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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, $\beta$ is sensitivity of QA to lubrication, $\gamma$ 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 $\gamma$ than tensile strength, since these QAs exhibited similar $\gamma$ 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 $\sigma_{SF=0.85,0}$, $\beta$, and $\gamma$ 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 |

**Table 2**
Nominal lubrication mixing times used in the experimental study.[a]

| Sampling point | 2:1 MCC:Lactose | | 2:1 MCC:DCP | |
|---|---|---|---|---|
| | 1250 and 500 mL bottles | 30 and 120 mL bottles | 1250 and 500 mL bottles | 30 and 120 mL bottles |
| 1 | 0.5 | 0.5 | 0.5 | 0.5 |
| 2 | 1.5 | 2.5 | 2.5 | 3.0 |
| 3 | 4.5 | 6.5 | 12.5 | 18.0 |
| 4 | 13.5 | 20.0 | 62.5 | 108.0 |
| 5 | 40.5 | 60.5 | 312.5 | 648.0 |
| 6 | 121.5 | 182.0 | 1562.5 | 3888.0 |

[a] Lubrication mixing times reported in minutes.

The Turbula blender (Model T2F, GlenMills, Inc.) was operated at a setting of 49 cycles/min. The duration of the lubrication blending was selected to ensure that the extent of lubrication was sufficient to reach the plateau region of the lubrication sensitivity profile for both formulations. The lubrication times used are reported in Table 2. In the case of the larger batches (i.e. both 1250 mL batches and the 500 mL, 30% headspace batches), a 10 g sample was removed from the main batch at six pre-determined extents of lubrication. For the smaller batches, six individual bottles were prepared, which were then processed according to the times listed in Table 2 to achieve different extents of lubrication. The impact of speed and mixing time for lubrication blending in the Turbula mixers was addressed previously and it was concluded that the number of revolutions was the fundamental blending duration parameter (Kushner and Moore, 2010).

### 3.5. Compression of lubricated blends

Tablets were manufactured from the ~10-g samples of the lubricated blends via direct compression using a compaction simulator both to utilize a material sparing approach and to avoid any potential contribution to the extent of lubrication from a tablet press feed frame (Mendez et al., 2010; Narang et al., 2010). For the compression of the lubricated MCC:Lactose blends, an in-house compaction simulator was used (Zinchuk et al., 2004). For the compression of the lubricated MCC:DCP blends, a Huxley-Bertram compaction simulator (Cambridge, England) was used. For both simulators, a Kilian T-100 rotary tablet press operating at 60 K tabs/h for a 9-station press with ~1 kN of pre-compression was simulated. Both compaction simulators were setup with 8-mm round, flat-faced tooling and the target tablet weight was 200 mg. For both formulations, tablets were compressed over a solid fraction range of 0.60–0.90 by varying the target punch separation during main compression. At each tablet thickness, 1–2 tablets were manufactured and measured for weight (Mettler Toledo XS201), thickness, diameter (Mitutoyo, Model ID-C112EBS), and hardness (Dr. Schleuniger Pharmatron Tablet Tester 8M).

### 3.6. Evaluation of tablet tensile strength and solid fraction

The tensile strength, $\sigma$, and solid fraction, SF, of the 8-mm flat-faced tablets were calculated using the following equations (Fell and Newton, 1970):

$$\sigma = \frac{f}{\pi R T} \tag{3}$$

$$\mathrm{SF} = \frac{m}{\rho_T \pi R^2 T} \tag{4}$$

where $f$ is the fracture force, $R$ is the tablet radius, $T$ is the tablet thickness, $m$ is the tablet mass, and $\rho_T$ is the true density of the powder. This data was used to create the tensile strength vs. solid fraction (i.e. compactability) profiles, from which the lubrication sensitivity profiles would be generated.

### 3.7. Analysis of compactability data

The compactability profiles for each lubrication blend sample were fit using the regression feature of Microsoft Excel (Richmond, WA) to the Ryshkewitch equation (Ryshkewitch, 1953):

$$\sigma = \sigma_0 \exp[b(1 - \mathrm{SF})] \tag{5}$$

The corresponding tensile strength at 0.85 solid fraction, $\sigma_{SF=0.85}$, which represents the middle of the typical tablet solid fraction range (i.e. 0.77–0.93) (Hancock et al., 2003), was then determined for each profile using values of $\sigma_0$ and $b$ obtained from regression analysis.

### 3.8. Regression analysis of lubrication sensitivity profiles

Lubrication sensitivity profiles were generated by plotting the tensile strength at 0.85 solid fraction as a function of the duration of lubrication blending in the Turbula mixer. Non-linear regression of the lubrication sensitivity profiles was performed with DataFit 9.0 (Oakdale Engineering) to determine the values of the initial tablet tensile strength, lubrication sensitivity parameter, and the lubrication rate constant (Kushner and Moore, 2010).

## 4. Results and discussion

### 4.1. Observations of Turbula bottle blending mixing dynamics

Fig. 1 provides an overview of the movement of the Turbula bottle blender over the course of a single mixing cycle. At first glance, the Turbula bottle blender appears to go through 2 rotations in a single mixing cycle – images 1–4 are similar to images 5–8. However, each of these rotations (i.e. images 1–4 and 5–8) comprise only half of a complete revolution imparted by a typical, low-shear diffusion mixer, as shown with the V-blender in Fig. 2. In a single mixing cycle of the Turbula bottle blender, there are four, 90° avalanching events, which is similar to a low-shear diffusion mixer. These events occur between images 2 and 4, 4 and 6, 6 and 8, and 8 and 2 for both the Turbula and V-blender.

In addition, the Turbula mixer also imparts a rotation along the radial axis of the bottle to the powder bed during each mixing cycle. This can be observed in Fig. 1 both by the movement of the light gray ball at one end of the bottle holder and by the location of the "Front" and "Back" stickers placed on opposite sides of the bottle in Fig. 1 (see images 3 and 7). This additional rotation enables turnover of the powder bed in the Turbula mixer, which, in the V-blender, is accomplished by the full 360° rotation of the low-shear blender along a single axis of rotation. This radial rotation of the bottle in a cycle of Turbula mixing provides an additional dimension over which powder avalanching can occur.

These observations suggest that that the characteristic length scale over which mixing occurs for the Turbula bottle blending is likely a combination of both the height and the diameter of the bottle used in the study, to reflect the two axes of rotation applied to the

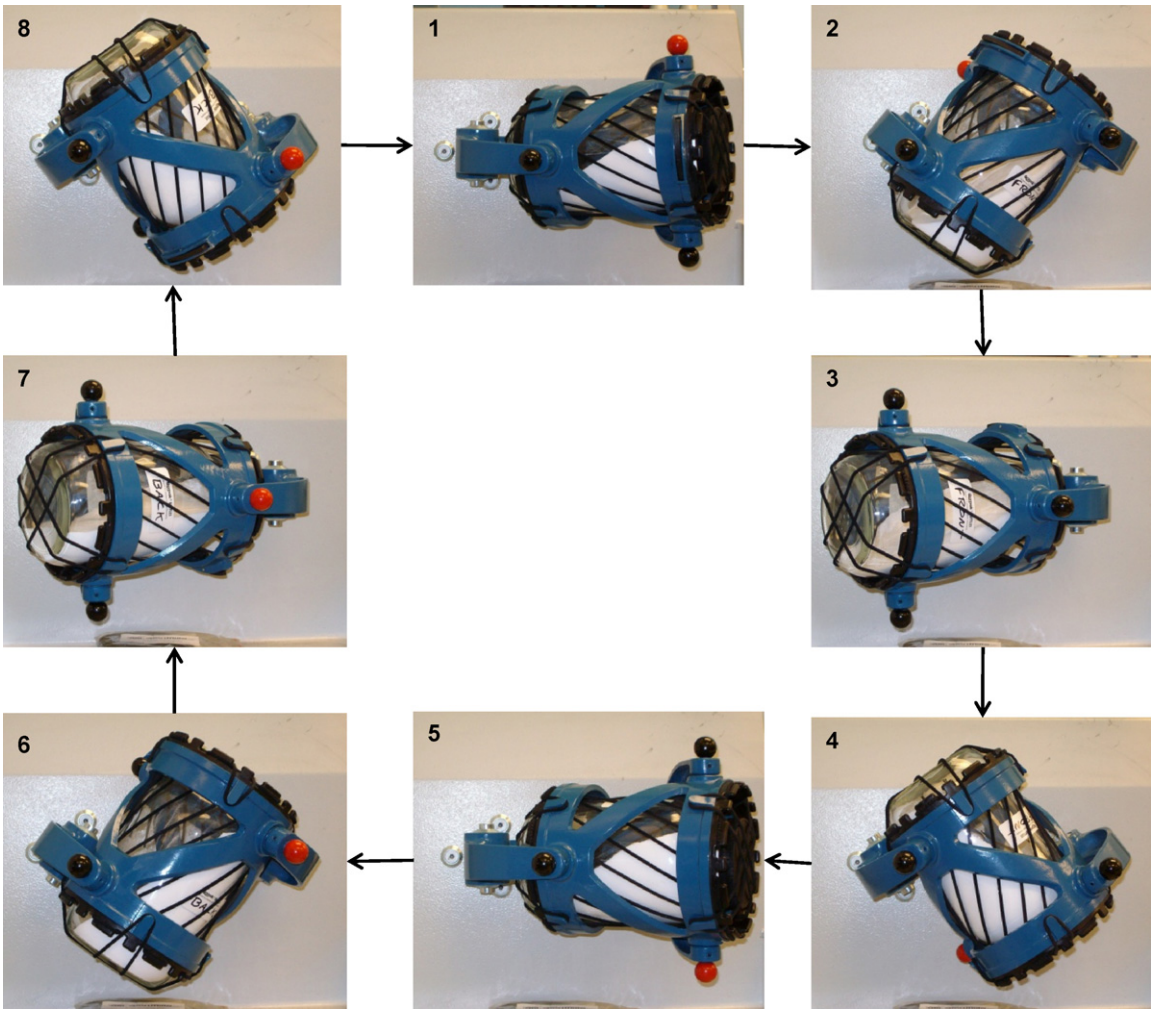


**Fig. 1.** Snapshots of the bottle blender orientation during a single blending cycle of the Turbula mixer. The Turbula mixer provides 4, 90° rotations of the bottle along the central axis, as well as a complete 360° rotation along the radial axis of the bottle, during a single mixing cycle.

bottle during mixing with the Turbula blender. For the bottle sizes tested in this study, the diameter of the bottle is approximately half of the height of the bottle (see Table 1). These measurements would suggest, then, that the characteristic length scale for mixing in the bottles used for the Turbula blender may be proportional to 1.5 times the height of the bottle. Previously, it was proposed that the characteristic length scale for simple diffusion mixers with a single axis of rotation was proportional to the cube root of the blender volume (Kushner and Moore, 2010). Building on this previous model framework, the mechanics of Turbula blending with the bottle sizes examined in this study may be described by the following equation:

$$K_{\text{Turbula}} = 1.5V^{1/3} \times F_{\text{headspace}} \times r \quad (6)$$

where the term $1.5V^{1/3}$ provides an estimate of the characteristic length scale for mixing in the amber bottles used with the Turbula blender.

### 4.2. Impact of Turbula bottle blender size and headspace on tablet tensile strength

Compactability profiles were generated from the tablets manufactured from the lubricated placebo blends processed with the Turbula mixer. Representative compactability profiles are shown in Fig. 3. The compactability profiles obtained for both the 2:1 MCC:Lactose with 1% MgSt formulation and 2:1 MCC:DCP with 1% MgSt formulation decrease as a function of the number of Turbula mixing cycles imparted during lubrication. The compactability data were regressed to the Ryshkewitch equation to estimate the tensile strength at 0.85 solid fraction at each lubrication condition. This data was used to generate the lubrication profiles in Figs. 4 and 5.

Figs. 4 and 5 present the tensile strength at 0.85 solid fraction vs. number of blender cycles as a function of the headspace in the blender (30% or 70%) and the size of the blender (A – 30 mL, B – 120 mL, C – 500 mL, and D – 1250 mL) for the 2:1 MCC:Lactose and 2:1 MCC:DCP formulations, respectively. From Figs. 4A–D and 5A–D, it can be seen that the profiles follow an exponential decay to an asymptotic value, similar to the profiles that were observed in the previous investigation (Kushner and Moore, 2010). The results from the regression analysis with Eq. (1) are reported in Table 3, along with the goodness-of-fit, $R^2$, value.

From the data in Table 3, the following observations can be made. First, the values of $\sigma$, the initial tensile strength, and $\beta$, the lubrication sensitivity, are similar across the blender volume and headspace conditions examined and are similar to the values observed in the prior lubrication studies (e.g. 2:1 MCC:Lactose – $\sigma_0 = 3.2$–$4.0$, $\beta = 0.61$; 2:1 MCC:DCP – $\sigma_0 = 6$, $\beta = 0.48$). These similarities suggest that these formulation parameters are not a function of the selected bottle size. Second, the lubrication rate constant, $c$, increases as the size of the blender and the amount of headspace increases. Both trends are in agreement with the trends observed in the prior lubrication studies for both V-blenders and Bin blenders (Kushner and Moore, 2010).

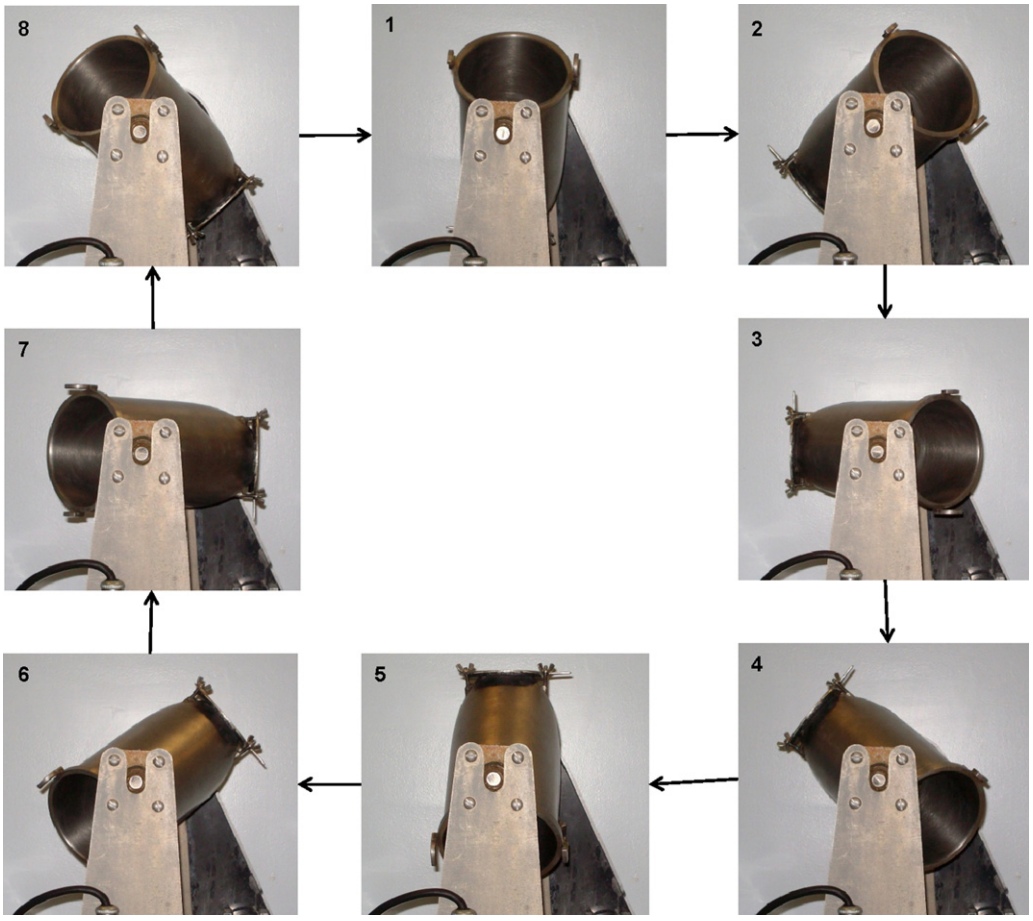


**Fig. 2.** Snapshots of the V-blender orientation during a single blending cycle. The V-blender only provides a complete 360° rotation along the central axis of the blender during a single mixing cycle.

**Table 3**
Summary of lubrication model parameter estimation for placebo formulations lubricated with 1% MgSt.[a]

| Lubrication conditions | 2:1 MCC:Lactose | | | | 2:1 MCC:DCP | | | |
|---|---|---|---|---|---|---|---|---|
| | $\sigma_{SF=0.85,0}$ (MPa) | $\beta$ | $c$ (cycles$^{-1}$)[b] | $R^2$ | $\sigma_{SF=0.85,0}$ (MPa) | $\beta$ | $c$ (cycles$^{-1}$)[b] | $R^2$ |
| 30-mL bottle, 70% load | 3.49 (0.38) | 0.55 (0.17) | 0.00054 (0.00052) | 95.3% | 5.66 (0.40) | 0.46 (0.13) | 0.000040 (0.000018) | 97.7% |
| 30-mL bottle, 30% load | 3.49 (0.44) | 0.54 (0.14) | 0.00098 (0.00094) | 95.4% | 5.53 (0.39) | 0.43 (0.08) | 0.000222 (0.000170) | 98.4% |
| 120-mL bottle, 70% load | 4.00 (0.59) | 0.59 (0.14) | 0.00140 (0.00128) | 95.5% | 5.72 (0.68) | 0.46 (0.17) | 0.000082 (0.000134) | 95.4% |
| 120-mL bottle, 30% load | 3.58 (0.60) | 0.56 (0.14) | 0.00192 (0.00196) | 94.4% | 5.56 (0.51) | 0.46 (0.10) | 0.000232 (0.000214) | 97.7% |
| 500-mL bottle, 70% load | 3.71 (0.32) | 0.60 (0.09) | 0.00144 (0.00084) | 98.3% | 5.88 (0.42) | 0.46 (0.10) | 0.000184 (0.000158) | 98.4% |
| 500-mL bottle, 30% load | 3.57 (0.41) | 0.56 (0.10) | 0.00244 (0.00170) | 97.3% | – | – | – | – |
| 1250-mL bottle, 70% load | 3.86 (0.32) | 0.60 (0.08) | 0.00156 (0.00084) | 98.4% | 5.79 (0.43) | 0.46 (0.09) | 0.000248 (0.000196) | 98.5% |
| 1250-mL bottle, 30% load | 3.74 (0.55) | 0.61 (0.12) | 0.00244 (0.00200) | 96.3% | 5.64 (0.46) | 0.47 (0.09) | 0.000520 (0.000400) | 98.4% |

[a] Data presented as value (95% confidence interval).
[b] $c$ is equal to (characteristic mixing length) $\times F_{headspace} \times \gamma$.

**Table 4**
Determination of the lubrication rate constant, $c$, for Turbula bottle blending using average values for the initial tensile strength and lubrication sensitivity for the placebo blends lubricated with 1% magnesium stearate.[a]

| Blender volume | 2:1 MCC:Lactose | | | | 2:1 MCC:DCP | | | |
|---|---|---|---|---|---|---|---|---|
| | 70% loading | | 30% loading | | 70% loading | | 30% loading | |
| | $c$ (cycles$^{-1}$) | $R^2$ | $c$ (cycles$^{-1}$) | $R^2$ | $c$ (cycles$^{-1}$) | $R^2$ | $c$ (cycles$^{-1}$) | $R^2$ |
| 30-mL bottle | 0.00056 (0.00022) | 95.4% | 0.00104 (0.00042) | 95.6% | 0.000042 (0.000017) | 97.3% | 0.000232 (0.000104) | 96.9% |
| 120-mL bottle | 0.00086 (0.00060) | 91.7% | 0.00184 (0.00078) | 95.8% | 0.000078 (0.000059) | 94.5% | 0.000260 (0.000130) | 96.7% |
| 500-mL bottle | 0.00136 (0.00044) | 98.1% | 0.00242 (0.00070) | 97.9% | 0.000138 (0.000074) | 96.7% | – | – |
| 1250-mL bottle | 0.00120 (0.00052) | 96.3% | 0.00232 (0.00102) | 96.3% | 0.000214 (0.000095) | 97.7% | 0.000579 (0.000237) | 97.9% |

[a] Data presented as value (95% confidence interval).

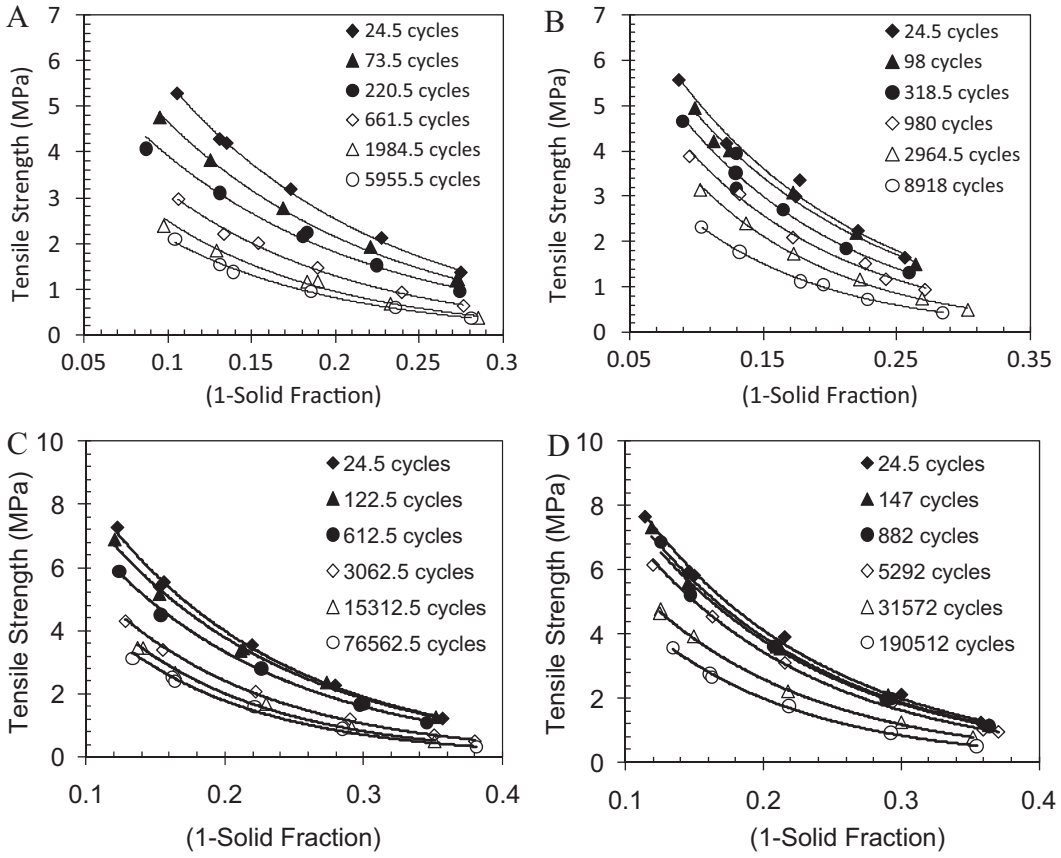


**Fig. 3.** Sample compactability profiles for the placebo formulations for various number of Turbula mixing cycles imparted during the lubrication process. *Key*: (A) 2:1 MCC:Lactose mixed with 1% magnesium stearate in a 1250-mL bottle at 70% headspace, (B) 2:1 MCC:Lactose mixed with 1% magnesium stearate in a 30-mL bottle at 30% headspace, (C) 2:1 MCC:DCP mixed with 1% magnesium stearate in a 1250-mL bottle at 70% headspace, and (D) 2:1 MCC:DCP mixed with 1% magnesium stearate in a 30-mL bottle at 30% headspace. The black curves represent the best fit of each data set to the Ryshkewitch equation.

As in the prior study, review of the data in Table 3 suggests that the lubrication rate constant, $c$, is likely the only parameter impacted by the change in the blender volume and blender loading. Therefore, average values of the initial tensile strength and lubrication sensitivity can be proposed (i.e. 2:1 MCC:Lactose – 3.68 MPa and 0.58; 2:1 MCC:DCP – 5.68 and 0.46, respectively). Using these values, the lubrication rate constant can be re-evaluated using Eq. (1), which gives the results reported in Table 4. Again, in general, $c$ increases as blender volume and the amount of headspace increases.

### 4.3. Incorporating Turbula bottle blenders into the previously developed lubrication science of scale model

Previously, the lubrication rate constant, $c$, was shown to be a function of the volume of the blender, the fraction of headspace in the blender, and the formulation rate constant for both V-blenders and Bin blenders (Kushner and Moore, 2010):

$$c_{\text{Bin and V-blenders}} = \gamma \times V^{1/3} \times F_{\text{headspace}} \quad (7)$$

In Eq. (7), the characteristic length scale for mixing in a diffusion mixer with a single axis of rotation is given by the $V^{1/3}$ term. From the observations of the Turbula mixing cycle discussed in Section 4.1, it was proposed that the characteristic length scale for mixing in the Turbula blender is proportional to the sum of the height and the diameter of the bottles, since powder mixing is occurring along two axes of rotation. In this case, Eq. (7) can be modified by a factor of 1.5 to account for the ratio of the bottle diameter to the bottle height, yielding the following equation for the lubrication rate constant, $c$, with the Turbula blenders:

$$c_{\text{Turbula}} = 1.5 \times \gamma \times V^{1/3} \times F_{\text{headspace}} \quad (8)$$

The data for $c$, reported in Table 4, can be analyzed with either of these two equations to determine if $c$ for the Turbula bottle blender is also a function of the volume of the bottle and the amount of headspace in the bottle. This analysis is reported in Fig. 6. As both Fig. 6A and B suggest, there does appear to be a linear correlation of the lubrication rate constant, $c$, to the term $(V^{1/3} \times F_{\text{headspace}})$, which agrees with the prior investigations on V-blenders and Bin blenders (Kushner and Moore, 2010). It should be noted that this correlation is stronger for the blending of the 2:1 MCC:DCP formulation (Fig. 6B, $R^2 = 0.95$), as compared to the blending of the 2:1 MCC:Lactose formulation (Fig. 6A, $R^2 = 0.68$). This reduced $R^2$ for the 2:1 MCC:Lactose data may be due to a low value for the 1250 mL, 30% fill blending condition. If this point were omitted, the value of $R^2$ improves to 0.88, strengthening the linear dependence of $c$ on the term $(V^{1/3} \times F_{\text{headspace}})$, and the slope would increase to 0.0046.

Also with Eqs. (7) and (8), the value of the formulation rate constant, $\gamma$, can be estimated from the values of the slopes of the linear regressions in Fig. 6. If Eq. (7) is used, which assumes a single bottle revolution per Turbula mixing cycle, then $\gamma$ would be equal to 0.0039 for the 2:1 MCC:Lactose formulation and 0.00075 for the 2:1 MCC:DCP placebo formulation. Comparison of the calculated values of the formulation rate constant from the data in Fig. 6 with the values obtained from the prior investigation (i.e. 0.0028 for 2:1 MCC:Lactose, 0.0006 for 2:1 MCC:DCP) suggest that use of Eq. (6), a single bottle revolution per Turbula mixing cycle, overestimates

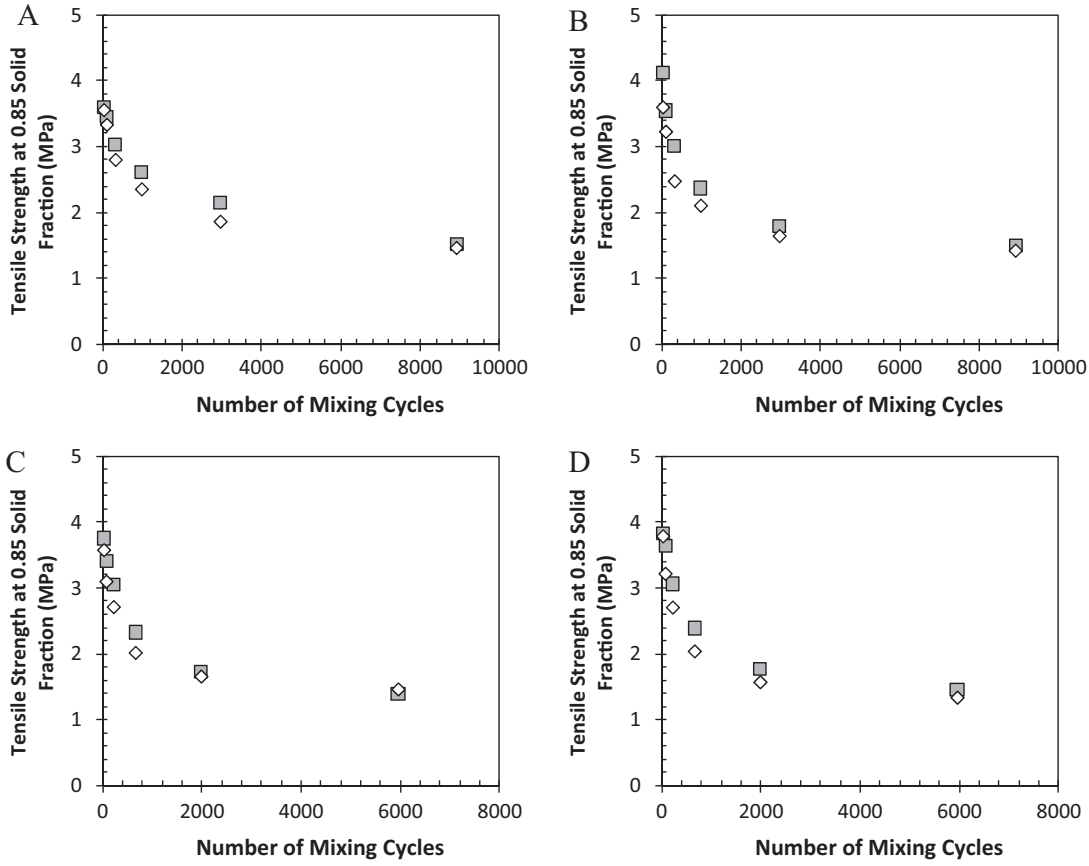


**Fig. 4.** Tensile strength at 0.85 solid fraction vs. number of Turbula mixing cycles for 2:1 MCC:Lactose with 1% magnesium stearate. *Key*: (A) 30 mL, (B) 120 mL, (C) 500 mL, and (D) 1250 mL. Gray squares – 30% headspace; open diamonds – 70% headspace.

the values of the formulation rate constants. However, if Eq. (8) is used, which assumes 2 bottle revolutions per Turbula mixing cycle, then $\gamma$ would be equal to 0.0026 for the 2:1 MCC:Lactose formulation and 0.0005 for the 2:1 MCC:DCP placebo formulation. The values of $\gamma$ obtained with Eq. (8), which more closely captures the blending mechanics of the Turbula mixer shown in Fig. 1, are in better agreement with the prior historical data, then the values of $\gamma$ obtained with Eq. (7), which assumes a single bottle rotation during one bottle blending cycle with the Turbula mixer. This finding is confirmed for both formulations in Fig. 7 which overlays the lab-scale Turbula data with the previously generated tensile strength vs. lubrication conditions data from the V-blender and Bin blender experiments (Kushner and Moore, 2010). The data in Fig. 7 show that, with appropriate scaling of the lubrication blending process, it should be possible to transfer the knowledge gained in lab-scale batches directly to larger sized blenders as high as 200 L.

### 4.4. Impact of lubrication blending on formulation bulk density and specific volume

During tablet compression of the various lubricated MCC:Lactose and MCC:DCP placebo Turbula samples, it was observed that the fill height required to achieve the target tablet weight decreased by 15–20% as the extent of lubrication applied to the samples increased. To confirm this observation, the bulk specific volume of the lubricated placebo Turbula samples was measured by loading a sample of the blend into a glass, graduated cylinder (while taking care not to tap down the powder column) to measure the volume of the powder column. The mass of the powder sample was measured with a balance. The bulk specific volume for each lubrication blending condition was repeated in triplicate.

Fig. 8A and B shows the results from the bulk specific volume measurements of the 2:1 MCC:Lactose and 2:1 MCC:DCP placebo blends, respectively, overlaid with the tensile strength data and the lubrication model with the formulation specific rate constant, $\gamma$. As these figures illustrate, the rate of decrease in the bulk specific volume of both placebo blends is similar to the rate of decrease in the tablet tensile strength of the blends, which agrees with the observations of Shah and Mlodozeniec (1977). This finding suggests that bulk specific volume (or bulk density) measurements, which are a non-consumable test, could be used to estimate the formulation lubrication rate constant, $\gamma$. However, the accuracy of the estimate in $\gamma$ using bulk specific volume changes will be dependent on the reproducibility and accuracy of these measurements–note that there is more spread in the MCC:Lactose bulk specific volume data (see Fig. 8A) than in the MCC:DCP bulk specific volume data (see Fig. 8B).

While the formulation lubrication rate constant, $\gamma$, appears to be similar for both bulk specific volume and tablet tensile strength, the bulk specific volume and tablet tensile strength have different degrees of sensitivity to lubrication, $\beta$. For the 2:1 MCC:Lactose formulation, $\beta$ is 0.61 and 0.22 for the sensitivity of tablet tensile strength and bulk specific volume, respectively, to lubrication. For the 2:1 MCC:DCP formulation, $\beta$ is 0.48 and 0.17 for the sensitivity of tablet tensile strength and bulk specific volume, respectively, to lubrication. The differences in $\beta$ are not an unexpected finding, as these are two different formulation properties. However, it is worth noting that the ratios of $\beta_\sigma$ and $\beta_{SV}$ for the two formulations are very similar (i.e. $\beta_\sigma$: 0.48/0.61 $\sim$ 0.77, $\beta_{SV}$: 0.17/0.22 $\sim$ 0.79). This similarity may suggest that there is an underlying formulation

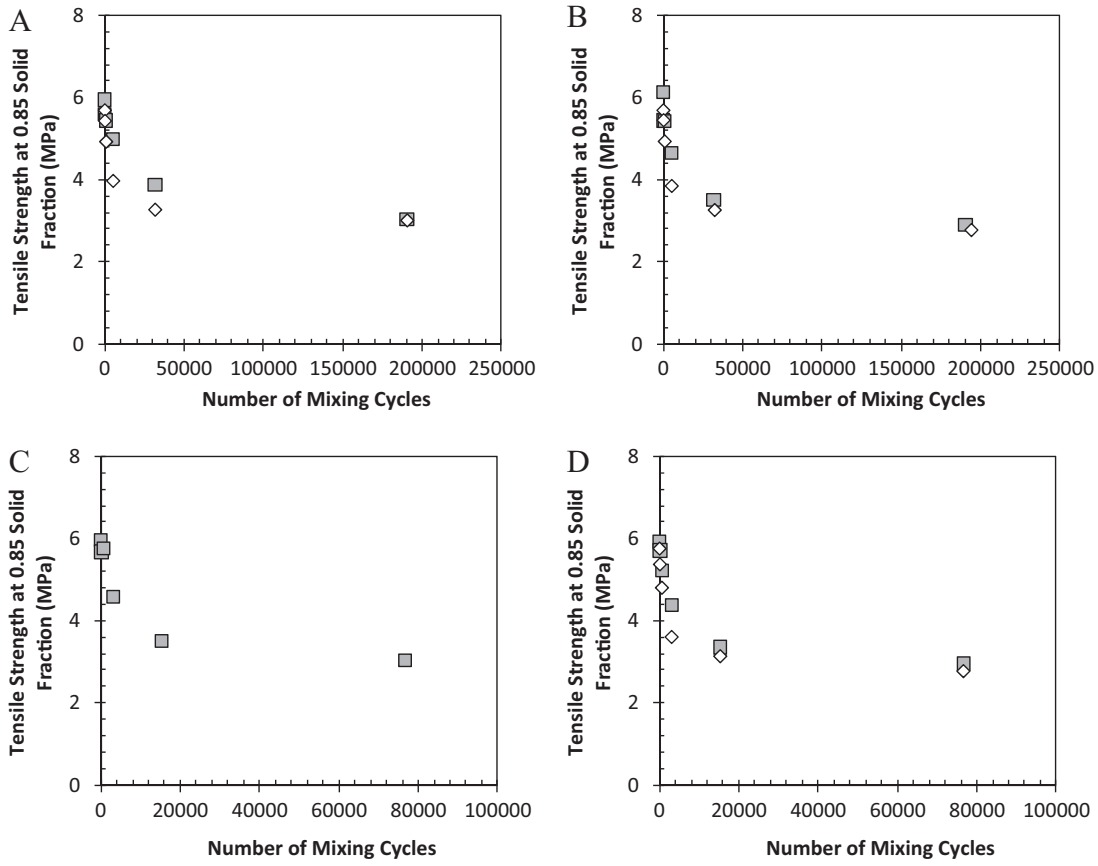


**Fig. 5.** Tensile strength at 0.85 solid fraction vs. number of Turbula mixing cycles for 2:1 MCC:DCP with 1% magnesium stearate. *Key*: (A) 30 mL, (B) 120 mL, (C) 500 mL, and (D) 1250 mL. Gray squares – 30% headspace; open diamonds – 70% headspace.

specific component of the sensitivity to lubrication parameter, $\beta$, which could be examined further as part of a deeper analysis on the effect of lubrication on a wider range of common pharmaceutical materials and their quality attributes.

### 4.5. Potential improvements to lubrication process development

The results presented in Figs. 7 and 8 suggest that effects of batch size, equipment scale, and the total number of revolutions imparted during lubrication blending on tablet tensile strength and bulk density can be successfully accounted for by the following generalization of Eq. (1):

$$\frac{QA_i}{QA_{i,0}} = (1-\beta_i) + \beta_i \exp(-\gamma \times L \times F_{headspace} \times r) \quad (9)$$

where $QA_i$ is the product quality attribute of interest (e.g. bulk specific volume or tensile strength), $QA_{i,0}$ is the initial value of QA, $\beta_i$ is the lubrication sensitivity parameter for the QA of interest, and $L$ is the characteristic mixing length scale (i.e. $1.5V^{1/3}$ for Turbula blenders, $V^{1/3}$ for simple diffusion mixers). The model presented in Eq. (9) expands upon the capabilities of Eq. (1) by: (1) more fully incorporating the Turbula bottle blending system into the model framework, and (2) extending the lower range of blender sizes from 0.75-Quarts to 30-mL. These model improvements make it possible to transfer lubrication blending process knowledge across blenders as small as 30-mL to blenders as large as 200-L, a range of nearly four orders of magnitude. Based on the results presented in Figs. 7 and 8, formulation and process developers can now achieve more consistent application of lubricant during the scale-up of the lubrication blending process for the same formulation by keeping the term, $L \times F_{headspace} \times r$, constant. Keeping this term constant should also result in maintaining the value of the product quality attributes of interest, QA, during the scale-up of the lubrication blending process. As such, the use of Eq. (9) can provide the formulation and process developer a means to reduce the incidence of over- or under-lubrication during scale-up of the lubrication blending process, which, in turn, should enable the manufacture of more consistent drug product during process scale-up.

Although the focus of the present study has been in improving the range of applicability for the previously developed lubrication blending process model, recent studies by Mendez et al. (2010) and Narang et al. (2010) suggest that additional lubrication mixing may also be occurring in the feed frames of rotary tablet presses. In these studies, increases in die fill weight and decreases in tablet tensile strength, respectively, were observed to occur when the powder residence time in the feed frame and the paddle speed were increased. Therefore, it may also be necessary to evaluate if any additional lubricant mixing occurring either in the feed frame of a rotary tablet press or in the feeders of other pharmaceutical process equipment (i.e. roller compactors, encapsulators) has an impact on product quality that could be modeled within the framework proposed in Eq. (9).

Since the generalized equation in Eq. (9) now incorporates the Turbula mixing system, the knowledge gained during lab-scale experiments performed with this equipment can be readily applied to manufacturing campaigns with larger scale equipment. For each new proposed formulation, a lubrication sensitivity profile (see Fig. 7) could be generated at the lab-scale with the Turbula mixer. From this profile, the values of the formulation lubrication rate constant, $\gamma$, and the lubrication sensitivity parameter, $\beta_i$, for the measured QA can be determined and used to assess how sensitive the formulation and its critical quality attributes are to

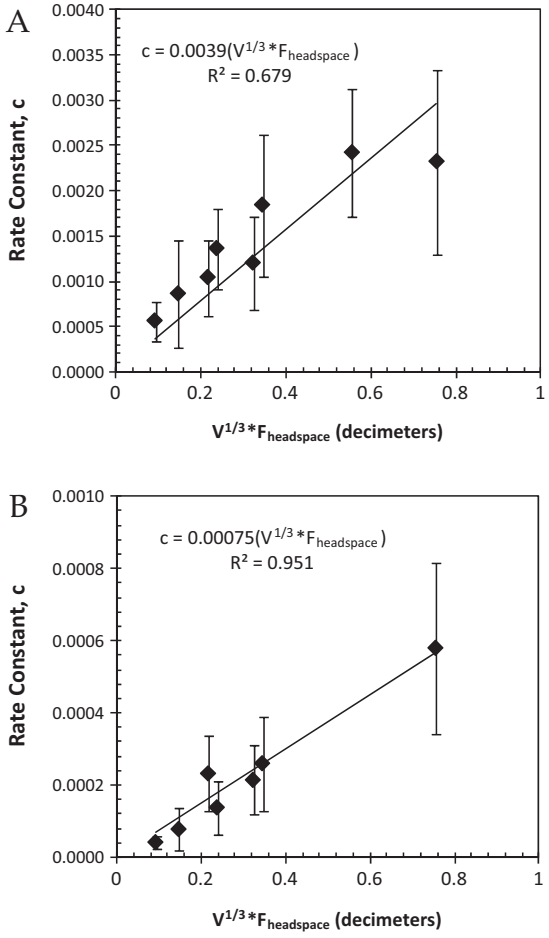


**Fig. 6.** Dependence of the rate constant, *c*, on the volume of the bottle and the amount of headspace present in Turbula bottle blending. *Key*: (A) 2:1 MCC:Lactose with 1% magnesium stearate and (B) 2:1 MCC:DCP with 1% magnesium stearate. Error bars: 95% confidence interval in regressed value of *c* from Table 4.

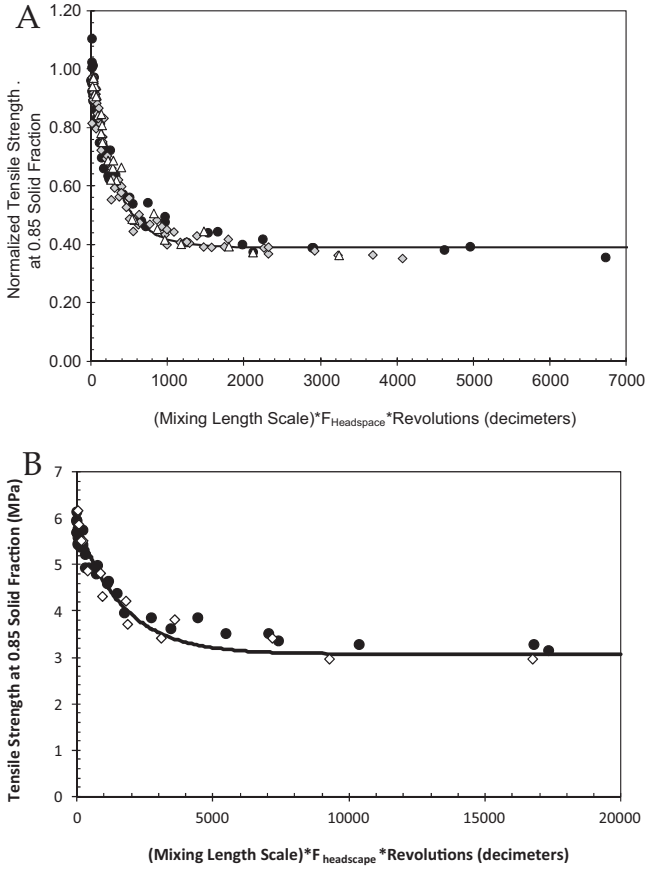


**Fig. 7.** Plot of the tensile strength at 0.85 SF for the placebo formulation as a function of the product of the mixing length scale, the fraction of blender volume occupied by headspace, and the number of revolutions. *Key*: (A) 2:1 MCC:Lactose with 1% magnesium stearate and (B) 2:1 MCC:DCP with 1% magnesium stearate. Black circles – Turbula data; gray or white diamonds – prior Bin blender data; white triangles – prior V-blender data; black curve – previously developed lubrication model (2:1 MCC:Lactose – $\beta = 0.61$, $\gamma = 0.0028\ \mathrm{dm}^{-1}$; 2:1 MCC:DCP – $\beta = 0.48$, $\gamma = 0.0006\ \mathrm{dm}^{-1}$). Prior V-blender data, Bin blender data, and lubrication model parameters were taken from Kushner and Moore (2010).

lubrication. Formulations with higher values of $\gamma$ will be more quickly affected by prolonged mixing of the lubricant than formulations with lower values of $\gamma$. This relationship can be seen in the values of $\gamma$ for the 2:1 MCC:Lactose and 2:1 MCC:DCP placebo formulations examined in this study. Replacing spray-dried lactose with DCP results in a formulation that has a lower value of $\gamma$, and, therefore, yields a formulation which is less impacted by prolonged lubricant mixing. Likewise, product quality attributes with higher values of $\beta$ are more sensitive to prolonged mixing of the lubricant than product quality attributes with lower values of $\beta$. For the 2:1 MCC:Lactose formulation, the percent reduction in the bulk specific volume decreased less than the percent reduction in the tensile strength, indicating that bulk specific volume is a less sensitive product quality attribute than tensile strength for this formulation. A similar finding was also observed for the 2:1 MCC:DCP formulation. In addition, it was observed that the value of $\gamma$ was the same for both quality attributes evaluated in this study for both placebo formulations. Finally, the values of both $\beta$ for bulk specific volume and tablet tensile strength and $\gamma$ for the 2:1 MCC:DCP formulation were all lower than the respective values for the 2:1 MCC:Lactose formulation. This observation suggests that spray-dried lactose is more sensitive to lubrication mixing than DCP. A brief examination of spray-dried lactose and DCP highlight a few differences that may impact the degree to which these excipients are sensitive to lubrication mixing. First, spray-dried lactose is an organic material, while DCP is an ionic material – this difference may impact the ability of magnesium stearate (a 16–18 carbon chain, organic salt) to adhere to the surface of these excipients. Second, spray-dried lactose is more ductile than DCP. This difference suggests that DCP will be more prone to fragment under compaction pressure, thereby producing more lubricant-free surfaces resulting in improved bonding (i.e. higher tensile strength) relative to spray-dried lactose. Finally, the grade of DCP used in this study appears to have a greater degree of surface roughness than the grade of spray-dried lactose, based on previously generated SEM images (Carlson and Hancock, 2006). Increased surface roughness may provide DCP with a greater total surface area than an equivalent amount of spray-dried lactose that would be coated by MgSt during lubrication blending. It is likely that a material with a smaller surface area would be more sensitive to lubrication, as the lubricant could more fully coat a material that has a smaller amount of surface area. However, additional studies examining a broader range of excipients would be needed to further elucidate which excipient material properties strongly impact the values of $\beta$ and $\gamma$.

While the values of $\beta$ and $\gamma$ for these two formulations do appear to be correlated (i.e. the 2:1 MCC:DCP formulation has lower values of both $\beta$ and $\gamma$ compared to the 2:1 MCC:Lactose formulation) and the value of $\gamma$ appears to be constant for the two quality attributes examined for each formulation studied here, it would again be necessary to examine a larger range of materials and product quality attributes to determine if these preliminary observations pertaining to $\beta$ and $\gamma$ hold true. Although the excipients examined

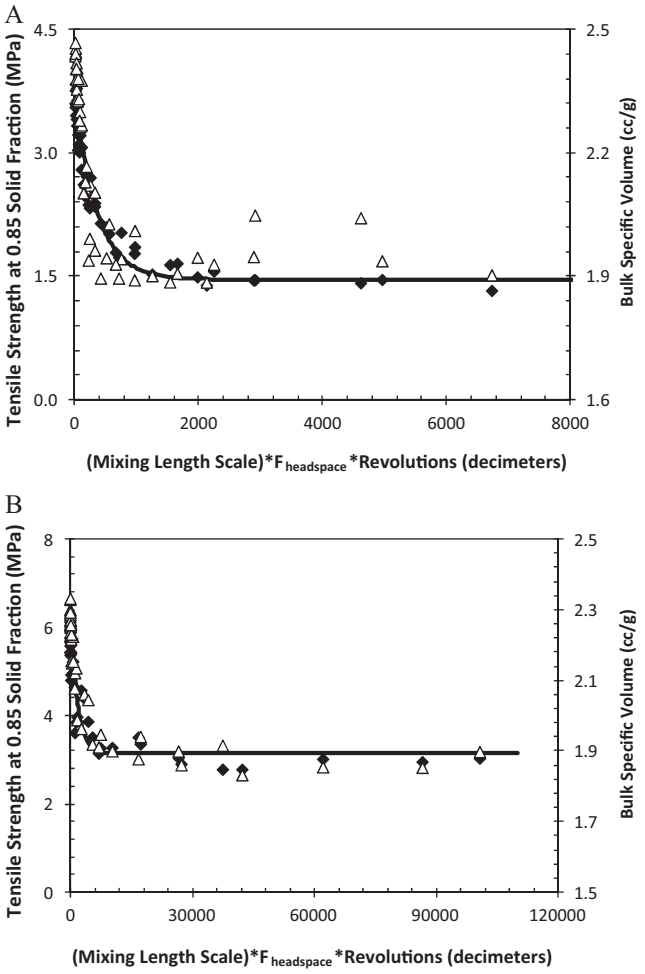


**Fig. 8.** Plot of tablet tensile strength and bulk specific volume of the lubricated placebo blends as a function of lubrication processing conditions. *Key*: (A) 2:1 MCC:Lactose with 1% magnesium stearate and (B) 2:1 MCC:DCP with 1% magnesium stearate. Black diamonds – tablet tensile strength data; white triangles – bulk specific volume data; black curve – previously developed lubrication model (2:1 MCC:Lactose – $\gamma = 0.0028\ \mathrm{dm}^{-1}$; 2:1 MCC:DCP – $\gamma = 0.0006\ \mathrm{dm}^{-1}$).
Formulation lubrication rate constants were taken from Kushner and Moore (2010).

in this study – MCC, lactose, and DCP – were selected as model excipients for their common use in immediate release tablet formulations, there remains a large number of excipients available to the formulator for use in solid, oral immediate release and modified release dosage forms for which minimal lubrication sensitivity data (i.e. values of $\beta$ and $\gamma$) have been gathered to date. Such studies may help provide insight into determining which attributes of the excipients or of the drug product formulation have an impact on the values of both $\beta$ and $\gamma$. Further, the addition of lubricant to the formulation has also been previously shown to impact other quality attributes of the formulation along with tablet tensile strength and bulk specific volume. These additional quality attributes may include powder flow, tablet disintegration, dissolution, tablet friability, and formulation sticking propensity (Wang et al., 2010). Future studies on these other quality attributes would help to confirm if the same formulation-specific, lubrication rate constant, $\gamma$, can be used for these additional quality attributes in the context of Eq. (9), as has been observed for tensile strength and bulk specific volume, and if a correlation exists between the values of $\beta$ and $\gamma$ for individual excipients or formulated drug products. Now that the Turbula mixing system has been incorporated into the previously developed, lubrication blending model framework through Eq. (9), material-sparing approaches can be utilized to prepare lab-scale batches with a Turbula mixer to examine both additional excipients and additional product quality attributes as part of future studies.

By evaluating the lubrication sensitivity of additional pharmaceutical excipients, it may also be possible to design formulations which are less sensitive to the detrimental effects of extended lubricant mixing. These lubricant-insensitive formulations would include excipients which have low values of the lubrication rate constant, $\gamma$, and/or low values of the critical product quality attributes, $\beta$. The primary advantage of developing lubricant-insensitive formulations lies in the ability to further broader the range of lubrication blending conditions (i.e. $L \times F_{\mathrm{headspace}} \times r$) that can be applied to the formulation without adversely impacting the product quality. From a Quality-by-Design perspective, a lubricant-insensitive formulation would support a broader design space for the corresponding lubrication blending process relative to a formulation that is highly sensitive to lubrication. Having a larger design space would be more desirable than a more narrow design space, since it gives the formulator and process developer the ability to build more flexibility into the commercial manufacturing process. This increased flexibility from a broad design space increases the overall robustness of both the proposed drug product formulation and its manufacturing process to the effects of extended lubricant mixing.

## 5. Conclusions

The lab-scale Turbula bottle blender was successfully incorporated into the lubrication blending scale-up model. Formulators now have the ability to apply lubrication process knowledge obtained from blenders as small as a 30-mL bottle blender to blenders as large as a 200-L Bin blender. It was observed that Turbula mixers provide two dimensions of powder avalanching, along the height and diameter of the bottle, which increases the characteristic length scale over which mixing occurs relative to V- or Bin blenders. For the dimensions of the bottles used with the Turbula mixer in this study, a characteristic mixing length scale of $1.5 \times V^{1/3}$ (the factor of 1.5 is related to the diameter of the bottle being about half the bottle height) yielded values of the formulation rate constant that were similar to values obtained in prior investigations over a large range of V- and Bin blender sizes. It was also observed that the decrease in the tensile strength of placebo tablets as the extent of processing increased occurred at the same rate as the decrease in the bulk specific volume of the placebo blends. This observation suggests that the rate of the extent of lubrication for each formulation, $\gamma$, may be a fundamental parameter to describe the rate of change in product quality attributes due to lubrication mixing.

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