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A quality by design approach to investigate the effect of mannitol and dicalcium phosphate qualities on roll compaction

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ABSTRACT

Roll compaction is a continuous process for solid dosage form manufacturing increasingly popular within pharmaceutical industry. Although roll compaction has become an established technique for dry granulation, the influence of material properties is still not fully understood. In this study, a quality by design (QbD) approach was utilized, not only to understand the influence of different qualities of mannitol and dicalcium phosphate (DCP), but also to predict critical quality attributes of the drug product based solely on the material properties of that filler. By describing each filler quality in terms of several representative physical properties, orthogonal projections to latent structures (OPLS) was used to understand and predict how those properties affected drug product intermediates as well as critical quality attributes of the final drug product. These models were then validated by predicting product attributes for filler qualities not used in the model construction. The results of this study confirmed that the tensile strength reduction, known to affect plastic materials when roll compacted, is not prominent when using brittle materials. Some qualities of these fillers actually demonstrated improved compactability following roll compaction. While direct compression qualities are frequently used for roll compacted drug products because of their excellent flowability and good compaction properties, this study revealed that granules from these qualities were more poor flowing than the corresponding powder blends, which was not seen for granules from traditional qualities. The QbD approach used in this study could be extended beyond fillers. Thus any new compound/ingredient would first be characterized and then suitable formulation characteristics could be determined in silico, without running any additional experiments.

1. Introduction

Roll compaction (RC) is a continuous process that has become increasingly popular within pharmaceutical industry for dry granulation of moisture and heat sensitive powder blends with poor flowing properties (Kleinebudde, 2004). Although roll compaction has become an established technique, some of the process variation remains unexplained. Compactability and flowability are considered as key material attributes for fillers in roll compaction, hence well flowing direct compression (DC) qualities of fillers are commonly used in the roll compaction process (Malkowska and Khan, 1983; Wu and Sun, 2007; Chang et al., 2008). The choice of filler depends on the feeding system of the equipment, but even more on the properties and proportion of the active substance in the formulation. If the active substance is very cohesive, free flowing excipients as direct compression qualities are preferred. When flowability is not an issue in the formulation, traditional filler qualities not designated to one specific use such as direct compression or roll compaction, are also usable.

Microcrystalline cellulose (MCC) is a plastic deforming material and one of the most popular fillers for roll compaction due to its high tensile strength. Several authors have studied the effect of MCC quality on the roll compaction (Herting and Kleinebudde, 2007; Sun and Himmelspach, 2006; Inghelbrecht and Remon, 1998a,b; Dumarey et al., 2011). In contrast, there are only few studies describing the effect of brittle filler qualities such as lactose, mannitol and dicalcium phosphate (DCP) on roll compacted granules and tablets. Inghelbrecht and Remon (1998a,b) investigated the influence of different lactose qualities on roll compaction. In their study, spray-dried lactose caused problems due to its excellent flow and only low pressures could be used, which resulted in a lower granule quality.

Modeling of the roll compaction unit operation was pioneered by Johanson (1965). A practical follow up was made by Reynolds

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et al. (2010), while the effects of the raw materials were included in the modeling by Dec et al. (2003) and Soh et al. (2008). The purpose of the study presented herein was to generalize the modeling in order to enable predictions for new raw material qualities in a quality by design (QbD) context. To fulfill this goal, it is not enough to model the outcome of the statistically designed experiments based on selected batches from individual vendors. Instead, it is important to understand how raw material and intermediate material properties as well as process parameters affect the outcome at different process steps. For this reason, orthogonal projections to latent structures (OPLS) (Trygg and Wold, 2002) was substituted for multiple linear regression, i.e. the standard regression tool for design evaluation. Since projections to latent structures based modeling techniques can cope with correlated variables, it is possible to directly use a series of raw material properties in the modeling while still supported by the systematic variation maximized by the underlying design of experiments (DoE). An advantage of OPLS is that variation not related to the studied product quality can be studied separately. In a QbD context, the ability to fit a significant model that relates the outcome of one or more process steps to material properties and process settings, enables a control strategy that includes a mathematical model to arrive at a desired product quality within the design space. If a significant model cannot be made, this is an indication that the outcome of the process is robust for the magnitude of property variations present within the design space.

In this study, the strategy for understanding the influence of raw material properties on roll compaction used by Dumarey et al. (2011) was applied for one brittle filler, dicalcium phosphate (DCP), and for one moderately brittle filler, mannitol. For both DCP and mannitol, additional qualities were studied as external test sets to evaluate the predictive capacities of the constructed OPLS models. Tablets made from roll compacted material were also compared with tablets compressed directly from the initial powder blends in order to study differences in critical quality attributes and the tensile strength reduction phenomenon. Finally, the utility of these models are discussed in a QbD context.

2. Theory

2.1. Orthogonal projections to latent structures

OPLS is a development of partial least squares (PLS) with the aim to increase the interpretability of models by separating the variation that is related to the response from the variation that is unrelated to the response. Using the same settings, the prediction properties are the same for PLS and OPLS (Trygg and Wold, 2002). Both methods involve the construction of a regression model maximizing the covariance between the descriptor variables ($\mathbf{X}$) and the response, i.e. the dependent variable, $\mathbf{y}$. Additionally, OPLS performs a filtering step, which captures structured variation not related to the response but overlapping with the related variation, in one or more orthogonal components. The loadings of the descriptor variables on those components indicate the origin of the uncorrelated, also called orthogonal, variation. The variation correlated with the response can be interpreted by the loadings on the predictive component of the OPLS model, i.e. the PLS component calculated from the filtered data after removal of the orthogonal components. The R^2X values of the predictive and orthogonal components are measures of the structured fraction of the original data variation describing the response and the fraction not correlated with the response. The quality of an OPLS model is described by the R^2Y value, i.e. the correlation between the observed and predicted values for the studied response, and the Q^2 value, i.e. the correlation between the observed and cross-validated predicted response. The higher the R^2Y and Q^2 value the better the response can be described and predicted as a function of the descriptor variables, respectively. The R^2X, R^2Y, and Q^2 values are normalized to have an upper limit of 1. The low end is around 0 but the results of the cross validation may cause Q^2 to be negative when no model is found.

3. Experimental

3.1. Raw material characterization

Seven different DCP qualities and thirteen different mannitol qualities were characterized by measuring their rheological properties using a FT4 Powder rheometer (Freeman Technology, Welland, UK). Dynamic methods (specific energy, basic flowability energy, flow rate index and stability index) measure the resistance of the powder to flow whilst the powder is in motion. The measurements were done using a 25 mm bore diameter, 40 ml volume split vessel with a 23.5 mm blade. The detailed description of the dynamic methods is provided by Freeman (2007).

In addition to dynamic methods, the powder rheometer can be used to measure bulk density, compressibility and permeability of the material. The compressibility test determines changes in a powder's density as a result of a directly applied consolidating load. The compressibility of raw materials and powder blends was measured by applying levels of normal stress with a porous piston whilst measuring the volume change. The permeability test applied to the raw materials and powder blends determines the air flow between particles and through the powder bed by measuring the pressure drop across a powder bed. These measurements are done by varying the applied normal pressure while maintaining the air velocity through the bed constant. Both increased compressibility and increased pressure drop indicate a worse flowing powder. The compressibility (%) and the permeability (mbar) were measured using a 25 mm bore diameter, 10 ml volume split vessel at an end stress of 15 kPa. Permeability testing has been described in detail by Cordts and Steckel (2012).

The particle size distribution curve was measured with laser diffraction (Mastersizer 2000, Malvern Instruments Ltd., Malvern, United Kingdom) for the pure mannitol and DCP grades as well as powder blends and granules. No dispenser pressure was applied in order to break neither the spray-dried particles nor the granules before the measurement. The 10th and 50th percentile of the particle size distribution was reported, which means that 10% (or 50%) of the particles have a diameter according to the $d(0.1)$ (or $d(0.5)$) value or smaller. The 90th percentile value and the width of the particle size distribution were also determined, but did not provide any additional information about the samples in this study. The correlation between $d(0.5)$ and $d(0.9)$ was 0.997, thus even if the nominal values of $d(0.9)$ are higher, they provide the same variation pattern as the $d(0.5)$.

Additionally, the tensile strength of each filler quality was determined by compressing 300 mg of the pure quality both at approximately 10 kN (three replicates) and 14 kN (three replicates) with a single punch tableting machine (Kilian SP300, Kilian & Co GmbH, Germany) using a round flat punch (10 mm diameter). Finally, the average of the normalized tensile strengths (tensile strength/compaction pressure ratio) of the six measurements was calculated and multiplied by 153 MPa (corresponds to a compression force of 12 kN). All measured properties (identical for DCP and mannitol designs) and their abbreviations can be found in Table 1, while the abbreviations for mannitol and DCP qualities are shown in Tables 2 and 3, respectively.