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Roller compaction scale-up using roll width as scale factor and laser-based determined ribbon porosity as critical material attribute

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ABSTRACT

Due to the complexity and difficulties associated with the mechanistic modeling of roller compaction process for scale-up, an innovative equipment approach is to keep roll diameter fixed between scales and instead vary the roll width. Assuming a fixed gap and roll force, this approach should create similar conditions for the nip regions of the two compactor scales, and thus result in a scale-reproducible ribbon porosity. In the present work a non-destructive laser-based technique was used to measure the ribbon porosity at-line with high precision and high accuracy as confirmed by an initial comparison to a well-established volume displacement oil intrusion method. The ribbon porosity was found to be scale-independent when comparing the average porosity of a group of ribbon samples (n = 12) from small-scale (Mini-Pactor®) to large-scale (Macro-Pactor®). A higher standard deviation of ribbons fragment porosities from the large-scale roller compactor was attributed to minor variations in powder densification across the roll width.

With the intention to reproduce ribbon porosity from one scale to the other, process settings of roll force and gap size applied to the Mini-Pactor® (and identified during formulation development) were therefore directly transferrable to subsequent commercial scale production on the Macro-Pactor®. This creates a better link between formulation development and tech transfer and decreases the number of batches needed to establish the parameter settings of the commercial process.

1. Introduction

Roller compaction for dry granulation has gained increasing interest in the pharmaceutical industry over the past decades. Improvements in the technology such as better control over the gap, leading to more uniform ribbon and granule properties, and improved roller side sealing and thus containment of fines, are key reasons for its increased popularity (Kleinebudde, 2004; Miller, 2005).

Roller compaction is a continuous unit operation, meaning that a primary batch may be split into several sub-batches and processed at various combinations of process parameters. This approach carries the potential of efficient formulation development as well as flexibility to shift between various scales by either adjusting press roller speed and/or gap size; however, only when their impact on granule quality is fully understood.

Scale-up from lab/pilot to commercial scale can pose challenges that are difficult to foresee as well as mitigate; not least because these issues occur late in development where the formulation composition is often fixed. This restricts scale-up control strategies to the adjustment of process parameters as well as equipment design alterations; the latter typically realistic only with new equipment as a part of its installation and qualification. Proper understanding of scale-up parameters stems from mechanistic insight into the given process technology and its various scales. The aim of a successful scale up is therefore to create similar process conditions for the powder material across scales through the adjustment of process parameters. For roller compaction, assuming a fixed granulator sieve size between pilot and commercial scale, ribbon porosity is the most important quality descriptor of the granules' compression properties and size distribution, as discussed by Allesø et al. (2013). The proper scale-factor for compaction pressure may be found through empirical testing at the larger scale or through the application of powder mechanics theory (Johanson, 1965) combined with experimental data (Reynolds et al., 2010; Rowe et al., 2013). Mechanics theory can be applied to determine the nip angle/in the compaction zone when switching to larger roll diameters. In roller compaction, the nip angle indicates the compaction zone from start to end of densification, which therefore dictates the total pressure applied to the powder (at a given roll force) and ultimately impacts ribbon porosity. There are studies demonstrating the use of instrumented roller compactors to acquire the pressure profile of the powder material in the nip region (Bindhumadhavan et al., 2005; Miguélez-Moran et al., 2008; Nesarikar et al., 2012) as well as a recent example of roller compaction modeling

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by computational FEM combined with experimental data (Cunningham et al., 2010). As an alternative to first-principle understanding, Liu et al. (2011) modeled historic data from a small-scale roller compactor by Joint-Y PLS regression and applied it to predict the scale factor for roll pressure on a larger scale compactor, having a larger roll diameter.

Parts of the scale-up challenges in roller compaction may also be averted through innovative designing of the different equipment scales. The flagship models of Gerteis® compactors include the Mini-Pactor® and the Macro-Pactor®. A scale-comparable front-view of the two compactors is shown in Fig. 1. The Mini-Pactor® is the *R&D* and *pilot-scale* machine although the continuous nature of this unit operation makes it suitable for production scale also depending on the processing time. The Macro-Pactor® is Gerteis®' *production scale* compactor. It is very similar to the Mini-Pactor®, the two most notable differences being four times wider press rollers (25 mm vs. 100 mm) and a feeding system with two tamp augers instead of one in addition to the single feed auger that both machines have. The fact that rollers have identical diameters between the two scales ensures an identical nip area and thus a similar impact of roll pressure and gap size on the conveyed powder material. Consequently, one may claim ribbon porosity to be scale independent for these particular roller compactor types. To the best of our knowledge there are no published studies demonstrating this.

Determination of ribbon porosity is not as trivial to determine as for a tablet. A tablet has well defined dimensions and, using punch drawings, for example, the volume of the tablet can be calculated at a specific tablet thickness. When the tablet mass and the density of the particles are known, the porosity can easily be acquired. Ribbons on the other hand are irregular in shape and a frequently used method to determine the volume of the inter-particular voids is a volume displacement method where a medium of known density is absorbed into the pores of the sample. A long-established technique in this category is mercury porosimetry, its major drawback being the toxicity of the mercury. Environmentally friendly alternatives are intrusion with low viscosity oil (Allesø et al., 2013; Khorasani et al., 2015) or a fine-particulate solid material such as the Dry Flo® medium used for the GeoPyc® (www.micromeretics.com).

Nkansah et al. (2008) have described a simple throughput approach to solid fraction[1] determination. Ribbons are collected in real-time within a certain process time frame and weighed. The volume of ribbon material produced in that time frame is calculated from the process parameters gap and roll speed as well as a correction for viscoelastic expansion. The mass and volume (per time unit) divided provide the at-gap ribbon density. An obvious drawback of this technique is the large sample size required for accurate porosity determination. The dimensional method is perhaps the most simple of all, where the volume of the ribbon is determined by cutting the ribbon to a rectangular shape with a trimming knife. This method, however, has a very limited use since fragile and small ribbons, which often are the case when API is present in the formulation, cannot be cut properly. Furthermore the dimensional approach does not take into account thickness variations of ribbons manufactured using knurled or serrated rollers. Spectroscopic techniques have also been described in the literature, though they do not directly measure the density of the compact but rather a property correlated with the density. These methods include near-infrared (NIR) spectroscopy (Lim et al., 2011; Acevedo et al., 2012; Khorasani et al., 2015; Souihi et al., 2015), where the impact of light scattering on the baseline is considered. Recently terahertz (THz) spectroscopy has been described, which measures the effective refractive index of the ribbon that can be correlated to the density (Sullivan et al., 2015).

The use of a laser-based direct volume measurement device is a recently introduced technique for determination of ribbon porosity (Iyer et al., 2014a,b). The large number of ribbons needed for scale-up investigations, call for a method that efficiently analyzes ribbon porosity at a higher speed than the previously described, well-established volume displacement approaches. The laser technique provides a result in approximately 2 min per ribbon, avoids the use of any consumable supplies and is simple to utilize. Although the technique is commercially available, literature demonstrating its performance is still sparse. Therefore, one aim of this study was to compare the laser-based porosity method against a volume displacement method using low viscosity oil (medium chain triglyceride, MCT). Another aim of the present study was to investigate the hypothesized scale independence of ribbon porosity, when roller compaction scale-up was done by means of a roll width increase from 25 mm to 100 mm on Gerteis® compactors.

2. Materials and methods

2.1. Materials

Microcrystalline cellulose (Avicel PH102) and croscarmellose sodium (Ac-Di-Sol) were sourced from FMC Health and Nutrition (Philadelphia, PA, USA) and used as filler/binder and superdisintegrant, respectively. Magnesium stearate (Peter Greven GmbH & Co.KG, Bad Münstereifel, Germany) was added as lubricant to reduce friction between the powder and metal surfaces of the roller compactor. Medium chain triglyceride was obtained from Delios V (Illertissen, Germany).

2.2. Experimental design

All samples consisted of microcrystalline cellulose (diluent) and 0.75% magnesium stearate. A two-factor, two level design was carried out at each roller compactor equipment scale, with the factor gap size at levels 2.0 and 4.0 mm and the factor, roll force at levels 3.0 and 11.0 kN/cm. The study included a center point with a gap of 3.0 mm and roll force of 7.0 kN/cm. For the comparison of the two porosity measurement techniques (laser and oil; see below), a total of six ribbons were analyzed per experiment (five in total) per equipment scale (two), i.e. $6 \times 5 \times 2 = 60$ ribbons in total. Every ribbon was first analyzed by the non-destructive laser method and finally subjected to the destructive oil intrusion method.

For comparison of roller compactor equipment scales, the sample population was increased from six to $n = 12$, the additional six ribbons only being analyzed by the laser method.

An additional four experiments were conducted separately with the intention to sample an entire 100 mm ribbon from the Macro-Pactor® (see below) and assess the within-ribbon porosity variability. Four combinations of gap and roll force where investigated, but this time at relatively high roll pressures, since whole ribbons are difficult to sample when they get too fragile. The investigated settings were 2.0 and 4.0 mm gap and 7.0 and 11.0 kN/cm.

2.3. Roller compaction

The microcrystalline cellulose was mixed with magnesium stearate in a Bohle LM40 bin blender of suitable size (L.B. Bohle, Ennigerloh, Germany). Dry granulation was carried out on the smaller scale Mini-Pactor® (Gerteis® Maschinen + Processengineering AG, Jona, Switzerland) equipped with 25 mm wide rolls as well as on its larger scale equivalent, the Macro-Pactor®, equipped with 100 mm wide rolls. Gap size and roll force were varied according to the design described in the previous section. Roll speed was 6.0 rpm and the feed/tamp auger ratio was 250%. Auger speed was automatically adjusted by the gap control feature in order to ensure a stable gap during processing. A stable gap was confirmed for all individual experiments of this study. Sample collection (see below) was performed once the roller compactor had reached its target setting for gap and roll force.

[1] Porosity = (1 − solid fraction) * 100%