Air entrapment during tablet compression – diagnosis, impact on tableting performance, and mitigation strategies

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Abstract

Air entrapment during powder compression, a phenomenon that can cause tablet defects upon decompression and ejection, was diagnosed for celecoxib powder by comparing its in-die elastic recovery profiles with and without precompression prior to the main compression. Without precompression, the elastic recovery of celecoxib compacts significantly increased from ~4% at a main compaction pressure of 150 MPa to ~14% at and above 200 MPa. The large increase in elastic recovery is eliminated when a precompression step is employed. The deaeration of powder by precompression resulted in higher tablet strength, accompanied by lower tablet porosity. Thus, precompression is an effective strategy to mitigate the deleterious effects of air entrapment in tablet manufacturing. We also found that, although entrapped air caused significantly higher elastic recovery, it does not affect the plasticity parameter derived from an in-die Heckel analysis.

Keywords: Precompression, air entrapment, tableting, defects, lamination

1 Introduction

During the unloading phase of a powder compression cycle, the elastic strain stored in a tablet is first relieved axially as the punch is withdrawn from the tablet, followed by radial relief upon ejection from the die. This elastic recovery can create defects in the tablet structure (Hiestand et al., 1977), leading to tablet capping or lamination either immediately upon ejection or upon exposure to some external stresses during physical testing, packaging, shipping, and handling. Although not always observed, lamination or capping is a common symptom of tablet overcompression (Paul and Sun, 2017a). Several factors can influence tablet lamination and capping, including tooling design (Hiestand et al., 1977; Sugimori et al., 1989; Sugimori and Kawashima, 1997), tolerance between punch and die (Mann et al., 1981), tableting speed (Kalies et al., 2020; Mann et al., 1981; Ruegger and Çelick, 2000), compression location within the die (Ritter and Sucker, 1980), stress distribution within tablet (Wu et al., 2008), powder deformation characteristics (Akseli et al., 2014, 2013; Kalies et al., 2020), air entrapment (Long and Alderton, 1960; Mazel et al., 2015; Tanino et al., 1995), in-die elastic recovery, Poisson's ratio, tablet tensile strength (Paul and Sun, 2017a), residual die wall pressure (Garner et al., 2014; Hiestand et al., 1977; Mazel et al., 2018; Paul and Sun, 2017a; Sugimori et al., 1989), and tablet thickness (Mazel et al., 2018, 2015).

Various approaches have been examined to address tablet capping and lamination, including 1) modifications of the unloading conditions to avoid the development of shear stress that contributes to capping (Mazel et al., 2019; Sugimori et al., 1989), 2) precompression to allow some degree of plastic deformation before the main compression (Hiestand et al., 1977), 3) triaxial decompression to allow more uniform stress relaxation (Amidon et al., 1981; Hiestand et al., 1977), 4) decreasing tableting speeds or increasing dwell time to allow for more extensive plastic

deformation during compression, which favors a larger bonding area (Hiestand et al., 1977; Mazel and Tchoreloff, 2021; Tye et al., 2005). The effectiveness of these approaches in addressing tablet lamination problems depends on the type of tablet defect (Mazel and Tchoreloff, 2021), including air entrapment (Type 1), development of shear stress during ejection (Type 2), and development of tensile stresses in the center of biconvex tablets (Type 3) (Mazel and Tchoreloff, 2021).

Air entrapment is particularly problematic for highly plastic materials with a low bulk density. FEM modeling results suggested that the pressure of entrapped air in a tablet could be on the order of 1-1.5 MPa, which is in the same order of magnitude of tablet diametrical tensile strength (Klinzing and Troup, 2019). Thus, the entrapped air is expected to measurably deteriorate tablet mechanical strength. When such a problem is observed, powder bed deaeration before the main compression event may be applied to overcome it by applying appropriate methods, e.g., 1) lower punch vibration prior to compression (Kalies et al., 2020), 2) extended compression cycle or a three-stage compression cycle composed of degassing compaction, precompression, and main compression (Tanino et al., 1995), 3) use of a precompression phase (Mazel et al., 2015; Mazel and Tchoreloff, 2021), 4) compaction speed reduction (Mazel and Tchoreloff, 2021). Among these strategies, simple precompression is the most practical since it is a widely available feature on modern tableting presses and does not require reducing manufacturing throughput.

Lamination due to air entrapment is easily diagnosed if cracks are visually observed on the ejected tablet, which signals the need for reformulation or processing parameter adjustment. However, when the defects are internalized for some borderline formulations, the discovery of such a problem is often delayed. In that case, hidden defects can cause misleading characterization of intrinsic material attributes, such as compressibility, tabletability, and compactibility, that

inform tablet formulation design. Thus, there is a need for a fast and reliable method for early detection of air entrapment issues to guide the effective design of robust tablet formulations.

2 Materials and Methods

2.1 Materials

Celecoxib (CEL; Aarti Drugs Pvt Ltd., Mumbai, India) was used as received.

2.2 Tableting

Tablets were prepared using a compaction simulator (Styl'One Evolution; MedelPharm, Beynost, France) using a symmetrical, force-controlled cycle at 2% speed (~2.8 mm/s punch traveling speed), composed of a 2 s compression (1 s rise and 1 s fall with no holding at the maximum force) followed by a 3 s relaxation and a 2 s ejection step. Precompression was employed where indicated. Round flat-faced tooling and a straight-bore die was used to compress tablets (300-400 mg). The punch tips were measured to be 11.25 mm, and the die diameter was measured to be 11.28 mm using a digital caliper. Magnesium stearate spray (STYL'One Mist) was used to lubricate the die wall and punch tips.

2.3 Tablet porosity

The true density (ρ_t) was determined using helium pycnometry (Quantachrome Instruments, Ultrapycnometer 1000e, Byonton Beach, Florida) with ~1.5 g of an accurately weighed sample filled about 75% of the volume of the sample cell. An analytical balance (Mettler Toledo, Columbus, Ohio, model AG204) was used for weighing. The experiment was stopped when the coefficient of variation between five consecutive measurements was below 0.005%, and the mean of the last five measurements was taken as the measured true density.

Out-of-die tablet density (ρ) was calculated by dividing tablet weight with tablet volume, calculated from tablet dimensions measured using a digital caliper. Tablet porosity (ε) was calculated according to Equation 1.

$$\varepsilon = 1 - \frac{\rho}{\rho_t} \quad (1)$$

2.4 Elastic recovery

In-die elastic recovery of the tablets was determined using Equation 2.

$$ER(\%) = \frac{h_1 - h_0}{h_0} * 100\% \quad (2)$$

Where h_1 is the in-die thickness at the end of the decompression, where the pressure is zero, and h_0 is the minimum thickness. Tablet thickness under pressure is extracted from the compaction simulator after correcting for machine deformation.

2.5 In-die Heckel analysis

In-die ε data was calculated from tablet thickness measured with the compaction simulator and the weight of the ejected tablet. P_y was obtained from a linear regression of the linear portion of the Heckel plot (i.e., -ln(ε) versus pressure), according to Equation 3 (Heckel, 1961a, 1961b).

$$-\ln(\varepsilon) = \frac{1}{P_y}P + A \quad (3)$$

2.6 Tablet mechanical strength

Tablet strength was evaluated using a texture analyzer to compress the tablet diametrically to failure between two platens. However, CEL tablets failed by lamination instead of breaking diametrically during testing (Video S1). Therefore, instead of tensile strength, tablet breaking force was used to quantify tablet strength in this work.

3 Results and Discussion

3.1 Tablet elastic recovery

The elastic recovery profile of CEL tablets shows a tilted "S" shape (Figure 1, blue curve). With increasing compaction pressure (CP), the elastic recovery of CEL tablets first decreased from 4.5% to 2.1% in the range of 20 - 100 MPa, followed by a slight increase in the pressure range of 100 – 150 MPa. Subsequently, elastic recovery increased to 13.5% at 200 MPa, rose to a maximum of 15.6% at 250 MPa, and then gradually decreased to 13.7% at 350 MPa. Since visual inspection did not reveal any signs of lamination, capping, or cracking, any defects associated with the profound elastic recovery above 200 MPa are hidden inside the tablets. The unique elastic recovery profile suggests that air entrapment likely occurred. This is possible when extensive plastic deformation of particles seals the tablet's surface to entrap the air at a sufficiently high compaction pressure. Upon axial pressure removal, both the expansion of the compressed air and the elastic recovery of the solid phase take place, leading to significant tablet axial expansion. When the pressure was ≤150 MPa, open channels allow the air to escape from the tablet so that mainly elastic recovery of solid contributes to the axial recovery of the tablet, which is much lower than that due to air expansion.

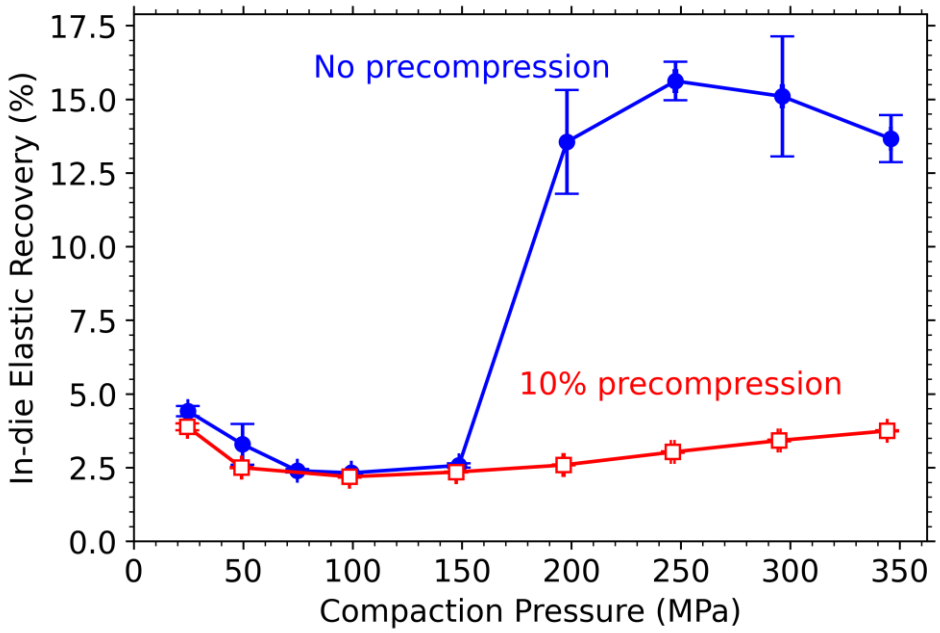
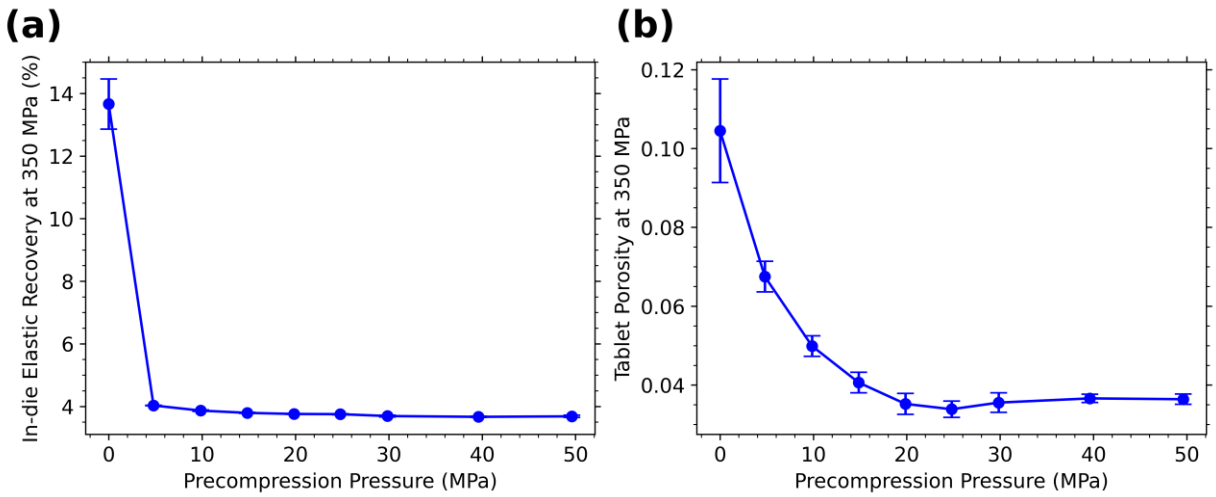


Figure 1. In-die tablet elastic recovery of CEL with and without 10% precompression.

To verify this, precompression pressure at 10% of the maximal CP during the main compression event was applied to deaerate the powder bed. The absence of a significant increase in the resulting axial tablet elastic recovery profile when precompression is applied (Figure 1, red curve) strongly supports the air entrapment mechanism. The elastic recovery profiles with and without precompression are similar up until 150 MPa but significantly differ above 150 MPa. Since the only difference between the two scenarios is the amount of air in the powder bed before the main compression event took place, the similar elastic recovery behaviors at CPs ≤150 MPa suggest that these pressures allow for air to escape from the compact during compaction. On the other hand, the large difference between the two profiles at CPs >150 MPa reflects the effect of entrapped air expansion, suggesting the inability of air escape. If this phenomenon is broadly applicable, comparing elastic recovery profiles with and without precompression may be a useful

approach to assess the propensity of powders to air entrapment, where a larger difference in elastic recovery indicates a higher propensity to air entrapment.

The effect of precompression pressure variation, from 5 to 50 MPa, on axial tablet elastic recovery was examined at a main CP of 350 MPa. A 5 MPa precompression pressure significantly reduced axial elastic recovery from ~14% to ~4% (Figure 2**a**). A further increase in precompression pressure only slightly reduced the axial elastic recovery. Thus, even a low pressure is effective in deaerating the powder, which is consistent with the high sensitivity of bulk density to pressure variation in the low-pressure region for cohesive powders with low bulk densities. Tablet porosity decreased from ~0.10 to ~0.035 when precompression pressure increased from 5 to 50 MPa (Figure 2**b**). Compared to the in-die elastic recovery profile, the change in porosity with increasing precompression pressure is more gradual. It is possible that, upon ejection from the die, most of the entrapped air in the tablet without precompression leaked out before tablet dimensions were measured (analogous to balloon deflation), which leads to the more gradual decrease in out-of-die tablet porosity compared to that expected from the sharp decrease in the in-die elastic recovery measured immediately after compression.



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148 **Figure 2.** Effects of precompression pressure on (**a**) In-die elastic recovery and (**b**) out-of-die
149 tablet porosity. The main compaction pressure was 350 MPa.

150 ### 3.2 Tablet strength and porosity

151 The entrapped air affected the mechanical strength of CEL tablets. Tablets are significantly
152 stronger at all pressures when 10% precompression pressure is applied (Figure 3**a**). Without
153 precompression, tablet breaking force gradually increased with increasing CP up to 150 MPa,
154 stayed approximately constant between 150 and 300 MPa, and significantly decreased at 350 MPa
155 (Figure 3**a**, blue line). The sharp decrease in tablet strength at 350 MPa corresponds well with the
156 significant tablet elastic recovery (Figure 3**a**). Such a high elastic recovery likely resulted in
157 microscopic or macroscopic defects within the tablet structure, leading to the phenomenon known
158 as overcompression (Paul and Sun, 2017b). The absolute difference in breaking strength of tablets
159 compressed with and without precompression increases linearly with CP (Figure 3**b**). The linearity
160 indicates that, if no air escapes from the tablet during the compression phase, the presence of air
161 pockets deteriorates the bonding area approximately proportional to CP. This may be because the
162 more extensive expansion of air during decompression compromises more bonding between

particles. The difference in tablet strength is supported by their different compressibility (Figure 3**c**). Without precompression, tablet porosity is higher at all CPs and porosity plateaus at ~0.10 above 150 MPa (Figure 3**c**, blue line). With precompression, the tablet porosity is lower at all pressures ≥50 MPa. Importantly, tablet porosity continues to decrease over the entire range of compaction pressures studied as predicted from powder compaction theory (Heckel, 1961a), assuming air is not entrapped (Figure 3**c**, red line). The absolute difference between tablet porosity with and without precompression (Figure 3**d**) increases linearly. The resemblance between the differential plots of breaking force and porosity further supports their inherent connection because a larger difference in porosity leads to a larger difference in mechanical strength based on the bonding area-bonding strength interplay model (Osei-Yeboah et al., 2016; Sun, 2011).

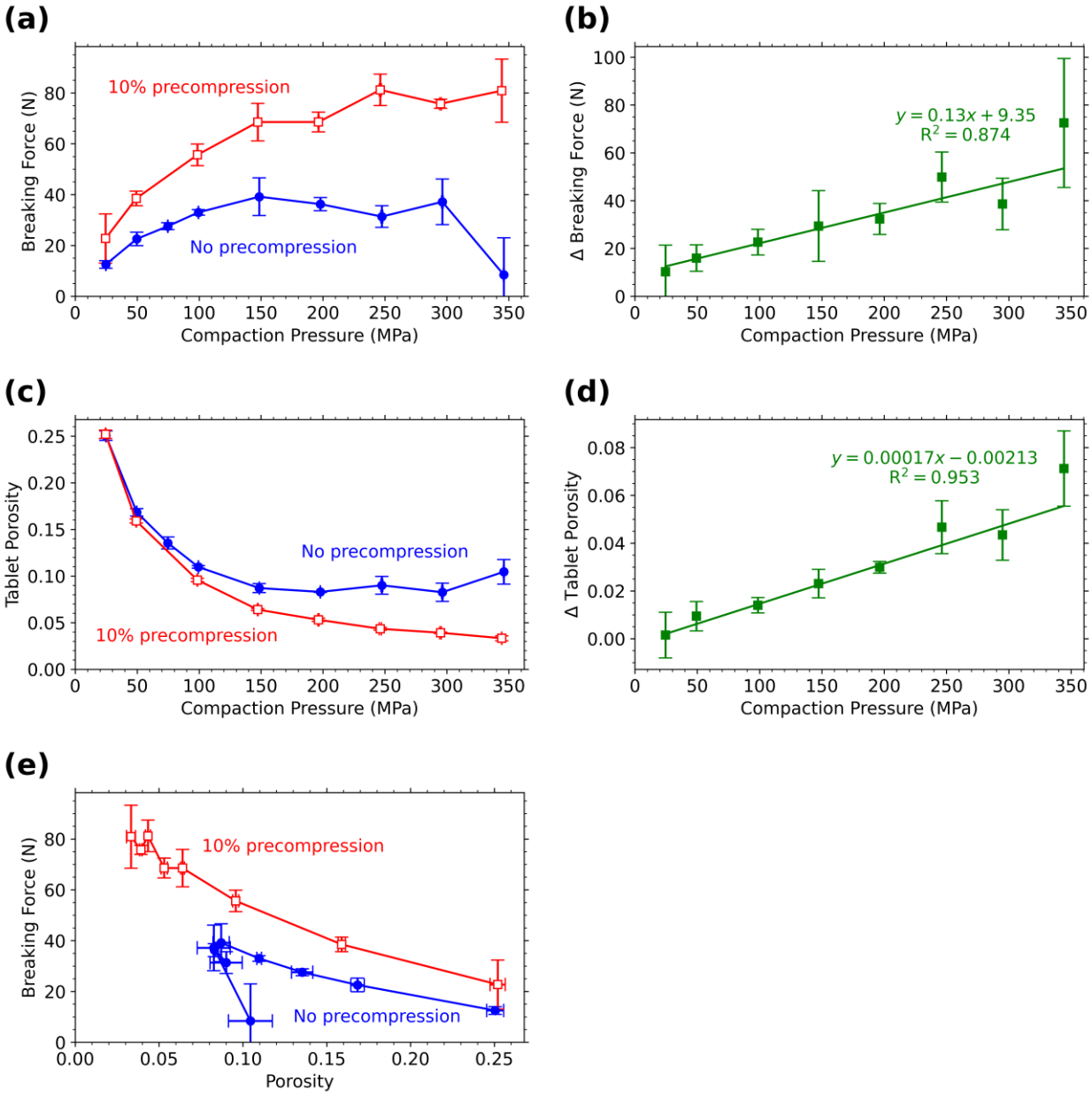

Figure 3. (**a**) Tablet breaking force with and without precompression as a function of compaction pressure, (**b**) absolute change in tablet breaking force by precompression as a function of compaction pressure, (**c**) tablet porosity with and without precompression as a function of compaction pressure, (**d**) absolute change in tablet porosity by precompression as a function of compaction pressure, and (**e**) tablet breaking force with and without precompression as a function of tablet porosity.

The observed reduction in the strength of the tablets by air entrapment may be a result of the following mechanisms: (1) the more uniform distribution of pressure onto the particles by air pockets, which lowers the extent of plastic deformation at contact points by avoiding very high local pressure, (2) air pockets in the tablet structure after compression lower the overall interparticulate bonding area available, and (3) more structural defects caused by air expansion during decompression. These mechanisms gain support from the observation that the breaking force of tablets prepared without precompression is lower than that with precompression at the same tablet porosity (Figure 3e). In the context of the first effect, it is useful to point out that the in-die P_y values, which measures material plasticity during the loading phase of compression (Heckel, 1961b, 1961a; Vreeman and Sun, 2021), is not significantly affected by precompression (both have a P_y value of ~79 MPa) (Figure 4). This indicates that the air pockets, although affecting local pressure at contact points, only minimally affect the bulk compressibility of the powder bed. This is reasonable because air is much more compressible than solids and can transmit pressure effectively through the powder bed.

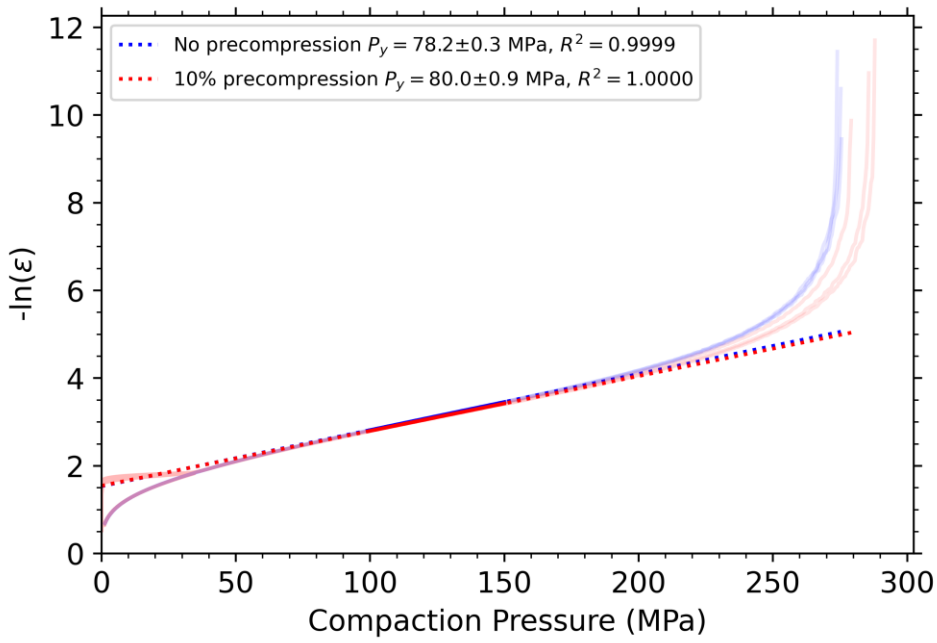

Figure 4. In-die Heckel plots of CEL with and without precompression (n = 3 under each condition). The Heckel profile of the powder with 30 MPa precompression pressure starts at a higher –ln(ε) value because the porosity was significantly reduced by precompression before the main compression event.

3.3 Strategies to mitigate air entrapment

When air entrapment does occur, its deleterious effects on tablet quality can be addressed by using a deaeration step during tablet manufacturing. Precompression, which is effective for CEL, may be considered when air-entrapment is positively identified by a large increase in elastic recovery (Figure 1). However, precompression alone may not be sufficient to overcome tableting problems caused by air entrapment in all cases. When possible, a combination of deaeration techniques should be employed to ensure a robust solution to problems caused by air entrapment. For example, since a larger clearance between the upper punch and die allows air to escape more easily as the punch enters the die, employing a tapered die is another approach that can be easily

implemented. This is especially helpful for low bulk density powders compressed using deep-cup punches during high-speed tableting (Natoli, 2013).

4 Conclusion

Air entrapment during the compression of CEL was demonstrated using the in-die elastic recovery profile obtained from a compaction simulator. Deaeration by precompression improved the tableting strength via an increase in the interparticulate bonding area. For powders having a low bulk density (i.e., higher air content) and high plasticity (i.e., more likely to form sealed air pockets in tablet), it is important to consider the impact of air entrapment when characterizing powder compression properties. In that case, the impact of precompression on the tableting performance of drugs should be assessed to attain a comprehensive understanding of their tableting properties to reliably guide formulation design. To this end, a compaction simulator is a valuable tool to assess the propensity to air entrapment, its potential impact on tableting performance, and the effectiveness of mitigation strategies.

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Declaration of interests

☒The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Credit Author Statement

Gerrit Vreeman: Methodology, Formal analysis, Investigation, Writing- Original draft preparation.

Changquan Calvin Sun: Supervision, Conceptualization, Writing- Reviewing and Editing, Resources, Funding acquisition

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