Worsened Punch Sticking by External Lubrication with Magnesium Stearate

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Abstract

External lubrication of tooling with magnesium stearate (MgSt) is a common strategy to eliminate punch sticking when compressing powders with a high sticking propensity, such as many pure active pharmaceutical ingredients (APIs). We found that it actually led to aggravated punch sticking at low compaction pressures. This counterintuitive phenomenon was explained based on interplay of forces among the punch tip, MgSt, and API. The explanation is supported by the observed effects of pressure and mechanical properties of APIs on this phenomenon.

1. Introduction

The tablet has been widely used in drug delivery due to its physical and chemical stability, low manufacturing cost, and good patient compliance (Kottke and Rudnic, 2002; Sun, 2017). A common problem during tablet manufacturing is punch sticking, which may be defined as the adherence of the powder material onto the tooling surface during powder compaction (Paul et al., 2017a). If not eliminated, punch sticking leads to tablet defects, low manufacturing efficiency, and even loss of batches (Chattoraj et al., 2018). Punch sticking occurs when the total force of an API particle bonding with the punch surface (F1) is higher than that between the API particle and neighboring particles in tablet (Paul et al., 2017a). With repeated compression, the severity of API sticking to the punch depends on the force between API particles adhered to punch and API particles in a new tablet (F2) relative to the force between the API particles in a new tablet and neighboring excipient particles (F3). After repeated compression, a monolayer is formed when $F2 < F3$, or multiple layers form when $F2 > F3$ (Paul et al., 2017a). Furthermore, the kinetics of punch sticking can be described by the Hill's equation (Paul et al., 2017a).

Strategies used to mitigate or eliminate punch sticking problems can be broadly divided into three categories: 1) API crystal and particle engineering, such as salt and cocrystal formation (Al-Karawi and Leopold, 2018; Paul et al., 2019; Wang et al., 2020), particle size and morphology modification (Capece, 2019; Waknis et al., 2014; Hooper et al., 2017; Paul et al., 2020; Chen et al., 2020), and containment of API in a porous carrier (Paul et al., 2023); 2) modification of process parameters, such as compaction pressure (Paul et al., 2017b; Al-Karawi et al., 2017; Capece, 2019; Billany and Richards, 1982; Mitrove and Augsburger, 1980; Danjo et al., 1997; Kakimi et al., 2010; Roberts et al., 2003; Roberts et al., 2004; Swaminathan et al., 2017; Waimer et al., 1999; Wang et al., 2015; Wang et al., 2004) and tooling design (Waimer et al., 1999; Roberts et al., 2004; Roberts et al., 2003); 3) formulation design, such as using different excipients (Abdel-Hamid and Betz, 2012; Badal Tejedor et al., 2015; Paul and Sun, 2018), reducing API loading (Hutchins et al., 2012; Capece, 2019), and changing lubricant level in tablet formulation (Gunawardana et al., 2023; Capece, 2019; Al-Karawi et al., 2017; Badal Tejedor et al., 2015; Roberts et al., 2004; Swaminathan et al., 2017; Billany and Richards, 1982; Mitrove and Augsburger, 1980; Patel and Dave, 2021).

It is known that mixing a powder with MgSt, i.e., internal lubrication, can significantly change tableting behaviors of some powders (Dun et al., 2020; He et al., 2007) and may lead to higher tablet friability and slower tablet dissolution performance (Paul and Sun, 2017; Li-Hua and Chowhan, 1990; Uzunović and Vranić, 2007; Billany and Richards, 1982). Given these known issues with internal lubrication, external lubrication has been pursued to reduce ejection force and punch sticking problem in commercial tablet manufacturing (de Backere et al., 2023). Compaction properties of pure APIs can offer invaluable insights into tablet formulation design, such as excipient selection. In such studies, it is common to lubricate tablet tooling with magnesium stearate (MgSt) before compression to avoid punch sticking (Jahn and Steffens, 2005).

However, we surprisingly observed that tablet tooling lubricated with MgSt sometimes worsened punch sticking during compression. For example, sodium cyclamate exhibited slight punch sticking after compression at both 50 MPa and 200 MPa when clean punches were used (Figure 1a, b). After coating the punch tip with a layer of MgSt, sticking was much more severe at 50 MPa compaction pressure (Figure 1c). However, punch sticking was absent at 200 MPa compaction pressure (Figure 1d). This unexpected deterioration of punch-sticking performance by external lubrication of tooling with MgSt and the effect of pressure cannot be explained by the existing punch sticking model, which was developed to explain behaviors of formulated API during compaction using a clean punch (Paul et al., 2017a). Hence, we propose a new punch-sticking model to explain this surprising phenomenon.

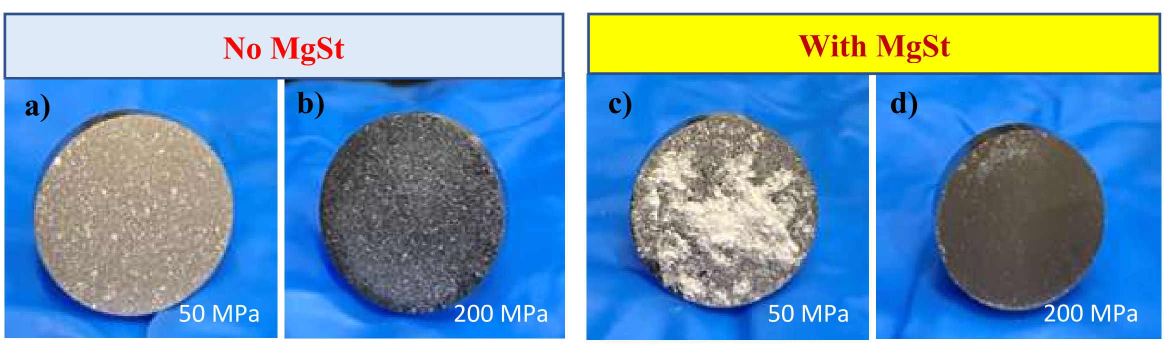

Figure 1. The sticking behaviors of sodium cyclamate under different compaction conditions; a) no MgSt, 50 MPa; b) no MgSt, 200 MPa); c) with MgSt (50 MPa); d) with MgSt (200 MPa)

2. A Punch Sticking Model for External Lubrication

The new punch sticking model for the scenario of external lubrication differs from the previous punch sticking model in two aspects: 1) punches used for compression, instead of being clean, are coated with a layer of MgSt, and 2) API is not mixed with an excipient. Consequently, whether or not sticking occurs depends on the interplay among a different set of forces, i.e., 1) the force between punch tip and MgSt (F_{pm}); 2) the force between MgSt and API (F_{ma}); and 3) the force between API and API (F_{aa}). In this new model, punch sticking takes place when F_{pm} and $F_{ma} > F_{aa}$, but is absent when $F_{pm} < F_{ma}$ and F_{aa}. It should be mentioned that the total force between any pair of particles depends on the effective bonding area (BA) and bonding strength (BS) (Osei-Yeboah et al., 2016). A larger BA or BS or both favors a higher total bonding force between two particles. While BS depends on chemical nature and surface energy of the particles, BA depends on compaction pressure, particle size, and hardness of the particles in contact (Sun, 2011).

There are a few important features of this model that are worth mentioning. First, the punch tip is covered by a continuous layer of MgSt prior to compression, i.e., the contact area between MgSt and punch is at the maximum. Consequently, F_{pm} would be independent of pressure for a given set of tooling and a batch of MgSt (Figure 2). In contrast, both F_{ma} and F_{aa} are pressure-dependent since BA usually increases with increasing compaction pressure due to more extensive plastic deformation till a maximum value is reached. Second, MgSt is a soft material (Sun, 2015), likely softer than most API particles. If so, API particles in contact with the MgSt layer penetrate into it during compression, leading to a sharper rise in BA between MgSt and API than that between API particles (Figure 2). For an API that is significantly harder than MgSt, a negligible BA between the first and second layers of API is developed when the maximum BA between MgSt and API has been attained. BA of API-API can also reach a maximum, but only at significantly higher pressures. The different BA growth profiles with increasing pressure lead to F_{ma} rising more quickly to a plateau than F_{aa} (Figure 2).

The curvatures of F_{aa} and F_{ma} are expected to be S-shaped, which is analogous of the full tabletability profiles of powders (Vreeman and Sun, 2022, Chang and Sun, 2020). Therefore, the condition of F_{pm} and F_{ma} are both greater than F_{aa} (F_{pm} and $F_{ma} > F_{aa}$) will be satisfied in a low-pressure range, leading to punch sticking (zone 1 in Figure 2). At high pressures, no sticking is observed because MgSt is peeled off the punch surface when the condition of F_{pm} is lower than F_{ma} and F_{aa} (i.e., $F_{pm} < F_{ma}$ and F_{aa}) is met (zone 2 in Figure 2).

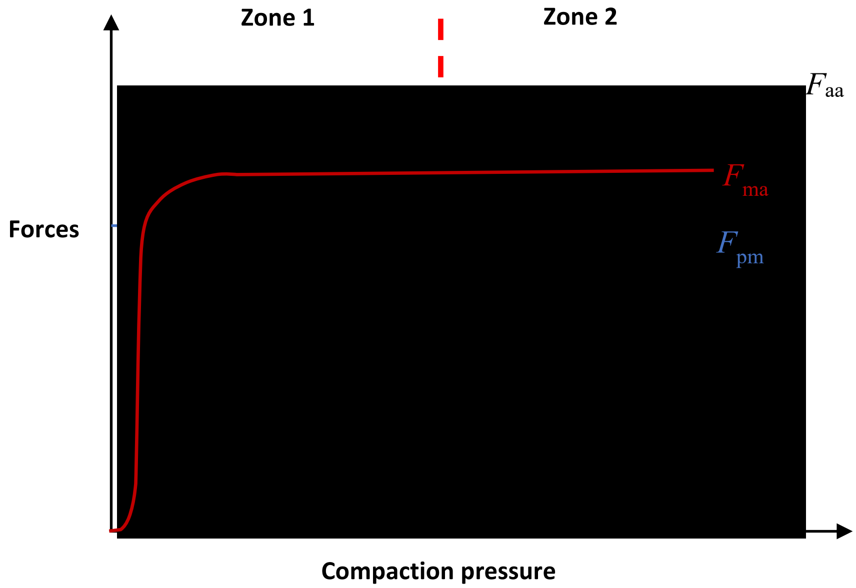

Figure 2. The conceptual profiles of F_{aa}, F_{ma}, and F_{pm} varying with compaction pressure. In zone 1, sticking is evident. In zone 2, sticking is avoided because MgSt is detached from punch surface when F_{aa} and F_{ma} are both higher than F_{pm}.

3. Materials and Methods

3.1 Materials

Ibuprofen (IBU; Sigma Aldrich, St. Louis, MO), celecoxib (CEL; Aarti Drugs Pvt Ltd., Mumbai, India), magnesium stearate (MgSt; non-bovine, HyQual™, Mallinckrodt, St. Louis, MO), sodium cyclamate (CycNa; Acros Organics®, Geel, Belgium), and acetaminophen (ACM, Form I) (Sigma Aldrich, St Louis, MO) were all used as received.

3.2. Methods

3.2.1. Powder compaction

Compaction of powders was conducted on a compaction simulator (Styl'One Evolution; MedelPharm, Beynost, France) using a force-controlled, symmetrical single compression cycle (2% speed, 2 s compression composed of a 1 s rise and a 1 s fall without holding at the maximum force, followed by 3 s relaxation, and a 2 s ejection step). A 12.7 mm round flat tooling (B type) with a removable upper punch tip was used for all the compaction and sticking assessment. A suspension of MgSt in ethanol (10%, w/v) was applied onto the punch surface with a brush and air-dried before compaction. Depending on the material, different compaction pressures (4 - 400 MPa) were used. At each pressure, 5 tablets were compressed following an identical procedure. The punch tip was cleaned and coated with a visually uniform layer of MgSt before each compression.

3.2.2. True density

The true density ($\boldsymbol{\rho_t}$) of IBU, CEL, CycNa, ACM, and MgSt was determined using a helium pycnometer (Quantachrome Instruments, Ultrapycnometer 1000e, Byonton Beach, Florida) with 1–2 g of an accurately weighed sample that 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 variation between five consecutive measurements was below 0.005% and the mean of the last five measurements was calculated, which was taken as the true density.

3.2.3. In-die Heckel analysis

In-die tablet porosity (ε) data was calculated from in-die tablet thickness measured with the compaction simulator, $\boldsymbol{\rho_t}$, and the weight of the ejected tablet. In-die mean yield pressure ($P_{y,i}$) was obtained from a linear regression of the linear portion of the $-\ln(\varepsilon)$ vs. P profile, i.e., the Heckel plot, according to Eq. (1). (Heckel, 1961a, 1961b)

$$-\ln(\varepsilon) = \frac{1}{P_{y,i}} P + A \qquad (1)$$

3.2.4. Assessment of sticking behavior by weight gains

Punch sticking was quantified by the weight gain of the removable upper punch tip after each tablet was compressed. The various weights of the removable upper punch tip, i.e., clean tip (W0), tip with MgSt coating (W1), and tip after compression (W2), were recorded. The weight of the MgSt layer (W1-W0) and the weight gain after compression (W2-W1) were calculated. A positive weight gain indicates sticking of API onto the punch tip, while a negative weight gain indicates peeling-off of the MgSt from the punch tip.

4. Results and Discussion

Although the extent of punch sticking varied among the four model APIs, i.e., IBU, CEL, CycNa, and ACM, they all showed a qualitatively similar pattern in their weight gain profiles (Figure 3). With increasing compaction pressure, the weight gain initially increases, then decreases, and eventually becomes negative.

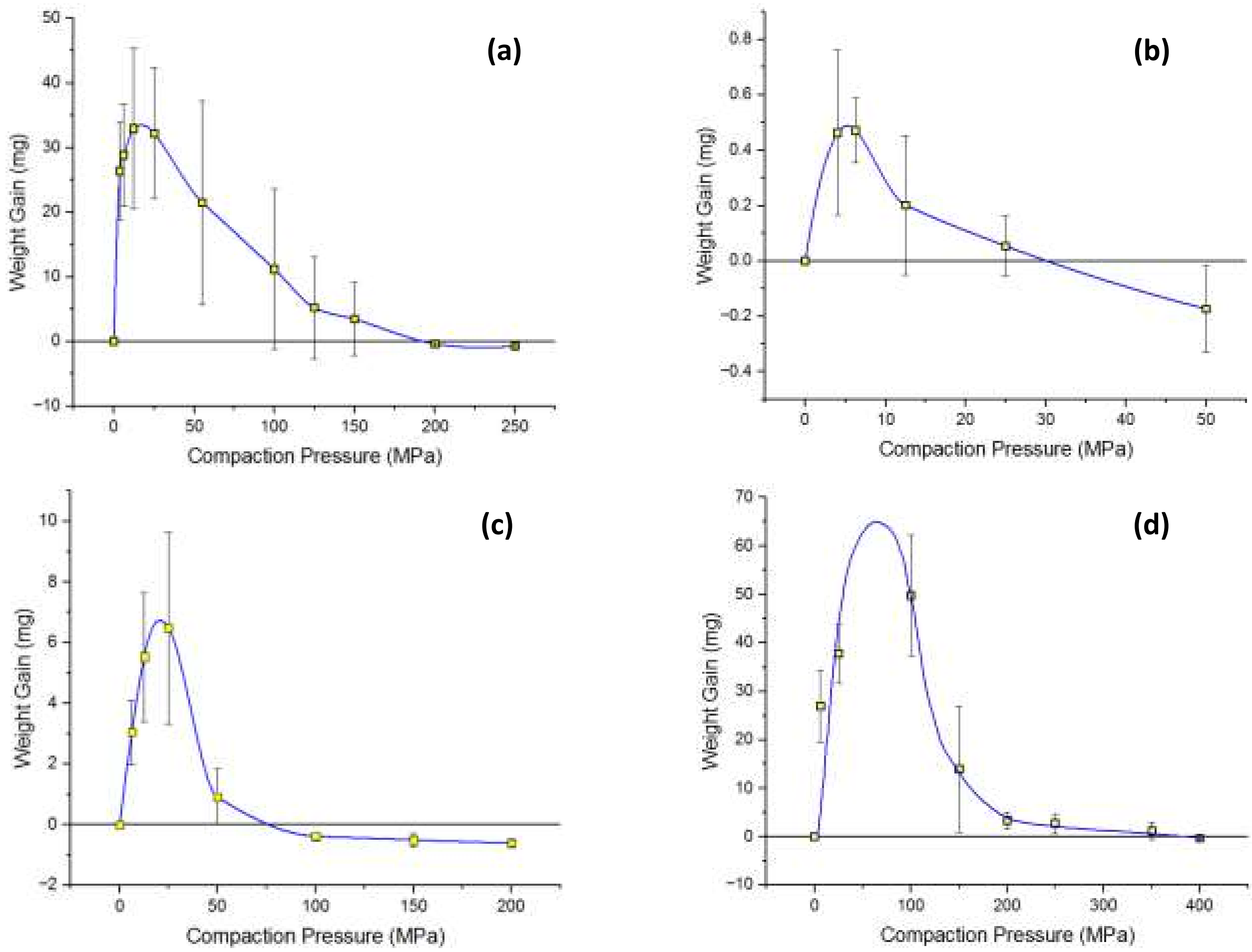

Figure 3. The plots of weight gain of punch tip after compression versus compaction pressure for a) sodium cyclamate (CycNa), b) acetaminophen (ACM); c) celecoxib (CEL); and d) ibuprofen (IBU).

This common shape of these plots is consistent with the observation that punch sticking was severe at low pressures (Figure 1c) but eliminated at high pressures (Figure 1d). The positive weight gain at low pressures suggests that the condition of F_{pm} and $F_{ma} > F_{aa}$ has been met, while the negative weight gain (an absence of punch sticking) at high pressures suggests that the condition of $F_{pm} < F_{ma}$ and F_{aa} has been met.

The validity of the model depends on the assumption that MgSt is softer than an API. This assumption is supported based on their $P_{y,i}$ values (Table 1), which suggests the plasticity follows the descending order of MgSt > IBU ≥ CEL > ACM > CycNa. Under this condition, the pressure-depending sticking behaviors can be explained by considering the pressure dependence of BA and, hence, total bonding force between different pairs (F_{pm}, F_{ma}, and F_{aa}), as explained below.

Table 1. In-die $P_{y,i}$ values of APIs and MgSt (n = 3).

Materials	**In-die P_y (MPa)**
Magnesium stearate	25.8 ± 4.5
Ibuprofen	40.5 ± 9.9
Celecoxib	47.1 ± 8.3
Acetaminophen	89.5 ± 2.7
Sodium cyclamate	108.3 ± 4.7

In the very low-pressure range (Figure 4a), MgSt particles deform much more than API particles due to the significantly higher plasticity of MgSt than API. Thus, the BA between MgSt and API is much larger than that between API particles. Note that the bonding force between MgSt and punch already reached the maximum at the beginning because of the MgSt layer was applied through drying a suspension of MgSt. As a result, F_{pm} and $F_{ma} > F_{aa}$ (Figure 4a) and sticking occurs. With increasing pressure, the BA between MgSt and API particles grows rapidly while that between API particles does not change much. Hence, the condition of F_{pm} and $F_{ma} > F_{aa}$ is still satisfied to assure sticking despite the changes in BA. However, since more API particles can encounter the MgSt layer at a higher pressure, the amount of API transferred to punch tip grows (Figure 4b). When the pressure further increases, the BA between MgSt and API particles starts to saturate, but the BA between API particles continues to increase. As some point, some of the API particles are removed from the MgSt layer when F_{aa} surpasses F_{ma}, leading to a decrease in the amount of API stuck onto the punch tip (Figure 4c). When the compaction pressure is sufficiently high, both MgSt and API particles undergo extensive plastic deformation, leading to maximum BA of MgSt-API and API-API, and the condition of $F_{pm} < F_{ma}$ and F_{aa} is met so that the MgSt layer is peeled off from the punch tip (Figure 4d), leading to a negative weight change.

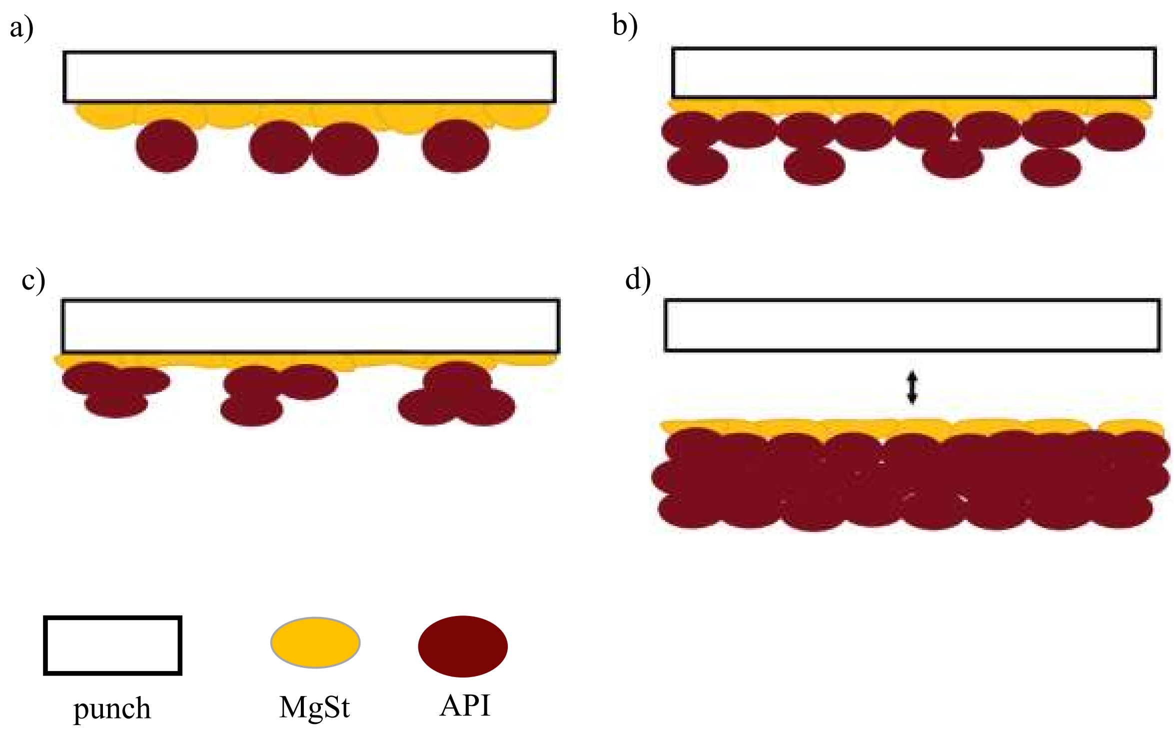

Figure 4. Evolution of bonding interactions among different particles as a function of compaction pressure. a) low pressure (positive weight gain due to API particles sticking to the MgSt layer); b) medium pressure (peak value of weight gain profiles), c) medium – high pressure (reduced weight gain), d) high pressure (negative weight gain corresponding to the peeling off of MgSt from punch)

The peak value of weight gain varied widely with API, from 0.5 – 50 mg, which is dictated by the size, density, and number of layers of API particles adhered to the punch. Given the complexity of this phenomenon and variability in weight gain, quantitative description of the maximal weight gain or the shape of the profiles cannot be predicted in this work. However, we note that the high peak values of weight gain profiles of IBU, CycNa, and CEL, are accompanied by capping or lamination of tablets upon ejection. Consequently, multiple layers of API particles were transferred onto the punch tip, leading to higher peak weight gains. The average of the maximum negative weight gain varied in a narrow range of 0.17 – 0.68 mg for the four APIs, roughly corresponding to the amount of MgSt coated onto punch tip (0.36 – 1.24 mg).

Lastly, this new punch-sticking model predicts that an API that is softer than MgSt may not exhibit punch sticking even at low pressures, if the BS between API particles is similar or higher than that between MgSt and API. However, we could not identify an API that is softer than MgSt to further test the model in this way.

5. Conclusions

The counterintuitive observation of a MgSt coating layer worsening punch-sticking of API at low pressures is explained using a model that considers the interplay among F_{pm}, F_{ma}, and F_{aa} as a function of pressure. This model predicts severe punch sticking at low pressures but an absence of punch sticking at sufficiently high pressures. Results from this investigation using four API powders support the proposed model. They suggest that increasing pressure is likely an effective approach to overcome punch sticking problems, if observed during tablet manufacturing when external lubrication is used. This work also affirms the validity of the approach to predict punch sticking behavior based on interaction forces between different pairs of materials, i.e., punch, API, and excipient (magnesium stearate in this work). Thus, it not only explains an intriguing phenomenon, but also offers a general approach for a fundamental understanding of the complex phenomenon of punch sticking in other scenarios during tablet manufacturing.

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