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Research paper

A practical approach for the scale-up of roller compaction process

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ABSTRACT

An alternative approach for the scale-up of ribbon formation during roller compaction was investigated, which required only one batch at the commercial scale to set the operational conditions.

The scale-up of ribbon formation was based on a probability method. It was sufficient in describing the mechanism of ribbon formation at both scales. In this method, a statistical relationship between roller compaction parameters and ribbon attributes (thickness and density) was first defined with DoE using a pilot Alexanderwerk WP120 roller compactor. While the milling speed was included in the design, it has no practical effect on granule properties within the study range despite its statistical significance. The statistical relationship was then adapted to a commercial Alexanderwerk WP200 roller compactor with one experimental run. The experimental run served as a calibration of the statistical model parameters. The proposed transfer method was then confirmed by conducting a mapping study on the Alexanderwerk WP200 using a factorial DoE, which showed a match between the predictions and the verification experiments. The study demonstrates the applicability of the roller compaction transfer method using the statistical model from the development scale calibrated with one experiment point at the commercial scale.

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1. Introduction

Roller compaction is a process typically used in the pharmaceutical and food industry to increase the flowability of a powder by forming granules of greater size and density [1]. In a roller compaction process, a powder blend containing active pharmaceutical ingredient (API) and excipients passes through two counter-rotating rolls that compact the blend into ribbons. The ribbons subsequently are milled into granules of a desired size distribution that are mixed with extragranular materials prior to tabletting or capsule filling. While milling can be a mechanically separate unit operation, some roller compactors have combined ribbon formation and milling mechanism, making it a continuous operation. In this study, we focus on the scale-up of such roller compactor.

As the granules are denser and larger compared to the pre-roller-compacted blend, the granules flow freely and result in consistent feeding on a tablet press or capsule filling machine. However, the trade-off of the roller compaction process is the reduction in compactibility as a result of the powder being stressed, which may cause chipping or capping in tablets. Therefore, a balance between increase in flow and reduction in compactibility is a key design consideration in the development of a roller compaction process for tablet products. The flow and compactibility are directly linked to ribbon density [2]. While there is no evidence that ribbon thickness could affect followability or compactibility, the ribbon thickness is used as a process stability index. Its variation is related to functionality of the feeding control system, i.e. the responsiveness of the control logic to the input material or other variations [2]. Consequently, maintaining appropriate ribbon attributes (both ribbon density and thickness) during process scale-up [3] is crucial in the development of solid dosage forms (tablet or capsule).

Roller compaction as a unit operation has been studied extensively. Based on the Johanson model which describes the principle of ribbon formation, various methods [4–7] with the emphasis of matching normal stress betweens scales have been derived and utilized for scale up. However, since measuring the material properties required in the models is challenging and there are variations in mechanical conditions among roller compactors, design of experiment (DoE) at the commercial scale is still conducted to identify proper conditions for operating roller compaction. Such tedious experiments at commercial scales consume valuable API due to the large batch size.

Aiming to streamline transfers to commercial scales without impacting the reliability of the process, we have developed the probability based method that maximizes the usage of

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Nomenclature

ρ	ribbon density (g/ml)	T	ribbon thickness (mm)
P	roll pressure (bar)	MS	milling speed (RPM)
G	roll gap (mm)		

development scale data, and only requires one batch at commercial scale to define the acceptable range of operational parameters.

2. Experimental method

2.1. Materials and preparation

A low drug loading formulation containing API X at 5% w/w was used in the study for the proposed transfer method. Other components in the formulation included microcrystalline cellulose (68.5%, FMC Biopolymer), lactose anhydrous (20%, Kerry Bioscience), crospovidone (4%, Ashland), silicon dioxide (1.5%, Evonik), and magnesium stearate (1%, Covidien). All ingredients except magnesium stearate were mixed in a bin blender for 108 revolutions, comilled through a Quadro Comil (with 0.6 mm screen opening) and mixed again in the bin blender for 120 revolutions with magnesium stearate. The milling operation was used for enhanced local mixing, rather than size reduction as previously reported [8]. Since lactose anhydrous, the largest ingredient in the formulation, had a particle size of about 200 μm, the particle size of blend was not expected to change after milling through the 600 μm opening. As API X had a small particle size (100% less than 30 μm) and was a cohesive material with a low bulk density of about 0.1 g/ml, the resulted powder had a poor mass flow at 5% drug loading and required roller compaction prior to tabletting. A drug loading higher than 5% increased risk of sticking, arching or rate holing during process.

2.2. Roller compactor

Alexanderwerk WP120 (pilot scale) and WP200 (commercial scale) roller compactors were used in the study. The major differences between the two roller compactors are roller width (120 mm vs 200 mm) and roller depth (40 mm vs 75 mm). While the WP120 uses a horizontal single screw feeder to deliver the powder from the hopper to the roller units, the WP200 uses a horizontal double screw feeder to accommodate the wider rollers. As a result, the WP200 can have a throughput up to 400 kg/h compared to 40 kg/h for the WP120.

### 2.3. Pilot scale roller compaction development

The process was developed on an Alexanderwerk WP120 roller compactor which has an incorporated milling operation (fine rotor granulators). A 3-factor central composite design or CCD (JMP 7.0.1, SAS Institute Inc.) as shown in Fig. 1 was used. The inscribed option was checked, which limited the experiment points within the minimum and maximum of design parameters. The design was rotatable, a desirable property of response surface design. In the design, roll pressure (hydraulic pressure, P, 50–70 bar), gap setting between the rolls (G, 2.0–2.6 mm), and milling speed (MS, 40–80 rpm) were studied. The response in this design is granules properties (flow, bulk density, and particle size distribution) as well as ribbon attributes (ribbon density and thickness). The development work was used to determine parameter ranges yielding acceptable granules or ribbons, i.e., flowability, compactibility and tablet dissolution rate.

As milling of ribbons proceeded ribbon formation, the 3-factor design could be used to study ribbon formation only, i.e., using ribbon density and thickness as the responses and only considering roll pressure and gap setting as the factors without milling speed. This transforms the design to a two-factor central composite design with factorial points repeated once and the center point repeated 6 times as shown in Fig. 2.

From each run, ribbon and powder samples were taken. Ribbon thickness was measured with a digital thickness gauge. Ribbon density was determined using the weight and volume of 1-in. ribbon disks cut from the ribbon samples [9]. Powders were characterized for particle size distribution with a sonic sifter. Bulk
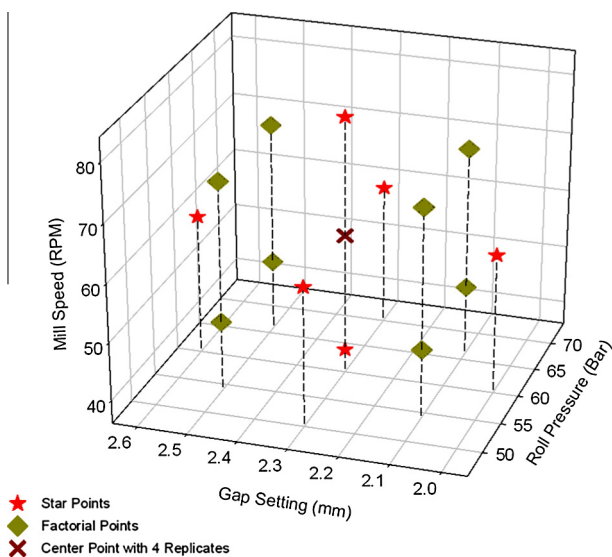
Fig. 1. Experimental design on Alexanderwerk WP120. A total of 18 experiments were conducted with 6 star points (star), 8 factorial points (diamond), and 4 replicates of the center point (cross).
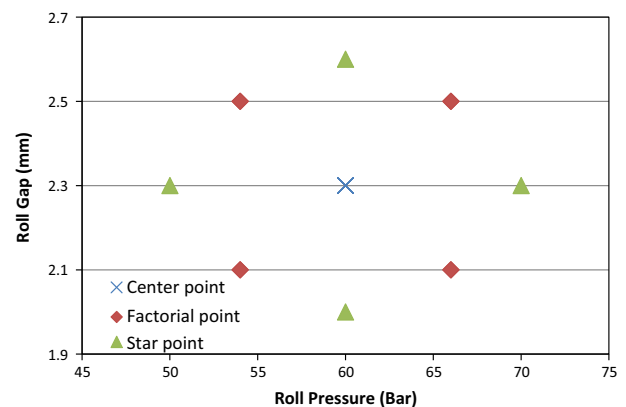
Fig. 2. Experimental design on Alexanderwerk WP120 for ribbon formation. Experimental design (ribbon formation) showing roll pressure and gap setting as the factors since milling occurs after ribbon formation and has no impact on ribbon formation.