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Scale-up model describing the impact of lubrication on tablet tensile strength

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ABSTRACT

Lubrication of 2:1 and 1:1 blends of microcrystalline cellulose and spray-dried lactose or dibasic calcium phosphate (DCP) with 0.33% or 1% magnesium stearate, as model free-flowing pharmaceutical formulations, was performed in rotary drum blenders. Blender process parameters examined in this study included type (Bin, V, and Turbula), volume (0.75-Quart to 200-L), fraction of headspace in the blender after the blend is loaded (30–70%), speed (6–202 rpm), and time (up to 225 min). Based on analysis of the experimental data, the following model for the impact of the lubrication process on tablet tensile strength at 0.85 solid fraction, $TS_{SF=0.85}$, was obtained, $TS_{SF=0.85} = TS_{SF=0.85,0}\left[\beta \exp\left(-\gamma \times V^{1/3} \times F_{headspace} \times r\right) + \left(1-\beta\right)\right]$, where V is blender volume, $F_{headspace}$ is the headspace fraction, r is the number of revolutions (i.e. speed × time), $TS_{SF=0.85,0}$ is the initial tensile strength of the blend, β is the sensitivity of the blend to lubrication, and γ is the lubrication rate constant of the formulation. This model can be used to maintain tensile strength during scale-up, by ensuring that $(V^{1/3}F_{headspace}r)_1 = (V^{1/3}F_{headspace}r)_2$. The model also suggests that formulations with DCP are less sensitive to lubrication and more slowly lubricated than formulations with spray-dried lactose (i.e. smaller β and γ values).

1. Introduction

Magnesium stearate (MgSt) is a lubricant commonly added to pharmaceutical powder blends for the purpose of improving the performance of these blends during compaction processes (i.e. roller compaction and tablet compression) (Swaminathan et al., 2006). For example, MgSt aides the compaction process by: (1) reducing wall friction during ejection from a tablet press (Sheskey et al., 1995), (2) improving powder flow (Podczeck and Miah, 1994), (3) increasing bulk powder density (Dansereau and Peck, 1987; Shah and Mlodozeniec, 1977), and (4) reducing the potential of the pharmaceutical formulation to adhere to exposed metal surfaces during powder compaction (i.e. tooling surfaces in tablet compression (Sabir et al., 2001; Yamamura et al., 2009), roll surfaces in roller compaction (He et al., 2007). However, increased levels of mixing during lubrication and increased percentages of MgSt in powder blends have previously been shown to reduce tablet hardness (Bossert and Stamm, 1980; Dansereau and Peck, 1987; Bolhuis et al., 1987; Kikuta and Kitamori, 1994; Sheskey et al., 1995), increase disintegration time (Kikuta and Kitamori, 1994), slow dissolution rates (Billany and Richards, 1982; Johannson and Nicklasson, 1986; Sheskey et al., 1995), and reduce the adhesion of film-coats to tablet surfaces (Rowe, 1977; Lethola et al., 1995). Therefore, MgSt is typically added to the process after a pharmaceutical formulation has been blended prior to the subsequent compaction operation, and blended for only a few minutes to balance the benefits of MgSt as a processing aid with the potential drawbacks to product quality (Wang et al., 2010). The use of alternative lubricants (e.g. sodium stearyl fumerate, glyceryl behenate, zinc stearate, calcium stearate, stearic acid (Shah et al., 1986; Baichwal and Augsburger, 1998; Wang et al., 2010)) and external lubrication, in which MgSt is sprayed directly onto compaction surfaces rather than incorporated into the formulation (Yamamura et al., 2009), have been proposed in the literature as a means of separating the benefits of lubrication to powder processing from the deleterious effects. However, at this time, the use of MgSt and its incorporation into the pharmaceutical powder blend remains the most common practice for the roller compaction and tablet manufacturing processes (Swaminathan et al., 2006).

It has been suggested that the mixing of MgSt during the lubrication process coats the individual particles of the pharmaceutical blend (Shah and Mlodozeniec, 1977; Densereau and Peck, 1987; Billany and Richards, 1982; Desai et al., 1993; Kikuta and Kitamori, 1994; Sheskey et al., 1995; Barra and Somma, 1996; Otsuka and Yamane, 2009). MgSt particles have a plate-like crystal structure (Rao et al., 2005). Under the shear of mixing, sheets of MgSt can be removed from these plate-like crystals and can adsorb onto the surfaces of the components of the pharmaceuti-

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cal powder blend (Dansereau and Peck, 1987; Rao et al., 2005). Since MgSt is hydrophobic (Billany and Richards, 1982), the formation of an external MgSt film on the blend particles can: (1) reduce surface wettability (Billany and Richards, 1982; Lethola et al., 1995), thereby reducing dissolution rates (Johannson and Nicklasson, 1986; Sheskey et al., 1995) and increasing disintegration times (Kikuta and Kitamori, 1994), (2) reduce the bonding properties of the blend due the poor bonding properties of MgSt (Bossert and Stamm, 1980; Dansereau and Peck, 1987; Bolhuis et al., 1987; Kikuta and Kitamori, 1994; Sheskey et al., 1995), and (3) increase the bulk density of the blend (Shah and Mlodozeniec, 1977; Dansereau and Peck, 1987), due to the ability of MgSt-coated particles to more easily slip by one another and pack into a denser formation, relative to unlubricated material. It has been proposed that the adsorption of MgSt onto pharmaceutical blend surfaces follows a Langmuir-type adsorption process (Shah and Mlodozeniec, 1977; Bolhuis et al., 1987). Increased processing during lubrication has previously shown that hardness and bulk density may follow exponential decay (Shah and Mlodozeniec, 1977). There is some evidence that hardness and bulk density decays to a non-zero asymptote (Shah and Mlodozeniec, 1977; Bossert and Stamm, 1980; Bolhuis et al., 1987; van der Watt, 1987), while others have suggested that reductions in hardness follow a bi-exponential decay (Kikuta and Kitamori, 1994). In either case, these profiles can be sub-divided into two regions: (1) a highly-sensitive domain at the beginning of the lubrication process, in which the extent of lubrication and the corresponding tablet quality attributes can change significantly as a result of small changes to processing time, and (2) a domain in which the extent of lubrication and corresponding tablet quality attributes are significantly impacted only by large changes in processing time. Since most pharmaceutical lubrication processes operate in this highly-sensitive domain, if there is a change to the process scale, it then becomes very important to select new process parameters which will maintain the same extent of lubrication as achieved with the original lubrication process, so that product quality remains unchanged.

However, at present, there is no general model that can be used to describe the impact of formulation and/or process parameters related to lubrication of a pharmaceutical blend that can guide lubrication process scale-up, or at-scale changes, to ensure that the product quality attributes are maintained. In this study, then, a series of experiments were performed to examine the reduction in tablet tensile strength due to lubrication as a function of blender process parameters (i.e. blender type, blender size, blender speed, blender fill level, and blending time) and formulation. From an analysis of this experimental data, an empirical model will be proposed which can describe the impact of both formulation and process parameters on the extent of lubrication in a pharmaceutical powder blend (as measured by the reduction in tablet tensile strength). Finally, the utility of the empirical model as an aid for maintaining the extent of lubrication across manufacturing scales and evaluating the lubrication sensitivity of new materials will be discussed.

2. Materials and methods

2.1. Materials

The materials used for the experiments and per-tablet formulation are listed in Table 1. Microcrystalline Cellulose (MCC) as Avicel PH102 was obtained from FMC Corporation (Philadelphia, PA), Spray-Dried Lactose (Lac) as Fast Flo Lactose 316 from Foremost Farms (Baraboo, WI), Dibasic Calcium Phosphate (DCP) as A-Tab from Innophos (Chicago Heights, IL) and magnesium stearate from Mallinckrodt (Hazelwood, MO).

Table 1
Formulations of the 100 mg standard round convex tablets.

Item	Component	*A*	*B*	*C*	*D*	*E*
1	MCC	66.00	49.50	66.00	49.50	66.45
2	Lactose	33.00	49.50	–	–	33.22
3	DCP	–	–	33.00	49.50	–
4	MgSt	1.00	1.00	1.00	1.00	0.33
Total weight	100 mg					

2.2. Pre-lubrication processing

Prior to lubrication, MCC and Lac and DCP were combined together using a blend-mill-blend procedure. For studies performed in the laboratory setting with small blenders, pre-blend batches were made using a 45-Qt V-blender, while at the clinical supply scale, pre-blend batches were made using a 200-L Bin Blender. In all cases, the excipients were blended for 10 min at 24 rpm. The blend was then passed through a 032R screen in the CoMil 193 (Quadro Engineering, Waterloo, Canada) operating at 1000 rpm. The blend was then replaced in the blender and mixed for another 10 min at 24 rpm. The blend was then bagged until required for lubrication with MgSt. For larger batch sizes, the pre-blend of the excipients was performed in the blender to be used in lubrication. In this case, the blend was retained in the blender until the lubrication process was begun.

2.3. Lubrication

When necessary, the pre-mixed placebo blend was weighed out to the desired amount and added to the blender selected for testing. Magnesium stearate was then added to the placebo blend in the blender such that it comprised 1% or 0.33% (w/w) of the final lubricated blend. Blender size, blender type, blender load level, blender speed, and time for lubrication were all varied according to Table 2. For lubrication of large batches (i.e. greater than 6 kg), ~500-g samples were taken from the blend at pre-determined time points for subsequent tableting (Otsuka and Yamane, 2009), to save material and processing time. For small batches, a new batch was generated for each lubrication time point.

2.4. Tablet manufacture

The ~500-g sample of the lubricated blends was tableted via direct compression using a Kilian T-100 (IMA S.p.A, Köln, Germany) rotary tablet press operating at 60K tabs/h for a 9-station press and 107K tabs/h for a 16-station press with feed frame speed of 10 rpm. Each rotary press was outfitted with three 1/4-inch (6.35-mm) standard round concave (SRC) punches and the target tablet weight was 100 mg. A pre-compression force of ~1 kN was used during production. After achieving the proper tablet weight, tablets were generated at 4–5 compression forces over the range of 2–15 kN.

2.5. Evaluation of tablet physical properties

Tablet hardness, thickness, diameter, and mass measurements were performed on ten tablets per compression force using a PharmaTest rotary tablet tester (Pharma Test Apparatebau GmbH, Hainburg, Germany).

2.6. Calculation of tensile strength and solid fraction for SRC tablets

The tensile strength, σ, of the SRC tablet was calculated from the values of the hardness, thickness, and diameter of the SRC tablets

Table 2
Summary of tested lubrication process parameters.

Type	Size	Supplier	Fill level (%)	Speed (rpm)	Max time (min)	Froude number[a]
V-blender[a]	0.75-Quart	Patterson-Kelley[b]	60	24	37.5	0.059
	6-Quart		34, 70	24	112.5	0.092
	45-Quart		34, 70	24	37.5	0.229
Bin blender	5-L	Bohle[c]	30, 70	6, 12, 18, 30	225	0.141
	10-L	Servolift[d]	30, 70	12	225	0.026
	50-L	Meto[e]	30, 70	12	75	0.059
	50-L	Servolift	30, 70	12	75	0.059
	100-L	Servolift	30, 70	12	75	0.075
	200-L	Servolift	30, 70	12	75	0.094
Turbula T2F	2-L	GlenMills[f]	50, 70	46, 68, 98, 144, 202	27	ND

[a] Froude Number was determined for highest blender speed examined. A value for the Turbula mixer was not determined (ND) due to the non-circular mixing path of the Turbula mixer.
[b] East Stroudsburg, PA 18301.
[c] L.B. Bohle Maschinen and Verfahren GmbH, Ennigerloh, Germany.
[d] Wharton, NJ 07855.
[e] Meto Corp, Franklin Lakes, NJ 07417.
[f] Clifton, NJ 07014.

using the following equation (Pitt et al., 1988):

$$\mathrm{TS} = \frac{10F}{\pi D^2}\left(2.84\frac{H}{D} - 0.126\frac{H}{H-2H_c} + 3.15\frac{H-2H_c}{D} + 0.01\right)^{-1} \quad (1)$$

where F is the tablet hardness, D is the diameter of the tablet, H is the total thickness of the tablet, and H_c is the thickness of the convex cups.

Solid fraction, SF, of the SRC tablets was calculated from the ratio of the apparent density to the true density of the powder blend (1.55 g/cm^3). Apparent density was calculated by dividing the mass of the SRC tablet by the volume of the SRC tablet, which was calculated using the following equation:

$$V_{\mathrm{SRC}} = V_{\mathrm{band}} + 2V_{\mathrm{cup}} \quad (2)$$

where V_{band} is calculated using the equation for the volume of disk:

$$V_{\mathrm{band}} = \pi(H - 2H_c)D^2 \quad (3)$$

and V_{cup} is calculated using the equation for the volume of a dome:

$$V_{\mathrm{cup}} = \pi H_c^2\left(r_c - \frac{H_c}{3}\right) \quad (4)$$

where r_c, the radius of curvature for a dome, is calculated from the following equation:

$$r_c = \frac{4H_c^2 + D^2}{8H_c} \quad (5)$$

2.7. Analysis of compactibility data

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

$$\mathrm{TS} = \mathrm{TS}_0 \exp[b(1 - \mathrm{SF})] \quad (6)$$

The corresponding TS at 0.85 solid fraction, 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 TS_0 and b obtained from regression analysis. The value of TS at 0.85 solid fraction was then plotted as a function of the number of revolutions imparted during lubrication blending. These values were then regressed using a non-linear regression software package (DataFit 8.1, Oakdale Engineering) to the following equation for exponential decay to a non-zero asymptote:

$$\mathrm{TS}_{\mathrm{SF}=0.85} = \mathrm{TS}_{\mathrm{SF}=0.85,0}\left[\left(1-\beta\right) + \beta\exp(-\mathrm{cr})\right] \quad (7)$$

where $\mathrm{TS}_{\mathrm{SF}=0.85}$ is the tensile strength at 0.85 solid fraction of the formulation after blending for r revolutions, $\mathrm{TS}_{\mathrm{SF}=0.85,0}$ is the initial tensile strength at 0.85 solid fraction of the formulation, β is the sensitivity of the formulation to lubrication and represents the total fraction of the initial tensile strength that can be lost as a result of lubrication, and c is the lubrication rate constant. This equation is similar in form to the analysis method undertaken by Shah and Mlodozeniec for tablet hardness and tapped density of lubricated blends (Shah and Mlodozeniec, 1977), and incorporates the concept of a lubrication sensitivity ratio (Bolhuis and Holzer, 1996; Almaya and Aburub, 2008), through the use of the β term. For the case of $\beta = 1$, Eq. (7) reverts to the equation for exponential decay to zero.

3. Results

3.1. Impact of blender speed and blending time during lubrication on tablet tensile strength

Fig. 1 shows the tablet hardness-compression profiles obtained from the lubrication of Formulation A with the 6-Qt V-blender, 5-L Bin blender, and 2-L Turbula operated at different speeds and durations during lubrication. As each plot shows, the hardness-compression profiles decrease as blend time or blend speed increases. However, the number of revolutions imparted during lubrication appears to be the fundamental parameter that controls the loss of tablet hardness, since speed and time combinations resulting in similar total revolutions yield similar hardness-compression profiles. For example, in Fig. 1B, the hardness-compression profiles obtained from lubricating at 12 rpm for 5 min (i.e. 60 revolutions) and at 6 rpm for 9 min (i.e. 54 revolutions) in the 5-L Bin Blender are very similar to one another. Further, the slight differences between these two profiles are no greater than the differences observed by repeating identical processing conditions, as shown in Fig. 1C for lubrication in the 2-L Turbula operated at 202 rpm for 9 min.

Compactability profiles, shown in Fig. 2, were also generated from the tablets analyzed in Fig. 1. Similar to the trend of the hardness-compression profiles in Fig. 1, the compactability profiles obtained for 2:1 MCC:Lac with 1% MgSt also decrease as a function of the number of revolutions imparted during lubrication. The compactability data were regressed to the Ryshkewitch equation to estimate the tensile strength at 0.85 solid fraction. These tensile strength values were then plotted as a function of the number of revolutions imparted during blending, as shown in Fig. 3.

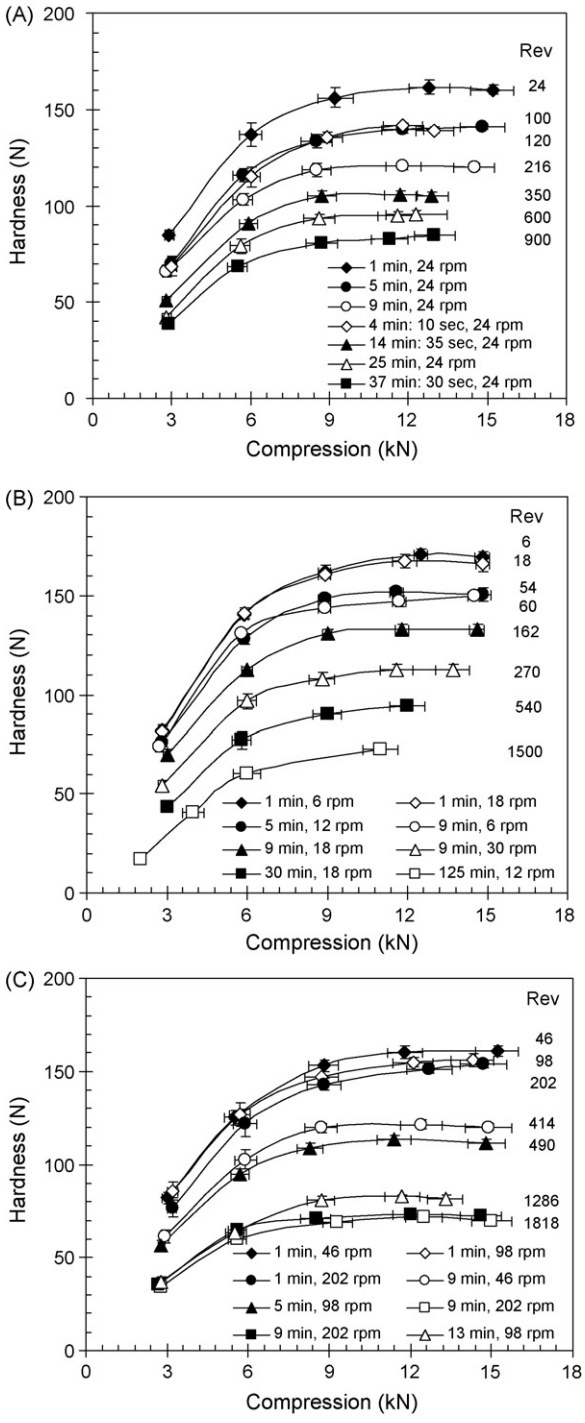

Fig. 1. Hardness-compression profiles for the 2:1 MCC:Lac formulation containing 1% MgSt. (A) 6-Quart V-Blender, (B) 5-L Bin blender, (C) 2-L Turbula mixer.

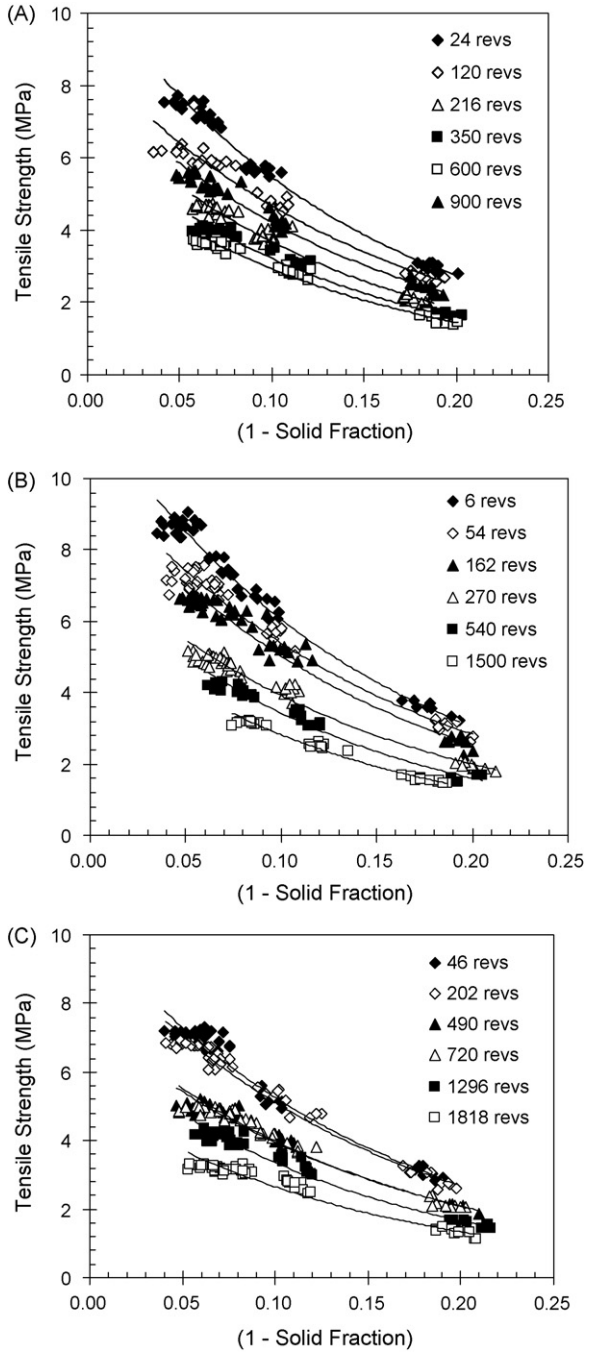

Fig. 2. Compactability profiles for the 2:1 MCC:Lac formulation containing 1% MgSt for various number of revolutions imparted during the lubrication process. (A) 6-Quart V-Blender, (B) 5-L Bin blender, (C) 2-L Turbula mixer. The black curves represent the best fit of each data set to the Ryshkewitch equation.

Equation (7) was then used to determine the values of the initial tensile strength at 0.85 solid fraction, the lubrication sensitivity, β, and the lubrication rate constant, c, of the 2:1 MCC:Lac blend with 1% MgSt. The values of these parameters corresponding to the data in Fig. 3 are reported in the first three rows of Table 3. It should be noted that each data point in Fig. 3 represents a single lubrication batch. The data in Fig. 3 are also plotted according to the day on which the batch was lubricated and tableted. Therefore, Fig. 3 also illustrates the extent of batch-to-batch and day-to-day variability in the lubrication and tableting process used in this study.

3.2. Effect of scale-up (blender size) and blender load level during lubrication on tablet tensile strength

Figs. 4 and 5 shows the impact of blender size and loading for the V-blenders and Bin blenders examined in laboratory setting and clinical supply manufacturing setting on the tensile strength at 0.85 solid fraction versus lubrication revolution profiles for the 2:1 MCC:Lactose blend. In both figures, for a constant number of revolutions, the tensile strength at 0.85 solid fraction decreases as the size of the blender increases and as the loading in the blender decreases in both V-blenders and Bin blenders.

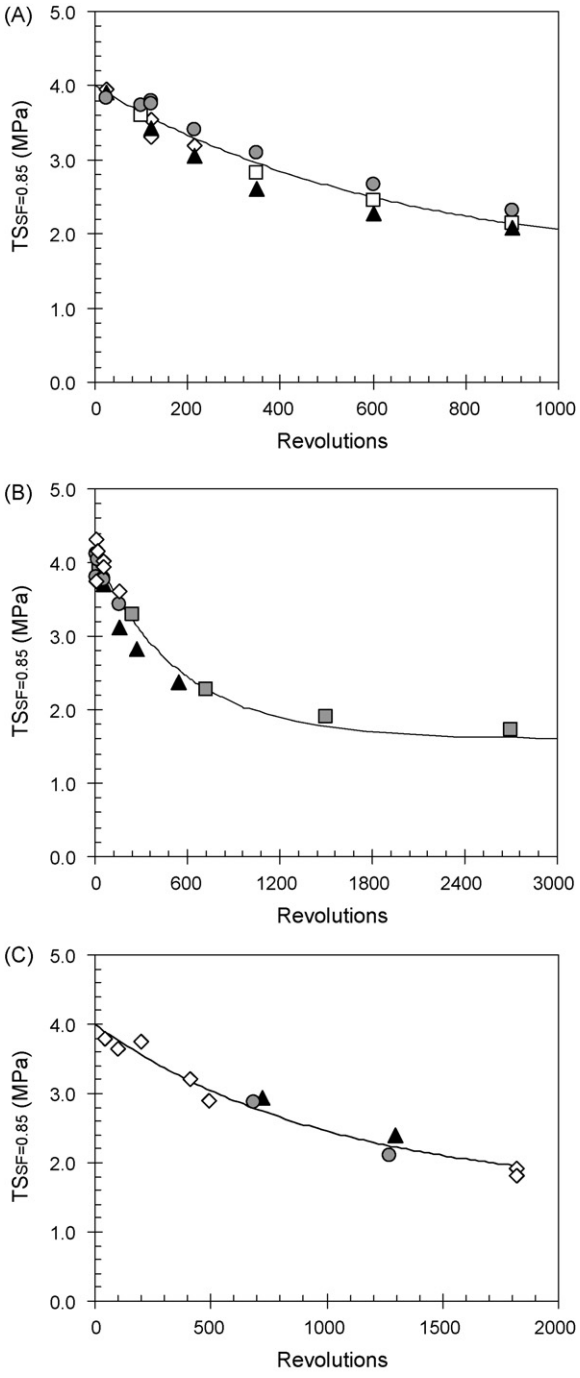

Fig. 3. Reduction in tensile strength at 0.85 solid fraction as a function of revolutions imparted during the lubrication process with small-scale blenders. (A) 6-Quart V-Blender, (B) 5-L Bin blender, (C) 2-L Turbula mixer. Key: white diamonds—Day 1, grey circles—Day 2, black triangles—Day 3, grey squares—Day 4, solid line–model fit of the data with Eq. (7).

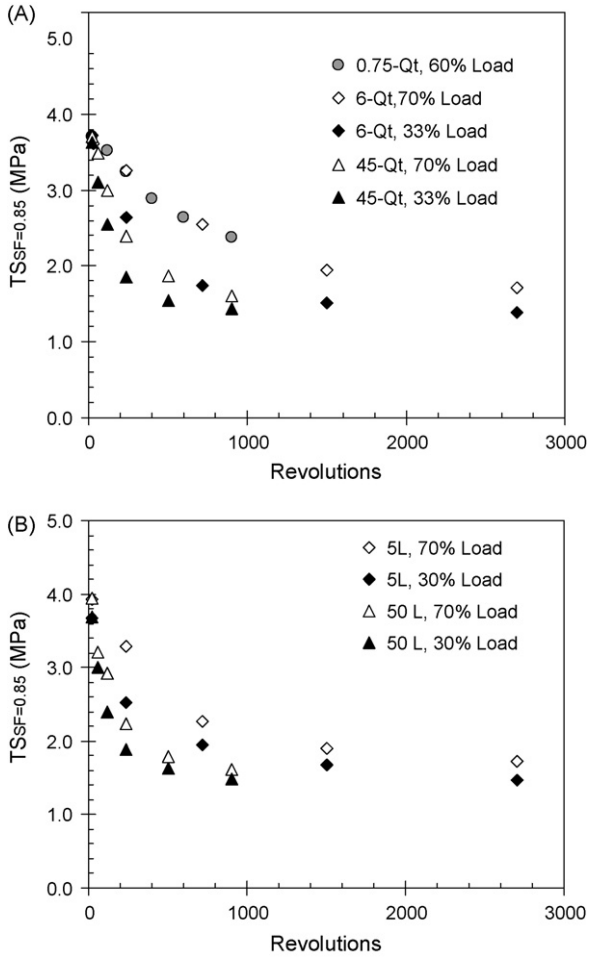

Fig. 4. Reduction in tensile strength as a function of the number of revolutions imparted during lubrication blenders in the laboratory setting. (A) V-blenders, (B) Bin Blenders.

Equation (7) was then used to determine the values of the initial tensile strength at 0.85 solid fraction, the lubrication sensitivity, β, and the lubrication rate constant, c, of the 2:1 MCC:Lac blend with 1% MgSt. The values of these parameters corresponding to the data in Figs. 4 and 5 are also reported in Table 3. Review of the data in Table 3 for the 2:1 MCC:Lac blend with 1% MgSt indicates that the lubrication sensitivity, β, is independent of the processing conditions, while the initial tensile strength at 0.85 solid fraction for each location is also independent of the processing conditions (i.e. blender type, blender size, and blender fill) (see Appendix A). The data in Figs. 3–5 were refit with Equation (7) with β set at 0.61 and the initial tensile strength at 0.85 solid fraction set at 4.00 and 3.25 MPa for the laboratory and clinical-scale experiments, respectively. This yielded revised values for the lubrication rate constant, c, for each of the conditions in Figs. 3–5, which are listed in Table 4.

The lubrication rate constants presented in Table 4 were then plotted as a function of the cube root of the blender volume for each blender load level, as shown in Fig. 6. The cube root of the blender volume was selected, since, if one assumes that the blender can be modeled as a cube and that shearing of the magnesium stearate is occurring at the free surface of the powder bed, the cube root of the blender volume can be used to describe a characteristic length scale over which lubrication via magnesium stearate particle shear is occurring in the powder bed. For both load levels, the lubrication rate constant increases linearly with the cube root of the blender volume. Further, the slopes of the lines in Fig. 6 appear to be proportional to the fraction of the blender occupied by the empty headspace (i.e. the ratio, 0.0022:0.0009 is similar to the ratio 70%:30%), which is in agreement with prior observations for the impact of fill volume on the mixing of free-flowing materials (Brone et al., 1988). Therefore, the values of the lubrication rate constant were plotted in Fig. 7 against the cube root of the blender volume multiplied by the fraction of headspace, $F_{\text{headspace}}$, present in the blender. This figure shows that the lubrication rate constant, c, increases linearly as the product $(V^{1/3} \times F_{\text{headspace}})$ increases over the range of 0.2–4.1 for this parameter. Also, Fig. 7 indicates that the performance of V-blenders and Bin blenders during lubri-

Table 3
Summary of lubrication model parameter estimation for 2:1 Avicel PH102:Fast Flo Lactose with 1% magnesium stearate placebo blend.[a].

Lubrication conditions	$TS_{SF=0.85,0}$ (MPa)	β	c (revs^{-1})	R^2 (%)
5-Liter Bin, 70% Load	4.06 (0.33)	0.58 (0.07)	0.0018 (0.0008)	99.7
6-Quart V, 60% Load	4.04 (0.20)	0.54 (0.11)	0.0022 (0.0012)	93.9
2-Liter Turbula, 50-70% Load	3.99 (0.20)	0.61 (0.06)	0.0010 (0.0001)	96.8
0.75-Quart V, 60% Load	3.81 (0.14)	0.50 (0.15)	0.0015 (0.0009)	99.6
6-Quart V, 70% Load	3.71 (0.18)	0.57 (0.07)	0.0011 (0.0004)	99.9
6-Quart V, 33% Load	3.89 (0.23)	0.63 (0.04)	0.0030 (0.0008)	99.9
45-Quart V, 70% Load	3.97 (0.18)	0.61 (0.04)	0.0043 (0.0011)	99.8
45-Quart V, 33% Load	4.03 (0.14)	0.64 (0.02)	0.0073 (0.0010)	99.9
5-Liter Bin, 30% Load	4.10 (0.48)	0.60 (0.08)	0.0040 (0.0033)	98.4
50-Liter Bin, 70% Load	4.31 (0.20)	0.62 (0.03)	0.0061 (0.0012)	99.9
50-Liter Bin, 30% Load	4.20 (0.37)	0.63 (0.04)	0.0094 (0.0029)	99.6
10-Liter Bin, 70% Load	2.76 (0.59)	0.56 (0.17)	0.0013 (0.0013)	95.2
10-Liter Bin, 30% Load	3.11 (0.41)	0.61 (0.09)	0.0034 (0.0021)	98.9
50-Liter Bin, 70% Load	3.14 (0.80)	0.62 (0.59)	0.0024 (0.0061)	91.8
50-Liter Bin, 30% Load	3.31 (0.77)	0.60 (0.14)	0.0079 (0.0080)	97.3
100-Liter Bin, 70% Load	3.15 (0.24)	0.59 (0.09)	0.0038 (0.0018)	99.4
100-Liter Bin, 30% Load	3.42 (0.42)	0.63 (0.04)	0.0126 (0.0043)	99.7
200-Liter Bin, 70% Load	3.33 (0.27)	0.62 (0.07)	0.0051 (0.0022)	99.5
200-Liter Bin, 30% Load	3.14 (0.23)	0.62 (0.03)	0.0110 (0.0029)	99.8

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

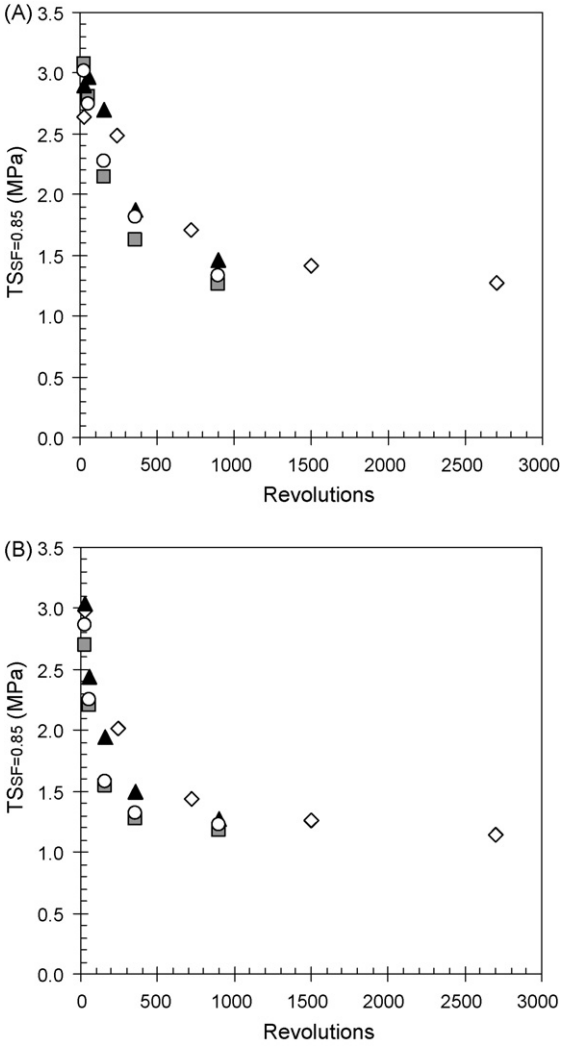

Fig. 5. Reduction in tensile strength as a function of the number of revolutions imparted during lubrication for Bin blenders in the clinical manufacturing facility. (A) 30% load level (70% headspace), (B) 70% load level (30% headspace). Key: white diamonds—10-L Bin Blender, black triangles—50-L Bin Blender, white circles—100-L Bin Blender, grey squares—200-L Bin Blender.

Table 4
Determination of the lubrication rate constant, c, using average values for $TS_{SF=0.85,0}$ and β for the 2:1 Avicel PH102:Fast Flo Lactose Placebo Blend with 1% magnesium stearate.[a,b].

Lubrication conditions	c (revs^{-1})	R^2 (%)
5-Liter Bin, 70% Load	0.0018 (0.0003)	94.3
6-Quart V, 60% Load	0.0015 (0.0012)	93.6
2-Liter Turbula, 50-70% Load	0.0010 (0.0001)	96.1
0.75-Quart V, 60% Load	0.0014 (0.0003)	94.0
6-Quart V, 70% Load	0.0013 (0.0005)	96.1
6-Quart V, 33% Load	0.0033 (0.0009)	99.2
45-Quart V, 70% Load	0.0044 (0.0003)	99.8
45-Quart V, 33% Load	0.0078 (0.0011)	99.2
5-Liter Bin, 30% Load	0.0035 (0.0010)	96.8
50-Liter Bin, 70% Load	0.0051 (0.0011)	98.1
50-Liter Bin, 30% Load	0.0084 (0.0012)	99.2
10-Liter Bin, 70% Load	0.0021 (0.0016)	79.5
10-Liter Bin, 30% Load	0.0040 (0.0011)	98.6
50-Liter Bin, 70% Load	0.0028 (0.0011)	94.0
50-Liter Bin, 30% Load	0.0070 (0.0017)	98.0
100-Liter Bin, 70% Load	0.0040 (0.0006)	99.1
100-Liter Bin, 30% Load	0.0111 (0.0015)	99.4
200-Liter Bin, 70% Load	0.0048 (0.0007)	99.4
200-Liter Bin, 30% Load	0.0127 (0.0016)	99.4

[a] Data presented as: Estimate (95% confidence interval).
[b] Average $TS_{SF=0.85,0}$ value for lab scale = 4.0 MPa, for clinical scale = 3.25 MPa.

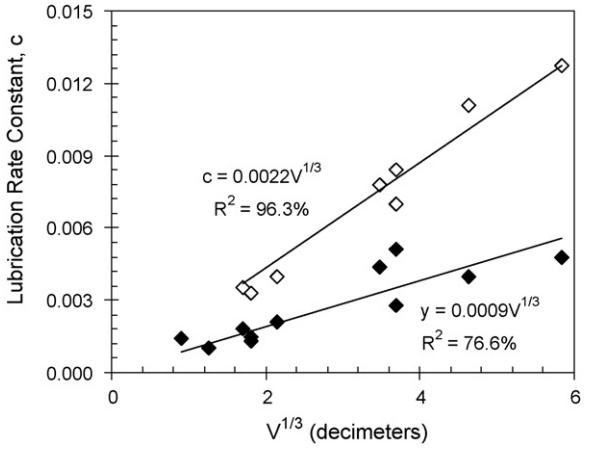

Fig. 6. Lubrication rate constant, c, from Table 4 as a function of the cube root of the blender volume for the 2:1 MCC:Lac data. Key: black diamonds—30% headspace, white diamonds—70% headspace, solid line–linear regression of data.

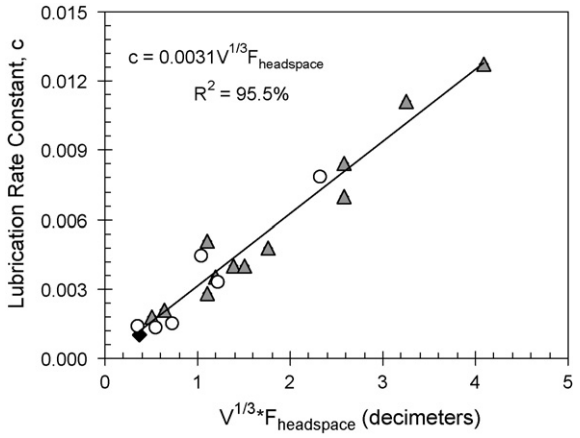

Fig. 7. Lubrication rate constant, c, from Table 4 as a function of the product of the cube root of the blender volume of the fraction of headspace in the blender for the 2:1 MCC:Lac data. Key: black diamond—Turbula data, white circles—V-blender data, grey triangles—Bin blender data, solid line–linear regression of all data.

cation is similar. Therefore, in Eq. (7), c may be replaced by the terms, $\gamma \times V^{1/3} \times F_{headspace}$, where γ for the 2:1 MCC:Lac formulation with 1% MgSt is equal to 0.0031. Finally, by normalizing the tensile strength at 0.85 solid fraction by the initial value, all of the data in Figs. 3–5 can be collapsed onto a single profile that is a function of the process parameters, $V^{1/3} \times F_{headspace} \times r$, as shown in Fig. 8.

3.3. Impact of formulation on the effect of lubrication on tablet tensile strength

To determine whether the slope of the line in Fig. 7, γ, is a constant or a formulation-dependent parameter, batches of 1:1 MCC:Lac, 2:1 MCC:DCP, and 1:1 MCC:DCP were lubricated with 1% MgSt in the 5-L and 50-L Bin Blenders used in the laboratory setting at a fill level of 30% ($F_{headspace}$ = 70%). In addition, a batch of 2:1 MCC:Lac with 0.33% MgSt was manufactured in the 6-Qt V-blender at a fill level of 60% ($F_{headspace}$ = 40%). The tensile strength at 0.85 solid fraction as a function of lubrication revolutions from these batches are shown in Fig. 9.

Values for the initial tensile strength, β, and γ for each formulation were obtained by fitting the data in Fig. 9 to Eq. (7), modified for the case where $c = \gamma \times V^{1/3} \times F_{headspace}$. The parameter values for

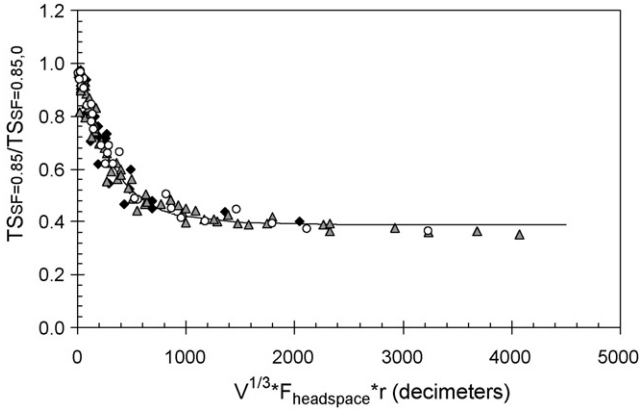

Fig. 8. Normalized tensile strength at 0.85 solid fraction of 2:1 MCC:Lac as a function of the lubrication process parameters. Key: black diamond—Turbula data, white circles—V-blender data, grey triangles—Bin blender data, solid line–model fit of all data with Eq. (8) for β = 0.61 and γ = 0.0031 decimeters^{-1}.

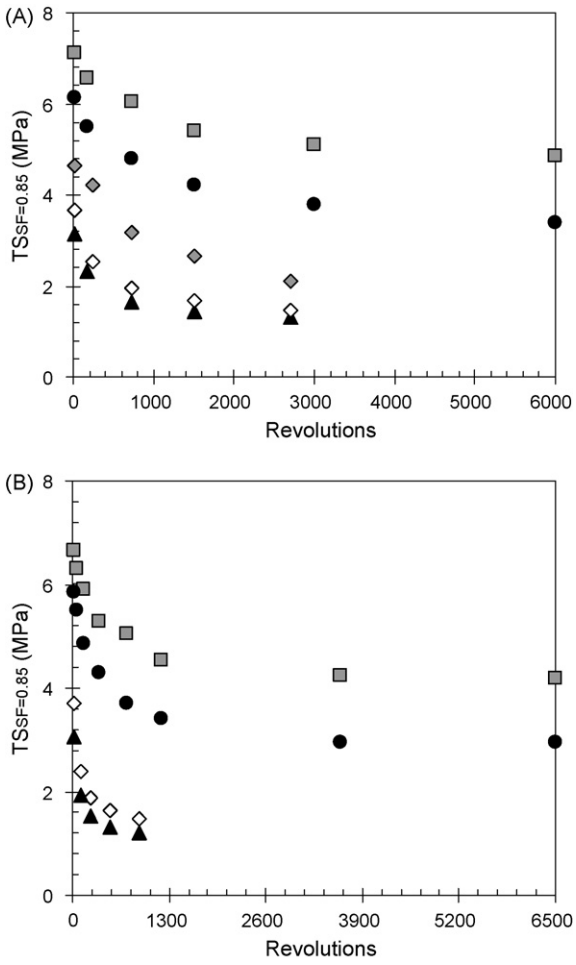

Fig. 9. Tensile strength at 0.85 solid fraction of Formulations A-E as a function of the number of revolutions imparted during blending. (A) 5-L Bin with 70% headspace (Note: Formulation E was lubricated in a 6-Quart V-blender with 40% headspace), (B) 50-L Bin with 70% headspace. Key: grey squares—1:1 MCC:DCP with 1% MgSt, black circles—2:1 MCC:DCP with 1% MgSt, grey diamonds—2:1 MCC:Lac with 0.33% MgSt, open diamonds—2:1 MCC:Lac with 1% MgSt, black triangles—1:1 MCC:Lac with 1% MgSt.

each formulation are reported in Table 5. As shown in Table 5, the initial tensile strength of the formulation improves when: (1) DCP is used in place of spray-dried lactose, and (2) the amount of MgSt is reduced. Furthermore, Table 5 shows that the lubrication sensitivity, β, of the MCC:Lac formulations are equally high, while the MCC:DCP formulation are both less sensitive to lubrication with 1% MgSt, with 2:1 MCC:DCP being more sensitive than 1:1 MCC:DCP. Finally, the lubrication rate constant, γ, also appears to be formulation dependent, with γ decreasing as MgSt% is decreased and when DCP is included in the formulation in place of lactose. To more clearly illustrate the trends in β and γ in Table 5, the tensile strength data in Fig. 9 was normalized and plotted as a function of the process parameters, $V^{1/3} \times F_{headspace} \times r$, in Fig. 10.

4. Discussion

4.1. Empirical equation for the impact of formulation and process parameters on tablet tensile strength

Based on the results in the previous section, the following equation is proposed to describe the decrease in tensile strength, TS, (at 0.85 solid fraction) as a function of formulation and blender process

Table 5
Summary of formulation-dependent parameter estimation for formulations A–E.[a].

Formulation	$TS_{SF=0.85,0}$ (MPa)	β	γ (decimeters^{-1})	R^2 (%)
A - 2:1 MCC:Lactose, 1% MgSt (Bin, lab scale)	4.05 (0.10)	0.600 (0.025)	0.0038 (0.0007)	96.6
A - 2:1 MCC:Lactose, 1% MgSt (V, lab scale)	3.84 (0.11)	0.607 (0.029)	0.0029 (0.0005)	97.6
A - 2:1 MCC:Lactose, 1% MgSt (Bin, clinical scale)	3.24 (0.08)	0.613 (0.015)	0.0028 (0.0003)	98.5
B - 1:1 MCC:Lactose, 1% MgSt	3.40 (0.20)	0.605 (0.044)	0.0035 (0.0012)	97.7
C - 2:1 MCC:DCP, 1% MgSt	6.01 (0.30)	0.480 (0.060)	0.0007 (0.0003)	94.0
D - 1:1 MCC:DCP, 1% MgSt	6.90 (0.40)	0.340 (0.066)	0.0007 (0.0004)	87.2
E - 2:1 MCC:Lactose, 0.33% MgSt	4.84 (0.14)	0.572 (0.055)	0.0017 (0.0004)	98.7

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

parameters:

$$\frac{TS_{SF=0.85}}{TS_{SF=0.85,0}} = \beta \exp\left(-\gamma \times V^{1/3} \times F_{headspace} \times r\right) + \left(1-\beta\right) \quad (8)$$

where $TS_{SF=0.85,0}$, β and γ are the formulation-dependent parameters, which correspond to the *initial tensile strength at 0.85 solid fraction*, *lubrication sensitivity*, and the *lubrication rate constant* of the formulation, respectively, and V, $F_{headspace}$, and r are the process-dependent parameters, which correspond to the *total blender volume*, *fraction of headspace in the blender*, and *total number of revolutions* imparted to the blend during lubrication. This model for tablet tensile strength reduction is presently valid for headspace fractions between 30 and 70% and blender volumes up to 200 L.

For the blends examined in this study, the number of revolutions was found to be a dominant process parameter, rather than blender speed and blender time, individually. This observation is consistent with prior studies which have shown that, for free-flowing blends, blender speed in the range considered here does not have an impact on the degree of mixing for a constant number of revolutions (Brone et al., 1988; Lemieux et al., 2007; Sudah et al., 2002). Conversely, for cohesive blends, it has been shown that blender speed can impact the degree of mixing for a constant number of revolutions (Arratia et al., 2005; Bossert and Stamm, 1980; Bolhuis et al., 1987). In some cases, pharmaceutical blends can be cohesive in nature, as were those used in prior studies (Arratia et al., 2005; Bossert and Stamm, 1980; Bolhuis et al., 1987). However, it has been shown that the formulations tested here, 2:1 and 1:1 mixtures of MCC:Lac and MCC:DCP, have excellent powder flow properties, and may be characterized as free-flowing materials (Guerin et al., 1999; Schneider et al., 2007).

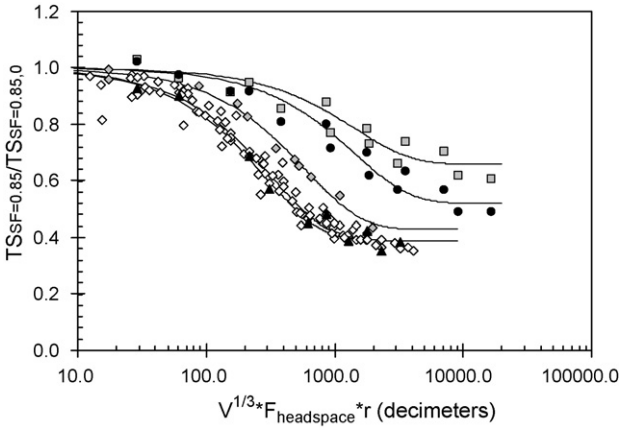

Fig. 10. Semi-log plot of the normalized tensile strength at 0.85 solid fraction of Formulations A–E as a function of the lubrication process parameters. Key: grey squares—1:1 MCC:DCP with 1% MgSt, black circles—2:1 MCC:DCP with 1% MgSt, grey diamonds—2:1 MCC:Lac with 0.33% MgSt, open diamonds—2:1 MCC:Lac with 1% MgSt, black triangles—1:1 MCC:Lac with 1% MgSt, solid lines–model fit of data with Eq. (8) for β and γ given by values in Table 5.

Of course, if the rotary blender is turned fast enough, centrifugal forces will begin to diminish powder mixing in the blender, as the powder material will not tumble and cascade as the blender rotates. To ensure that the blender speed is not so high that mixing is impeded by centrifugal forces, a Froude Number for the blending process can be calculated, using the following equation (Brone et al., 1988):

$$Fr = \frac{v^2}{gL} \quad (9)$$

where v is the tip speed of the blender, g is the gravitational constant, and L is the rotational length of the blender. Previous contributors have suggested three main blending domains, as a function of blender speed: tumbling ($Fr < 0.4$), partial inertial ($0.4 < Fr < 2$), and centrifugal ($Fr > 2$) (Brone et al., 1988). All conditions tested with Bin and V-blenders in this study were contained with the tumbling domain, as shown in Table 2. Therefore, it should be noted that Eq. (8) is valid only in the tumbling domain of the blender mixing process.

As the data in Fig. 8 show, it appears that the type of rotary blender used during lubrication – Bin, V-blender, or Turbula – does not significantly impact the extent of lubrication over the range of blender volumes, fill levels, and speeds examined here. This observation would suggest that, for the blenders considered in this study, the geometry of the blending vessel does not have a large impact on the lubrication of the powder blend, thereby making it easier to move the lubrication blending process into different types of rotary blenders.

Finally, it should be noted that the formulation-dependent parameters, $TS_{SF=0.85,0}$, β, and γ may also be functions of other properties of the formulation. As Table 5 has shown, a change in the level of MgSt in the formulation can impact the initial tensile strength, as well as the lubrication rate constant. The physico-chemical parameters of MgSt have also been shown to have an impact on tablet tensile strength and other critical tablet attributes (Barra and Somma, 1996; Rao et al., 2005). Material properties of the other formulation components (i.e. degree of ductility (Jarosz and Parrott, 1984)), particle size (van der Watt, 1987)) may also have an impact on the values of the formulation-dependent parameters in Eq. (8), as seen in the differences in the formulation-dependent parameters between the MCC:Lac and MCC:DCP formulations. Understanding the role of formulation properties on the lubrication process, as described by the model proposed in Eq. (8) could be the focus of additional study in this area, and could provide a means for identifying improved pharmaceutical formulations.

4.2. Maintaining extent of lubrication across scales

Equation (8) can be used to scale the lubrication process from the lab scale through clinical supply manufacture scale, and possibly also to commercial scale manufacture. For an adjustment to the manufacturing process scale where the formulation undergoes no modifications (i.e. β and γ do not change), to maintain the extent of lubrication, as measured by the reduction in ten-

sile strength given by $TS_{SF=0.85}/TS_{SF=0.85,0}$, the exponential term, $\gamma \times V^{1/3} \times F_{headspace} \times r$, needs to remain constant. One reason for maintaining the extent of lubrication or reduction in tensile strength across scales can be illustrated by examining the data in Fig. 2. As shown in Fig. 2, the TS vs. SF fraction profiles decrease as the number of revolutions during lubrication is increased. Since the tensile strength and solid fraction are both intrinsic properties of the tableted lubrication formulation, increasing the number of revolutions during lubrication for a formulation fundamentally alters the intrinsic material properties of the processed formulation. In a sense, one could consider a blend lubricated for 24 revolutions and the same blend lubricated for 900 revolutions as *two unique materials*, each with their own intrinsic material properties, even though the formulation components are identical. If the batch size and blender volume of the new process is known, the number of revolutions to be used at the new process condition can be evaluated using the following equation:

$$r_2 = \frac{\left(V^{1/3} F_{headspace} r\right)_1}{\left(V^{1/3} F_{headspace}\right)_2} \quad (10)$$

For example, if the original lubrication process developed in the laboratory used a 1-L blender, with 50% headspace, and was blended for 200 revolutions, then, for clinical supply manufacture where lubrication will occur in a 100-L blender with 30% headspace, the corresponding number of revolutions required to maintain the same extent of lubrication would be ~72 revolutions.

While the blender size examined in this study was limited to 200 L, it should be noted that Eq. (8) could be used to scale up the lubrication process to a fully-loaded (i.e. 30% headspace), commercial scale blender. For example, if the lubrication process is going to be scaled-up to a 2000-L blender that will be run at full capacity (i.e. 30% headspace fraction), then the value of the $V^{1/3} \times F_{headspace}$ parameter is 3.7, which is within the range of this parameter examined with lab scale and clinical supply scale equipment utilized in this study (see Fig. 7). Therefore, with this model, it is possible to scale the lubrication process directly from the lab scale to the commercial scale. This attribute of Eq. (8) should enable formulation designers and process developers to save considerable time and material scaling-up the manufacturing process by reducing the number experiments required to ensure consistent product quality at the new scale. Furthermore, the ability of Eq. (8) to enable movement from lab scale to commercial scale could also be used to modify the initial process development work at lab scale to lubricate a new formulation to a condition that would be more representative of the extent of lubrication obtained with typical commercial scale manufacturing processes. For instance, if lubrication of a pharmaceutical blend at commercial scale (2000-L vessel at 30% headspace) is generally conducted for 5 min at 12 rpm (60 revolutions), then the corresponding lab scale lubrication process, using a 0.5-L vessel, filled to 50% headspace, would require ~570 revolutions (~47 min at 12 rpm) to mimic the extent of lubrication expected under commercial-scale processing conditions. Therefore, in general, it may be necessary to lubricate new formulations that are examined at the lab scale for a much longer duration to more effectively understand how lubrication will impact the final product at commercial scale.

In the context of Eq. (8), tensile strength is presently used as the quantitative response for assessing the extent of lubrication imparted to the pharmaceutical blend. However, it would be more convenient to assess the extent of lubrication directly on the uncompressed pharmaceutical blend *in situ* to ensure that the blend is lubricated to the desired extent at any scale of manufacture. This task would seem to be well suited for the application of a process analytical technology (PAT). Unfortunately, a commonly-used PAT in pharmaceutical manufacture, near infrared (NIR) spectroscopy, does not appear to possess the level of scrutiny needed to properly assess the impact of extended lubrication of pharmaceutical blends on tablet strength. Duong et al. (2003) have shown that magnesium stearate can be detected in pharmaceutical blends with NIR, but the utility of this method seems to be only to determine if magnesium stearate is uniformly distributed throughout the blend. In their study, the RSD in magnesium stearate distribution in a 2:1 MCC:Lactose placebo formulation dropped from ~200% after 10 revolution to ~20% after 160 revolutions in a 40 L Bohle Bin blender filled to 85% of the total volume, which would suggest blend uniformity of magnesium stearate was achieved after 160 revolutions. At 160 revolutions, the value of $V^{1/3} \times F_{headspace} \times r$ for these conditions is ~80. From the data for 2:1 MCC:Lactose in Fig. 10, this value corresponds to about a 10% reduction in the initial tensile strength, which is only a small portion of the total reduction in tensile strength that could be achieved with additional mixing of the lubricated blend. While this example suggests that NIR may not be appropriate for tracking the extent of lubrication, perhaps another method or technique could be developed in the future to properly track the extent of lubrication in a pharmaceutical powder, which could be used to control the end point of batch lubrication processes to ensure desired tablet tensile strengths.

4.3. Evaluating the lubrication sensitivity of APIs, excipients, or pharmaceutical blends

As shown in Figs. 9 and 10, the 1:1 MCC:DCP formulation yields the formulation with the highest initial tensile strength, as well as the formulation that is both the least sensitive to lube and the least impacted by mixing during the lubrication process (e.g. smallest values of β and γ in Table 5, respectively). This is due to: (1) the use of DCP, which has a higher tensile strength than lactose and MCC (Sheskey et al., 1995; Busignies et al., 2006), and (2) the reduced amount of MCC, which is known to be very sensitive to lubrication (Zuurman et al., 1999).

Since Eq. (8) has separated out the process parameters from the formulation-dependent parameters, it is possible to evaluate these formulation-dependent parameters for individual APIs, excipients, or new pharmaceutical blends. Specifically, a series of experiments can be run at lab scale with minimal material usage and a known set of blender process parameters during lubrication to evaluate the reduction of tensile strength (and the impact on other product attributes, such as bulk density, Carr's Index, and dissolution) with increased lubrication. In performing such experiments, it is recommended that multiple samples be taken at the early stages of the lubrication process to account for a possible lack of lubricant blend uniformity, which may lead to greater sample-to-sample variability (as observed in Fig. 3B for the 5-L Bin Blender, see white diamond data points). The corresponding TS vs. process parameter data can be fit to Eq. (8) to determine the values of the initial tensile strength, lubrication sensitivity, and lubrication rate constant for the new material or blend. This information could then be used to determine what extent of lubrication should be selected for the new lubrication process to avoid the deleterious effects of over-lubrication with the new material or blend, while maximizing tableting performance of the material or blend.

While the effect of process changes are predicted by Eq. (10), the model cannot currently be used to mathematically determine the effect of a change in the formulation. β, γ, and $TS_{SF=0.85,0}$ are all formulation-dependent, which prevents a single equation from predicting the change of either of these parameters individually. Further, it may also be necessary to adjust the process parameters if a change to the formulation is made to maintain similar tablet tensile strength. In this case, experiments will likely be needed to evaluate the effects of a formulation change on the formulation-specific parameters.

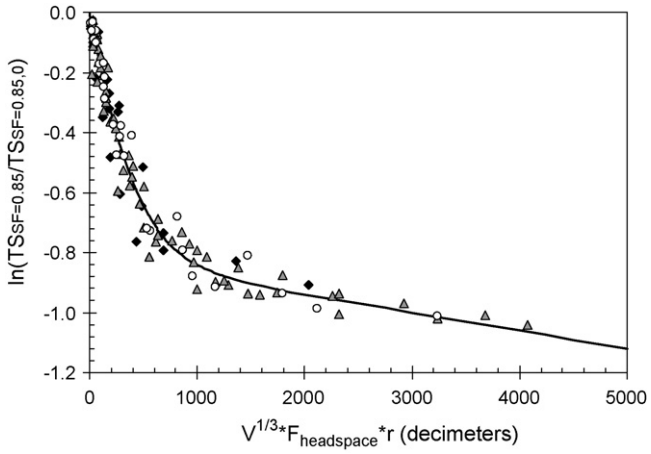

Fig. 11. Natural logarithm of normalized tensile strength at 0.85 solid fraction of 2:1 MCC:Lac as a function of the lubrication process parameters. Key: black diamond—Turbula data, white circles—V-blender data, grey triangles—Bin blender data, solid line–bi-exponential model described in Eq. (11) with $\beta = 0.56$, $\gamma_1 = 0.0035$, and $\gamma_2 = 0.00006$.

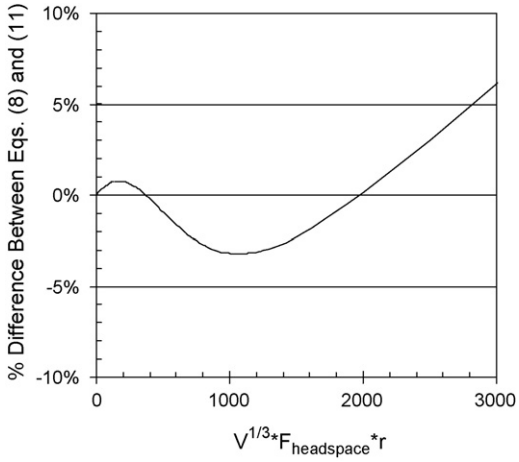

Fig. 12. Percent difference in reduction in tensile strength between Eq. (8) for $\beta = 0.61$ and $\gamma = 0.0031$ and Eq. (11) for $\beta = 0.56$, $\gamma_1 = 0.0035$, and $\gamma_2 = 0.00006$.

Predicting values for γ and β parameters as a function of formulation (e.g. 1.3:1 MCC:Lac, 1.7:1 MCC:Lac) could be the focus of an additional study by evaluating a spectrum of formulation variants under known processing conditions. A database of excipient and formulation γ and β parameters would be useful for elucidating the effects of excipient properties on γ and β as well as for predicting the properties of new formulations.

4.4. Use of a single exponential vs. bi-exponential model equation for describing tensile strength reduction due to lubrication

According to the observations of Kikuta and Kitamori, reductions in tablet hardness and tablet ejection due to lubrication appear to follow a combination of two first-order rate processes (Kikuta and Kitamori, 1994). As they propose, based on analysis of their experimental data and other previous investigations, these two first-order rate process could be accounted for by a rapid rate of distribution of MgSt throughout the blend and adsorption onto the blend particles followed by a slower rate of distribution of sheared MgSt on the surface of the blend particles (Kikuta and Kitamori, 1994). However, there was no statistical evidence presented to support that the second, slower first-order rate process was significant. Therefore, prior to this study, it was not certain that a bi-exponential model is superior to the single exponential model utilized in this study.

It should be noted, however, that there is only a small difference in the form of Eq. (7) and the corresponding bi-exponential model. Specifically, the lubrication process, as proposed by Kikuta and Kitamori, could be described by the following equation:

$$\frac{TS_{SF=0.85}}{TS_{SF=0.85,0}} = \beta \exp(-c_1 r) + \left(1-\beta\right) \exp(-c_2 r) \qquad (11)$$

where c_1 and c_2 are the fast and slow first-order rate processes for lubrication. For the case when c_2 is zero in Eq. (11), the reduction in tensile strength approaches a non-zero asymptote, and returns to the form presented in Eq. (8). Therefore, Eq. (8) is a simplified case of the lubrication mechanism proposed by Kikuta and Kitamori.

It should also be noted that both c_1 and c_2 in Eq. (11) are dependent on the lubrication process parameters, as shown in Fig. 11 for the 2:1 MCC:Lac formulation with 1% MgSt, but the formulation component of the rate constant, γ, is likely different for the two processes. Furthermore, since the only difference between the forms of Eq. (8) and Eq. (11) is the value of the second, slower rate constant, the difference in the values of the reduction in tensile strength is very small over the range of typical processing conditions. As shown in Fig. 12, the difference between the two models is less than 5% for values of the term, $V^{1/3} \times F_{headspace} \times r$, between 0 and 2800. A value of 2800 would correspond to over 700 revolutions in a full, 2000-L commercial scale blender. Therefore, it is unlikely that the use of the bi-exponential decay model (Eq. (11)) in place of the single exponential model with decay to a non-zero value (Eq. (8)) will have any significant impact on maintaining tensile strength reduction across manufacturing scales, since the point at which the two models diverge is far greater than typical operating conditions during lubrication. However, it is likely that, in practice, it will be easier to utilize the simpler form of Eq. (8) for the modeling of the lubrication process across scales.

5. Conclusions

An empirical model that describes the reduction of tablet tensile strength during the lubrication of a free-flowing blend with magnesium stearate, as a function of both lubrication process parameters (blender volume, headspace fraction, and the number of revolutions imparted during lubrication) and formulation-dependent parameters (initial tensile strength, lubrication sensitivity, and lubrication rate constant), has been proposed. This model can aid formulation scientists and process developers maintain tablet tensile strength as the lubrication process is scaled-up from lab scale to commercial scale manufacture.

Acknowledgements

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Appendix A.

To determine whether the three parameters in Eq. (7) were dependent on the processing conditions reported in Table 3, an initial statistical screen was performed using the following linear

Table A1
ANOVA summary for initial tensile strength (R^2 = 0.893).

	df	SS	MS	*F*	Significance *F*
Regression	3	3.42	1.14	41.7	1.63E−07
Residual	15	0.41	0.0274		
Total	18	3.83			

	Coefficients	Standard error	*t* Stat	*P*-value	Lower 95%	Upper 95%
Intercept	3.16	0.139	22.8	4.82−13	2.86	3.45
Site	0.957	0.0943	10.1	4.13E−08	0.756	1.16
Volume	0.00156	0.000778	2.00	0.0636	−0.000100	0.00322
Load	−0.00255	0.00205	−1.24	0.233	−0.00693	0.00183

Table A2
ANOVA Summary for β (R^2 = 0.328).

	df	SS	MS	*F*	Significance *F*
Regression	3	0.00747	0.00249	2.44	0.104
Residual	15	0.0153	0.00102		
Total	18	0.0228			

	Coefficients	Standard error	*t* Stat	*P*-value	Lower 95%	Upper 95%
Intercept	0.621	0.0268	23.2	3.70E−13	0.564	0.678
Site	0.00745	0.0182	0.409	0.688	−0.0314	0.0463
Volume	0.000255	0.000150	1.69	0.111	−6.57E−05	0.000575
Load	−0.000749	0.000397	−1.89	0.0786	−0.00159	9.69E−05

Table A3
ANOVA summary for *c* (R^2 = 0.724).

	df	SS	MS	*F*	Significance *F*
Regression	3	0.000158	5.26E−05	13.2	0.000177
Residual	15	5.99E−05	3.99E−06		
Total	18	0.000218			

	Coefficients	Standard error	*t* Stat	*P*-value	Lower 95%	Upper 95%
Intercept	0.00804	0.00168	4.80	0.000236	0.00447	0.0116
Site	0.000697	0.00114	0.612	0.550	−0.00173	0.00313
Volume	3.61E−05	9.41E−06	3.84	0.00162	1.60E−05	5.61E−05
Load	−0.000107	2.48−05	−4.31	0.000618	−0.000160	−5.4E−05

model:

$$\mathrm{TS},\ \beta,\ c = A + B \times \mathrm{Site} + C \times \mathrm{Volume} + D \times \mathrm{Load} \quad \text{(A1)}$$

where *A*, *B*, *C*, *D* are regression coefficients. The results of this initial regression analysis are shown in Tables A1–A3. Tables A1 and A2 show that the initial tensile strength and β are both independent of volume and load ($P > 0.05$). However, the results for the *c* parameter in Table A3 suggest that blender volume and blender loading do have an impact on the value of *c*. In addition, the results of Table A1 indicate the presence of a significant site effect on the value of the initial tensile strength parameter.

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