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Research Article

Mechanism and Kinetics of Punch Sticking of Pharmaceuticals

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ABSTRACT

Adherence of powder onto tablet tooling, known as punch sticking, is one of the tablet manufacturing problems that need to be resolved. An important step toward the resolution of this problem is to quantify sticking propensity of different active pharmaceutical ingredients (APIs) and understand physicochemical factors that influence sticking propensity. In this study, mass of adhered material onto a removable upper punch tip as a function of number of compression is used to monitor sticking kinetics of 24 chemically diverse compounds. We have identified a mathematical model suitable for describing punch sticking kinetics of a wide range of compounds. Chemical analyses have revealed significant enrichment of API content in the adhered mass. Based on this large set of data, we have successfully developed a new punch sticking model based on a consideration of the interplay of interaction strength among API, excipient, and punch surface. The model correctly describes the general shape of sticking profile, that is, initial rise in accumulated mass followed by gradual increase to a plateau. It also explains why sometimes sticking is arrested after monolayer coverage of punch surface by API (punch filming), while in other cases, API buildup is observed beyond monolayer coverage.

Introduction

Punch sticking refers to the adherence of the powder material on to the tooling surface during compaction of tablets. Mild punch sticking results in a film of material on the punch tip after successive compactions and can be visualized by inspecting the tooling. Severe punch sticking leads to significant tablet surface defects.[1] Since a sticking problem of a borderline formulation usually does not occur in early stages of clinical manufacturing, it is often not identified until late stage of development when more tablets are needed, at which point a change of the formulation is expensive and time consuming. Sticking during tablet manufacturing leads to compromised tablet quality and loss in manufacturing efficiency due to intermittent cleaning of tooling surface. In the majority of cases, punch sticking issues originate from the active pharmaceutical ingredients (APIs) instead of commonly used pharmaceutical excipients in the formulation.[2] In addition, while this problem has been amply documented over the years,[3-5] there is still a lack of clear understanding of this complex phenomenon. Current literature has mostly focused on correlating sticking phenomenon with various factors, such as temperature, humidity,[6] lubrication,[7] melting point of API,[7] particle size, excipient type and grade,[8] and punch-surface finishing.[9] Understanding the relationship between material's property and sticking propensity, although critical for solving this problem as per the materials science tetrahedron principle,[10] has been an elusive goal to attain. A main reason for the limited progress in this direction is the relatively poor ability to directly quantify the sticking propensity of a powder at small scales, which is required for fundamental understanding of sticking kinetics. Recently, API punch sticking propensity was quantified using an upper punch with a removable tip where API was added to a common matrix consisting of microcrystalline cellulose (MCC) and magnesium stearate.[11] In that study, ibuprofen (IBN) or mannitol at different loadings was mixed with the placebo matrix and the influence of API/excipient and lubricant concentration on sticking was investigated by directly quantifying the adhered mass. This technique has the potential to fill a critical technological gap in studying punch sticking. In the present study, we have adopted the same technique for quantifying sticking propensity of a wide range of compounds.

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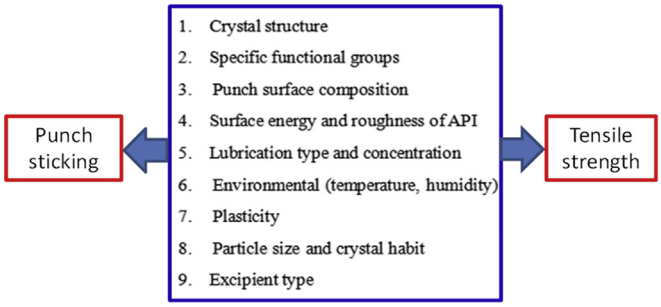

Figure 1. A short list of factors that affect both punch sticking and tablet tensile strength.

Evidences have suggested that sticking is impacted by the adhesive force between powder and the punch surface. For example, the same IBN-based formulations exhibited different extent of sticking when the punch construction material was changed, suggesting a key role played by the punch-tablet adhesion in sticking propagation.[12] Along this line of thinking, particle-punch adhesion was determined by measuring the force required to detach particles deposited on to substrates of steel, brass, or polytetrafluoroethylene inside a centrifuge tube[13] or by atomic force microscopy (AFM).[5] Powder-punch adhesion, estimated using scrapper force, was also used to evaluate influence of powder properties, temperature, and humidity conditions on punch sticking.[6,14] Although insight has been gained by studying API-punch adhesion alone, these techniques are still insufficient to explain a wide range of sticking behaviors of pharmaceutical materials.

Ideally, the interplay between particle-particle cohesion/adhesion and particle-punch adhesion forces must be simultaneously studied for better understanding of sticking behaviors. For example, compounds that exhibit strong adhesion to punch tips can still avoid occurrence of sticking if the particle-particle cohesion is even stronger than the adhesion. Therefore, factors observed to impact sticking outcomes, such as temperature, humidity, molecular structure, and solid-state characteristics of an API, likely act through influencing the interplay between particle-punch and particle-particle interactions. In fact, many factors that influence punch sticking (Fig. 1) also influence tablet strength, which is related to particle-particle cohesion/adhesion. The inherent crystal structure and exposed functional groups of an API could affect the particle-punch adhesion force[15] as well as particle-particle cohesion and tablet tensile strength.[16,17] The different faces on the same crystal also normally possess different surface energy that can lead to different adhesion susceptibility[18] and tabletability.[19] Particle size has also been observed to influence both tabletability[20] and particle-punch adhesion, for example, pull-off force of TiO_2 is higher when its particle size is smaller than the larger dimension of the substrate surface asperity.[21] Fresh particle surface generated by fragmentation is expected to impact both tabletability and sticking. For quartz and pyrex particles, adhesion force to punch increased linearly with relative humidity as a result of increased moisture film thickness.[22] Meanwhile, moisture content also significantly influences powder tableting performance.[23] Lubrication generally reduces adhesion to punch but also reduces tablet tensile strength. In addition, deformation characteristics of the API (brittle or plastic), surface roughness, could also influence both the sticking kinetics and tableting behaviors. Factors that only influence particle-punch adhesion, such as punch-surface roughness, impact punch sticking but do not impact tablet tensile strength.[24]

In the present work, sticking kinetics were quantified at 2 compaction pressures for a set of 24 chemically diverse compounds by directly quantifying sticking propensity using the removable upper punch tip technique. The sticking data were mathematically modeled to estimate the maximal sticking amount of a material. In addition, composition analysis of material adhered on to the punch tip was also conducted for sticky APIs to gain further insight on sticking mechanism.

Table 1
Summary of Extrapolated Parameters by Fitting Experimental Data to Equation 4

Compounds	Fitted Parameters at 100 MPa				Fitted Parameters at 200 MPa			
	M_{max}	a	b	R^2	M_{max}	a	b	R^2
Theophylline_A	446	110	2	0.971	93	51	2	0.85
Theophylline_B	470	76	1.9	0.94	$6.7 \times 10^{6*}$	$3.2 \times 10^{5*}$	1.2	0.983
Amlodipine	460	29	1.8	0.998	262	51	2	1.000
Glyburide	1038	37	1.7	0.988	1504	46	2.1	0.999
Sildenafil citrate	497	73	1.9	0.997	343	34	2.9	0.999
Ibuprofen	1485	92	1.3	0.982	1023	42	2	0.999
Flurbiprofen	899	53	1.3	0.999	740	35	1.8	0.996
DCPD	648	83	1.3	0.994	265	43	1.9	0.997
Caffeine	740	75	1.5	0.955	560	85	1.4	0.997
Mannitol	223	25	2.4	0.959	936	169	1.1	0.999
Mefenamic acid	667	37	1.8	1.000	717	37	2	1.000
Me Paraben	724	123	1.2	0.988	212	22	3.4	0.998
LM	$2.4 \times 10^{8*}$	$9.9 \times 10^{7*}$	1.0	0.987	421	210	1.4	0.999
AL	339	100	1.7	1.000	78	38	2.6	0.962
Esreboxetine	567	66	1.7	0.999	1301	169	1.4	0.999
Celecoxib_A	1156	51	1.7	0.988	4003*	223	1.1	0.996
Celecoxib_B	1678	418	1.0	0.990	771	51	1.0	0.870
Tofacitinib	1076	40	2.2	0.996	1648	68	1.9	0.982
Compound A	43	37	3.1	0.982	43	37	3.1	0.982
Compound B	801	54	1.9	1.000	903	65	1.8	0.995
Compound C	$5.8 \times 10^{6*}$	$1.8 \times 10^{5*}$	1.3	0.988	480	91	1.9	0.994
Compound D	652	64	1.5	0.999	1186	90	1.7	0.984
Compound E	1287	64	1.7	0.998	2138	97	1.4	0.987
Compound F	571	54	2.2	1.000	529	42	2.4	1.000
Compound G	635	44	2.1	0.998	668	39	2.2	0.994
Compound H	223	41	1.6	0.999	289	87	1.8	0.974

Materials with highly linear sticking profiles up to 100 compressions yielded unrealistic hill parameters and are marked with an asterisk.
DCPD, dicalcium phosphate dihydrate; LM, lactose monohydrate; AL, anhydrous lactose.