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Process analytical technology in continuous manufacturing of a commercial pharmaceutical product

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ABSTRACT

The implementation of process analytical technology and continuous manufacturing at an FDA approved commercial manufacturing site is described. In this direct compaction process the blends produced were monitored with a Near Infrared (NIR) spectroscopic calibration model developed with partial least squares (PLS) regression. The authors understand that this is the first study where the continuous manufacturing (CM) equipment was used as a gravimetric reference method for the calibration model. A principal component analysis (PCA) model was also developed to identify the powder blend, and determine whether it was similar to the calibration blends. An air diagnostic test was developed to assure that powder was present within the interface when the NIR spectra were obtained. The air diagnostic test as well the PCA and PLS calibration model were integrated into an industrial software platform that collects the real time NIR spectra and applies the calibration models. The PCA test successfully detected an equipment malfunction. Variographic analysis was also performed to estimate the sampling analytical errors that affect the results from the NIR spectroscopic method during commercial production. The system was used to monitor and control a 28 h continuous manufacturing run, where the average drug concentration determined by the NIR method was 101.17% of label claim with a standard deviation of 2.17%, based on 12,633 spectra collected. The average drug concentration for the tablets produced from these blends was 100.86% of label claim with a standard deviation of 0.4%, for 500 tablets analyzed by Fourier Transform Near Infrared (FT-NIR) transmission spectroscopy. The excellent agreement between the mean drug concentration values in the blends and tablets produced provides further evidence of the suitability of the validation strategy that was followed.

1. Introduction

This publication describes the integration of Process Analytical Technology (PAT) and continuous manufacturing within a facility where current Good Manufacturing Practices are followed. Continuous manufacturing has been recognized as an innovation with significant potential to improve agility, flexibility, and robustness in the manufacture of solid oral dosage forms (Ierapetritou et al., 2016; Osorio and Muzzio, 2016; Osorio et al., 2015), and polymeric thin films (Krull et al., 2015; Zhang et al., 2014). Continuous manufacturing is also being developed for the manufacture of active pharmaceutical ingredients with the subsequent production of solid oral dosage forms (Adamo et al., 2016). Pharmaceutical continuous manufacturing is one of the advanced manufacturing initiatives with potential for driving long term economic prosperity and growth as indicated by the Subcommittee for Advanced Manufacturing of the National Science and Technology Council (Subcommittee for Advanced Manufacturing of the National Science and Technology Council, 2016). Innovation companies have been focused on the discovery of new active pharmaceutical ingredients, but there is a need to improve the product development process to reduce the time to market of new products (Ierapetritou et al., 2016). Continuous manufacturing will provide benefits for patients and the investment community as the product development time is shortened.

The Food and Drug Administration (FDA) has recognized that “the lack of agility, flexibility, and robustness in the pharmaceutical manufacturing sector poses a potential public health threat as failures within manufacturing facilities that result in poor product quality can lead to drug shortages” (Lee et al., 2015; Throckmorton, 2014). The FDA has also stated that continuous manufacturing, compared to batch

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manufacturing, “often involves a higher level of process design to ensure adequate process control and product quality”(Lee et al., 2015) Continuous manufacturing eliminates the need to store and relocate intermediate products obtained during the manufacture of solid oral dosage forms thus avoiding segregation and degradation problems(Lee et al., 2015). Continuous manufacturing could help a product reach market in less time by eliminating the need to perform process scale up, and pharmaceutical companies have been increasingly investigating the implementation of continuous processes (Byrn et al., 2015; Colón et al., 2017; Martinez et al., 2013; Roth et al., 2017; Shi et al., 2016). Designed experiments could be performed in just a few days to optimize a process with significant savings in materials and time (Osorio et al., 2015). A number of studies have been performed to thoroughly understand the feeding and mixing steps in the continuous manufacturing of solid oral dosage forms (Engisch and Muzzio, 2015; Engisch and Muzzio, 2016; Vanarase and Muzzio, 2011; Vanarase et al., 2013; Wang et al., 2017). However, a continuous manufacturing system is not easily achieved as it involves: (1) an integrated manufacturing process where individual unit operations are connected, (2) real time monitoring and control through process analytical technology (PAT), and (3) the implementation of engineering process control to mitigate the effect of process and raw material variability on the final product (Lee et al., 2015). This publication describes progress in continuous manufacturing and PAT and their implementation in commercial manufacturing. The FDA recently approved the change of a process from batch to continuous manufacturing (Brennan, 2016; Gray, 2016; Langhauser, 2016; MacDonald, 2016; Yu, 2016) and this publication describes the PAT and continuous manufacturing advances for this process.

PAT provides information to a control system (Joglekar et al., 2014; Román-Ospino et al., 2016; Singh et al., 2015, 2014) to monitor the critical quality attributes of the product during the continuous manufacturing process. The manufacture of solid oral dosage forms in continuous processes has included the use of near infrared (NIR) spectroscopy to monitor the mixing of the active pharmaceutical ingredient (API) and excipients (Martinez et al., 2013; Shi et al., 2016; Vanarase et al., 2010; Vargas et al., 2017). Mixing is a crucial step in the manufacturing process and therefore, control strategies must be implemented for powder blending (Singh et al., 2014). The drug concentration results obtained by the NIR method are used to determine whether the blend is accepted for compression or rejected (diverted to waste) prior to compression. The amount of drug that a patient receives in a tablet is determined by the uniformity of the blend and the powder density which may be also monitored by NIR spectroscopy (Román-Ospino et al., 2016; Singh et al., 2015). The NIR method monitors the mixing process after steady state is reached, and large data sets are created as the manufacturing runs may be lengthy as shown in this study. The objective of NIR spectroscopic monitoring during continuous processing is not to detect an endpoint as in batch blending, but to monitor the blending process in real time and determine whether the blend meets the product specification (Fonteyne et al., 2016). The NIR method must monitor the process for a longer time than in batch processes where the mixing is stopped after a certain level of drug distribution is achieved (Alcala et al., 2010; Alcalà et al., 2012; Igne et al., 2013, 2011; Romañach et al., 2016). The NIR method for continuous manufacturing must be designed for flowing powder systems, and two studies have described difficulties in meeting this challenge (Martinez et al., 2013; Shi et al., 2016). The NIR probe could be placed over the blend (Colon et al., 2014) or at the outlet of the continuous blender (Román-Ospino et al., 2016), and the distance between the NIR probe and the powder must be taken into consideration. Thus, a number of challenges must be met during the implementation of PAT for continuous manufacturing.

This publication describes the implementation of continuous manufacturing within a commercial manufacturing plant and a process run that consisted of a 28 h runtime, a significant advance over previous studies that described the development of continuous processes in research facilities (Colon et al., 2014; Shi et al., 2016; Singh et al., 2013, 2015). This implementation has required a system’s approach, as outlined by the PAT Guidance (U.S. Department of Health and Human Services, 2004), and diagnostic tests that are necessary in a commercial manufacturing setting. The system includes an air spectrum diagnostic test to indicate that spectra were obtained when powder is not present in the NIR interface. The system also includes two different tests to identify the formulation, before the drug concentration is predicted by a PLS calibration model, and immediately after mixing.

The validation of the PLS method includes estimates of the analytical errors as well as the sampling error. PAT methods are usually thoroughly validated providing excellent estimates of the analytical errors (Corredor et al., 2015). However, sampling errors are usually unknown in PAT methods. This study presents the first evaluation of sampling and analytical errors during a commercial continuous manufacturing process. The systems necessary to achieve a continuous manufacturing run throughout 28 h are described.

2. Materials and methods

2.1. Formulation Components

The formulation included a cohesive API with a concentration greater than 50% (w/w) and silicified microcrystalline cellulose (SMCC) as the filler (Prosolv® from JRS Pharma). The formulation also included crospovidone NF/PH EUR (disintegrant) and magnesium stearate NF/EP (lubricant).

2.2. Continuous manufacturing system

The system included volumetric feeders that are connected to the gravimetric feeders as shown in Fig. 1. The API and Prosolv® volumetric feeders are filled by pneumatic transfer from the containers received at the manufacturing plant. The magnesium stearate is manually loaded to a volumetric feeder. The continuous system included four K-tron (Model: K-PH-MV-KT20-P20) gravimetric feeders, as shown in Fig. 1. The gravimetric feeders for the API, magnesium stearate and Prosolv® were automatically refilled by a coupled volumetric feeder. Crospovidone was manually loaded to a gravimetric feeder.

The API, Prosolv®, and magnesium stearate were dispensed to volumetric hoppers at a specific frequency determined by level sensors in each volumetric feeder. The volumetric feeders were used to fill the gravimetric feeder hoppers during the refill cycle. The volumetric feeding refill cycle was initiated once the amount of API, Prosolv®, or magnesium stearate in their gravimetric feeder hoppers reached the minimum refill set point. The refill cycle involved a pre-set screw speed in the volumetric feeder to add the API or excipients to the gravimetric feeder hopper. The gravimetric feeders added the API, Prosolv®, crospovidone, and magnesium stearate to create the desired drug product formulation. The gravimetric feeder operated under two modes: gravimetric (feeding material to the line) and volumetric (refill cycle). The loss in weight (LIW) control was used when the feeder was in the gravimetric mode. LIW determined the rate at which the material decreased in the hopper to update the screw speed and maintain the mass flow rate. No weight measurements were performed when the feeder was in volumetric mode. During the short volumetric period (refill cycle), the LIW control is not performed and the screw speed is fixed. Gravimetric feeders were used for accurate material dispensing and as the reference method for the calibration set blends used for the development of the NIR spectroscopic calibration model.

After the gravimetric feeders, the API and excipients passed to an in-line conical mill and then entered an in-line continuous paddle blender (Glatt GCG 70). The NIR spectrometer was installed after the blender. Fig. 1 shows the interface where the in-line NIR spectra were obtained as the powder flowed from the blender to the tablet press. The blend level in the interface was determined with a laser level sensor and