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Multivariate monitoring for the industrialisation of a continuous wet granulation tableting process

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ABSTRACT

The pharmaceutical industry is undergoing a significant change in product development and manufacturing strategies with the progressive shift from batch to continuous processes. These typically feature vast volumes of data generated by the numerous sensors connected to several unit operations running over the period of several hours or even days and that demand the application of increasingly efficient tools for process understanding, monitoring and control. This paper describes the use of multivariate statistical process modeling by means of chemometric methods to monitor the continuous wet granulation tableting process for a drug product currently under development. Models are tailored to the different units that make up the continuous tableting line, from material feeding and granulation up to tablet compression, where the solutions devised reflect the different dynamics of each unit and are used as maintenance and intervention tools to optimise manufacturing and associated operations retrospectively as well as in real-time, as part of the product industrialisation programme.

1. Introduction

In the pharmaceutical industry, the progressive shift from traditional batch to continuous processes has the potential to bring significant advantages in terms of minimising cost of operations, reduce materials waste, improve product quality and increase compliance to desired operational and safety standards (Khinast and Rantanen, 2015; Lee et al., 2015). However, the intake of continuous manufacturing technologies comes with its own challenges, e.g. new infrastructure requirements, data analytics capabilities, technical upskilling of the organisation etc. that are also reflected in the emerging regulatory expectations (Allison et al. 2015). This changing environment presents numerous opportunities particularly for process modeling: the availability of more integrated processes where manual intervention is minimised and unit operations are closely integrated lends itself to approaches such as holistic system based models that have more limited applicability to batch manufacturing (Kumar et al., 2013; Rehrl et al., 2016; Singh et al., 2015; Su et al., 2017). In this regard, also the possibility to carry out more experiments with reduced quantities of materials enables to test earlier and more extensively hypothesis on process dynamics and estimate models parameters. However, this also comes with the need to develop new paradigms, for example on models maintenance and update, where the model output needs to be contextualised and used in the appropriate manner within the traditional pharmaceutical production environment (Miyano et al., 2015).

In the context of continuous tableting operations, multivariate statistical process modeling by means of chemometric methods comes to the fore due to the large trains of data continuously generated, often highly collinear in nature, enabling the derivation of data driven models to foster understanding, monitoring and control (MacGregor and Kourti, 1995; Nomikos and MacGregor, 1994; Wold et al. 1993). Here, the application of data driven models may also be favoured by the scarcity of methods available to derive robust models from first principles for certain unit operations such as for granulation (Iveson et al., 2001; Iveson 2002; Kemp and Oakley 2002). Indeed, these types of models, whose application is well established in other industries, are likely to rapidly become a standard for pharmaceutical continuous manufacturing (Silva et al., 2017; Tomba et al. 2013). The use of chemometric methods for this purpose often relies on latent variables techniques such as Principal Components Analysis (PCA) and Partial Least Squares (PLS) as the core components (Wold et al., 1986, 2001). Amongst the many advantages, these techniques have proved to be extremely versatile, robust, and able to deliver sets of easily understandable diagnostics suitable for review. In fact, these have been so successful over the years to trigger custom adaptations to fit a variety of manufacturing scenarios (Camacho and Pico, 2006; Facco et al. 2009;

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Wang et al. 2012; Zhu et al. 2012). It is also noted that, to support to development of continuous processes, chemometric methods underpin numerous other spectroscopic applications. Examples are illustrated in the scientific literature in relation to all main unit operations, i.e. for continuous material transfer, granulation, drying, blending and compression (Benedetti et al. 2007; Chablani et al., 2011; Fonteyne et al., 2012, 2014; Hattori and Otsuka, 2017; Järvinen et al., 2013; Martinez et al. 2013; Vanarese et al. 2010). A comprehensive review on the take up of Process Analytical Technologies (PAT) for the continuous manufacturing of oral solid dose forms is provided by Fonteyne et al. (2015).

This paper demonstrates the application of multivariate statistical process modeling by means of chemometrics methods on data from a pharmaceutical oral solid dose product under development, where manufacturing occurs using the the continuous tablet production line (CTL) ConsiGma™-25 (GEA Pharma Systems, Collette™ Wommelgem, Belgium) (Vercruysse et al., 2015). The CTL includes a train of closely integrated units, i.e. materials feeding, granulation, drying, milling, blending and tablet compression, where materials are continuously charged and tablet cores are continuously discharged from the system and where the overall process may last from a few hours to several days. Modeling is used to determine the *common cause* variation of the system, derived from the historical data acquired from the process running under Normal Operating conditions (NOCs). This in turn enables its deployment as multivariate monitoring tool for the detection of *special cause* variation, i.e. associated to new, unpredictable or previously neglected phenomena within the system and that can be retrospectively investigated, e.g. at the end of a batch or a campaign, as well as in real-time, i.e. during manufacturing operations (MacGregor and Kourti, 1995).

In this application, the CTL is equipped with ports to discharge intermediate materials of undesirable quality on certain steps, based on robust univariate parametric controls. Therefore, multivariate monitoring is not being implemented with the purpose to define materials to be rejected, but rather as a mechanism to monitor equipment performance to provide the opportunity to intervene and adjust should the process drift from typical (e.g., clean, adjust or replace an equipment component) as well as to enable progressive improvement on the CTL based on periodic retrospective review of the data against the historical experience. The use of multivariate monitoring in this fashion reflects the late stage development and industrialization phase of the product used as example in this paper, where the drug formulation and process have been defined, but the relatively limited manufacturing experience may require further optimization of the process and associated operations. As more data and experience is gathered in the future, multivariate monitoring may also be integrated as a tool to support the continued process verification approach thus contributing to confirm product quality prior to release, for the remaining phase of commercialization (Allison et al., 2015; ICH 2008).

The paper is organized as follows: the *methods* section provides an overview of the manufacturing process, the sensors selected as in scope for the modeling and the workflow adopted for model development. The *process characterization* section provides detail on the *common cause variation* observed for the process operating at NOCs and used as basis for the modeling. The *results* section describes the process drifts detected, i.e. *special cause variation*, through the application of the models. The concluding section discusses additional considerations of interest for the practical deployment in a manufacturing environment, i.e. in relation to *models use*, *validation* and *update*.

2. Materials & methods

2.1. Manufacturing process overview

Fig. 1 illustrates the process workflow for the drug product used as model in this application. Input materials are supplied to the

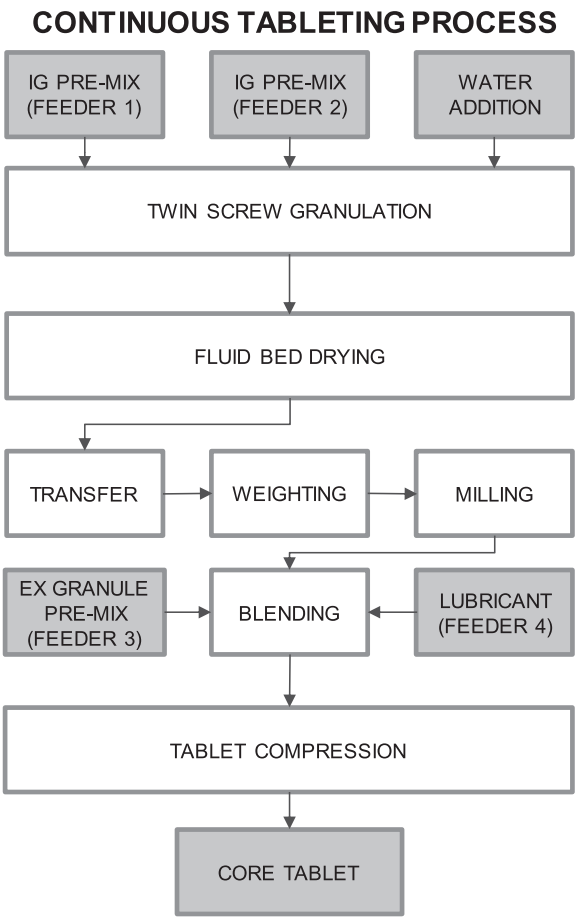

Fig. 1. Continuous tableting process workflow.

ConsiGma™-25 CTL in the form of two intragranular pre-mixes via two loss-in-weight gravimetric feeders (Coperion K-Tron Inc. Sewell, New Jersey, United States). The materials flow from the feeders into a twin screw granulator where water is added through a peristaltic pump. The twin screw alternates conveying and kneading elements to favour the formation of granules of desired characteristics. Exiting granules fall into fluid bed dryer segmented into six cells. The dryer operates continuously, but from this point onwards the product is managed as discrete aliquots of material, termed Product Keys (PKs), which are separately dried in each cell. Dried granules are pneumatically conveyed to a hopper and then transferred via gravity through a mill and onto a weigh cell. The dried milled granules are then automatically transferred into a blender where further extra granular excipients and lubricant are added. The blend then flows into the hopper of a tablet press (Curtoy GEA Pharma Systems, Collette™ Wommelgem, Belgium) where it is compressed as tablet cores. The tablet cores manufactured on the CTL are coated in a coater using conventional coating techniques. The whole process is fully automated where the materials and product are continuously charged into and discharged from the system, respectively, throughout the duration of operations. Univariate parametric controls, not discussed in this paper, are enacted so to divert material to waste when associated limits are exceeded. Controls have been designed to ensure that only intermediate materials of acceptable quality progress through the various stage that make up the CTL and are used to form tablet cores.

2.2. Process sensors

The entire process is connected to a multitude of electro-mechanical process sensors that continuously log data for the duration of