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# Powder properties and compaction parameters that influence punch sticking propensity of pharmaceuticals

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ABSTRACT

Punch sticking is a frequently occurring problem that challenges successful tablet manufacturing. A mechanistic understanding of the punch sticking phenomenon facilitates the design of effective strategies to solve punch sticking problems of a drug. The first step in this effort is to identify process parameters and particle properties that can profoundly affect sticking performance. This work was aimed at elucidating the key material properties and compaction parameters that influence punch sticking by statistically analyzing punch sticking data of 24 chemically diverse compounds obtained using a set of tooling with removable upper punch tip. Partial least square (PLS) analysis of the data revealed that particle surface area and tablet tensile strength are the most significant factors attributed to punch sticking. Die-wall pressure, ejection force, and take-off force also correlate with sticking, but to a lesser extent.



## 1. Introduction

The term “punch sticking” refers to the adherence of powder material on to the tooling surface during compaction. Punch sticking is a phenomenon that commonly occurs in tablet manufacturing and is usually more severe for debossed tablets (Waimer et al., 1999a). In severe cases of sticking, obvious tablet defects, due to removal of material from the tablet surface, are observed shortly after the compression run starts (Simmons and Gierer, 2012; Waimer et al., 1999b). In mild cases, dulling of tablet surfaces and removal of material at the sharp debossing corners and edges with the punch (commonly referred as “picking”) can be observed. Previous work by the authors suggested that sticking primarily originates from active pharmaceutical ingredients (API) in a formulation, instead of commonly used pharmaceutical excipients (Paul et al., 2016). Due to the complexity, it is not yet possible to reliably predict punch sticking for a given formulation. Therefore, the development of a sticking-free tablet formulation and a robust manufacturing process for a given API still relies on assessing the sticking propensity of a formulation by repeatedly compressing tablets on a press. As per the Materials Science Tetrahedron principle (Sun, 2009), process parameters and material properties that can affect sticking performance need to be mechanistically understood before effective strategies can be designed to proactively address the potential for punch sticking. This necessitates the identification of suitable parameters for enabling reliable prediction of sticking issues by material sparing approaches. In spite of some pioneering work on sticking, the current literature does not render the ability to predict punch sticking behavior based on easily accessible process parameters or material properties. Previous work mainly focused on the role of adhesion in sticking, different methods of adhesion quantification, and influence of lubricants and punch geometry (Bejugam et al., 2015; Kakimi et al., 2010; Sakata and Yamaguchi, 2011). Roberts et al. reported a systematic study on the influences of lubricant type and concentration, tooling type and embossment designs on various ibuprofen formulations (Roberts et al., 2003; Roberts et al.,

*Abbreviations:* μ, friction coefficient; CEL, celecoxib; $D_{[3,2]}$, surface-mean diameter; EF, ejection force; GLY, glyburide; IBN, ibuprofen; MA, mefenamic acid; MCC, microcrystalline cellulose; MDP, maximum die-wall pressure; PLS, partial least square; RDP, residual die-wall pressure; SA, surface area; TOF, take-off force; TS, tensile strength of pure compound; TS′, tensile strength of the formulation; VIP, variable importance for projection; *X*, variable Input variables.

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2004a,b). Wang et al. demonstrated the usefulness of atomic force microscopy as a quantitative tool to elucidate the adhesion between a family of profen compounds and a tooling surface (Wang et al., 2003). Use of scrapper force data during tablet detachment was also suggested as an indicator of sticking (Otsuka, 1998). Using different filler-binders, it has been recently reported that degree of radial expansion of tablets could correlate with the sticking of mefenamic acid formulations (Abdel-Hamid and Betz, 2012). Waknis et al. explained the effect of crystal habit on punch sticking of mefenamic acid based on the crystal facet-dependent exposure of specific functional groups (Waknis et al., 2014). Some recent studies elucidated the feasibility of using take-off force as a predictor of sticking. However, conflicting conclusions were drawn from these studies (Saniocki et al., 2013; Wang et al., 2004). Generally, each study only focused on a limited number of compounds and different methods were employed in different studies. Hence, extrapolating findings from an individual study or based on an analysis of the literature is difficult.

Clearly, there is still the need for better understanding of punch sticking. A successful study will require characterizing a large number of compounds across a range of different sticking performances, while having access to both material properties and compaction parameters. Once clear correlations are firmly established, more thorough investigations can be carried out to derive knowledge that can be used to guide the prediction of punch sticking for a given formulation. To address this knowledge gap, it is useful to conduct a quantitative study that includes a reasonably large number of chemically diverse compounds using the same set of characterization methods. Subsequent statistical analyses of such a data set then yields insights into factors that significantly influence punch sticking, which is the first step towards mechanistic understanding of this phenomenon.

Among the available statistical methods, partial least square (PLS) analysis is a simple and frequently used method for extracting significant variables from a large pool of possible variables (Cui et al., 2012a). Therefore, we used PLS analysis to identify dominating factors that influence punch sticking. Both particle properties (e.g., particle size) and process related parameters (e.g., compaction pressure) were carefully characterized and assessed for their correlation with punch sticking.

## 2. Materials and methods

### 2.1. Materials

Sticking assessment was conducted on 24 compounds, including both excipients and APIs. The names and bulk properties of these compounds are presented in Table 1. Compounds were either provided by Pfizer Inc. (Groton, CT) or available in our chemical library. Compounds in the investigational stages were denoted by coded names (A to I). Two batches with different particle sizes were obtained for celecoxib and theophylline. Microcrystalline cellulose (MCC) (Avicel PH102, FMC Biopolymer, Philadelphia, PA) and magnesium stearate (Mallinckrodt, St Louis, MO) were used as binder and lubricant, respectively. All materials were used as received.

### 2.2. Determination of particle size and surface area

The particle size of the model compounds were determined using a laser scattering particle size analyzer (Sympatec Inc., Clausthal-Zellerfeld, Germany) with a relatively low dispersion pressure (0.1-1.0 bar) to avoid break down of agglomerates into API primary particles. Such agglomerates interact with punch surface similar to enlarged API particles and, hence, they are more relevant to punch sticking than primary particles. The surface area (SA) of

**Table 1**
Bulk properties and compaction parameters of 24 model compounds.

| Coded name | SA ($m^2$/g) | $D_{[3,2]}$ (μm) | TS (MPa) | | TS′ (MPa) | | EF (N) | | TOF (N) | | Sticking (μg) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 100 MPa | 200 MPa | 100 MPa | 200 MPa | 100 MPa | 200 MPa | 100 MPa | 200 MPa | 100 MPa | 200 MPa |
| Celecoxib_1 | 0.13 | 11.8 | 1.59 | 2.50 | 3.01 | 5.25 | 114.3 | 112.3 | 1.48 | 1.97 | 340 | 530 |
| Celecoxib_2 | 0.805 | 30.5 | 3.18 | 4.8 | 3.69 | 5.03 | 121.2 | 132.7 | 0.93 | 1.32 | 890 | 1160 |
| Theophylline_1 | 0.25 | 16.1 | 0.48 | 0.70 | 4.11 | 7.33 | 94.3 | 74.5 | 1.31 | 0.34 | 290 | 350 |
| Theophylline_2 | 0.93 | 4.3 | 1.02 | 1.35 | 3.76 | 7.23 | 101.1 | 98.5 | 2.16 | 1.63 | 200 | 70 |
| Amlodipine | 0.59 | 7.6 | 1.54 | 2.28 | 3.88 | 5.52 | 93 | 107.2 | 1.85 | 2.88 | 420 | 210 |
| Glyburide | 3.69 | 9.2 | 1.06 | 1.41 | 3.19 | 6.6 | 126.8 | 179.4 | 0.71 | 2.09 | 890 | 1250 |
| Sildenafil citrate | 0.46 | 9.1 | 1.12 | 2.79 | 3.23 | 6.3 | 126.5 | 151.4 | 1.67 | 2.27 | 320 | 330 |
| Ibuprofen | 0.08 | 78.9 | 1.15 | 1.35 | 1.42 | 2.3 | 82.8 | 92.3 | 1.38 | 2.01 | 750 | 860 |
| Flurbiprofen | 1.15 | 5.2 | 0.69 | 0.98 | 3.15 | 3.15 | 114.7 | 143.4 | 1.72 | 1.4 | 620 | 640 |
| DCPD* | 0.05 | 117.7 | 0.96 | 2.24 | 2.91 | 5.6 | 98.4 | 108.3 | 1.81 | 2.53 | 360 | 280 |
| Caffeine | 0.09 | 67.6 | 0.76 | 1.53 | 2.62 | 4.35 | 105.6 | 111.4 | 1.94 | 2.03 | 460 | 310 |
| Mannitol | 0.23 | 26.4 | 1.07 | 1.89 | 2.53 | 4.15 | 100.1 | 105 | 2.54 | 2.47 | 340 | 220 |
| Mefenamic acid | 0.59 | 10.2 | 0.65 | 1.07 | 2.46 | 3.84 | 125.1 | 153.4 | 1.46 | 1.79 | 570 | 630 |
| MP** | 0.03 | 187.5 | – | – | 1.52 | 2.7 | 105.2 | 116.2 | 0.61 | 0.64 | 320 | 210 |
| LM* | 0.18 | 17.7 | 0.55 | 1.64 | 3.75 | 6.12 | 110.2 | 123.5 | 1.3 | 1.6 | 250 | 110 |
| AL* | 0.12 | 27.7 | 1.70 | 4.15 | 3.75 | 6.37 | 122.2 | 148.7 | 1.44 | 1.6 | 170 | 70 |
| Esreboxetine | 0.25 | 11.6 | 0.87 | 1.41 | 3.92 | 5.26 | 199.8 | 287.3 | 2.36 | 1.4 | 380 | 420 |
| Tofacitinib | 1.51 | 10.8 | 1.34 | 2.53 | 4.3 | 6.32 | 106 | 101.6 | 2.2 | 1.16 | 950 | 1100 |
| Compound_A | 1.55 | 67.4 | 1.11 | 2.28 | 3.21 | 5.75 | 94.3 | 96.2 | 1.63 | 1 | 40 | 40 |
| Compound _B | 0.52 | 20.2 | 0.38 | 0.63 | 2.87 | 5.8 | 258.9 | 257.5 | 1.25 | 2.27 | 540 | 600 |
| Compound _C | 0.26 | 5.43 | 1.06 | 1.99 | 2.9 | 6.2 | 130.3 | 126.5 | 1.7 | 2.53 | 260 | 360 |
| Compound _D | 2.18 | 14.1 | 1.58 | 2.43 | 3.85 | 6.54 | 180.9 | 162.5 | 2.5 | 1.93 | 430 | 640 |
| Compound _E | 1.25 | 12.2 | 0.28 | 0.4 | 3.51 | 5.81 | 385.8 | 342.6 | 1.63 | 1.8 | 870 | 1080 |
| Compound _F | 0.78 | 8.4 | 0.87 | 1.10 | 2.88 | 5.46 | 112 | 129.6 | 1.45 | 2.21 | 450 | 470 |
| Compound _G | 5.37 | 11.5 | 1.35 | 2.58 | 3.67 | 5.66 | 225.4 | 522.4 | 1.33 | 1.03 | 610 | 620 |
| Compound _H | 0.19 | 24.7 | 2.49 | 3.15 | 3.19 | 6.2 | 121.2 | 130.4 | 1.74 | 2.89 | 180 | 180 |

* (DCPD = dicalcium phosphate dehydrate, LM = lactose monohydrate, AL = anhydrous lactose).
** Methyl Paraben (MP) could not form an intact tablet.