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Incorporating Turbula mixers into a blending scale-up model for evaluating the effect of magnesium stearate on tablet tensile strength and bulk specific volume

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ABSTRACT

Turbula bottle blenders are often used in lab-scale experiments during early-stage pharmaceutical product development. Unfortunately, applying knowledge gained with these blenders to larger-sized diffusion mixers is limited by the lack of blending models that include Turbula mixers. To address this need for lubrication blending scale-up, 2:1 blends of microcrystalline cellulose and spray-dried lactose or dibasic calcium phosphate were mixed with 1% magnesium stearate using Turbula bottle blenders, varying bottle volume, V (30–1250 mL); bottle headspace fraction, $F_{headspace}$ (30–70%); and the number of blending cycles, r (24 to ~190,000 cycles). The impact of lubrication blending on tensile strength and bulk specific volume quality attributes, QA, was modeled by:

$$\frac{QA}{QA_0} = (1-\beta) + \beta \exp(-\gamma \times L \times F_{headspace} \times r),$$

where QA_0 is initial QA value, β is sensitivity of QA to lubrication, γ is formulation-specific lubrication rate constant, and L is characteristic mixing length scale (i.e. $1.5V^{1/3}$ for Turbula blenders, $V^{1/3}$ for simple diffusion mixers). The factor of 1.5 captures the bottle dimensions and the more complex mixing dynamics of the Turbula blender. This lubrication blending process model is valid for scale-up from 30-mL to 200-L blenders. Assessing bulk specific volume may provide a simpler, more material-sparing means for determining γ than tensile strength, since these QAs exhibited similar γ values.

1. Introduction

For initial formulation development work, Turbula bottle blending offers the ability to generate very small, material-sparing batches. For example, batches as small as 5 g can be prepared using 30-mL amber glass bottles with the Turbula mixer. In contrast to experiments performed with kilo-scale blenders, use of Turbula mixers can enable the formulator to perform the experiments necessary to identify a suitable commercial drug product formulation with a significantly smaller quantity of the active pharmaceutical ingredient (API). The ability to reduce the amount of API required for initial development of the commercial drug product formulation is an attractive aspect of Turbula mixers, since those studies often occur at a time when the API supply is both limited and in high demand to support clinical and toxicological studies.

The method of mixing employed by the Turbula blenders may provide the formulator an additional advantage through more efficient mixing relative to simple diffusion mixers. Unlike simple diffusion mixers (i.e. V-blenders and Bin blenders) which provide mixing primarily through rotation along a single axis, the Turbula mixer provides rotation, translation, and inversion of the powder bed (Porion et al., 2004; Sommier et al., 2001) by making use of the Schatz geometry (Schatz, 1998). These three modes of mixing present in the Turbula blender should, in theory, provide more efficient mixing than in a simple one-dimensional diffusion blender. The potential for improved mixing efficiency offered by the Turbula mixers may, therefore, lead to decreased processing times relative to simple diffusion mixers of comparable size, improving the efficiency of lab-scale pharmaceutical blend preparation.

Therefore, in light of these potential advantages, it is not surprising that the use of Turbula mixers in the pharmaceutical industry is well-documented, as they have been used for over 35 years in investigations related to formulation and process understanding. For example, Turbula mixers have been used to study drug substance deagglomeration and its impact on dissolution (de Villiers, 1997; Kale et al., 2009; van der Watt and de Villers, 1995), adhesion of drug substance to pharmaceutical powders (Nilsson et al., 1988; Song and de Villiers, 2004; Zhu et al., 2007; Selvam et al., 2011), and the role of colloidal silicon dioxide (Jonat et al., 2004; Chang et al., 1999) and other silicas (Mueller et al., 2008) as flow regulating

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agents. In addition, Turbula mixers have been used in previous investigations examining the impact of lubrication on drug product performance attributes including low dose blend uniformity (Hess et al., 1975), tablet hardness (Bolhuis et al., 1987; Bossert and Stamm, 1980), bulk density (Harding et al., 1989), disintegration (Harding et al., 1989; Bossert and Stamm, 1980), and dispersion for inhaled powders (Tay et al., 2009). Unfortunately, the ability to leverage data and understanding from lab-scale experiments is often limited by the lack of a validated blending process scale-up model that includes the Turbula mixer.

For the lubrication blending process, a recent study examined the impact of blender type (i.e. V-blenders, bin blenders, and Turbula mixers) and blending process parameters (blender size, fill level, and number of blending revolutions) on changes in the tensile strength of lubricated placebo formulations (Kushner and Moore, 2010). However, this study examined only a limited range of processing conditions for the Turbula mixing system (i.e. a 2-L bottle with 50% and 70% fill level). The following study was performed to more fully incorporate the Turbula bottle blender system into the previously developed lubrication scale-up model (Kushner and Moore, 2010). The results of the present study will enable formulators to better: (1) perform formulation and lubrication process understanding experiments using material sparing approaches, thereby reducing API requirements, and (2) maintain product quality during scale-up from the Turbula bottle blenders to larger scale blenders by providing a model-based approach to maintain a constant extent of lubrication of the formulation across scales.

2. Theory

A previous experimental investigation has shown that the reduction in tablet tensile strength at 0.85 solid fraction, $\sigma_{SF=0.85}$, can be modeled according to the following equation (Kushner and Moore, 2010):

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

where $\sigma_{SF=0.85,0}$, β, and γ are initial tensile strength at 0.85 solid fraction, the sensitivity of the blend to lubrication, and the lubrication rate constant of the formulation, respectively. K captures the contribution of the blending process parameters and is described by the following equation:

$$K = V^{1/3} \times F_{headspace} \times r \quad (2)$$

where V is blender volume (dm^3), $F_{headspace}$ is the fraction of the blender occupied by headspace, and r is the number of revolutions applied to the formulation during blending.

The $V^{1/3}$ term was proposed as an estimate of the length of the free powder surface in the blender over which powder avalanching occurs and, therefore, serves as an estimate of the characteristic length scale for powder mixing. As the blender size increases, the distance over which a blend particle is exposed to shear along the free powder surface increases. The number of times that a typical blend particle travels down the avalanching domain is a function of the amount of headspace in the blender and the number of blender revolutions imparted during the lubrication blending process. The dependence of the latter parameter on the total number of avalanching events experienced by a typical blend particle should be straight-forward. For $F_{headspace}$, as the load level in the blender decreases, the average number of avalanching events experienced by a typical blend particle, per blender revolution, will increase. Since the perimeter of the bed decreases as the load level decreases, an increase in the ratio of the blender perimeter to the powder blend perimeter is obtained, yielding a greater number of avalanching events per blender revolution for low fill levels than for high fill levels. Therefore, the blending process parameters in Eq. (2) can be viewed as an estimate of the total distance over which mixing shear forces are applied to the powder blend. Eq. (1) has been shown to be valid for low-shear, diffusion mixers (e.g. V-blenders, Bin blenders) ranging in volume from 0.75-Quarts to 200-L (Kushner and Moore, 2010). In the present study, the low end of this range will be expanded to include a range of bottle sizes (i.e. 30–1250 mL) that are compatible with a lab-scale Turbula mixer.

3. Materials and methods

3.1. Materials

Microcrystalline cellulose (MCC) as Avicel PH102 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

MCC and either Lactose or DCP were combined together using a blend-mill-blend procedure. The blends contained a ratio of excipients as follows:

- 2 parts MCC and 1 part DCP
- 2 parts MCC and 1 part Lactose

After loading the two excipients into a 20-L Bin blender, the two powders were blended for 10 min at 12 rpm. The blend was then passed through a 032R (aperture diameter = 32/1000th in.) screen in the CoMil 193 operating at 1000 rpm. The blend was then returned to the Bin blender and mixed for another 10 min at 12 rpm. The blend was then bagged and stored in a controlled environment to reduce the likelihood of caking until required for lubrication with MgSt.

3.3. Selection of bottles for blending in the Turbula blender

30 mL, 120 mL, 500 mL, and 1250 mL amber wide mouth packer bottles (VWR, Bridgeport, NJ) were selected to cover a range of bottles sizes compatible with a lab-scale Turbula mixer. The height and diameter of the bottles are presented in Table 1.

3.4. Lubrication of placebo blend with 1% magnesium stearate

Prior to lubrication, the pre-mixed placebo blend was weighed out to the desired amount and added to the appropriate amber bottle selected for testing. Two batch sizes for each of the four bottle sizes were examined, corresponding to 30% and 70% headspace in the bottle. MgSt was then added to the placebo blend in the bottle such that it comprised 1% of the final lubricated blend. MgSt was not passed through a screen prior to addition to the placebo blend to be consistent with the previously used approach (Kushner and Moore, 2010) and to avoid additional variability in the results that may result from applying shear to the MgSt in an uncontrolled manner as it is forced through a screen.

Table 1
Dimensions of the amber bottles used with the Turbula mixer.

Nominal bottle size	Bottle height (cm)	Bottle diameter (cm)	Diameter/height
30 mL	6.8	3.5	0.51
120 mL	9.8	5.4	0.55
500 mL	15.0	7.7	0.51
1250 mL	19.5	10.5	0.54