



Commercial scale validation of a process scale-up model for lubricant blending of pharmaceutical powders



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ABSTRACT

An experimental study was conducted to verify that lubrication mixing in commercial-scale bin blenders can be described by a previously-reported lubrication blending process scale-up model. Specifically, the mixing of two placebo formulations (2:1 MCC:lactose, and 2:1 MCC:DCP) with 1% magnesium stearate in 100, 400, and 2000 L bin blenders at 30% and 70% blend fill levels for several extents of lubricant mixing was examined. The lubricated powder blends were assessed for bulk/tapped density and powder flow, as measured by Hausner's ratio. The blends were then compressed into tablets and evaluated for tensile strength, friability, and disintegration. It was observed that the lubrication rate constant, γ , for tablet tensile strength and for bulk specific volume were similar. Furthermore, powder flow, as measured by Hausner's ratio, improved with increased extent of lubrication. Tablet disintegration and tablet friability were both minimally affected as a result of extended lubrication for the placebo blends evaluated in this study. The results of this study confirm that the lubrication mixing model can be applied to scale-up the lubrication blending process from batches made in 30 mL bottle blenders to batches made in 2000 L bin blenders, which is a range of nearly five orders of magnitude.

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1. Introduction

Development and scale-up of the pharmaceutical manufacturing processes is a key aspect of drug product development. One of the process steps for solid dosage forms, powder lubrication, is particularly important, due to concerns about under- and over-lubrication of the drug product blend upon scale-up impacting the quality and performance of the drug product. It is well-known that magnesium stearate and other lubricants – other metal stearates, fatty acids, surfactants, polymers, and inorganic compounds (Wang et al., 2010) – can provide some benefit to downstream compaction processes (e.g., reducing wall friction during tablet ejection and reducing powder sticking to metal surfaces during roller compaction (He et al., 2007) and/or tablet compression (Yamamura et al., 2009)). However, these lubricants can also often impact the quality attributes – powder flow (Zhou et al., 2011; Horio et al., 2013; Morin and Briens, 2013), tablet hardness and friability (Perrault et al., 2011; Soh et al., 2013; Uchimoto et al., 2013), tablet disintegration (Taylor and Elhissi, 2011; Abe and Otsuka, 2012; Soh et al., 2013; Uchimoto et al., 2013), and dissolution (Abe and Otsuka, 2012) – of the proposed drug

product. Several formulation-related factors can determine the degree to which one or more of the drug product quality attributes can be affected by the powder lubrication step, including selection of the lubricant (Wang et al., 2010), the levels of lubricant in the formulation (Taylor and Elhissi, 2011; Uchimoto et al., 2013), and the physico-chemical properties of the lubricant (Dansereau and Peck, 1987). In addition, blending process parameters can also affect the extent of lubrication of the lubricated powder. Previously, it has been shown that blender type, batch/equipment size, and blending speed and duration (Bossert and Stamm, 1980; Bolhuis et al., 1987) can have an impact on drug product performance attributes of lubricated blends.

Within the quality-by-design development paradigm, pharmaceutical manufacturers can propose a design space, i.e., a range of material attributes and process parameters ranges within which acceptable product can be made. In an ideal situation, a design space for the lubricant blending process could be determined with small-scale experiments and, with appropriate, validated process scale-up models, could be transferred to the commercial-scale manufacturing operation. This has proven to be challenging for the lubricant blending process, due to concerns of under- and over-lubrication of the pharmaceutical formulation, and a lack of a good scale-up model for the lubricant blending process. Several approaches have recently been examined to better incorporate the lubrication blending process into the scale-up of a pharmaceutical manufacturing

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process. Maeda et al. (2012) examined the approach of developing a large-scale (3 kg) design space for powder flow, tablet hardness and dissolution, through a combination of small-scale (0.3 kg) experiments, Bayesian estimation methods, and a few large-scale batches to validate the model. This proposed approach has the benefit of reducing the amount of validation at large-scale for an individual formulation, but may need to be repeated for subsequent new formulations. Lakio et al. (2013) examined the use of process analytical technology (PAT) approaches to determine the extent of lubricant blending with Raman chemical imaging. This approach, and other in situ PAT approaches, would allow the blending process to be terminated when the desired extent of lubricant coverage of the formulation was achieved. Presently, Raman chemical imaging was only able to distinguish differences between samples blended for 2 min and for 60 min. Nakagawa et al. (2013) have also examined NIR and thermal effusivity of magnesium stearate as a means for in-process control of the lubricant blending process across scales, evaluating this method at both 4.8 kg and 500 kg batch sizes. Finally, NIR was used to develop a method of detecting the extent of magnesium stearate coverage on a theophylline, lactose, and potato starch tablet surfaces for the purpose of predicting theophylline dissolution performance (i.e., time to 50% dissolved) with a PLS model rather than by conducting future dissolution experiments (Abe and Otsuka, 2012).

In addition to these methods, a model for the lubrication blending process was previously developed and shown to be suitable for the scale-up of the lubrication blending process from lab-scale manufacture (i.e., 30 mL Turbula bottle blending) to clinical scale manufacture (i.e., 200 L bin blending) (Kushner and Moore, 2010; Kushner, 2012). However, there has yet to be any investigation on whether powder lubrication in commercial-scale blenders (i.e., greater than 200 L blenders) follows the previously-developed lubricant blending scale-up model. Therefore, the following study was performed to determine if the previously developed lubricant blending scale-up model (Kushner and Moore, 2010; Kushner, 2012) also applies to powder lubrication in commercial-scale blending units. From the results of the present study, it will be possible to better: (1) perform formulation and lubrication process understanding experiments using material sparing approaches, thereby reducing API requirements, and (2) scale the lubrication blending process from lab-scale (30 mL Turbula bottle blending) to commercial scale (2000 L bins) such that extent of lubrication of the formulation, and the associated product quality attributes, remain constant.

2. Theory

Previous experimental investigations have shown that the reduction in tablet tensile strength, σ , and bulk specific volume, SV , can be modeled according to the following expressions (Kushner and Moore, 2010; Kushner, 2012):

$$\sigma_{SF=0.85} = \sigma_{SF=0.85,0}[(1 - \beta) + \beta \exp(-\gamma \times K)] \quad (1)$$

$$SV = SV_0[(1 - \beta) + \beta \exp(-\gamma \times K)] \quad (2)$$

where β and γ are the sensitivity of the blend to lubrication and the lubrication rate constant of the formulation, respectively, and K is the amount of mixing applied to the lubricated formulation. K has previously been defined as the lubrication mixing imparted by the blender, as described by the following equation (Kushner, 2012):

$$K = (L \times F_{\text{headspace}} \times r) \quad (3)$$

where L = mixing length scale (V and bin blenders: $V^{1/3}$, Turbula blenders: $1.5V^{1/3}$), $F_{\text{headspace}}$ = the fraction of the blender occupied by headspace, and r = number of revolutions.

While Eqs. (1)–(3) were obtained empirically from experimental data, they can be used to provide some insight into the physical process occurring during lubricant mixing. The formulation parameters, β and SV_0 or $\sigma_{SF=0.85,0}$, describe the theoretical initial and final (i.e., at infinite mixing extent) material properties, while γ describes the rate at which the lubricant interacts with the formulation. For high values of γ , the formulation will approach the infinite mixing extent material property value more rapidly than a formulation with a low value of γ . The rate of lubrication is also impacted by the process parameters – L , $F_{\text{headspace}}$, and r . The L term serves as an estimate of the length of the free powder surface in the blender over which powder avalanching occurs, and serves as an estimate of the characteristic length scale for powder mixing. $F_{\text{headspace}}$ and r is related to the number of passes through the free powder surface the formulation will be exposed to during the blending process. As $F_{\text{headspace}}$ and r increase, the number of passes through the free powder surface increases. To maintain product quality of the same formulation throughout process scale-up, it is then necessary to maintain a constant value for K by adjusting the number of revolutions applied to the formulation during lubricant mixing to account for changes in the blender volume and blender fill level during process scale-up.

Eqs. (1)–(3) have been shown to be valid for low-shear, tumble blenders (e.g., V-blenders, bin blenders) ranging in volume from 30 mL to 200 L (Kushner and Moore, 2010; Kushner, 2012). In the present study, the high end of this range will be expanded to include the range of commercial-scale, low-shear bin blenders (i.e., 100–2000 L).

3. Materials and methods

3.1. Materials

Microcrystalline cellulose (MCC) as Avicel PH-102 was obtained from FMC Corporation (Philadelphia, PA), spray-dried lactose (lactose) as Fast Flo lactose 316 from Foremost Farms (Baraboo, WI), dibasic calcium phosphate (DCP) as A-Tab from Rhodia (Chicago Heights, IL) and magnesium stearate (MgSt) from Mallinckrodt (Hazelwood, MO). All materials were used as received.

3.2. Preparation of placebo blend

Microcrystalline cellulose and either spray-dried lactose or dibasic calcium phosphate anhydrous were combined together in the following ratios:

- 2 parts MCC and 1 part DCP,
- 2 parts MCC and 1 part lactose.

The two excipients were loaded into the corresponding bin blender (100 L, 400 L, or 2000 L) at either a 70% or 30% fill level and blended for 20 min at 12 rpm.

3.3. Lubrication of placebo blend with 1% magnesium stearate

Magnesium stearate (Mallinckrodt) was then added to the placebo blend in the bins such that it comprised 1% of the final lubricated blend. The 100 L and 400 L bins were operated at a speed of 12 rpm, while the 2000 L bins were operated at a speed of 8 rpm. The lower speed was used for the 2000 L bins to maintain a Froude number within the tumbling flow regime (i.e., $Fr < 0.4$) (Brone et al., 1988; Kushner and Moore, 2010; Maeda et al., 2013). At 12 rpm, the Froude number was 0.51 for the 2000 L bins, while at 8 rpm, the Froude number was 0.34. The duration of the lubrication blending was selected to ensure that the extent of lubrication was

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