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Development of mechanistic reduced order models (ROMs)for glidant and lubricant effects in continuous manufacturing of pharmaceutical solid-dosage forms

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Abstract

As the pharmaceutical industry transitions from batch to continuous manufacturing, real-time monitoring, and mechanistic model-based control are essential to conform to FDA quality standards. Glidants and lubricants are known to affect the Critical Quality Attributes (CQAs) of a tablet such as tensile strength, tablet porosity, and dissolution profile (Razavi et al., 2018; Apeji and Olowosulu, 2020). Quantitative models for predicting these effects are essential for enabling centralized control strategies of lubricant and glidant feeding and blending in direct compression tableting lines. This work presents the development of mechanistic reduced order models to capture the effects of lubricant (magnesium stearate) and glidant (silica) on CQAs and Critical Process Parameters (CPPs). A Latin Hypercube experimental campaign with thirty different mixing conditions of silica with MCC (Avicel PH200) and APAP (Acetaminophen) was carried out using a Natoli NP400 tablet press and a SOTAX AT4 tablet tester. Experiments show that the tensile strength and blend bulk density are significantly affected by the mixing conditions of silica. Similarly, adding magnesium stearate (MgSt) changes the bulk density of the blend, compaction force required to form a tablet, and tensile strength of the tablet, depending on the lubrication conditions (Mehrotra et al., 2007; Razavi et al., 2018).

Keywords: Lubricant effects, glidant effects, continuous pharmaceutical manufacturing

1. Introduction

The production of tablets in the pharmaceutical industry has predominantly been operated in batch mode, where tablets are produced using a specified amount of raw materials within a given time frame. In recent years, with the advent of process analytical technology (PAT) sensors, the transition from batch to continuous manufacturing has been made possible. However, modeling and advanced understanding of the tablet production process is essential to implement continuous manufacturing in the pharmaceutical industry. In particular, active process control using the Quality-by-Control (QbC) approach (Su et al., 2019) requires predictive and fast models of the tablet Critical Quality Attributes (CQAs). Therefore, steady-state mechanistic models which can predict Critical Process Parameters (CPPs) and CQAs of tablets are essential to the implementation of robust control strategies in the direct compression tableting line.

In continuous manufacturing, it is essential that the powder has good flowability. A glidant, such as colloidal silica (Silica), is an excipient added to improve powder flowability. A lubricant, such as magnesium stearate (MgSt), helps reduce internal friction during compaction and tablet-tooling

friction during ejection. Typically formulations use 0.25%-1% w/w of MgSt and 0-0.02% w/w of Silica. Even when added in such small amounts, these excipients significantly affect the bulk properties of the powder, such as bulk density (Mehrotra et al., 2007), and surface properties, such as the strength of solid bridges formed during compaction. This change in the properties of the blend naturally impacts the tableting process and the CQAs of the final tablet (Razavi et al., 2018; Van Veen et al., 2005), including its dissolution profile, and in turn, the bioavailability of the active pharmaceutical product (API).

It is well-known that MgSt increases the bulk density of the powder and reduces the tensile strength of the tablets (Mehrotra et al., 2007). Quantitative models to describe the effects of MgSt on the tensile strength and elastic modulus of tablets were proposed by Razavi et al. (2018). However, little research has been carried out to quantify the effects of Silica. In this paper, mechanistic reduced-order models of the entire tableting process, i.e., algebraic models based on the understanding of the underlying physical mechanisms which describe the effects of Silica and MgSt on tablet CQAs, are proposed and calibrated. These models are a means to implement moving horizon estimation-based non-linear model predictive control (MHE-NMPC) for the tablet press at Purdue's pharmaceutical continuous manufacturing pilot plant (Huang et al., 2021).

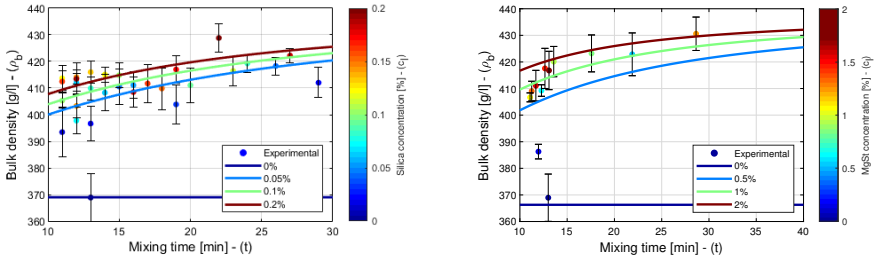
The paper is organized as follows. In Section 2, the design of experiments (DoE) to study both MgSt and Silica is described. In Section 3, the quantitative models proposed for CPPs and CQAs of the tableting process are discussed, with a special focus on the differences between MgSt and Silica effects. Section 4 discusses conclusions and directions for future work.

2. Materials and Methods

Two experimental campaigns were carried out, one to study the effects of Silica and the other to study the effects of MgSt. The materials used in this study were microcrystalline cellulose Avicel PH200 (MCC), 10% w/w acetaminophen (APAP), and Silica and MgSt at different concentrations. The DoE to study the effects of Silica was carried out using a mixture of MCC, APAP, and Silica. MCC and APAP were mixed in a Tote blender with 0-0.2% w/w Silica for 10-30 minutes. The in-die thickness was kept constant at 3.1 mm and the dosing position was chosen to be 7-11 mm, to manufacture tablets having a broad range of relative densities, i.e., 0.6-0.9. The tablet press turret speed was varied between 25-35 rpm. A Latin Hypercube sampling (Viana, 2013) of turret speed, dosing position, concentration, and mixing time for 30 experiments was created using the MATLAB function `lhsdesign`. The same procedure was repeated for the second DoE to characterize the effects of MgSt. Blends with 0-2% w/w MgSt, APAP, and MCC were prepared by mixing in a Tote blender for 11-30 minutes. The in-die thickness was also chosen to be 3.1 mm, the dosing position 9-13 mm, and the tablet press turret speed 11-20 rpm. Tablets formed with MgSt blends required higher dwell time as compared to Silica blends and hence lower turret speeds were used in the MgSt DoE. In this case, a Latin hypercube design of 20 experiments was created. Next, tablets were manufactured using a Natoli-NP400 tablet press using D-type tooling with shallow cup depth. For each run in the DoE, a SOTAX AT4 tablet tester was used to measure tablet thickness, diameter, weight, and hardness of 50 tablets under steady-state manufacturing conditions. The tablet press hopper was filled with 0.5 kg of the blend at the start of each experimental run.

3. Reduced Order Models

The bulk density of a powder ρ_b is observed to be affected by shear strain γ imparted to the powder during mixing (Mehrotra et al., 2007). As the total shear increases, the bulk density initially increases and ultimately reaches a plateau, during which no further change in the bulk density is observed. The following asymptotic relationship between the bulk density and total shear is



(a) Variation w.r.t Silica

(b) Variation w.r.t MgSt

Figure 1: Bulk density increases with increase in concentrations for both Silica and MgSt.

proposed to capture this trend

$$\rho_b = \rho_{b,\infty} - \frac{\rho_{b,\infty} - \rho_{b,0}}{1 + C_\rho} \quad \text{with} \quad C_\rho = \frac{c_l^{r_1}(\gamma+\gamma_0)^{r_2}}{r_3} \tag{1}$$

where $\rho_{b,\infty}$ and $\rho_{b,0}$ represent the bulk densities when the shear imparted is infinite and zero respectively, C_ρ is a lumped parameter which defines the glidant or lubricant mixing conditions, where c_l is glidant or lubricant concentration, γ is the shear imparted to the powder during mixing, γ_0 is the initial shear imparted during pre-blending, and r_1, r_2, r_3 are fitting parameters. The total shear $\gamma+\gamma_0$ is considered proportional to mixing time. Figure 1 shows that increasing the concentration or mixing time of Silica or MgSt results in an increase in bulk density. The bulk density gradually increases and reaches an asymptotic value.

The tablet weight, W, is affected significantly by the process parameters such as the turret speed (n_T), feeder speed (n_F), dosing position (fill depth -H^fill) and diameter of the tablet (D). If turret speed is too high, then the die may be filled unevenly, resulting in undesired deviation in tablet weight, ultimately affecting the dosage of the active ingredient. The weight of a doubly-convex tablet formed by Natoli D-type tooling with cup-depth, h, is computed as follows:

$$\frac{W}{\rho_b V^\mathrm{fill}} = -\xi_1 \frac{n_\mathrm{F}}{n_\mathrm{T}} + \xi_2 \frac{H^\mathrm{fill}}{D} + \xi_3 \left(\frac{H^\mathrm{fill}}{D}\right)^2 \tag{2}$$

with the volume of die-cavity, V^fill, given by

$$V^\mathrm{fill} = \frac{\pi D^2 H^\mathrm{fill}}{4} + \frac{\pi h}{6}\left(\frac{3D^2}{4} + h^2\right) \tag{3}$$

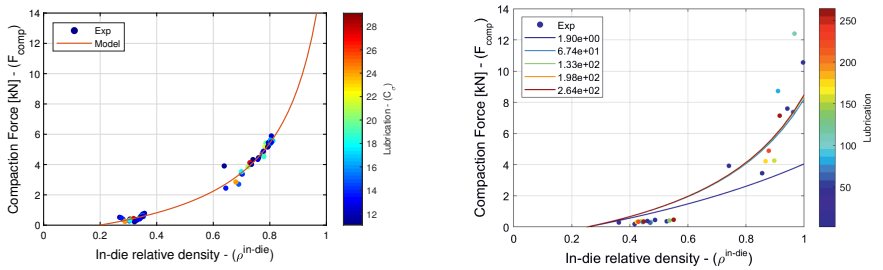
where ξ_1, ξ_2, ξ_3 are fitting parameters. The same model describes the trends for both MgSt and Silica blends.

The main compaction force F_punch for the effect of Silica can be estimated using Kawakita equation (Kawakita and Lüdde, 1971):

$$\sigma_\mathrm{punch} = \frac{4F_\mathrm{punch}}{\pi D^2} = \frac{\rho^\mathrm{in-die} - \rho_b/\rho_t}{[\rho^\mathrm{in-die}(a-1) + \rho_b/\rho_t]\, b} \tag{4}$$

with the in-die relative density, $\rho^\mathrm{in-die}$, given by

$$\rho^\mathrm{in-die} = \frac{W}{\rho_t V^\mathrm{in-die}} \tag{5}$$



(a) Variation w.r.t Silica

(b) Variation w.r.t MgSt

Figure 2: (a) shows that compaction force is independent of mixing conditions of Silica. (b) shows that compaction force decreases with increase in lubrication.

where σ_{punch} is the compaction pressure, ρ_t is the true density of the blend, a and b (MPa) are Kawakita parameters, $V^{\text{in-die}}$ is the volume of die-cavity with main compression thickness $H^{\text{in-die}}$, given by

$$V^{\text{in-die}} = \frac{\pi D^2 H^{\text{in-die}}}{4} + \frac{\pi h}{3}\left(\frac{3D^2}{4} + h^2\right) \tag{6}$$

The compaction force for MgSt blends depends on lubrication conditions (Figure 2b). This effect is incorporated by modeling the parameter a as

$$a = \frac{a_0 - a_\infty}{1 + C_c} + a_{0,\infty} \quad \text{with} \quad C_c = \frac{c_l^{p_1}(\gamma+\gamma_0)^{p_2}}{p_3} \tag{7}$$

with C_c where $a_0, a_\infty, p_1, p_2, p_3$ are fitting parameters. The compaction force does not depend on the mixing conditions of Silica (Figure 2a), whereas it increases with increasing lubrication 2b.

Elastic recovery, ε_ρ, of a tablet is defined as

$$\rho^{\text{tablet}} = \rho^{\text{in-die}}(1 - \varepsilon_\rho) \tag{8}$$

with the out-of-die tablet relative density, ρ^{tablet}, given by

$$\rho^{\text{tablet}} = \frac{W}{\rho_t V^{\text{tablet}}} \tag{9}$$

and the out-of-die tablet volume after elastic recovery, V^{tablet}, with bellyband, H^{tablet} given by

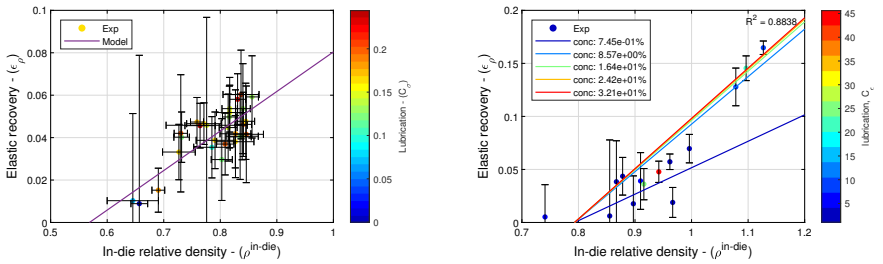
$$V^{\text{tablet}} = \frac{\pi D^2 H^{\text{tablet}}}{4} + \frac{\pi h}{3}\left(\frac{3D^2}{4} + h^2\right) \tag{10}$$

Elastic recovery is not sensitive to mixing conditions of Silica (Figure 3a) and is governed by (Gonzalez, 2019)

$$\varepsilon_\rho = \varepsilon_0 \frac{\rho^{\text{in-die}} - \rho_{c,\varepsilon}}{1 - \rho_{c,\varepsilon}} \tag{11}$$

However, with increase in lubrication with MgSt, the elastic recovery increases (Figure 3b). This trend is captured by modifying the ε_0 as follows:

$$\varepsilon_0 = \varepsilon_\infty + \frac{\varepsilon_\phi - \varepsilon_\infty}{1 + C_\varepsilon} \quad \text{with} \quad C_\varepsilon = \frac{c_l^{q_1}(\gamma+\gamma_0)^{q_2}}{q_3} \tag{12}$$



(a) Variation w.r.t Silica

(b) Variation w.r.t MgSt

Figure 3: (a) shows that elastic recovery is independent of mixing conditions of Silica, (b) shows that elastic recovery increases with increase in lubrication.

where ε_∞, ε_ϕ, q_1, q_2, q_3 are fitting parameters.

Tensile strength of a tablet is an important CQA since it is correlated with tablet dissolution. The tensile strength σ_t of a tablet depends on lubricant or glidant concentration and mixing time as follows (Kuentz and Leuenberger, 2000)

$$\sigma_t = \sigma_0 \left[1 - \left(\frac{1-\rho^{\text{tablet}}}{1-\rho_{c,\sigma_t}} \right) e^{(\rho^{\text{tablet}} - \rho_{c,\sigma_t})} \right] \tag{13}$$

where, ρ_{c,σ_t} is the critical relative density at which the tablet starts forming and σ_t goes to zero. The tensile strength at zero-porosity, σ_0, is given by

$$\sigma_0 = \frac{\sigma_{0,\phi}}{1+C_\sigma} \quad \text{with} \quad C_\sigma = \frac{c_l^{b_1}(\gamma+\gamma_0)^{b_2}}{b_3} \tag{14}$$

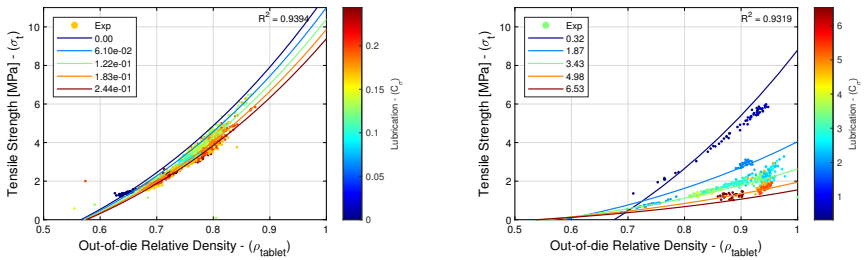
and

$$\rho_{c,\sigma_t} = \frac{\rho_{c,\sigma_t,\phi} - \rho_{c,\sigma_t,\infty}}{1+C_\rho} + \rho_{c,\sigma_t,\infty} \tag{15}$$

where $\rho_{c,\sigma_t,\phi}$, $\rho_{c,\sigma_t,\infty}$, b_1, b_2, b_3 are the fitting parameters (Razavi et al., 2018). $\sigma_{0,\phi}$ and $\rho_{c,\sigma_t,\phi}$ represents the tensile strength and critical relative density corresponding to no lubrication, $C_\sigma = 0$. As the concentration or mixing time of Silica or MgSt increases in the formulation, softer tablets with lower tensile strength are formed (Figure 4). The decrease in tensile strength of lubricated tablets would be due to a combination of changes in physical properties of the blend, as well as the increased elastic recovery of lubricated tablets. Whereas, the tensile strength of tablets formed with Silica blends decreases solely due to changes in physical properties of blended material since elastic recovery is independent of Silica mixing conditions.

4. Conclusion

The results of the experiments demonstrate that the glidant Silica affects the bulk density of the blends, and the tensile strength, and consequently, the dissolution profile, of tablets. In particular, bulk density increases with an increase in glidant concentration or mixing time, whereas tensile strength decreases. However, interestingly, compaction force and elastic recovery show no dependency on the mixing conditions of Silica. In contrast, the lubricant MgSt affects all the CQAs of a tablet. Specifically, bulk density increases with an increase in lubrication, and tensile strength decreases. The elastic recovery and compaction force increase with the increase in lubrication.



(a) Variation w.r.t Silica

(b) Tensile strength with increase in lubrication

Figure 4: Tensile strength decreases with increase in concentration or mixing time, for both Silica and MgSt.

The effects of Silica and MgSt differ for compaction force and elastic recovery. The practical application of mechanistic models is to use them as steady-state models in MHE-NMPC control of rotary tablet press (Huang et al., 2021). Future work includes integrating the lubricant and glidant feeder with the tablet press to control tablet properties. Additionally, Residence time distribution models (RTDs) will be added to the MHE-NMPC framework to enhance real-time process control.

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