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Multivariate statistical process control of a continuous pharmaceutical twin-screw granulation and fluid bed drying process

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ABSTRACT

A multivariate statistical process control (MSPC) strategy was developed for the monitoring of the ConsiGma™-25 continuous tablet manufacturing line. Thirty-five logged variables encompassing three major units, being a twin screw high shear granulator, a fluid bed dryer and a product control unit, were used to monitor the process. The MSPC strategy was based on principal component analysis of data acquired under normal operating conditions using a series of four process runs. Runs with imposed disturbances in the dryer air flow and temperature, in the granulator barrel temperature, speed and liquid mass flow and in the powder dosing unit mass flow were utilized to evaluate the model's monitoring performance. The impact of the imposed deviations to the process continuity was also evaluated using Hotelling's T^2 and Q residuals statistics control charts. The influence of the individual process variables was assessed by analyzing contribution plots at specific time points. Results show that the imposed disturbances were all detected in both control charts. Overall, the MSPC strategy was successfully developed and applied. Additionally, deviations not associated with the imposed changes were detected, mainly in the granulator barrel temperature control.

1. Introduction

In the last years there has been an increasing interest of pharmaceutical companies to shift from the traditional batch processing to continuous production. Continuous manufacturing has the potential of reducing production costs while simultaneously delivering a product of consistent quality, providing an answer to the need of the pharmaceutical industry to develop more cost-efficient processes, without compromise product quality (Fonteyne et al., 2015). The strong competition between pharmaceutical companies that produce innovative medicines, which largely invest in research and development, and the generics industry reinforces this necessity as it deepens the gap between the increasing development costs and the decreasing market prices, hindering profitability. In continuous manufacturing the production volume can be increased by running the process for a longer period of time and/or by increasing flow rate, thus eliminating the time-consuming, labor-intensive, and expensive scaling-up studies. Areas dedicated to off-line quality control are reduced as well, as ideally continuous processes rely on in-process measurements to assess quality (Fonteyne et al., 2015; Schaber et al., 2011). Continuous processes also require smaller facilities as the conversion of raw-materials to final products can fit a single room, minimizing materials transportation needs, energy intake, material handling, and storage of intermediates (Aksu et al., 2012). Continuous pharmaceutical processes are inherently more flexible; in order to obtain a larger amount of product process time is extended, which allows to quickly deal with changes in market demands and avoiding shortages, as well as overstock and stockpiling. These factors contribute to shortening supply chains allowing a faster product release and reducing the risk of product degradation (Allison et al., 2015; Byrn et al., 2015; Malet-Sanz and Susanne, 2012; Mascia et al., 2013). Despite the numerous advantages, the pharmaceutical industry has been slow in

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adopting steps toward this manufacturing principle. The high investment costs and the risk of delays in regulating authorities' approvals, the need of skilled professionals, and technical reasons related with in-process control (IPC) are the main reasons (Byrn et al., 2015; Lee et al., 2015). To guarantee product quality and safety without annulling the benefits of the process continuity, monitoring and control of a continuous process needs to be accomplished in real-time, and for this a solid understanding of the process dynamics is essential. This comes in alignment with the quality-by-design (QbD) paradigm for pharmaceutical development, framed by the ICH Q8 guideline, which presents a systematic scientific and risk-based approach to pharmaceutical development (International Conference on Harmonization, 2009). This approach advises manufacturers to relate product quality with process operation. The goal is to use process and product knowledge to implement effective process supervision, and quality control strategies, working toward the development of a robust process.

Most modern manufacturing lines record data in real-time acquired from sensors such as, flow rates, temperatures and pressures. These data are readily available and contain valuable information about the ongoing process. Latent variable projection models such as principal component analysis (PCA) are ideal for dealing with this type of data which can be highly collinear (Wikstrom et al., 1998). Multivariate statistical process control (MSPC) is the designation of the approach, which utilizes multivariable models for the purposes of process monitoring. This strategy is well documented in the literature (Barla et al., 2014; Burggraeve et al., 2011; Kona et al., 2013; Kourti, 2002, 2003, 2005; MacGregor and Cinar, 2012; Macgregor and Kourti, 1995; MacGregor et al., 2005; Rosas et al., 2011).

The ConsiGma™-25 is a fully continuous tablet manufacturing line composed by a high-shear twin-screw wet granulator, a fluid bed dryer, a product control unit and a tablet press (Chablani et al., 2011; Fonteyne et al., 2013). Continuous high-shear twin-screw granulation has received much attention in the last decade, being described by different groups in this period (Dhenge et al., 2012; Djuric and Kleinebudde, 2008; El Hagrasy et al., 2013; Keleb et al., 2004; Thompson and Sun, 2010; Van Melkebeke et al., 2008). It provides a suitable solution for processing at low production rates unlike continuous fluid bed granulators which could only produce at higher material throughputs which are rarely necessary in the pharmaceutical industry. It can also deal with the shortcomings of other types of continuous agglomeration processes such as spray-drying, instant granulation and roller compaction. An in-depth description of these limitations are found in the work of Vervaet et al. (Vervaet and Remon, 2005, 2009) and Vercruysse et al. (2013).

The ConsiGma™-25 has multiple sensors standardly implemented at different locations, which can monitor several process variables such as flow, pressure, temperatures, humidity, etc. The line does not include by default direct measurements of product

Table 1
Variables logged by the ConsiGma™ –25 included in the MSPC model.

Variable ID	Variable description	Type	Units	Set point value	ConsiGma™ 25 Unit
V1	Flow sensor – dryer air	Setpoint	$m^3\ h^{-1}$	360	Dryer
V2	Flow sensor – wet granule transfer line	Setpoint	$m^3 h^{-1}$	3.6	Wet granule transfer line (dryer)
V3	Humidity sensor – dryer air inlet	Setpoint	%RH	10	Dryer
V4	Humidity sensor – dryer air outlet	Measured	%RH	N/A*	Dryer
V5	Mass flow granulation liquid	Setpoint	$g\,min^{-1}$	58	Liquid addition module (granulator)
V6	Mass Flow – Powder dosing	Setpoint	$Kg\,h^{-1}$	25	Powder dosing unit (granulator)
V7	Power – granulator drive	Measured	W	N/A	Granulator
V8	Pressure sensor – differential pressure over the dryer filters	Measured	mbar	N/A	Dryer
V9	Pressure sensor – differential pressure over the hole plate	Measured	mbar	N/A	Dryer
V10	Pressure sensor – differential pressure at the HEPA filter of the dryer air outlet	Measured	mbar	N/A	Dryer
V11	Pressure sensor – differential pressure over the HEPA filter at the product control unit	Measured	mbar	N/A	Product Control Unit
V12	Pressure sensor – differential pressure over the HEPA filter at the wet transfer line inlet	Measured	mbar	N/A	Wet transfer line (dryer)
V13	Pressure sensor – differential pressure over the wet transfer line	Measured	mbar	N/A	Wet transfer line (dryer)
V14	Pressure sensor – dryer air inlet	Measured	mbar	N/A	Dryer
V15	Pressure sensor – dryer air outlet after HEPA filter	Measured	mbar	N/A	Dryer
V16	Pressure sensor – dryer air outlet before HEPA filter	Measured	mbar	N/A	Dryer
V17	Pressure sensor – dryer top	Measured	mbar	N/A	Dryer
V18	Pressure sensor – product control unit after HEPA filter	Measured	mbar	N/A	Product Control Unit
V19	Pressure sensor – product control unit before HEPA filter	Measured	mbar	N/A	Product Control Unit
V20	Speed control – fan/blower	Measured	%	N/A	Fan/blower system (dryer)
V21	Speed – granulator screws	Setpoint	rpm	700	Granulator
V22	Speed – motor powder dosing	Measured	rpm	N/A	Powder dosing unit (granulator)
V23	Temperature sensor – air handling unit	Measured	°C	N/A	Air handling unit (dryer)
V24	Temperature sensor – dryer air inlet	Setpoint	°C	50	Dryer
V25	Temperature sensor – dryer air outlet	Measured	°C	N/A	Dryer
V26	Temperature sensor – temperature dryer cell 1	Measured	°C	N/A	Dryer
V27	Temperature sensor – temperature dryer cell 2	Measured	°C	N/A	Dryer
V28	Temperature sensor – temperature dryer cell 3	Measured	°C	N/A	Dryer
V29	Temperature sensor – temperature dryer cell 4	Measured	°C	N/A	Dryer
V30	Temperature sensor – temperature dryer cell 5	Measured	°C	N/A	Dryer
V31	Temperature sensor – temperature dryer cell 6	Measured	°C	N/A	Dryer
V32	Temperature sensor – granulator barrel	Setpoint	°C	25	Granulator
V33	Temperature sensor – outlet temperature control unit	Measured	°C	N/A	Temperature control unit (Granulator)
V34	Temperature sensor – tank temperature control unit	Measured	°C	N/A	Temperature control unit (Granulator)
V35	Torque sensor – granulator	Measured	N/A	N/A	Granulator

*N/A: not applied.