Worsened Punch Sticking by External Lubrication with Magnesium Stearate

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May everyone have a bright and blessed future!

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). However, we found that coating tooling with MgSt surprisingly led to aggravated punch sticking at low compaction pressures. We developed a model to explain this counterintuitive phenomenon based on the consideration of interplay of forces among the punch tip, MgSt, and API. The model is supported by the observed effects of pressure and mechanical properties of APIs on this phenomenon using 4 APIs.

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CHAPTER 1.

INTRODUCTION

1.1 Background

Tablet dosage forms, one of the most widely used pharmaceutical dosage forms, account for up to 70% of over-the-counter (OTC) and prescribed medications. [1] This popularity is attributed to several key factors. Firstly, tablets are favored by patients due to their ease of administration. From a manufacturing perspective, tablets are preferred because of their high efficiency and cost-effectiveness. Additionally, tablets offer high chemical and physical stability of APIs, making transportation and storage straightforward. Lastly, tablets provide exceptional precision and minimal variation in dosing, ensuring a more reliable clinical performance in disease management.

A wide range of performance criteria of tablets need to be monitored and controlled against stringent standards to ensure quality. Potential problem facing tablets include variable weight or hardness, sticking, capping, lamination, and so on. Among them, punch sticking is a persistent problem, which may be defined as the adherence of the powder material onto the tooling surface during powder compaction. [2] If not eliminated, punch sticking leads to tablet failure, low manufacturing efficiency, and even loss of batches. [3]

Strategies generally used to avoid sticking during drug product manufacturing are modifications of process parameters and formulation design, such as changing the compaction pressure [4], tooling design, and compositions of excipients [5]. A common formulation strategy for mitigating punch sticking is to increase the level of lubricant. [6]

Many APIs stick to punches when compressed. Since systematic characterization of API compression properties requires intact tablets compressed over a range of pressures, it is necessary to prevent punch sticking of pure APIs during compression. The common method

adopted is to lubricate tablet tooling with magnesium stearate (MgSt) before compression. [7] Surprisingly, we observed that tablet tooling lubricated with a layer of MgSt sometimes exacerbated punch sticking during compression. Hence, we initiated a project to understand the mechanism of this counterintuitive phenomenon. The primary objective of this thesis research is to propose a model that can explain this pheromone and test it using different model compounds.

1.2 Punch Sticking

Punch sticking is a well-known issue in tablet manufacturing, referring to the problem of the powder material adhering to the surface of the tablet press tooling during the compaction of tablets. This adherence can range from mild filming of material on the punch tip to severe loss of material to punch tips and defects on the tablet surface. [8]

A significant challenge with punch sticking is that it often does not manifest in the early stages of formulation development but appears later when larger numbers of tablets are compressed. Addressing this issue at a later stage can be expensive and time-consuming. If not resolved quickly, such a problem can compromise tablet quality and lead to low manufacturing efficiency due to the need for intermittent cleaning of the tooling surfaces.

Punch sticking occurs when the force of an API particle adhering to the punch surface (F1) is greater than the force between the API particle and neighboring particles within the tablet (F3). [2] The severity of API sticking to the punch, as a result of repeated compressions, depends on the force between the API particles adhered to the punch and the API particles in a newly formed tablet (F2). When F2 is less than F3, repeated tablet compression leads to the formation of a monolayer of API coating the punch. However, if F2 exceeds F3, multiple layers of API can

accumulate on the punch. [2] The kinetics of punch sticking can be described using the Hill's equation, which helps model and understand how the sticking phenomenon evolves over time. [2]

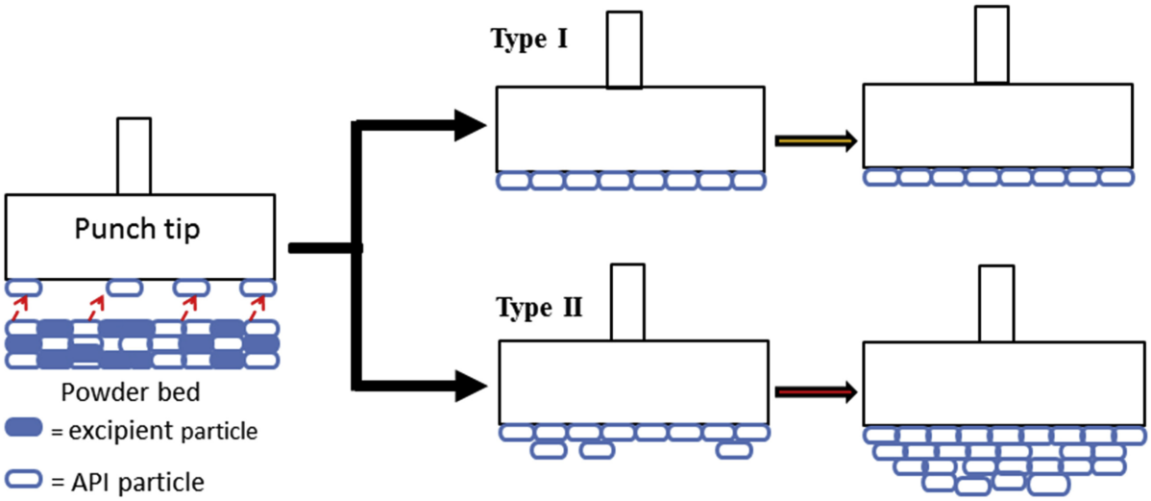

Figure 1.1. Schematic representation of different types of punch sticking behaviors (reproduced from ref. 2).

Three main strategies to mitigate or eliminate punch sticking problems have been identified, including: 1) API crystal and particle engineering, such as forming salts and cocrystals [9 10], modifying particle size and morphology [11 12], and containing the API within a porous carrier. [13] 2) Process modification, such as compaction pressure and tooling design. [4] 3) Formulation design: such as using different excipients [5], reducing the amount of API in the formulation [14], and adjusting the level of lubricants [6].

1.3 Lubricant and Magnesium Stearate

Lubricants are essential components in tablet formulations, with the primary function of reducing the friction between the tablet and the die wall. [15] Among tablet lubricants, magnesium

stearate (MgSt) the most favored choice due to its high lubrication efficiency. [16] Depending on the formulation, a concentration of 0.25% to 1.0% (w/w) of MgSt can effectively reduce ejection force and prevent punch sticking. [2, 17] Typically, lubricants are mixed with the powder blend before tablet compression during commercial manufacturing. Internal incorporation of MgSt has been associated with several noteworthy drawbacks, including a decline in tablet tensile strength [19], elevated tablet friability [20], and a delay in tablet dissolution performance [21]. These adverse effects raise concerns about the use of internal MgSt within tablet formulations. In laboratory-scale settings, MgSt is often applied externally, by spraying or brushing the suspension of MgSt, or dusting the MgSt powder onto the surfaces of the tablet tooling [18], to make intact tablets for assessing the tableting properties of pure materials. [7]

In the context of addressing punch-sticking issues by external lubrication, we observed a counterintuitive effect, where external lubrication with MgSt exacerbated the punch-sticking problem. This unexpected observation calls for a mechanistic explanation, given it is so commonly employed in laboratory studies of tableting performance of powders.

CHAPTER 2.

WORSENED PUNCH STICKING BY EXTERNAL LUBRICATION WITH MAGNESIUM STEARATE

2.1 Introduction

The tablet has been widely used in drug delivery due to its physical and chemical stability, low manufacturing cost, and good patient compliance [22]. 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 [2]. If not eliminated, punch sticking leads to tablet defects, low manufacturing efficiency, and even loss of batches [3]. 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 ($F3$) [2]. 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, $F2$. A monolayer is formed when $F2 < F3$, or multiple layers form when $F2 > F3$ [2]. Furthermore, the kinetics of punch sticking can be described by the Hill's equation [2]. 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 [9,10], particle size and morphology modification [11,12], and containment of API in a porous carrier [13]; 2) modification of process parameters, such as compaction pressure [4] and tooling design; 3) formulation design, such as using different excipients [5], reducing API loading [14], and changing lubricant level in tablet formulation [6].

To avoid punch sticking of pure APIs, it is common to lubricate tablet tooling with magnesium stearate (MgSt) before compression [7]. 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 2.1a, b). After coating the punch tip with a layer

of MgSt, sticking was much more severe at 50 MPa compaction pressure (Figure 2.1c). However, punch sticking was absent at 200 MPa compaction pressure (Figure 2.1d). 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 model, which was developed to explain punch sticking of formulated API during compaction using a clean punch [2]. Hence, we propose a new punch-sticking model to explain this surprising phenomenon.

2.2 A Punch Sticking Model

The new punch sticking model 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 $F_{pm} > F_{ma} > F_{aa}$, but is absent when $F_{pm} < F_{ma} < F_{aa}$. It should be mentioned that the total force between any pair of particles depends on the effective bonding area (BA) and bonding strength (BS) [23]. 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.

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 used to coat the punch tip (Figure 2.1). 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 likely softer than most API particles. Thus, 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 2.2). 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 2.2).

The shape of F_{aa} and F_{ma} profiles is expected to be S-shaped, which is analogous of the full tabletability profiles of powders [24 25]. Therefore, the condition of F_{pm} and F_{ma} are both greater than F_{aa} ($F_{pm} / F_{ma} > F_{aa}$) will be satisfied in a low-pressure range, leading to punch sticking. At high pressures, no sticking is observed because MgSt is peeled off the punch surface when the condition of F_{pm} is lower than both F_{ma} and F_{aa} ($F_{pm} < F_{ma} / F_{aa}$) is met.

2.3 Materials and Methods

2.3.1 Materials

Ibuprofen (IBN; 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 used as received.

2.3.2 Methods

2.3.2.1 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 - 200 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.

2.3.2.2 True density

The true density (ρ_t) of IBN, 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.

2.3.2.3 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). [26] [27]

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

2.3.2.4 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.

2.4 Results and Discussion

Although the extent of punch sticking varied among the four model APIs, i.e., IBN, CEL, CycNa, and ACM, they all showed a qualitatively similar pattern in their weight gain profiles (Figure 2.3). With increasing compaction pressure, the weight gain initially increases, then decreases, and eventually becomes negative.

This common shape of these plots is consistent with the observation that punch sticking was severe at low pressures (Figure 2.1c) but eliminated at high pressures (Figure 2.1d). The positive weight gain at low pressures suggests that the condition of $F_{\mathrm{pm}} > F_{\mathrm{ma}} > F_{\mathrm{aa}}$ 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 2.1), which suggest a descending order of plasticity: 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.

In the very low-pressure range (Figure 2.4a), 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, $F_{pm} / F_{ma} > F_{aa}$ (Figure 2.4a) 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 $F_{pm} / F_{ma} > F_{aa}$ is still satisfied to assure sticking despite the changes in BA. However, since more API particles can come in contact with the MgSt layer at a higher pressure, the amount of API transferred to punch tip grows (Figure 2.4b). When the pressure further increases, the BA between MgSt and API particles starts to saturate, but the BA between API particles continues to increase. At 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 2.4c). 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 $F_{pm} < F_{ma} < F_{aa}$ is met.

Consequently, the MgSt layer is peeled off from the punch tip (Figure 2.4d), leading to a negative weight change.

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. 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 stuck onto the punch tip. 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).

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 of MgSt-API. However, we could not identify an API that is softer than MgSt to further test the model in this way.

2.5 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. This work 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 a surprising

phenomenon, but also offers a general approach for a fundamental understanding of the complex phenomenon of punch sticking during tablet manufacturing.

Table 2.1. In-die $P_{y,i}$ values of four model APIs and MgSt.

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

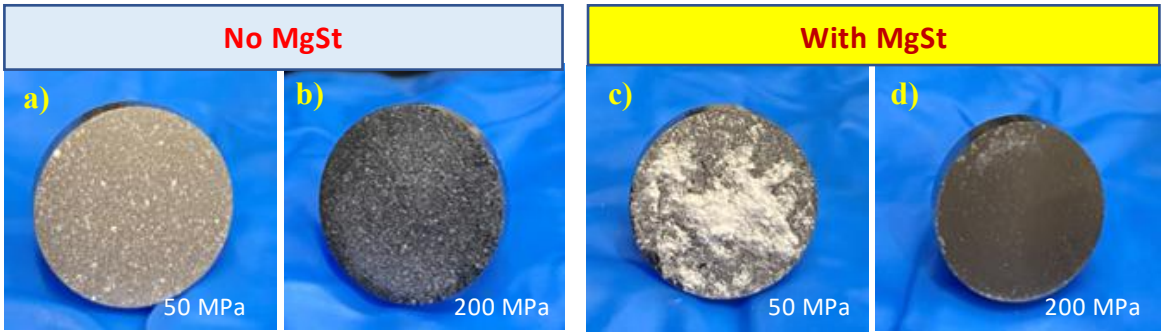

Figure 2.1. The sticking behaviors of sodium cyclamate under different compaction conditions; a) no MgSt, 50 MPa; b) no MgSt, 200 MPa); c) with MgSt (50 MPa); d) with MgSt (200 MPa)

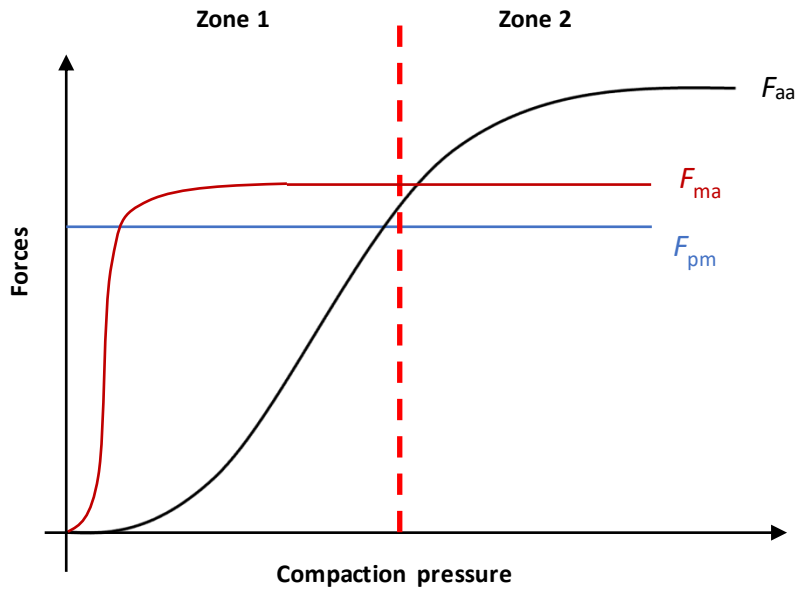

Figure 2.2. The conceptual profiles of F_{aa}, F_{ma}, and F_{pm} varying with compaction pressure. In zone 1, sticking is evident. In zone 2, sticking is avoided because F_{aa} and F_{ma} are both higher than F_{pm}, leading to detachment of MgSt from punch surface.

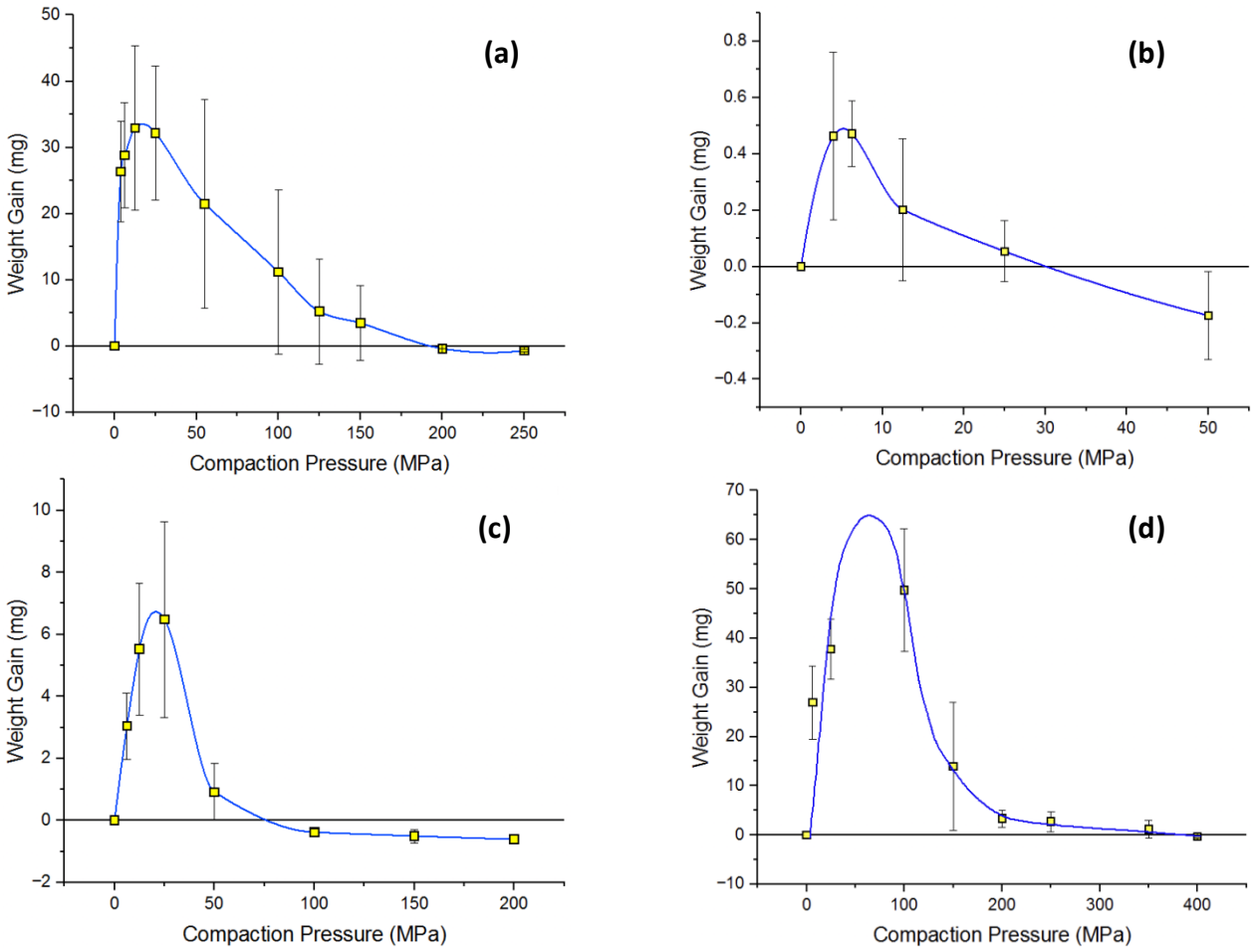

Figure 2.3. The weight gain plots of punch tip versus compaction pressure for a) sodium cyclamate (CycNa), b) acetaminophen (ACM); c) celecoxib (CEL); and d) ibuprofen (IBU).

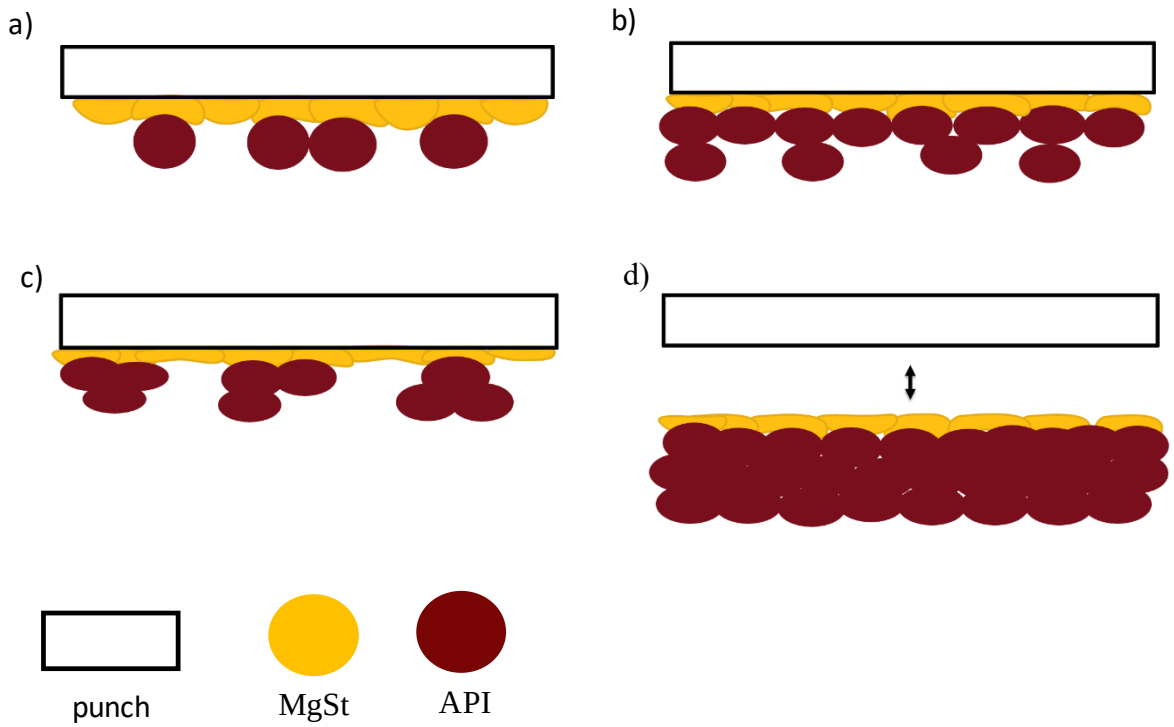

Figure 2.4. Evolution of bonding interactions among different particles as a function of compression pressure. a) low pressure (API particles stuck in the MgSt layer); b) medium pressure (peak value of stuck API particles), c) medium – high pressure (less API sticking than b), d) high pressure (peeling off of MgSt from punch)

CHAPTER 3.

RESEARCH SUMMARY AND FUTURE WORK

3.1 Research Summary

A new model for understanding the unexpected phenomenon of deteriorated sticking issues caused by external lubrication with magnesium stearate (MgSt) has been developed. This model explains the pressure-dependent sticking behaviors by considering the pressure dependence of the total bonding force between different pairs, including punch-MgSt, API-MgSt, and API-API. The sticking propensities of four APIs were assessed by creating weight gain plots to validate the model.

3.2 Future Work

The fundamental assumption of this model is that magnesium stearate (MgSt) is softer than most active pharmaceutical ingredients (APIs). To test the hypothesis and further validate the model, several experiments can be conducted. These experiments involve substituting MgSt with alternative external lubricants that are also softer than APIs, like sodium dodecyl sulfate (SDS), to see if a similar pressure-dependent sticking behavior is observed. If this behavior persists with these alternative lubricants, it will provide additional evidence supporting the model.

Another avenue for testing the hypothesis is to replace MgSt with other excipients of varying plasticity, like polyvinylpyrrolidone (PVP). Results from those studies, can either validate the model or provide information to further improve it.

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