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A mechanistic study on tablet ejection force and its sensitivity to lubrication for pharmaceutical powders

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ABSTRACT

Pharmaceutical powders can exhibit markedly different tablet ejection forces. The purpose of this study is to understand the factors leading to the variability of the tablet ejection force and its sensitivity to lubrication. The study showed that the tablet ejection force is mainly governed by 1) tablet diameter and thickness, 2) compact-die wall friction coefficient, and 3) residual die wall stress upon ejection; the latter was further controlled by the maximum compression pressure, as well as the degree of non-elastic deformation during compression. Brittle powders, such as lactose or dicalcium phosphate, often exhibit exceeding ejection force because of their significant contribution from the non-elastic deformation during loading. These conclusions were verified through compaction experiments of five pharmaceutical powders with diverse compaction properties. Additionally, we found that boundary lubrication was highly effective in reducing tablet ejection force, achievable through decreasing the compact-die wall friction coefficient, but not through altering the intrinsic consolidation behavior of powders. High ejection force is indicative of the sub-optimal stress condition of the tablet post-unloading. Therefore learnings from this study are beneficial for practitioners to harness the ejection force as an effective metric to identify and mitigate risks of tablet defects.

1. Introduction

In pharmaceutical tablet manufacturing, the tablet ejection force is a common parameter monitored during the compression run. In absolute scale, the tablet ejection force is typically lower than the main compression force by one to two orders of magnitude. Nevertheless, a higher-than-expected tablet ejection force, usually judged based on an operator's experience, is an alarming sign that the process or product is susceptible to such risks as capping, lamination, or punch sticking (Paul and Sun, 2017; Sun, 2015).

Ejection force arises from the constraint of a compressed tablet residing in a die, applied by the residual die wall stress along the radial direction (Briscoe and Rough, 1998). The ejection of the tablet out of the die therefore requires an axial force to overcome the radial restraint. Obviously, the greater radial die wall stress and higher friction coefficient at the compact-die wall interface, the higher tablet ejection force is anticipated. Pharmaceutical powders can exhibit markedly different tablet ejection forces (Nelson et al., 1954). The diverse ejection force among different materials suggests that the magnitude of radial restraint and the compact-die wall friction coefficient can differ significantly among pharmaceutical powders.

The common approach to lower tablet ejection force is through powder (internal) or die-wall (external) lubrication, even though the sensitivity of the ejection force to lubrication can be broadly different (Bolhuis and Hölzer, 1996). On some occasions, lubrication is effective to mitigate the risk of punch sticking or tablet defects, while on other occasions such approach does not provide meaningful improvement. In other words, although high ejection force could implicate potential erratic tablet compression, it is not always a reliable indicator. The relationship between the tablet ejection force and the tablet stress state or tablet coherence remains elusive.

The ejection force is a routine measurement for tablet manufacturing notwithstanding, research dedicated to the understanding of this important parameter is scarce in pharmaceutical literature. Furthermore, information gathered from non-pharmaceutical powders is not always directly applicable for pharmaceutical use. For example, a recent study conducted by Sun, using microcrystalline cellulose and compressible sugar, showed that the ejection force increases with increasing tableting speed, which the author attributed to the higher friction coefficient (Sun, 2015). While in another study on alumina powder, such speed dependence of ejection force was not observed (Briscoe and Rough, 1998). There appears to be a need to intensify the

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understanding of tablet ejection force in pharmaceutical manufacturing, so that formulation scientists can make more frequent and informed use of this parameter to probe or troubleshoot the tableting process. This study is therefore an effort aimed to develop mechanistic understanding of the factors leading to the ejection force of pharmaceutical powders. To capture the diversity of tablet ejection, five pharmaceutical excipients known to possess different compaction behaviors, i.e. pregelatinized starch, microcrystalline cellulose (MCC), lactose, mannitol, and dicalcium phosphate (DCP) were chosen for this study. The experiments were performed on a compaction simulator equipped with load and position sensors and a die instrumented with radial stress sensors, so that the tablet compaction and ejection process can be studied in a constitutive manner.

2. Materials and methods

2.1. Materials

Five pharmaceutical excipients were chosen in this study: microcrystalline cellulose (Avicel® PH-102, FMC Biopolymer, abbrev. MCC); spray dried lactose (Fast Flo® 316, Foremost Farms USA, abbrev. lactose); dicalcium phosphate anhydrous (A-TAB®, Innophos, abbrev. DCP); mannitol (Parteck® M200, Millipore Sigma); and pre-gelatinized starch (SPRESS® B818, Grain Processing Corporation, abbrev. starch). Magnesium stearate (HyQual™ 2257, Mallinckrodt) was selected as the lubricant.

2.2. Methods

2.2.1. Tablet compaction

Round, flat-face, 10 mm tablets were compacted using an HB Servo-Hydraulic Compaction Simulator (Huxley Bertram Engineering Ltd, Cambridge, UK). The compaction simulator measured punch forces and displacements; it was also equipped with an instrumented die to measure die wall pressure. The data acquisition frequency was 5000 Hz. For all compaction runs, the lower punch was kept stationary, whereas the upper punch followed a V-profile at a constant speed of 10 mm/s during loading and unloading. The minimum punch gap, which was the minimal distance between the upper and lower punch surface during compaction, was set at 2.2 mm. There was no holding time at the minimum punch gap. Upon completion of the unloading step, the lower punch ejected tablets through an upward motion at 10 mm/s. The weights of all specimens were adjusted to achieve a target solid fraction of 0.85 at the minimum in-die punch gap. An exception was made on DCP, where the target solid fraction at the minimum in-die punch gap was set at 0.70 instead, due to the strong resistance to volume reduction and the abrasive nature of the material. Before each powder specimen (different type of powder, or the same type of powder with different level of lubrication) was loaded for compaction, the punch surface and inside of the die were thoroughly cleaned to minimize potential cross contamination. The in-die solid fraction was calculated from true density measured by a helium pycnometer (AccuPyc II 1340, Micromeritics, Norcross, GA, USA). All the data generated by the compaction simulator was processed and visualized using the programing language R version 3.4.2 with packages data.table (Dowle and Srinivasan, 2017), dplyr (Wickham et al., 2017), gtable and ggplot (Wickham, 2017).

2.2.2. Determination of Janssen constant and Poisson's ratio

Janssen (Janssen, 1895; Sperl, 2006) defined a ratio between the horizontal radial stress, σ_{rr}, and the vertical axial stress, σ_z. This proportionality constant is commonly referred as Janssen constant, $K = \sigma_{rr}/\sigma_z$. Using the differential slice method and assuming the vertical stress was isotropic in the horizontal direction, Janssen derived that the vertical axial pressure acting on the bulk solid retained by twin walls was an exponentially decaying function of the confinement geometry, solid bulk density and the Janssen constant. Following Janssen's analysis in a circular die and by neglecting the weight of the solid (Cunningham et al., 2004), it could be shown that:

$$\sigma_z = \left(\sigma_T^{\frac{z}{H}} \sigma_B^{\left(1-\frac{z}{H}\right)}\right)$$

where σ_z is the axial stress at the position from the top punch by a distance of z, σ_B is the axial stress at the lower punch, σ_T is the axial stress at the upper punch, and H is the distance between upper and lower punch. The Janssen constant K in this study was determined at the maximum in-die solid fraction as:

$$K = \sigma_{rr}/\left(\sigma_T^{\frac{z}{H}} \sigma_B^{\left(1-\frac{z}{H}\right)}\right)$$

The Poisson's ratio ν was determined based on the following assumptions: For a linear elastic, homogeneous and isotropic material subjected only to compressive forces (assuming frictionless die wall),

$$\varepsilon_{rr} = \frac{1}{E}[\sigma_{rr} - \nu(\sigma_{rr} + \sigma_{zz})]$$

where ε_{rr} is the radial strain; E is Young's modulus; and ν is Poisson's ratio. Because the die wall is assumed to be rigid, the radial strain is zero. ν can then be evaluated by rearranging the differential form of the equation as:

$$\nu = \frac{1}{1 + \frac{d\sigma_z}{d\sigma_{rr}}}$$

Hence the Poisson's ratio was measured from the slope of σ_z vs. σ_{rr} during unloading step in the current study.

2.2.3. Powder mixing and lubrication

Each pharmaceutical excipient was blended with magnesium stearate for 0 min, 5 min, 15 min and 60 min at 25 rpm in a 1-quart table top V-blender. Magnesium stearate concentration in excipients was fixed at 1% (wt). To ensure all testing materials received the same extent of lubrication, we kept the bulk volume of the powder, and thereby headspace fraction inside blender, identical for all blending. The extent of lubrication was quantitated by the lubrication scaling factor (Kushner and Moore, 2010): c = (Blender Volume in Liter)$^{1/3}$ × (Headspace Fraction) × (Number of Revolutions). The 5, 15, and 60 min lubrication corresponded to c values of 87, 261, and 1044 decimeters, respectively. Prior to use, all lubricated excipients and the unlubricated counterparts were equilibrated at ambient temperature and under 33% relative humidity for at least 48 h in a desiccator over saturated magnesium chloride solution.

3. Results and discussion

3.1. Factors governing tablet ejection force of pharmaceutical powders

During a usual tablet ejection process, the compressed table is pushed out of the die through an upward axial movement exerted by the lower punch. The tablet ejection force is the force endured by the punch upon ejection, which overcomes the friction between the tablet side band and the die wall. Pharmaceutical powders can exhibit markedly different ejection forces when compressed at a pressure typical of tablet manufacturing. The sensitivities of ejection force to lubrication are also different. These phenomena were apparent in Fig. 1, where the tablet ejection forces of five pharmaceutical excipients, i.e. pregelatinized starch, MCC, lactose, mannitol, and DCP, directly measured by the load sensor of the lower punch, were displayed. Presented in Fig. 1 are the ejection forces of the non-lubricated powders, as well as the powders lubricated with magnesium stearate for various durations. In order to compare among different materials, the same tablet punch and die set was used. The targeted tablet in-die thickness (t = 2.2 mm) and relative