Quantitative and Miniaturized Assessment of External Lubrication to Reduce Tooling Adhesion in Early Formulation Development

Susan Lum[1], [2], Adam Heckman[1], Junfu Huang[1], Maureen McLaughlin[1] and Kwok Chow[1]

[1]Development Services, Patheon Inc., Mississauga, Ontario L5N 7K9, Canada, [2]To whom correspondence should be addressed www.patheon.com

ABSTRACT

Purpose: To assess the effect of externally applied magnesium stearate lubricant on the compression of unlubricated refractory blends with mini-tooling on a development scale rotary tablet press.

Method: Nonlubricated adhesive formulation blends (sorbitol in MCC 4:1 to 7:3 with folic acid 1% as a chemical tracer) were compressed in duplicate with less than 100g runs on an instrumented rotary press (Piccola) at 20 rpm under compression forces up to 5.6 x 10^2 MPa. External lubrication was applied by volumetric feed of magnesium stearate powder at 2 g per hour into a venturi system with nitrogen at 20 psi to deliver fluidized magnesium stearate powder directly onto the punch faces and die during operation of the rotary press. Punch tips were examined (Scalar USB, MATLAB, HPLC analysis of rinsates) with image analysis after a minimum of 400 revolutions of the press to quantify the amount of powder adhered to the tooling. Dissolution profiles of the lubricated folic acid tablets were compared to assess dissolution retardation.

Results: Ejection forces, as a measure of punch adhesion, were reduced from > 300N in some cases to below 100N on average with the application of < 0.6% externally applied magnesium stearate. Moreover residue analysis of the upper punches showed that less than ca. 15% powder remained on the punches after external lubrication as contrasted with ca. 5.8 - 100% post compression for internally blended, lubricated tablets. Infilling of the pad areas of the embossing was reduced after compression with external lubrication. Chemical analysis confirmed a statistically significant drop in folic acid tracer on the punch faces after external lubrication.

Conclusions: A material sparing process to quantify the effectiveness of externally applied lubricants to prevent sticking to tooling under conditions for rotary compression was developed. Removing a portion of magnesium stearate from the blend and applying it at the tooling interface improves the effectiveness of the lubricant in reducing adhesion.

INTRODUCTION

External lubrication technology has the potential benefit to improve hardness and reduce tooling adhesion of tablets under manufacture. Commercialized and validated systems such as the K-tron or the Kikusui External Lubrication System (ELS-P1) are available for GMP manufacture on larger rotary systems; the latter uses an electrostatic charge to hold lubricant films to the upper punches prior to compression. However, development-scale proof-of-concept external lubrication technologies for limited material is lacking.

Miniaturized tooling run on a rotary tablet press augmented with external spray lubrication was used in this study to check on the intrinsic stickiness of blends and the degree to which that stickiness may be prevented with lubricants. It was a tool to probe the effectiveness of different levels of blend lubrication within and on tablets while conserving API. Adhesive blends with and without a chemical tracer and with varying levels of lubricant were run at high speeds for sufficient long periods of time to simulate normal production. The effect of externally applied magnesium stearate on compression was assessed to:

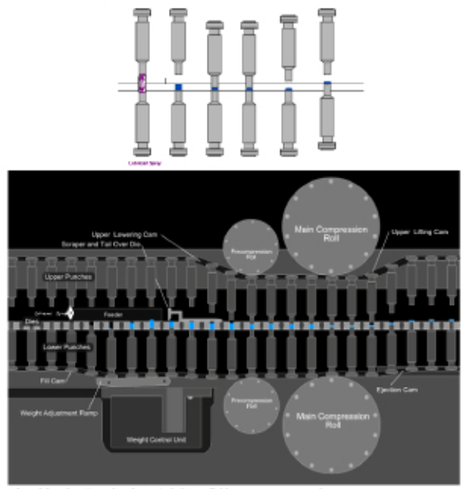
- Quantify and evaluate the effect on ejection forces and sticking on tooling faces
- Examine the utility of a diagnostic tool to probe potential issues for sticking in formulations

METHODOLOGY

Blending and Compression

Adhesive powder blends each consisting of MCC (PH102) and sorbitol (USP) with folic acid 1% as a chemical tracer (Table 1) were run unlubricated or with various amounts of magnesium stearate as a lubricant. Compression was performed in duplicate on an instrumented rotary press (Piccola) with less than 100g for a minimum of 400 revolutions at 20 rpm. External lubrication was applied by feeding fluidized magnesium stearate in nitrogen (input regulated at 20 psi) at ca. 2g per hour using a venturi system directly onto punch surfaces (Figure 1). The upper and lower punch tips were examined under a portable microscope camera and the degree of surface coverage (filming) was quantified by image analysis of digital scans with a MATLAB program. The results were compared with the folic acid content of the rinsate of each tooling face by HPLC. Dissolution profiles of the lubricated vs. non lubricated tablets were also compared.

Figure 1–Schematic of external lubrication application



Adapted from http://en.wikipedia.org/wiki/Image:Tablet_press_animation.gif

Experimental Design

A 2^2 screening design with point augmentation is presented in Table1. Statistical analyses were performed using a statistical software package (JMP 5.0, SAS Institute).

Table 1–Experimental screening design – matched pair response on compression before and after external spray lubrication application

Run #	Code of Design	Magnesium stearate (%)	Sorbitol (%)	External lubrication spray
1	--	0	70	With and without
2	-+	0	80	With and without
3	+-	0.5	70	With and without
4	++	0.5	80	With and without
5	-0	0.15	70	With and without

RESULTS AND DISCUSSION

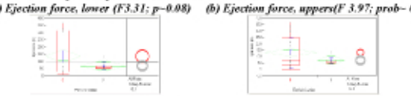
Reduction of Tooling Adhesion by External Lubrication

The aim of the present study is to examine the degree to which externally applied lubrication may reduce material adhesion with adhesive blends to tablet tooling. As shown in Figure 2 (a) through (d), analysis of variance (ANOVA) of the tooling surface coverage, ejection force and recovered punch rinsates stratified to either with or without externally applied lubrication showed that sticking or filming was statistically significantly reduced with external lubrication in all cases for both tablets with and without internally blended magnesium stearate. The α level for inclusion was set to 0.10 in consideration of the small sample size.

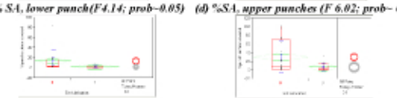
Figures 3 and 4 along with Tables 3 and 4 also indicated that a combination of both internal and externally applied lubrication can produce synergistic effects in reducing tooling adhesion.

Figure 2 ANOVA for compression either with or without external lubrication

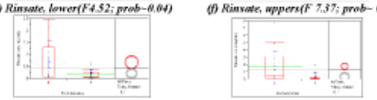
(a) Ejection force, lower (F3.31; p=0.08) (b) Ejection force, uppers(F 3.97; prob= 0.05)



(c) % SA, lower punch(F4.14; prob=0.05) (d) %SA, upper punches (F 6.02; prob= 0.02)



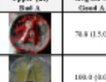
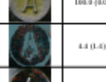
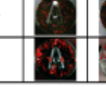
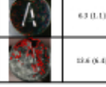
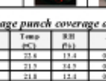
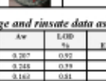
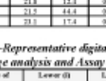
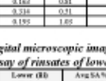
(e) Rinsate, lower(F4.52; prob=0.04) (f) Rinsate, uppers(F 7.37; prob= 0.01)



Differences in Tooling Adhesion on Upper and Lower Punches

Tables 3, 4, 5, 6 summarize the upper and lower punch face images, the ejection force, and the recovered punch rinsate data for before and after external lubrication spray. The results showed improvement of punch sticking with external lubrication between the upper and lower punch is statistically significant with less adhesion occurring on the lower punches in all cases. The results are consistent with the industrial experience that tooling adhesion occurs less frequently on the lower punches.

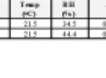
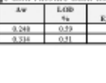
Table 3–Representative digital microscopic images used for image analysis of adhesion
(a) Image analysis and Assay of rinsates of upper punches before external lubrication

Code of Design	Upper (i) Good A	Upper (ii) Bad A	Avg SA% Good A	Avg Conc. Good A	Avg SA % Bad A	Avg Conc Bad A
--			78.8 (15.0)	2.193 (0.3)	72.8 (0.3)	4.949 (0.2)
-+			100.0 (0.0)	0.305 (0.5)	100.0 (0.0)	0.265 (1.5)
+-			4.4 (1.6)	0.691 (0.3)	11.3 (0.8)	1.535 (0.2)
++			6.3 (1.1)	0.218 (0.02)	5.5 (0.0)	0.110 (0.01)
-0			13.6 (8.4)	2.190 (0.6)	58.0 (17.0)	3.995 (0.0)

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

Code of Design	Temp (oC)	RH (%)	Aw	LOD %	Avg Net Ejection Force	Avg Upper Punch SA %	Avg Rinsate conc (ug/mL)
--	22.8	19.4	0.207	0.92	243	75.4	5.671
-+	21.5	34.7	0.248	0.59	528	100.0	5.286
+-	21.8	12.3	0.162	0.81	86	7.8	1.212
++	21.5	44.4	0.316	0.51	59	5.8	0.188
-0	23.1	17.4	0.195	1.05	247	55.8	5.192

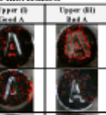
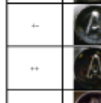
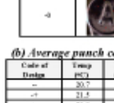
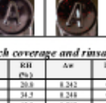
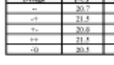
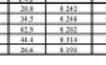
Table 4–Representative digital microscopic images used for image analysis of adhesion
(a) Image analysis and Assay of rinsates of lower punches before external lubrication

Code of Design	Lower (i) Good A	Lower (ii) Bad A	Avg SA% Good A	Avg Conc. Good A	Avg SA % Bad A	Avg Conc Bad A
-+			19.1	2.274	57.4	1.218
++			4.5	0.222	2.6	0.162

(b) Average punch coverage and rinsate data associated with lower punch adhesion

Code of Design	Temp (oC)	RH (%)	Aw	LOD %	Avg Net Ejection Force	Avg Lower Punch SA %	Avg Rinsate conc (ug/mL)
-+	21.5	34.7	0.248	0.59	318	30.6	1.746
++	21.5	44.4	0.316	0.51	59	3.5	0.192

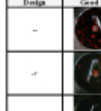
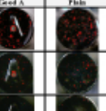
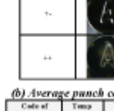
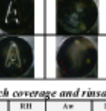
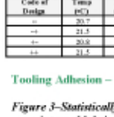
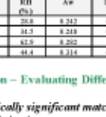
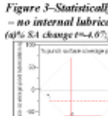
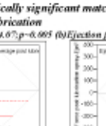
Table 5–Images analysis of adhesion and rinsate assay of upper punches
(a) After external lubrication

Code of Design	Upper (i) Good A	Upper (ii) Bad A	Avg SA% Good A	Avg Conc. Good A	Avg SA% Bad A	Avg Conc Bad A
--			11.3	0.825	18.8	1.816
-+			12.6	0.171	5.7	0.804
+-			0.2	0.110	8.2	0.110
++			0.3	0.073	3.0	0.891
-0			0.3	0.171	2.5	0.161

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

Code of Design	Temp (oC)	RH (%)	Aw	LOD %	Avg Net Ejection force	Avg Upper Punch SA %	Avg Rinsate conc (ug/mL)
--	20.7	20.8	0.242	0.67	93	15.0	0.928
-+	21.5	34.7	0.248	0.59	67	9.2	0.128
+-	20.8	12.9	0.202	1.17	61	0.2	0.114
++	21.5	44.4	0.314	0.51	59	0.4	0.108
-0	20.5	26.6	0.199	1.03	63	1.5	0.166

Table 6–Images analysis of adhesion and rinsate assay of lower punches
(a) After external lubrication

Code of Design	Lower (i) Good A	Lower (ii) Flats	Avg SA% Good A	Avg Conc. Good A	Avg SA% Bad A	Avg Conc Bad A
--			2.6	0.505	5.2	0.424
-+			3.4	0.233	2.2	0.113
+-			0.2	0.001	8.3	0.877
++			0.2	0.099	8.2	0.860

(b) Average punch coverage and rinsate data associated with lower punch adhesion

Code of Design	Temp (oC)	RH (%)	Aw	LOD %	Avg Net Ejection force	Avg Lower Punch SA %	Avg Rinsate conc (ug/mL)
--	20.7	20.8	0.242	0.67	93	3.9	0.405
-+	21.5	34.7	0.248	0.59	67	2.6	0.172
+-	20.8	12.9	0.202	1.17	61	0.2	0.108
++	21.5	44.4	0.314	0.51	59	0.2	0.179

Tooling Adhesion – Evaluating Difference with External Lubrication

Figure 3–Statistically significant matched response (80% sorbitol) – no internal lubrication
(a)% SA change t=-4.67; p=0.005 (b)Ejection force t*=-24.4; p<0.0001 (c) Rinsate change t*=-3.03; p=0.01*

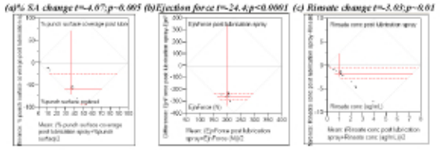
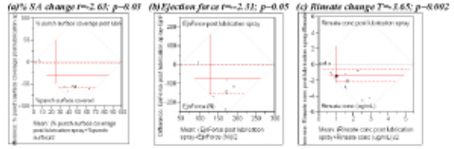


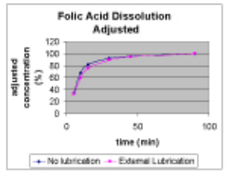
Figure 4–Statistically significant matched response (70% sorbitol) – no internal lubrication
(a)% SA change t=2.68; p=0.03 (b)Ejection force t*=-2.33; p=0.05 (c) Rinsate change T*=3.65; p=0.002*



Influence of Surface Lubricant Level on Dissolution Profile

Slight but statistically significant dissolution retardation is observed at early timepoints (Figure 5). Based on spray rate control of 1g to 4.5g 450 rotations and assuming all of the lubricant adhered solely to the 4 sets of tooling, the maximum externally applied lubricant load is 0.6%. The results suggest that adding a hydrophobic component to the tablet surface may change the wetting and dissolution.

Figure 5–Dissolution profile before and after external lubrication(70% sorbitol; 0.13% internally blended magnesium stearate)



CONCLUSIONS

Sticking particularly on the small scale to embossing is a first sign of potentially poor tablet quality and production failure on scale up. Ejection forces together with image analysis of lower punches are effective in ascertaining adhesion issues. Image analysis appears to be a more sensitive and direct measure of the sticking/picking potential for upper punch control. Imaging of tooling faces revealed material adhesion that was not detected by ejection force levels (< 100N).

Externally applied lubrication reduces punch surface coverage, ejection forces and recovered chemical rinsate levels; all indicators of the degree of punch adhesion. Removing a portion of magnesium stearate from the blend and applying it at the tooling interface improves the effectiveness of the lubricant in reducing tooling adhesion. The relative amount of magnesium stearate applied to the inside and outside of a tablet should be rationalized, eg. by the ratio of surface area relative to tablet mass and the flow properties of the blend, to maximize the processing capability and minimize dissolution retardation.