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In-line monitoring and optimization of powder flow in a simulated continuous process using transmission near infrared spectroscopy

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ABSTRACT

In-line monitoring of continuous powder flow is an integral part of the continuous manufacturing process of solid oral dosage forms in the pharmaceutical industry. Specifically, monitoring downstream from loss-in-weight (LIW) feeders and/or continuous mixers provides important data about the state of the process. Such measurements support control of the process and thereby enhance product quality. Near Infrared Spectroscopy (NIRS) is a potential PAT tool to monitor the homogeneity of a continuous powder flow stream in pharmaceutical manufacturing. However, the association of analytical results from NIR sampling of the powder stream and the homogeneity (content uniformity) of the resulting tablets provides several challenges; appropriate sampling strategies, adequately robust modeling techniques and poor sensitivities (for low dose APIs) are amongst them. Information from reflectance-based NIRS sampling is limited. The region of the powder bed that is interrogated is confined to the surface where the measurement is made. This potential bias in sampling may, in turn, limit the ability to predict the homogeneity of the finished dosage form. Further, changes to the processing parameters (e.g., rate of powder flow) often have a significant effect on the resulting data. Sample representation, interdependence between process parameters and their effects on powder flow behavior are critical factors for NIRS monitoring of continuous powder flow system. A transmission NIR method was developed as an alternative technique to monitor continuous powder flow and quantify API in the powder stream. Transmission NIRS was used to determine the thickness of the powder stream flowing from a loss-in-weight feeder. The thickness measurement of the powder stream provided an in-depth understanding about the effects of process parameters such as tube angles and powder flow rates on powder flow behaviors. This knowledge based approach helped to define an analytical design space that was specific to flow properties and to determine the optimum process parameters for successful quantitation of powder stream. A PAT method based on transmission NIRS was developed to monitor the homogeneity of API in a continuously flowing powder stream.

1. Introduction

Pharmaceutical unit operations are shifting from batch processing to continuous processing (Poechlauer et al., 2012). Continuous processing provides a more efficient means of increasing the total output of a process, or scale-up, when compared to batch processes. Continuous processes provide a greatly enhanced ability to control the quality of the finished product at a much smaller scale, by process intensification (Calabrese and Pissavini, 2011). Solid oral dosage form is one of the potential candidates to be manufactured by continuous processing. Manufacturing solid oral dosage forms by continuous processes effectively requires real-time quality monitoring of the process stream. The combination of real-time analytical data and responsive control of the manufacturing process results in substantially reduced hold times for the product when compared to batch manufacturing. This typically results in a substantial decrease in cycle time for manufacturing. Ultimately, continuous pharmaceutical processes are more efficient and controllable than batch processes (Vanarase et al., 2010). However, there are some initial hurdles that are critical to the adoption of continuous processing in pharmaceutical setup. Uncertainty of the regulatory requirement, high initial investment and uncertainty of the return-

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on-investment have resulted in reluctance among pharmaceutical industries towards continuous processing (Desai et al., 2015). Beside these, there are several challenges from manufacturing point of view for successful implementation of continuous processing in pharmaceutical operations (Plumb, 2005). Manufacturing of solid oral dosage forms requires handling and processing of powders. A typical approach to controlled addition of tablet ingredients to the continuous process is the use of loss-in-weight feeders. Cohesive and adhesive powders create challenges to manufacturing adequately homogenous tablets. Specifically, during the tableting operation, cohesive powders may limit the performance of a conventional gravimetric feeder, causing surges of API or excipients resulting in poor content uniformity of the finished tablets. It is critical to monitor the process downstream to verify the uniformity of the powder. The monitoring method needs to accurately sample and correctly analyze the powder stream to assure homogeneity at the final stage of tableting.

Different flow rates of the powder stream are necessary to match the production requirements of a continuous tableting process. High volume of production might be required for a high demand drug or to meet an emergency need, requiring the powder flow to set at high rate; whereas for low volume drugs such as orphan drugs, a low powder flow rate might be necessary to meet the production requirements. Powder flow rate for the same drug might also need to be adjusted to meet the production requirements. As the flow rates change, other process parameters, such as the descent angle of powder transport tubes and tablet press speed are adjusted to maintain consistent performance of the process. It is critical that the monitoring of the process is consistent across a range of process parameters. The monitoring method should also be integrated with the optimization and control strategy to produce desired powder flow behavior consistently.

Deviation from the desired flow behavior can affect the process outcomes in various ways. It can cause the process to fail to meet quality standards for the end products. It can also affect the performance of the analytical models, which subsequently cause erroneous control decisions, altering the process outcomes. Ultimately, a design space should be developed within which the process is demonstrated to perform as expected. Further, the powder monitoring method must be included in any process optimization schemes. Measure and control are explicitly required by the US Food and Drug Administration's (FDA) Process Analytical Technology (PAT) guidance (FDA, 2004). An in depth understanding of the interaction between the process parameters and its effect on powder flow properties is a pre-requisite for successful implementation of PAT method for continuous powder flow.

Several PAT tools are used to monitor continuous processes involving powdered materials. These include fluorescence spectroscopy (Lai and Cooney, 2004; Lai et al., 2001), light reflectance (Gratton-Liimatainen, 1995; Harwood et al., 1972; Weinekötter and Reh, 1994), thermal effusivity (Léonard et al., 2008; Mathews et al., 2002; Yoshihashi et al., 2013), Raman spectroscopy (De Beer et al., 2008; Vergote et al., 2004) and near infrared (NIR) spectroscopy (Berntsson et al., 2002; Blanco et al., 2002; Hailey et al., 1996; Sekulic et al., 1998; Shi et al., 2008). Among these techniques, NIR reflectance spectroscopy is the most widely applied technique to monitor powder blending and mixing (Shi et al., 2016; Singh et al., 2014; Vanarase et al., 2013). Both qualitative and quantitative approaches were reported using NIR spectra to monitor powder blending (Corredor et al., 2015; El-Hagrasy et al., 2006a, 2006b; El-Hagrasy and Drennen, 2006; Järvinen et al., 2013; Martínez et al., 2013; Vargas et al., 2017). NIR spectroscopy was used to analyze blend homogeneity and determine the blend end point (Sulub et al., 2011, 2009; Zacour et al., 2011) that directly affected the critical quality attributes of tablets such as content uniformity and hardness. A similar strategy of blend monitoring using NIR reflectance spectroscopy and imaging (Ma and Anderson, 2008) has been translated to powder flow monitoring. However, establishing homogeneity upstream does not assure it will remain through downstream processing. Specifically, vibration inside a feed hopper for a tablet press can induce segregation that results in reduced content uniformity of the subsequent tablets. Monitoring and controlling the powder stream immediately before the tablet compression more accurately represents the state of the process with respect to the finished dosage form. Considerable efforts have been made to monitor powder in the tablet feed frame using reflectance NIR (Durão et al., 2017; Mateo-Ortiz et al., 2014; Šašić et al., 2015; Ward et al., 2013). NIR reflectance spectroscopy has been also used to monitor powder bulk density (Román-Ospino et al., 2016; Singh et al., 2015) and control direct compression tableting process (Singh et al., 2015).

There are several off-the-shelf NIR reflectance systems that are ready to integrate with continuous processes. However, one of the limitations of these systems is that NIR reflectance spectra derive most of their information about the sample from the first few millimeters of the powder. Homogeneity and mixing state at the bulk phase assumes that the powder near the sampling point is representative of the bulk powder. This assumption has the potential to lead to a bias in sampling, leading to poor control decisions. Moreover, NIR reflectance offers limited understanding on the interaction between the process parameters (i.e., flow rate and tube angles) and its effect on the powder stream and its flow behavior. Such an understanding is critical to design a process and optimize the process parameters. An example of a parameter that is dynamically adjusted, based on the state of the powder stream, is the angle of the descent tube in which the NIR spectra is measured. An optimization strategy must ensure that the analytical method performs consistently across different powder flow rates set by process operators.

In this study, transmission NIR is proposed as a technique for monitoring and controlling continuous powder flow. Transmission NIR provides information from the bulk phase of the powder stream. It also provides critical information regarding the powder stream thickness. Powder stream thickness has the potential to affect the quantitative analysis of the powder stream using NIR. Powder stream thickness also acts as a response factor to gain an in-depth understanding about the interaction between process parameters such as flow rate and tube angles, and its effect of powder flow properties. The objectives of this study were as follows

- Develop a method for quantitatively monitoring powder stream constituents using transmission NIR spectroscopy.
- Develop a method for determining powder stream thickness using transmission NIR spectroscopy.
- Investigate the effect of process parameters (powder flow rates and tube angles) on powder flow behavior using transmission NIR spectroscopy.
- Develop an analytical design space of process parameters (powder flow rates and tube angles) for which the quantitative monitoring method using transmission NIR can be successfully deployed.

A quantitative method was developed in this study to determine the powder stream thickness using transmission NIR spectroscopy. This quantitative ability of the transmission NIR was used to analyze the effect of process parameters such as powder flow rates and tube angles on powder flow behavior. This strategy allowed the development of a design space to determine the optimum process parameters for producing desired powder flow behavior and ensuring consistent analytical model performance. The design space offers flexibility in processing conditions while