthermore, the footprint of the production line is typically smaller compared to a batch facility. The amount of produced material is mainly affected by the production time and not only by the size of the used equipment. Thus, in many situations, the same equipment can be used for laboratory experiments/development and for the final production of the drug. Consequently, no scale-up studies of the laboratory equipment to the production equipment are necessary (Benyahia et al., 2012) and the time from the successful laboratory-scale production to the final production can be significantly reduced. Hence, the time period of patent exclusivity is exploited more efficiently.

However, in order to operate a continuous production line, new challenges have to be overcome. For the proper operation of a continuous manufacturing line, on the one hand, a sophisticated process analytical technology (PAT) concept is advantageous for in-line and/or off-line measurement of critical process parameters (CPPs) and critical quality attributes (CQAs) (Markl et al., 2013; Wahl et al., 2013; Sacher et al., 2012; Treffer et al., 2013; Singh et al., 2014a, 2010; Kumar et al., 2013). On the other hand, advanced control strategies are desirable in order to keep the CPPs close to their desired set points and to keep intermediates and product within specification (Sacher et al., 2015; Rantanen and Khinast, 2015). Model-based control concepts are a promising technique in order to fulfill this requirement. In many other industries, model-based controller design is already well established, e.g., in robotics (Niu and Zhang, 2011; Zarghami et al., 2014), in the heating, ventilating and air conditioning industry (Komareji et al., 2008; Schwingshackl et al., 2013; Rehrl et al., 2014, 2009; Rehrl and Horn, 2011, 2009), in the automotive industry (Fei et al., 2013; Zhang et al., 2013; Zhou et al., 2015) or in chemical process control (Mesbah et al., 2012) – to mention just a few examples. For model-based controller design, the availability of an appropriate dynamic process model is essential. The derivation of such a model for pharmaceutical manufacturing is presented in this paper.

In case of continuous pharmaceutical production, typically several unit operations (e.g., feeding units, blenders, wet or dry granulation, drying, tabletting, coating, etc.) are involved. The combination of (at least two) feeders and a blender is referred to as feeding blending unit (FBU) in the following. In almost all continuous plants, a FBU is necessary. In continuous tablet or capsule

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http://dx.doi.org/10.1016/j.ijpharm.2016.06.024
0378-5173/

Nomenclature

k_{AW}	anti-windup constant of the PI controller
ω	blender speed in rev/min
k_u	blender speed feedback constant
$C(t)$	concentration as a function of time t
C_n	concentration as a function of normalized time θ
c_i	concentration at the inlet
$c_{k,i}$	concentration of component k at the inlet
c_o	concentration at the outlet
$c_{k,o}$	concentration of component k at the outlet
T_d	dead time in seconds
θ	dimensionless time
D	feedthrough matrix
I	identity matrix of appropriate dimension
$\dot{m}_{c1,i}$	inlet mass flow to the blender in kg/h
$\dot{m}_{cj,i}$	inlet mass flow to compartment j in kg/h
B	input matrix
$\dot{m}_{k,i}$	mass flow feeder k in kg/h
$m_{hu,cj}$	mass hold-up of compartment j in kg
m_{hu}	mass hold-up of the blender in kg
ω_{max}	maximum blender speed in rev/min
$m_{hu,\max}$	maximum mass hold-up in kg
τ	mean residence time in seconds
ω_{min}	minimum blender speed in rev/min
$m_{hu,\min}$	minimum mass hold-up in kg
n_G	normally distributed random signal with a variance of 1
N	number of compartments of the hold-up model
M	number of inlet mass flows
n_s	number of samples
n	number of state variables of the discrete time system
m	number of system outputs
$\dot{m}_o$	outlet mass flow of the blender
$\dot{m}_{cj,o}$	outlet mass flow of compartment j in kg/h
C	output matrix
Pe	Péclet number
k_P	proportional gain of the PI controller
T_N	reset time of the PI controller in seconds
$E(t)$	residence time distribution
T_s	sampling interval in seconds
A	system matrix
t	time in seconds
T	time constant in seconds
$\sigma(t)$	unit step signal
u	vector of inputs
x	vector of state variables (state vector)
y	vector of outputs
W	weight matrix for the outputs
R	weight matrix for the actuating signals

production lines, the optimal operation of the FBU is crucial in order to meet the critical quality attributes of the final product. Especially the content uniformity is strongly affected by the blender performance (Haack, 2014).

Here, we will consider the "minimum" configuration of a FBU, consisting of two feeders and one continuous blender, where the blender speed can be set by the operator. On the one hand, one wants to have a narrow residence time distribution in order to be able to perform better particle tracking (i.e., to track the position of a specific particle within the production line as a function of time). On the other hand, a narrow distribution typically causes performance degradation in terms of blend homogeneity. Blender speed has significant impact both on the residence time and the width of its distribution. A possible compromise is to set the blender speed such that the number of blade passes a specific particle experiences is maximized. However, by setting one constant blender speed, feed fluctuations at the blender inlet are conveyed to the outlet mass flow of the blender. If no buffer is installed after the blender, these outlet mass flow fluctuations are undesired, because the outlet mass flow of the blender has to meet the required steady input mass flow of the downstream unit operation, e.g., the tablet press.

In recent literature, many papers dealing with the control concept of pharmaceutical plants, including FBUs, can be found. Zhao et al. (2013) demonstrated the application of a feedback loop based on a standard PI controller in order to improve the blender performance during concentration set point changes. The authors highlighted the improved blender performance under closed-loop control compared to an open loop operation with a fixed blender speed. The studies by the Rutgers group (Singh et al., 2015a,b,c) demonstrated the development of a control concept for a direct-compaction continuous tablet manufacturing pilot-plant. The presented concept utilizes a feed-forward/feedback structure in the control strategy of the tablet press. The concept is demonstrated via simulation runs.

In our study, we also investigate a feed-forward/feedback structure as one possible strategy for the FBU control. We highlight its advantages compared to a standard feedback structure and additionally, we suggest a model-predictive control (MPC) technique which shows significant advantages compared to the feed-forward/feedback structure.

In Ramachandran et al. (2011), a direct compaction process consisting of three feeders, a blender and a tablet press was analyzed. Via the relative gain array method (Skogestad and Postlethwaite, 2005), the assignment of the actuating signals to the control variables is specified. The authors demonstrate that standard controllers show poor performance in case of high process interaction. The approach we suggest in our study overcomes this problem, because the possible interactions are inherently taken into account in the control concept.

The studies Campo and Morari (1989) and McDonald et al. (1986) deal with the control of the outlet flow of a tank. The authors propose a predictive control strategy, which allows keeping the fill level in the tank within given bounds, while the outlet mass flow is smoothened. They compare their approach to a PI-strategy proposed in Cheung and Luyben (1979). Although their setup is similar to the investigated blender, the methods given in Campo and Morari (1989), McDonald et al. (1986) and Cheung and Luyben (1979) are not directly applicable to our setup due to the following reason: the plant in the mentioned paper shows integrating behavior, i.e., its transfer function has a pole located at zero. In contrast, the system investigated here shows low pass characteristics (see the model in Section 2.5), rendering the direct application of the methods proposed in Campo and Morari (1989), McDonald et al. (1986) and Cheung and Luyben (1979) impossible.

In Mesbah et al. (2015), a model predictive control strategy is presented for a continuous pharmaceutical manufacturing process. The authors compare their approach to a conventional one which consists of multi-loop PI controllers. In Singh et al. (2012) a dynamic sensitivity analysis of a pharmaceutical process was proposed. The results of the sensitivity analysis were the basis for the selection of the control loops. Cascaded structures of standard PID controllers were used for the individual loops. Simulation studies of the overall system were performed. The obtained results highlight the performance improvement when using a closed-loop control system compared to the open loop operation of the plant. In Singh et al. (2013), the authors replaced some of the PID controllers by MPC strategies (hybrid MPC-PID control). The linear models used in the MPC controllers were identified from simulation data. The