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Impact of roll compactor scale on ribbon density

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ABSTRACT

Limited work has been performed regarding the scalability in the roll compaction process. Most of those studies available focus their efforts on developing models to successfully scale-up the process and only few of them strive to analyse the effect of the roll compaction scale on the product's properties. Therefore, in this work a double evaluation is performed focusing on process understanding and modelling application. In order to achieve this aim, ribbons of MCC, mannitol and a binary 1:1 mixture were roll compacted on 2 scales of compactors developed by Gerteis and L.B. Bohle, respectively. All compactors have a roll diameter of 250 mm in common but they differ in the roll width. The production was carried out following a common design of experiments in which the effect of the specific compaction force, the gap width and the roll speed were also investigated. The ribbons obtained were collected and characterized regarding their relative density. After statistical evaluation, it was found that the relative density of the mannitol and the mixture's ribbons produced using the Gerteis and L.B. Bohle compactors, are significantly affected by the scale, i.e. the roll width. For MCC, the impact of the compactor scales on the process was not so critical. The data collected was also modelled using the approach developed by Reynolds et al. 2010 in order to successfully scale-up the process. Excellent prediction was found for MCC, and although for mannitol and the mixture, the quality of the models decreased, they are still in good agreement, indicating the great utility of this approach when scaling-up a roll compaction process.

1. Introduction

The production of tablets in the pharmaceutical industry often requires a granulation process in order to achieve adequate flowability and compactability of the material by size enlargement. Roll compaction/dry granulation is a continuous process which popularity has increased in recent years [1]. This process comprises compaction of feed powder by passing through the gap formed between two counter-rotating rolls. The denser product ‘ribbon’ is subsequently milled into granules that can be later compacted into tablets. Many parameters and process conditions can be modified in order to obtain the desirable product characteristics. The properties of the compacted material also have a significant impact on the process. Two types of compaction behavior are relevant: plastic deformation and fragmentation (brittle character). A plastic material like microcrystalline cellulose (MCC) is able to remain deformed once the compaction stress is removed. A brittle material such as mannitol, will suffer fragmentation of its particles by the stress applied [2]. These two materials were chosen for this study as they are both widely used as diluents in the pharmaceutical industry [3,4].

As for any process of high interest for the pharmaceutical industry, it is necessary to investigate its scale-up, i.e. the transfer of the process from smaller to larger scale. For achieving this objective, the critical parameters involved on this procedure must be identified and their influence understood, so that it is possible to adapt them in order to obtain the same product quality at both scales. This is important to consider in research and a critical step in the industry, as it is desirable that the results obtained in the laboratory can also be transferred to pilot, production or commercial scale. Roll compaction process vendors use two scale-up strategies based on how the size of the rolls are modified between scales: by changing the roll diameter together with the roll width or by just varying the roll width while keeping the diameter constant.

Despite the importance of the roll compaction process, limited scale-up work has been reported in the literature. Several authors have performed multiple studies in the roll compaction field which resulted in different tools considered for the investigators as useful for scale-up [5–7]. Sheskey et al. [8] performed a scale-up study using three compactors from Freund-Vector (TF-Mini, TF-156 and TF-3012) to transfer a drug-containing formulation where production conditions were optimized for the TF-Mini. Freund-Vector Corporation applies a change in roll diameter and width scale-up strategy for its equipment. It was observed that the roll force (expressed as tons/in.) and speed can be easily scaled by adapting those parameters in order to obtain

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the same total roll force (depending on the roll width) and the same linear speed (depending on the roll diameter) in all compactors. The screw and its relationship with the roll speed caused minimum problems. Recently, Allesø et al. [9] investigated the scale-up between two compactors from Gerteis (Mini-Pactor® and Macro-Pactor®) which have a common roll diameter, thus, only the width of the rolls is different between both scales. A design of experiments (DOE) was performed in the two scales using mainly MCC. Ribbon porosity was determined using two different methods (laser-based technique and an oil intrusion method) and the values obtained for the same process conditions in the two scales were compared and an excellent correlation was found. They concluded that ribbon porosity was scale-independent when the roll width is used as the scale factor and the specific compaction force (SCF) is constant, i.e. when only the roll width differs between both pieces of equipment.

Many of the scale-up studies more recently published include the development of models which allow prediction of the density of the ribbons and the parameter settings required for achieving a target ribbon density value. These models are interesting tools as they can be used for the diverse scales. The models for scale-up can be primarily classified as mechanistic models or dimensionless variables. Nevertheless, there are many other papers in which statistical and multivariate models are described [6,10–21]. However, these approaches were not described to be applicable for the scalability of the process and for this reason, they will not be considered. The mechanistic models are based on physical principles and considerations of the roll compaction process and most of them rely on the rolling theory developed by Johanson [22]. On the other hand, the dimensional analysis to develop a scaling variable and therefore allows transfer of the process.

Johanson [22] developed a model which considers the geometry of the roll compactor and it could be useful for scale-up predictions. His theory is based on predicting the density of the ribbon by calculating the differences on volume between the nip area and the gap. The nip area is the zone where the densification starts and it is defined by the nip angle [23]. In order to calculate the nip angle, Johanson equates the normal stress generated in both regions. Once this value has been determined, the volume of the nip region is calculated by determination of the roll force. Then, the density of the ribbon is obtained by calculating the differences in volume between the nip region and the gap. Nevertheless, in the Johanson's model, the pressure on the nip angle (nip pressure) is used to calculate the roll force. However, this value cannot be accurately estimated and several authors have developed different approaches to overcome this limitation.

Reynolds et al. [24] proposed a practical approach in which the need for the nip pressure is avoided by using a preconsolidation relative density that can be used directly to relate the ribbon density to the modelled peak pressure, P_{max}, between the rollers. Another novel point is an alternative form of the model that includes the feed screw speed, showing how this has an effect on the incoming material. The model was validated using experimental data obtained using Alexanderwerk WP 120. For this compactor two roll widths are available: 25 and 40 mm but both of 120 mm diameters. The relative density of the ribbons was obtained, proving that the model provides excellent correlation between the predicted and experimental values. This approach is not only applicable for scale-up but also for other types of roll compactor. Souihi et al. [25] used the Reynolds's model to examine a formulation using two roll compactors with different feeding systems: Alexanderwerk WP 120 and Pharmapaktor C250 (from Hosokawa Bepex company). Results showed an excellent prediction of the ribbon porosity with overall root-mean-square error (RMSE) between 1.0 and 1.5%, and therefore, they confirmed the applicability of the model not only for scale-up but also for different systems. However, only two formulations were tested in total, although they involved plastic and brittle excipients and commonly used active pharmaceutical ingredients (API).

Another mechanistic model for scale-up was developed by Nesarikar et al. [26] in which the nip pressure requirement is eliminated. This approach calculates the relative density as a function of the gap and the roll force per unit of roll width (RFU) which are two variables independent on the roll compactor. An instrumented Alexanderwerk WP 120 (120 mm roll diameter and 40 mm roll width), which allows measuring the normal stress on the ribbon and hence the nip angle, was used. In this manner, the nip angle is calculated as a function of gap and RFU which is subsequently used for calculating the roll force, and therefore, the ribbon density. Placebo was used to calibrate the model and three active blends to validate this approach, obtaining reasonably accuracy for the ribbon density. Then, an uninstrumented Alexanderwerk WP 200 (200 mm and 75 mm of roll diameter and width respectively) was used for the scale-up study. As no data regarding normal stress or nip angle was collected for the WP 200, the equation obtained for the WP 120 was then used. Considering this assumption, the ribbon densities for a placebo mixture were calculated for the WP 200 and these values compared well with those obtained experimentally using the WP 200. The limitations of this approach are the requirement of extensive calibration data using materials with different compaction behaviors, and the need of an instrumented roll in order to obtain the nip angle.

Other authors applied dimensionless analysis for scale-up. Rowe et al. [27] developed the so-called modified Bingham number (Bm^*), and proposed a model based on the Johanson's theory and including some modifications from Reynolds's approach, specifically the consideration of the feeding zone. The same experimental data collected in Nesarikar's work [26] was used. The Bm^* is plotted against the relative density and a linear correlation was obtained for the two scales considered. As in the case of the previous model, it covers a broad range of materials and process combinations, however, in this case, the authors stressed the need of parameters which are easy to measure or obtain. More recently, Boersen et al. [28] proposed another dimensionless relationship, called as dimensionless variable (DV) which considered the roll pressure, roll speed, feed screw speed, the true density of the material and the roll diameter. This variable was correlated to the ribbon density obtaining a linear relationship. This DV was used to evaluate the roll compaction process using an Alexanderwerk WP 120 and a Fitzpatrick IR220. Only a small percentage of error was found when comparing the ribbon relative density in both compactors for those conditions resulting in similar values of DV. Although this model was applied to different sieve fractions of MCC and their mixture with APIs and requires further validation, it looks promising, in particular because of the limited effort required to calculate the DV. The authors concluded that it could be a good approach for scale-up.

Nevertheless, other techniques or approaches can be also used in order to predict the ribbon relative density at larger scales, and therefore, scale the process up. For instance, Shi et al. [29] developed a practical approach to scale-up the roll compaction process from the Alexanderwerk WP 120 to the Alexanderwerk WP 200 roller compactor. This methodology consists of the development of a linear equation which describes a property and is later adjusted for the large scale. The authors adapted the equation considering that the slopes of the previous equations are powder-dependent. The success of this methodology was later confirmed and it has as great advantage of being simple to implement. Another tool was proposed by Liu et al. [30], in which a new statistical methodology is used to scale-up a roll compaction process between the Fitzpatrick IR220 and the Fitzpatrick IR520: joint-Y partial least squares. The results confirmed that this methodology could be used for scaling-up. However, this model requires a large amount of data to perform its calibration.

2. Objectives

In this work, the scale-up with two roll compactors from Gerteis and two produced by L.B. Bohle is investigated by producing ribbons of MCC, mannitol and a binary mixture of both, following a common DOE. These compactors are seldom reported in the literature, and for the specific

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