

# Quantitative and Miniaturized Assessment of Tooling Adhesion – Mapping the Boundary of Lubricant Failure/Effectiveness

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## ABSTRACT

**Purpose:** To define the design space for blend lubrication by quick and quantitative tooling adhesion predictions using miniaturized tooling tests

**Method:** A d-optimal quadratic response surface design examined adhesive blends (sorbitol in MCC 4:1 to 7:3 with folic acid 1% as a chemical tracer) with magnesium stearate lubricant loads up to 2%. This design focused on the tipping point of lubricant success within blends. The impact of well and poorly designed embossing on powder (or blend) sticking to stainless steel tooling was also screened. Compressions were run in duplicate on an instrumented rotary press (Piccola) at 20 rpm for a minimum of 1000 revolutions. Surface water activity (Rotronic HygroLab) was monitored. Digital punch image analysis (Scalar USB and MATLAB programs) was employed to predict the percentage residue adhering to the tooling. The tooling adhesion was compared with HPLC assay of the rinse of each tooling face.

**Results:** With less than 100g of blend consumed in each tableting run, tooling sticking by image analysis noted surface coverages from 1 to 98%. The results were congruent with the concentration of the tracer folic acid on the punch faces determined by HPLC (corr. coeff. 0.92). As expected, higher lubrication levels showed reduced ejection forces and sticking as assessed by both image and chemical analysis. But similar blends with decreased surface water activity exhibited lower ejection forces (p<0.002) and adhesion. Therefore, the data may explain the day-to-day variations in sticking occurring during compression. Defectable punch residue was linked with increased humidity of the environment during compression (p<0.001). Punch sticking of these adhesive blends under various conditions was invariant to the type of embossing design. The boundary of success/failure was defined primarily by the effects of the lubricant level, the dilution ratio of sorbitol to MCC and the surface moisture level and its effects on the surface material characteristics of the blends.

**Conclusions:** This material sparing method uses only gram quantities of API for the prediction of tooling adhesion. The results correlated with traditional chemical analysis, and may define and predict the design space for processing incoming lots of drugs and excipients.

## INTRODUCTION

Although much has been learned about the compression of powders in pharmaceutical development, our ability to predict and prevent tooling adhesion on scale up is poor. Adhesion or sticking to punch surfaces during compression, creates defects on tablet surfaces that directly impact quality and productivity. Sticking during tablet production scale up is often related to boundary failure magnified from small scale formulation and processing designs. Sensitive diagnostic tools are valuable to assess the robustness of a formulation and process prior to regulatory commitments for formulation compositions and processes.

An API conserving method was evaluated to predict the propensity for adhesion of powders under compression. A cohesive model compound, sorbitol was used to quantify punch adhesion and the effects of lubricant levels on sticking. A d-optimal quadratic response surface design with point substitution is run with the adhesive blends spiked with a chemical tracer (folic acid) and changing lubricant loads up to 2% to:

- Define the failure envelope for sticking with different levels of adhesive excipient
- Quantify and evaluate the effect of different levels of lubricant during compression on the propensity for adhesion
- Examine the utility of a diagnostic tool to probe potential issues for sticking in formulations

## METHODOLOGY

### Blending and Compression

Miniaturization refers to limiting the quantities of expensive APIs used, and not to the scale of the equipment used in manufacturing; the aim is to consume small amounts of API in order to gain more information about drug products. Adhesive powder blends, each consisting of MCC (PH102) and sorbitol (USP) with folic acid 1%, were blended with various amounts of magnesium stearate as a lubricant in a d-optimal response surface design (Table 2). Compression was run in duplicate typically using ~100 gm for a minimum of 30 minutes on an instrumented rotary press (Piccola) at 20 rpm with two types of miniaturized tooling; embossed with an “A” with increased break radius, lower pad area, tapered peninsula and corner radii contrasted with a poorly designed “A” mini-tooling. Upper and lower punch tips were examined under a portable microscope camera and the degree of surface coverage (filming) quantified by image analysis of digital scans with a MATLAB program. Surface water activity (Aw) was monitored using a Rotronic HygroLab. The tooling adhesion was also measured by HPLC assay of the rinseate of each tooling face.

### Experimental Design

Statistical analyses were performed using statistical software packages (JMP 5.0, SAS Institute and Design-Expert DX7, Stat-Ease).

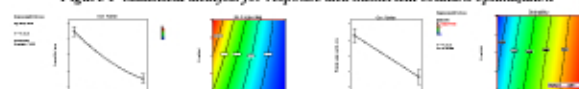
Table 1—Experimental design for d-optimal quadratic response surface

Run #	Code of Design	Magnesium stearate (%)	Sorbitol (%)	Tooling type
1	-0.5/-1	0.13	70	Good/BadUpper/Lower
2	-1/+1	0.00	80	Good/BadUpper/Lower
3	+1/+1	0.50	70	Good/BadUpper/Lower
4	+0.5/-1	0.38	70	Good/BadUpper/Lower
5	-1/-1	0.00	70	Good/BadUpper/Lower
6	+1/+1	0.50	80	Good/BadUpper/Lower
7	-1/+1	0.00	80	Good/BadUpper/Lower
8	+1/-1	0.50	70	Good/BadUpper/Lower
9	+1/+1	0.50	80	Good/BadUpper/Lower
10	+4/-1	1.25	70	Good/BadUpper/Lower
11	--	2.00	80	Good/BadUpper/Lower
12	--	2.00	70	Good/BadUpper/Lower
13	--	2.00	90	Good/BadUpper/Lower

## RESULTS AND DISCUSSION

As expected, ejection force and punch surface coverage – both orthogonal measures of punch sticking – increased with increased levels of adhesive powder and lower levels of lubricant (Figure 1).

Figure 1—Statistical analysis for response and numerical solution optimization



With compression on a rotary press, the heat generated assists in plastic deformation and interparticulate bonding. Heating also makes powders more susceptible to sticking in embossed areas. (Waimar 1999; Wang 2004) Therefore, sticking often occurs on both the upper and lower punch faces as well as within the die cavity. Traditional monitoring of sticking has included both tablet ejection and take off forces, however neither are a measure of upper punch adhesion. Instrumented upper punches are not robust and the signals are often not interpretable (Levine 2002). Ejection must occur before tablet scrape off and ejection forces are a complex measure of the force required to overcome residual die wall pressure and the friction between the punches/dies and the tablet contained within. Moreover variation in machine setup, lower punch position alignment with the scrape-off bar, and the angle has been shown to influence tablet take-off (and adhesion) readings (Aoki 1998). Overall either ejection or removal force measurements when combined with physical visual observations of sticking to upper/lower punch faces and sticking to the die wall may be used to set criteria to judge potential adhesion in development and during production.

### Tooling Design – Embossing

As shown below in Figures 2(a) through (f), analysis of variance (ANOVA) of the tooling surface coverage stratified to level of sorbitol, punch design and placement showed that sticking or formation of a visible film as a precursor to sticking was invariant to the type of embossing design in this study. Based on post compression examination and quantified analysis of the punch tips, the embossed area is prone to adhesion as expected since a concentration of shear stresses occur at the lateral faces of punch engravings (Roberts 2004). Data from tooling design types may therefore be pooled for subsequent model analysis of ejection forces, and punch surface coverage.

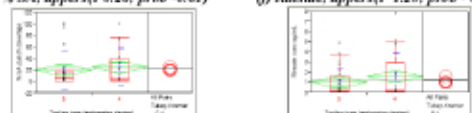
Figure 2—ANOVA for embossing designs, stratified to sorbitol level, upper or lower position (a) % SA, 70% sorbitol, upper (b) % SA, 80% sorbitol, upper (F 0.28; prob= 0.60)



(c) % SA, lower punch (F 1.15; prob= 0.30) (d) Ejection force, lower (F 1.01; prob= 0.33)



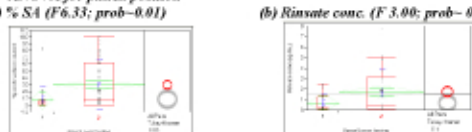
(e) % SA, uppers (F 0.26; prob= 0.61) (f) Rinstate, uppers (F 1.20; prob= 0.28)



### Tooling position – upper and lower punches

A statistically significant difference exists as to the extent of punch sticking when comparing punch position placement for surface coverage and rinstate analysis (Figure 3, Table 2).

Figure 3—ANOVA for punch position (a) % SA (F 6.33; prob= 0.01) (b) Rinstate conc. (F 3.00; prob= 0.09)



As shown below in Table 2(a), punches were physically examined post compression to quantify the surface area covered with powder and which zones were susceptible in the embossed area.

Table 2—Representative digital microscopic images used for image analysis of adhesion (a) Image analysis and Assay of rinstate of upper punches

Code of Design	Upper (B) Good A	Upper (B) Bad A	Avg SA % Good A	Avg Conc. Good A	Avg SA % Bad A	Avg Conc. Bad A
0			1.9 (1.4)	0.182 (8.94)	1.4 (0.8)	0.657 (0.01)
--			78.4 (15.0)	2.380 (0.3)	72.9 (0.3)	4.549 (0.2)
+-			4.4 (1.4)	0.381 (0.5)	13.7 (0.5)	1.357 (0.2)
+			12.6 (0.4)	2.390 (0.6)	38.0 (17.0)	3.595 (0.6)
+-			100.0 (0.0)	4.385 (0.5)	100.0 (0.0)	6.262 (0.5)
++			6.3 (1.1)	0.230 (0.32)	5.3 (0.8)	0.130 (0.01)

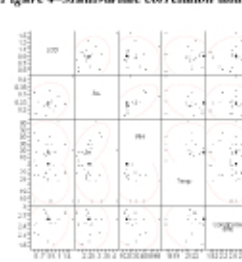
(b) Average punch coverage and rinstate data associated with upper punch adhesion

Code of Design	Temp (°C)	RH (%)	Aw	ESD (µm)	Avg No. of Ejection Force	Avg Upper Punch S.A. %	Avg Rinstate conc. (µg/ml)
--	21.3	16.3	0.201	0.89	21	1.6	0.680
0	21.6	13.4	0.207	0.92	242	75.4	3.671
+-	21.6	12.4	0.192	0.81	20	7.0	1.212
+	21.1	17.4	0.199	0.80	227	35.0	3.192
+-	21.2	24.3	0.248	0.79	324	190.8	7.284
++	21.2	44.4	0.324	0.71	92	5.0	0.180

### Adhesion to Tooling within the Design Space

Examining the data within this design by multivariate analysis for correlations between variables revealed partial positive correlations between surface water activity (Aw) and relative humidity.

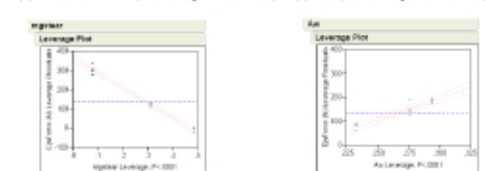
Figure 4—Multivariate correlation analysis



Ejection force analysis which is an indicator of sticking for the instrumented lower punches by stepwise forward/backward regression with Cp (Mallow's statistic) → p (number of parameters) showed (Figure 5) increased ejection force with decreased magnesium stearate levels and increased surface water activity (R<sup>2</sup><sub>adj</sub> 0.99):

Figure 5—Stepwise model regression for Ejection force (lower punches)

(a) lubricant level (F 710.7; prob= 0.0001) (b) Aw (F 90.90; prob= 0.0001)



Model Term	Estimate	Std Error	Prob.
Intercept	-117.83	45.9	0.03
Mg Stearate	-776.02	20.1	<0.0001
Aw	1798.488	188.6	<0.0001

Therefore, monitoring the surface moisture level is important for controlling sticking and picking. Most material sticking occurs easily with an increase in water content (Patel 2006). However, it has also been reported that the adhesive sticking force (measured by take off force) had a tendency to increase up to a water content of 3% w/w and decrease at high water content (Danjo 1997).

### Correlation of Punch Surface Image Analysis with HPLC

The average results of testing from this design space are presented in Table 2 (b) for ejection force, punch surface coverage and rinstate concentrations. Image analysis of surface coverages are well correlated to HPLC results (Figure 6). As expected, higher lubrication levels showed reduced sticking by both chemical and imaging methods as shown in Table 2a. The severity of sticking was more readily detected by the imaging technique.

Figure 6—Correlation of upper punch surface adhesion with chemical analysis

(a) (R<sup>2</sup><sub>adj</sub> 0.93)

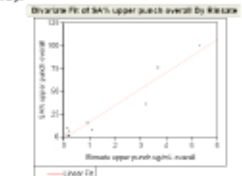
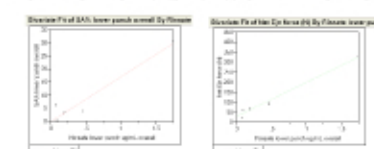


Figure 7—Correlation of lower punch surface adhesion

(a) by image analysis with ejection force (R<sup>2</sup><sub>adj</sub> 0.92) & (b) by rinstate with ejection force (R<sup>2</sup><sub>adj</sub> 0.97)



### Practical Implications of Lubricant Effectiveness

The results show ejection forces and image analysis of lower punches are effective in ascertaining adhesion issues, however image analysis is a direct probe of the sticking probability for upper punch control. As shown in Figures 1, 5a lubrication levels are inversely correlated with statistically significant effects on punch adhesion (p<0.001). Low lubrication levels amplify sticking potential and is statistically significantly affected by surface moisture levels (F=90.9, p<0.001). The boundary of failure for lubricity varies per surface moisture properties from day to day. Thus, inter days testing of gram quantities of blends to define this envelope with targeted environmental controls will help accurately define the envelope of failure.

## CONCLUSIONS

A material sparing (miniaturized) process was developed to qualitatively assess the tendency of various formulations for tooling adhesion during rotary press compression. Mini-tooling may be used as a predictive diagnostic tool in formulation and process optimization and process understanding. The screening method is quantitative, accurate, and quick and typically requires only gram quantities of API.

## REFERENCES

Aoki, S and K. Danjo, Effect of tableting conditions on the sticking of tablet using ibuprofen, Yakugaku Zasshi-Journal Of The Pharmaceutical Society Of Japan 118 (11): 511-518 Nov 1998  
 Danjo, K. et al. Effect of Water Content on Sticking during Compression, Chem. Pharm. Bull. 45(4) 1997 pp 706-709  
 Levine, M., Tablet Press Instrumentation in Swarbrick, J (ed.) Encyclopedia of Pharmaceutical Technology 3<sup>rd</sup> ed., 2002.  
 Patel, S. et al. Compression Physics in the Formulation Development of Tablets, Critical Reviews in Therapeutic Drug Carrier Systems, 23(1) 2006 pp 1-65  
 Roberts, M. et al. Effect of punch tip geometry and embossment on the punch tip adherence of a model ibuprofen formulation, J. Pharm. Pharmacol. 56 (2004) pp. 947-950  
 Waimar, F. et al. A Novel Method for the Detection of Sticking of Tablets, Pharm. Dev't Technol., 4(3) 1999 pp 359-367  
 Waimar, F., The Influence of Engravings on the Sticking of Tablets. Investigations with an Instrumented Upper Punch, Pharm. Dev't Technol., 4(3) 1999 pp 369-375  
 Wang, J. et al. Modeling of Adhesion in Tablet compression I. Atomic Force Microscopy and Molecular Simulation, J. Pharm. Sci., 92(4) 2003 pp 798-814