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Modeling of feed-forward control using the partial least squares regression method in the tablet compression process

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ABSTRACT

In the pharmaceutical industry, the implementation of continuous manufacturing has been widely promoted in lieu of the traditional batch manufacturing approach. More specially, in recent years, the innovative concept of feed-forward control has been introduced in relation to process analytical technology. In the present study, we successfully developed a feed-forward control model for the tablet compression process by integrating data obtained from near-infrared (NIR) spectra and the physical properties of granules. In the pharmaceutical industry, batch manufacturing routinely allows for the preparation of granules with the desired properties through the manual control of process parameters. On the other hand, continuous manufacturing demands the automatic determination of these process parameters. Here, we proposed the development of a control model using the partial least squares regression (PLSR) method. The most significant feature of this method is the use of dataset integrating both the NIR spectra and the physical properties of the granules. Using our model, we determined that the properties of products, such as tablet weight and thickness, need to be included as independent variables in the PLSR analysis in order to predict unknown process parameters.

1. Introduction

Over the past decade, a great deal of effort has been put towards the implementation of continuous pharmaceutical manufacturing in lieu of the traditional batch manufacturing (Leuenberger, 2001; Plumb, 2005; Singh et al., 2015a). Continuous manufacturing is expected to replace the traditional batch manufacturing approach and holds a significant potential in terms of innovation and brings flexibility, cost, and robustness to pharmaceutical manufacturing processes. In particular, the system enables flexible control of production volume per manufacturing time unit (Leuenberger, 2001; Plumb, 2005). Additionally, the traditional scale-up procedure, which classically requires changing the size of the manufacturing machine in accordance with sample volume, is no longer necessary in the continuous manufacturing system (Leuenberger, 2001; Plumb, 2005). Process analytical technology (PAT) is an indispensable tool for the continuous manufacturing system to ensure product qualify throughout the manufacturing process and offers the opportunity to automate the inter-process transportation of products (El-Hagrasy et al., 2001, 2005; Hattori et al., 2013; Hayashi et al., 2013; Otsuka et al., 2014b; Yu, 2008). In addition, the adoption of the quality-by-design (QbD) paradigm ensures quality of the end products during pharmaceutical development.

In most systems, PAT is implemented to monitor and control the output quality in real-time during continuous manufacturing. It may be sufficient to operate a continuous system which integrates PAT for the purpose of auto-testing. Similarly, if the process is controlled on the basis of the prospective data by PAT, the product quality will be automatically and accurately adjusted to the properties expected of the end products.

Near-infrared (NIR) spectroscopy is widely used as a monitoring tool for pharmaceutical manufacturing processes such as powder blending (Berntsson et al., 2002; Blanco et al., 2002; El-Hagrasy et al., 2001, 2005; Hailey et al., 1996; Hattori et al., 2013; Maesschalck et al., 1998; Sekulic et al., 1996), drying of wet granules (Hayashi et al., 2013; Otsuka et al., 2014b), granule coating (Andersson et al., 1999, 2000; Lee et al., 2011), and for quantifying tablet content (Dyrby et al., 2002; Ito et al., 2010; Järvinen et al., 2013). Järvinen et al. reported on the implementation of PAT using

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NIR for monitoring the content uniformity of active pharmaceutical ingredient (API) in powder blend and tablet (Järvinen et al., 2013). In their report, the authors described that in-line monitoring is an effective approach to determine the appropriate endpoint of blending and to ensure product quality. The use of PAT allows for a huge amount of informative data to be collected and processed in real-time during the manufacturing process, not only to ensure quality, but also towards a more effective retrospective use of the monitoring data.

Singh and Ramachandran demonstrated the utility of feed-forward control in the continuous manufacturing of tablets on the basis of in-line monitoring data collected through PAT (Singh et al., 2012, 2015a,b,c). For instance, the tablet compression process was significantly improved upon implementation of feed-forward control. The critical process parameters (CPPs) of compression need to be determined in order to adjust the tablet properties such as weight and thickness. It is empirically known that these CPPs are dependent on the chemical and physical properties of powder blends or granules, such as composition, moisture content, polymorphisms, particle size, bulk density, and flowability. When the initial CPPs are predicted through feed-forward control, deviations are minimized and anomalies are prevented hence ensuring overall product quality.

Singh et al. demonstrated the utility of feed-forward/feed-back control in the direct compression process using NIR spectroscopy real-time monitoring to predict powder bulk density (Singh et al., 2015b). Powder density is a significant quality attribute affecting the tablet weight and bulk density, hence the process parameters of compression need to be carefully monitored and controlled depending on the density. In the present study, we hypothesize that the granule compression process requires taking into consideration a number of attributes, not only including bulk density but also particle size and size distribution, chemical composition and crystallinity of all ingredients. When wet granulation is utilized to prepare the granules, moisture content and pseudo-polymorphism are also critical material attributes (CMAs) to be considered (Otsuka et al., 2014a).

Singh et al. also demonstrated that a control over the direct compression process was possible through a feed-forward control model empirically based on the powder bulk density (Singh et al., 2015b). It may be sufficient to apply a single input variable to the direct compression process. For a more universal feed-forward controller of both direct and granule compression process, chemical composition, moisture, and crystalline states of all ingredients are desirable parameters to be factored in the feed-forward control. Fortunately, these chemical characteristics are presented in the NIR spectroscopic data; hence chemical information and moisture content may be monitored and promote universal feed-forward control system.

To handle the intricate multi input variables, in this study, the partial least squares regression (PLSR) method was applied to prepare a feed-forward control model for predicting the process parameters of tablet compression. To determine CMAs using PAT, the PLSR method is often used on the basis of the NIR spectroscopic input variables (Hattori et al., 2013). Since the PLSR algorithm is based on the singular value decomposition method of multidimensional array, the key advantage of using PLSR is that the multiple input variables are permissible (Lorber et al., 1987). Additionally, it is also possible to use a hybrid input of multiple types of variables such as NIR spectra, particle size distribution, and granule bulk density.

In order to control the process based on the granule properties, tablet properties of weight and thickness are also required to use for the control model together with the input variables of the granules. The data set of total input variables for PLSR is eventually composed of both granule and tablet properties. The output variables are the process parameters of compression such as the displacements of upper and lower punches. In the present study, the PLSR feed-forward control model was applied to the prediction of CPPs for single punch compression and the fundamental attributes in the control of granule compression are discussed. To validate the model, the processes of powder blending, granulation, drying and compression were carried out as a batch method, while the NIR spectral measurements and other granule characterisation procedures were carried out using off-line methods.

2. Experimental methods

2.1. Materials

Riboflavin was purchased from Sigma-Aldrich (St. Louis, MO) and used as the API. The other additives, such as lactose monohydrate (200 M), anhydrous lactose (21AN), micro-crystalline cellulose (MCC, PH101), potato starch, hydroxypropyl cellulose (HPC-L), and magnesium stearate were purchased from DFE Pharma (Goch, Germany), DEF Pharma, Asahi Kasei (Tokyo, Japan), Kozakai pharmaceutical (Tokyo), Nippon soda (Tokyo), and Wako pure chemicals (Osaka, Japan), respectively and were used as received. A total of twenty-six batches of powder blends were prepared and were used in the ensuing processes of granulation and compression.

One variable was introduced: two types of lactose were used as excipient: either monohydrate or anhydrous lactose. A total of twenty-one batches were used for model preparation i.e., five batches of lactose monohydrate and sixteen batches of anhydrous lactose. External validation of the model was performed using four batches. The prediction and compression based on CPP output

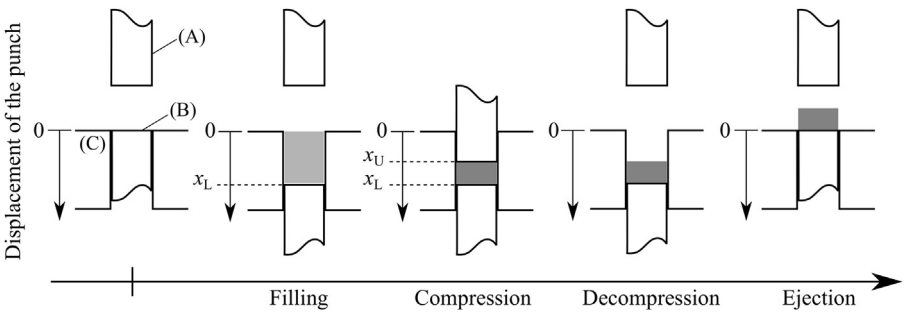

Fig. 1. Compression process flow using single punch tableting machine with an upper punch (A), a lower punch (B), and a die (C). x_U and x_L indicate the maximum displacements of the upper and lower punches, respectively. The minimum distance between punches is given by Eq. (1).