Transferable mini-blender performance impact on continuous direct compaction tablets using a modified Kushner-Moore approach.

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Abstract

Small-scale blenders capable of operating in batch mode are a key tool for many pharmaceutical R&D programs and production processes. In current times there is a strong drive to increase efficiency and reduce waste and development time, and there is high utility in transferable modelling approaches that allow the use of one blender to determine the performance in another. In the present work a modified Kushner-Moore approach is used to model the sensitivity to lubrication for tablets produced by Direct Compaction. A model formulation has been mixed in a Gericke GBM 10 P Mini Blender at intensities inaccessible to most batch blenders, with the blends then used to produce tablets, the properties of which have been analysed. The modified Kushner-Moore approach presented here shows a lubrication sensitivity trend that is also applicable in a Pharmatech bin blender, allowing transferability between mixing regimes that have significantly low intensity (Froude number *Fr* < 0.4) and high intensity (*Fr* >> 1), as well as equipment types.

**Keywords**: modelling, powder, blending, lubrication, compaction.

* 1. Introduction

Increasing R&D costs and a drive to improve efficiency and product quality have led to significant research interests in alternative production methods for pharmaceutical products (Cervera-Padrell et al., 2011; Gerogiorgis and Barton, 2009; Lee et al., 2015; Plumb, 2005). In particular, Continuous Direct Compaction (CDC) is attractive as a way to reduce material use and development time during the production of solid dosage forms, from key benefits of a simple manufacturing route and a reduction in scale-up needs (Ierapetritou et al., 2016; Vanarase and Muzzio, 2011). Understanding powder mixing phenomena becomes key, and models that are transferable across mixing durations, intensities and scales have high utility (Gao et al., 2013; Moghtadernejad et al., 2018).

In the literature, various batch blenders have been characterized and their operation in terms of impact on tablet tensile strength at solid fraction of 0.85 (*σ*SF=0.85) can be generalized by the following equation (Kushner and Moore, 2010):

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Where there are three formulation-dependent fitting parameters (*σ*SF=0.85,min, lowest achievable tensile strength; *σ*SF=0.85,max, theoretical tensile strength of an unblended mixture; *γ*, a rate constant) and three process-dependent variables (*V*1/3, cube root of volume and a measure of mixing length scale; *F*, headspace fraction; *R*, number of revolutions and the product of blending time and speed *i.e.* rotation rate). Batch blenders to which Eq. (1) applies are restricted to mixing speeds that result in a Froude number *Fr* value below 0.4 due to centrifugal forces (Brone et al., 1998); Froude number (dimensionless) is the ratio of gravitational forces to inertial forces:

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Where *v* is rotation rate, *r* is radius of mixing, and *g* is the gravitational constant.

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| **Table 1.** Mini blender run conditions. a: standard conditions in mini-blender (66 % MCC, 33 % lactose, 1 % MgSt). b: bin blender runs. Bulk density of the formulation was measured at 0.42 g/cm3, giving headspace fraction values of 0.38 for the mini-blender and 0.29 for the bin-blender. | | | | | | | | |
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| **Run** | **Blend time (s)** | **Blend speed (RPM)** | **Blend mass (kg)** |  | **Run** | **Blend time (s)** | **Blend speed (RPM)** | **Blend mass (kg)** |
| 01a | 5 | 100 | 3.00 |  | 16a | 112 | 200 | 3.00 |
| 02a | 10 | 100 | 3.00 |  | 17a | 50 | 300 | 3.00 |
| 03a | 30 | 100 | 3.00 |  | 18a | 659 | 50 | 3.00 |
| 04a | 120 | 100 | 3.00 |  | 19a | 1198 | 50 | 3.00 |
| 05a | 60 | 100 | 3.00 |  | 20a | 1797 | 50 | 3.00 |
| 06a | 60 | 200 | 3.00 |  | 21a | 2396 | 50 | 3.00 |
| 07a | 60 | 300 | 3.00 |  | 22a | 2995 | 50 | 3.00 |
| 08a | 600 | 100 | 3.00 |  | 23a | 187 | 200 | 3.00 |
| 09a | 1200 | 100 | 3.00 |  | 24a | 83 | 300 | 3.00 |
| 10a | 600 | 300 | 3.00 |  | 25b | 180 | 20 | 1.50 |
| 11a | 600 | 200 | 3.00 |  | 26b | 300 | 20 | 1.50 |
| 12a | 41 | 200 | 3.00 |  | 27b | 1800 | 20 | 1.50 |
| 13a | 18 | 300 | 3.00 |  | 28b | 3600 | 20 | 1.50 |
| 14a | 75 | 200 | 3.00 |  | 29b | 8400 | 20 | 1.50 |
| 15a | 33 | 300 | 3.00 |  | 30b | 26400 | 20 | 1.50 |

In the present work the impact on lubrication extent of mini-blender is evaluated. A mini-blender is a horizontal cylinder with blades about a mixing shaft that can be operated semi-continuously as well as in batch mode. As mixing is imparted by rotating blades and not rotation of the vessel itself, significantly higher Froude numbers (in practice meaning higher mixing speeds) can be used (Jaspers et al., 2023). The present work evaluates how applicable Eq. (1) is to a mini-blender, and if any modifications are required.

* 1. Materials and Methods
     1. Materials and equipment

The formulation is based on a literature composition of 2:1 microcrystalline cellulose (Pharmacel® 102, DFE) to lactose monohydrate (SuperTab® 11 SD) adding up to 99 weight % of the blend and 1 weight % magnesium stearate (Ligamed® MF-2-V, Peter Greven). Fixed composition allows exploration of blending effects on lubrication extent. The blenders used are a 10 L horizontal, single-shaft GBM 10 P Mini Blender (Gericke AG Switzerland) and a 5 L bin blender (Pharmatech). A KORSCH XP 1 single-punch tablet press was used for tablet compaction.

* + 1. Mini-blender operation

Blending speed and time were varied (Table 1) to explore degrees of mixing covering all potential regimes (Jaspers et al., 2023). For all experiments, a fixed routine of blend material addition and experiment execution is followed: 1) stationary blades and open inlet; 2) add Pharmacel® 102 followed by SuperTab® 11 SD (2:1 ratio, total mass 3.0 kg) set blade speed to 10 RPM for 1 s (complete equipment filling stage with minimal mixing; 4) pre-blend major components at 100 RPM for 60; 5) stationary blades and open inlet; 6) add Ligamed® MF-2-V; 7) set blade speed to 10 RPM for 1 s; 8) blend time and speed according to Table 1; 9) discharge at 10 RPM for 1200 s to allow complete discharge.

* + 1. Bin blender operation

Bin blends were prepared with a Pharmatech bin blender (5 L vessel, internal agitator present but not used during experiments). Pharmacel® 102 added first followed by SuperTab® 11SD (2:1 ratio, total mass of 1.5 kg) with pre-blending of 600 s at 20 RPM. For the lubricant addition a fixed speed of 20 RPM was used and blending time was varied as described in Table 1.

* + 1. Tablet compaction and analysis

Tableting was performed with a KORSCH XP1 tablet press equipped (9 mm round flat faced punches, 20 strokes per minute). Target tablet mass of 200 mg. Tablets were compressed at 8 upper main compression forces (UMCF) from 1–36 kN. A total of 100 tablets were prepared for each compression point. From these 10 were used for hardness/ tensile strength determination, with thickness measured; remaining ones were retained for further analysis. Tablet weight was measured with a 5DP analytical balance. Tablet thickness and hardness were measured using a calibrated hardness tester (Kraemer Elektronik) with two different load cells: 0–50 N or 50–500 N crushing force according to the expected tablet hardness. Tensile and porosity data have been used to regress Ryshkewitch-Duckworth equation parameters (Duckworth, 1953; Ryshkewitch, 1953):

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Where *σ* is tensile strength, fitting parameters are tensile strength at zero porosity *σ*0 and bonding capacity and *kb*, and *ε* is porosity (1 – solid fraction). Regression has been done in Matlab with error bars included in weighting. For further analysis values of tensile strength at 0.85, 0.80 and 0.75 solid fraction have been used (typical range for tablets of target tensile strength 1.5 – 2.5 MPa, (Nassar et al., 2021).

* 1. Results and discussion

Interpolating for tensile strength values at 0.85 solid fraction using Eq. (3) and plotting (Figure 3) mini-blender data according to Eq. (1) shows that while there are common maximum (*σ*SF=0.85,max) and minimum (*σ*SF=0.85,min) tensile strength parameters in across the four Froude number datasets, multiple rate constants *γ* are required which should not be the case as these should be process-dependent parameters (Kushner and Moore, 2010).

As stated previously, Eq. (1) was developed using batch blenders that are restricted to low Froude numbers due to mixing otherwise being prevented by centrifugal forces (Brone et al., 1998; Kushner and Moore, 2010). Given that Figure 3A shows clear differences in data trends between datapoints with different Froude numbers, modifications to Eq. (1) that incorporate an *Fr* term in some form have been explored.

The approach which showed promise is to include the root of *Fr* but only for conditions where *Fr* is above 1 – the hypothesis being that below this value it is number of revolutions *R* experienced that matters, and that above it is both the number of revolutions experienced and the intensity at which they are experienced (represented by Froude number) which matters. Whilst *Fr* values below 2.5 are described as one regime of mixing in the literature (Nassar et al., 2021) there is a clear difference in data between *Fr* values of 0.33 and 1.33 (Figure 3). In summary, the modified equation approach is:

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| **Figure 1.** Compaction data for varying with blending speed and time (Table 1). Speeds of 50, 100, 200 and 300 RPM correspond to Froude number *Fr* values of 0.33, 1.33, 5.32, and 11.97. Mini-blender data (runs 01–24, Table 1) plotted according to Eq. (1); regressed parameters in Table 2). |

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| **Table 2.** Regressed parameters of Eq. (1), regressed under assumption that datasets share a common maximum and minimum (*σ*SF=0.85,max and *σ*SF=0.85,min, respectively). | | | | |
| ***ν* (RPM)** | ***Fr* (-)** | ***σ*SF=0.85,max (MPa)** | ***σ*SF=0.85,min (MPa)** | ***γ* (-)** |
| 50 | 0.33 | 5.299 | 1.266 | 0.0023 |
| 100 | 1.33 | 5.299 | 1.266 | 0.0037 |
| 200 | 5.32 | 5.299 | 1.266 | 0.0061 |
| 300 | 11.97 | 5.299 | 1.266 | 0.0132 |

Plotting the data in this manner results in a collapse of all datapoints into one overall trend (Figure 3), with regressed parameters *σ*SF=0.85,max = 4.761 MPa, *σ*SF=0.85,min = 1.369 MPa, *γ* = 0.0027. The approach also holds for other pharmaceutically relevant (Nassar et al., 2021) solid fractions of 0.85, 0.80 and 0.75 (Figure 3).

The overall trend represented by Eq. (4) could, for a given formulation, allow use of experiments conducted at one RPM (*i.e.* Froude number) for predicting performance at any RPM, or alternatively, runs across several RPMs (but few in each specific RPM) to be used to predict said performance. Whilst the present work has been developed on one scale of equipment, the fact that bin blender data is overlaid with mini-blender data when Eq. (4) is used suggests that the approach shows promise (Figure 3), especially as the literature shows that there is a commonality of performance across many batch blenders (Kushner, 2012; Kushner and Moore, 2010; Kushner and Schlack, 2014).

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| **Figure 2.** Compaction data for varying with blending speed and time (Table 1). Speeds of 50, 100, 200 and 300 RPM correspond to *Fr* values of 0.33, 1.33, 5.32, and 11.97. Mini-blender data (runs 01–24, Table 1) plotted alongside bin-blender data (runs 24–30, Table 1) according to Eq. (4). |

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| **Figure 3.** Compaction data for varying with blending speed and time (Table 1). Speeds of 50, 100, 200 and 300 RPM correspond to *Fr* values of 0.33, 1.33, 5.32, and 11.97. Mini-blender data (runs 01–24, Table 1) according to Eq. (4) for solid fraction (SF) of 0.85, 0.80, and 0.75. |

* 1. Conclusions

There is significant research interest in novel pharmaceutical production methods, and this is the case for dry powder blending, relevant for Continuous Direct Compaction. Evaluations of existing approaches in literature for modelling the impact that batch blender operation has on lubrication extent (assessed via tablet tensile strength) suggests that modifications are required to extend the model to devices such as a mini-blender (that can operate at substantially higher blending speeds). Results show that modifying the existing approach to include a new term based on the root of the Froude number shows promise, with this modification resulting in one overall trend across different blending speeds. Moreover, the approach appears to work for batch blender data as well.

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