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Formulation and process optimization to eliminate picking from market image tablets

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Abstract

A tablet formulation when compressed using market image tooling may cause picking of powder. A D-optimal statistical experiment was designed to optimize the direct compression formulation and the process to alleviate picking of powder. The effects of levels of magnesium stearate, colloidal silicon dioxide (CSD), and lubrication time on picking were investigated using original compression tooling. These optimization results provided a small robust manufacturing region, hence a change in the cut angles of embossed letters and numbers from 70° to 90° in the modified compression tooling was evaluated. A statistical analysis of the data identified a robust manufacturing region that included formulations containing magnesium stearate 1–1.25% w/w, CSD 0.1–0.3% w/w, with a lubrication time of 5–10 min when compressed using modified compression tooling. The results indicate a significant reduction in picking by increasing the cut angles of embossed letters and numbers in the modified compression tooling. By evaluating interactions between various variables, we demonstrate a concentration dependent effect of CSD on the lubrication efficiency of magnesium stearate and compactability of microcrystalline cellulose containing formulation. In addition, the lubrication efficiency of magnesium stearate is maintained by blending CSD with powder blend prior to lubrication with magnesium stearate.

Keywords: Compression tooling; Experimental design; Formulation optimization; Picking; Lubrication

1. Introduction

Manufacture of tablets by direct compression of powder blend is a process of choice because it offers considerable advantages such as simplicity of process, cost effectiveness, reduced production and processing time, and elimination of contact with moisture and heat. A direct compression process places a greater emphasis on the physical and mechanical properties of drug substance and powder blends to allow manufacture of tablets. The impact of drug substance properties can be more profound in cases of high drug loading. During formulation development, scale-up and manufacturing, various issues including reduction in hardness, effect of press speed, capping, lami-

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nation, sticking, picking, filming, chipping and weight variation may be encountered during compression. Picking refers to adherence of powder to the punch surface and non-adherence to the debossing of the tablet (Gunsel and Kanig, 1976). This paper describes picking and punch filming (powder adherence to the face of tooling only) observed during direct compression of market image tablets containing high drug load (approximately 40–50% w/w). Various approaches to resolve these challenges by optimizing tooling, formulation and processing variables during process scale-up are reported. The utility of experimental design in identifying critical formulation and processing variables to achieve a robust compression process for debossed tablets is highlighted.

In this study, the goal of the experimental design was to find the optimal combination of formulation and process factors to eliminate picking during compression of market image tablets. The effect of different levels of magnesium stearate, colloidal silicon dioxide (CSD or Cabosil®), and lubrication time on picking during process scale-up was investigated using an experimental design. As the efficiency of mixing process is dependent on the mixer size and geometry, batch size and mixing dynamics, the 50 kg batches utilized in the design were processed using pilot scale equipment that follow the same principle and design as production equipment. Hence, the data obtained from this pilot scale study is relevant to production batches. Initially, the experimental design was conducted using the original embossed tooling (70° cut angle). The impact of compression tooling design was further evaluated by compressing selected batches with modified chrome-plated compression tooling (90° cut angle).

The discussion in this article is divided into three sections, one for the original compression tooling, a second for the modified compression tooling, and the last section deals with effects of various factors on tablet hardness. Based on the results, from the statistical optimization procedure, the formulations containing magnesium stearate 1–1.25% w/w, CSD 0.1–0.3% w/w, with a lubrication time of 5 min, and compressed with the modified compression tooling produced acceptable market image tablets by eliminating picking. Higher levels of CSD reduced lubrication efficiency of magnesium stearate and the lack of lubricity of magnesium stearate was manifested as picking on tablets. In-process data indicated that average weight, friability, disintegration time, and hardness of the tablets remained well within specification limits at all parameter levels for the experimental design batches.

2. Materials and methods

2.1. Materials

The following materials were used as received: Active (Glaxo Wellcome, Montrose, UK), microcrystalline cellulose NF (Avicel® PH102-FMC Corporation), sodium starch glycolate NF (Explotab®-Mendell Company), colloidal silicon dioxide NF (Cab-O-Sil® M-5 – Cabot Corporation), and magnesium stearate NF, (vegetable source – Ackros Inc).

2.2. Methods

2.2.1. Manufacturing process

The manufacturing process involved the following unit operations.

2.2.1.1. Weighing and sieving. Components were weighed from bulk containers into polyethylene-lined drums, sieved through a Russell-SIV and were transferred to the bulk blending bins for blending. A 630 μm/30 mesh sieve was used for all excipients, except magnesium stearate which was sieved through 125 μm/120 mesh to produce a smaller particle size. Decreasing the particle size of magnesium stearate has been shown to improve the lubricant properties of magnesium stearate (Leinonen et al., 1992). To facilitate the screening of CSD, it was combined with a portion of microcrystalline cellulose during screening.

2.2.1.2. Blending. A 250 l bulk bin blender was charged with active ingredient, Sodium starch glycolate NF, CSD NF/microcrystalline cellulose NF

screened mixture and the remainder of Microcrystalline cellulose NF, and blended for approximately 20 min at 17 rpm. Magnesium stearate NF was added and blended for lubrication for 5 or 10 min (as per experimental design) at 17 ± 2 rpm.

2.2.1.3. Compression. The lubricated blend was compressed using either original or modified embossed tooling. The typical parameters for compression using a Manesty Unipress are presented in Table 1. In-process controls for tablet weight, thickness, and hardness was applied at appropriate intervals throughout the compression process and adjustments to the tablet press were made if necessary. Friability and disintegration time tests were performed at the start-up and end of compression.

In order to understand the interactions between magnesium stearate, CSD and lubrication time, compaction profiles were obtained at the start of compression. The tablets were compressed at compression forces of 13–14 kN, 18–20 kN, and 25 kN and tablet hardness was determined.

2.2.2. Experimental design

A 10-run D-optimal experimental design was generated using Design Expert 5 (DX-5®) to evaluate the following factors at the corresponding levels.

- Magnesium stearate (0.75, 1.0 and 1.25% w/w).
- Colloidal silicon dioxide (0.1 and 0.3% w/w).
- Lubrication time (5 and 10 min).

Table 1
Typical parameters for compression (Manesty, Unipress)

Compression parameter	Target setting
Compression speed	1400 tablets/min
Feeder speed	1.0
Main compression force	17.5 kN
Precompression force	0
Penetration depth for main compression	5 mm
Penetration depth for precompression	5 mm
Fill depth	13.75 mm

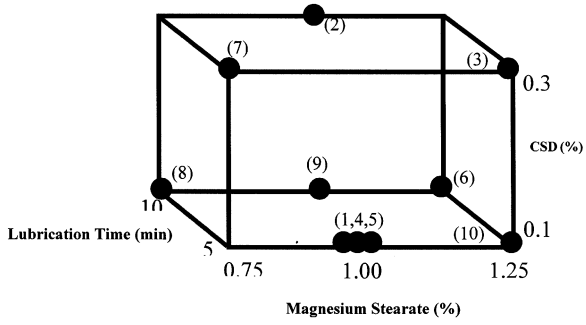


Fig. 1. Graphical representation of the D-optimal design: various factors and their levels.

This design was utilized to evaluate critical formulation and process parameters by compressing pilot scale batches (50 kg) on a 27 station Manesty Unipress tablet press using original (70° cut angle) compression tooling. The D-optimal design allowed studying multiple factors with varying levels using a minimal number of experiments. The graphical representation of the design is given in Fig. 1. This design also allows estimation of main effects, two factor interactions and the quadratic effect of magnesium stearate. The design included three replicates of a run to allow estimation of variability. The factors evaluated, interactions studied, and responses measured are presented in Table 2.

The number of tablets, tooling and letters picked were measured as responses by visual inspection of punch and tablet surfaces. A random sample of 800 tablets taken from each experimental run was above the requirements of military standard 105 for a batch size of approximately 63 000 tablets. A total of 27 tooling each embossed with five letters/numbers, was used in the Manesty press to compress each batch. The total number of tablets, tooling and letter picked using original compression tooling are shown in Table 3. The hardness, thickness, disintegration time and weight variation of the tablets from each batch were also recorded. The impact of modifications in cut angles in embossed letters and numbers was investigated by compressing selected batches from the experimental design with modified chrome-plated compression tooling (90° cut angle).

3. Results and discussion

The actual experimental layout is presented with summarized results in Table 3. Detailed results specific to tooling type and other factors are discussed below.

3.1. Analysis of data – original compression tooling (70° cut angle)

For each response, a model was selected using a backward elimination selection procedure (cut-off P-value = 0.1). The selected models were hierarchical in nature, i.e., if an interaction term was deemed appropriate for the model, the associated linear terms were also retained irrespective of their individual significance levels. Table 4 shows the reduced models (along with the significance levels associated with each model term) selected for each response.

Fig. 2(A) shows a two-dimensional contour plot of the predicted number of letters picked as the CSD and magnesium stearate levels are varied while the lubrication time is fixed at 5 min. Since lubrication time showed no effect within the range of 5–10 min on the degree of picking, plots are not shown for 10-min lubrication times. The degree of picking was very high at the highest level of CSD (0.3% w/w). The curvature in the plot is due to quadratic dependence on magnesium stearate concentration. The predicted numbers of letters picked was near zero at 0.1% w/w CSD and magnesium stearate levels between 1.12 and 1.25% w/w. The number of tooling picked also showed similar tendencies (Fig. 2(B)). For the number of tablets picked, the residual plot of residual versus predicted indicated that a transformation of the response may be required. Hence, a transformation (the number of tablets picked + $0.01)^{0.2}$ was applied. The results indicated that only magnesium stearate and CSD significantly affected number of tablets picked as shown in Fig. 2(C). The lubrication time had no effect on the number of tablets picked. The predicted number of tablets picked was nearly zero only at low CSD and high magnesium stearate concentrations.

The tablet hardness remained within the desired range of 23–27 kP for each combination of magnesium stearate and at lubrication times of 5 min (Fig. 3(A)). At the 10-min lubrication time, the predicted tablet hardness was slightly less than 23 kP at low CSD and high magnesium stearate levels (Fig. 3(B)). Tablet thickness alternatively was only impacted by CSD. The tablets were thicker at high levels of CSD. Furthermore, there was greater variability in thickness values at low CSD values. The disintegration time marginally increased with increases in magnesium stearate concentration but remained well within specifications. None of the factors affected the weight variation of the tablets indicating that material flow was similar for all batches.

Table 2
Factors, interactions, and responses included in design of experiments

Factors evaluated	Interactions studied	Responses measured
Magnesium stearate level (0.75, 1.00, and 1.25% w/w)	Magnesium stearate × magnesium stearate (quadratic effects of magnesium stearate)	Letters picked[a]; tooling picked[b]; tablets picked[c]; hardness; thickness; disintegration time
CSD level (0.1 and 0.3% w/w)	Magnesium stearate × CSD	Weight variation RSD; dissolution
Lubrication time (5 and 10 min)	Magnesium stearate × lubrication time Lubrication time × CSD	

[a] Letters picked refer to the total number of letters picked (out of 135) as determined by visual inspection of punch surfaces.
[b] Tooling picked refers to the total number of punches (out of 27) where picking was observed as determined by visual inspection of the punch surfaces.
[c] Tablets picked refer to the total number of tablets (out of 800 sampled) where picking and filming were observed as determined by visual inspection of cores.

Table 3
Responses from experimental design runs using original compression tooling

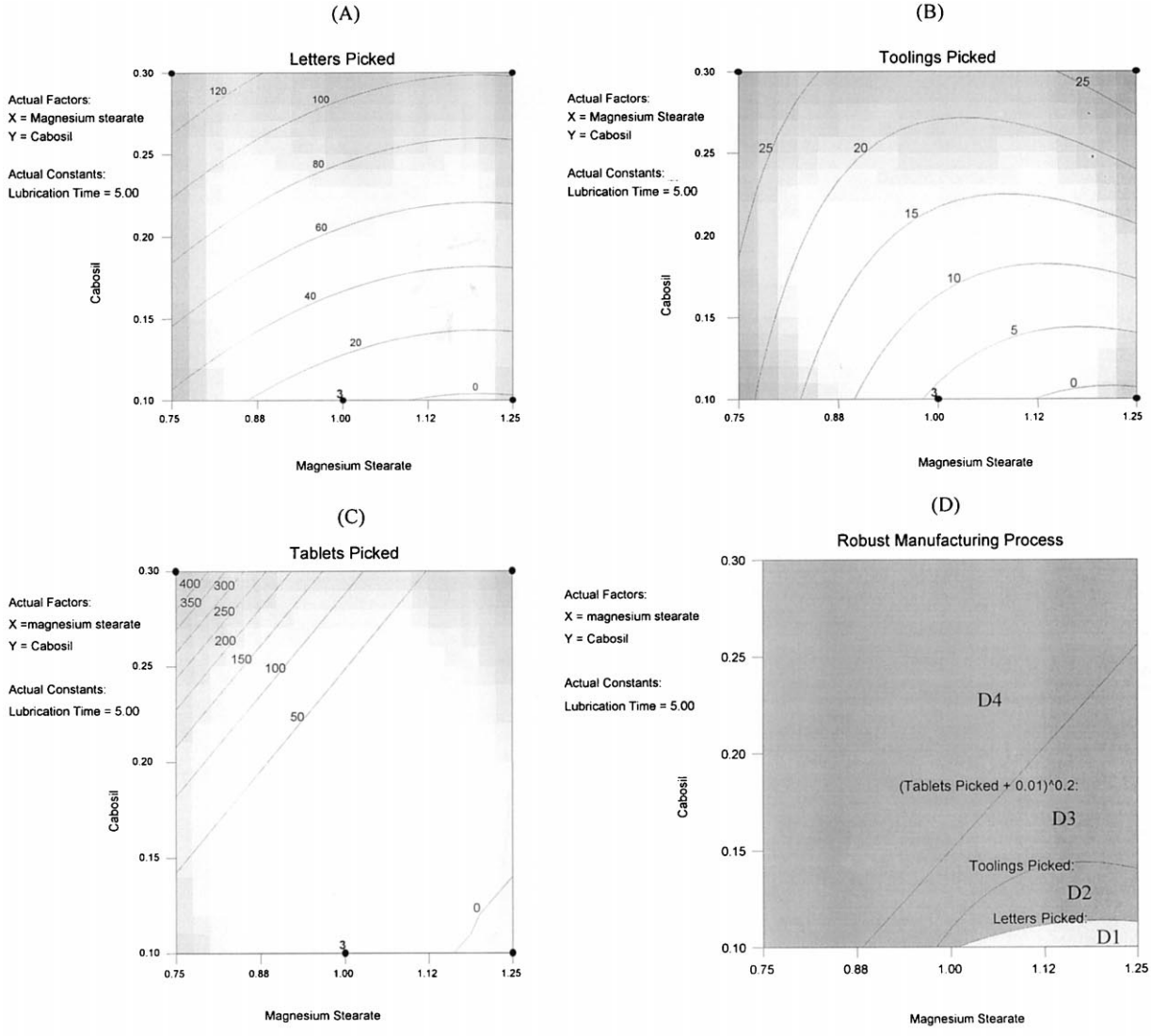
Run	Mg St (% w/w)	Lubrication time (min)	CSD (%w/w)	Letters picked (# out of 135)	Tooling picked (# out of 27)	Tablets picked (# out of 800 sampled)	Hardness (kP)	Thickness (mm)	Compression force (kN)	DT[a] (min)	RSD weight (%)
1	1	5	0.1	13	10	21	24.08	6.36	13.9	30	0.33
2	1	10	0.3	116	27	68	25.06	6.38	13.7	39	0.5
3	1.25	5	0.3	98	27	14	23.83	6.36	13.9	36	0.34
6	1.25	10	0.1	0	0	0	22.24	6.256	19.2	45	0.4
9	1	10	0.1	0	0	0	22.78	6.194	17.5	63	0.5
4	1	5	0.1	2	2	0	23.77	6.24	13.6	45	0.38
5	1	5	0.1	0	0	0	24.86	6.274	14	48	0.42
7	0.75	5	0.3	135	27	800	24.8	6.375	12	20	0.4
8	0.75	10	0.1	41	24	38	24.9	6.116	18.6	22	0.39
10	1.25	5	0.1	0	0	0	24.2	6.244	14.6	38.5	0.53

[a] DT – disintegration time.

Table 4
Reduced statistical model selected for each response with original compression tooling

Letters picked	Tooling picked	Tablets picked[a]	Hardness	Thickness	Compression force	Disintegration time	RSD weight
Intercept	Intercept	Intercept	Intercept	Intercept	Intercept	Intercept	Intercept only
MgSt ($P = 0.0006$)	MgSt ($P = 0.0442$)	MgSt ($P = 0.0106$)	MgSt ($P = 0.0317$)	CSD ($P = 0.0189$)	MgSt ($P = 0.0428$)	MgSt ($P = 0.0677$)	
CSD ($P < 0.0001$)	CSD ($P = 0.0024$)	CSD ($P = 0.0037$)	CSD ($P = 0.1403$)		CSD ($P = 0.0013$)	MgSt*MgSt ($P = 0.0483$)	
MgSt*MgSt ($P = 0.0296$)	MgSt*MgSt ($P = 0.0925$)		Lubrication time ($P = 0.9300$)		Lubrication time ($P = 0.0016$)		
	MgSt*CSD ($P = 0.0442$)		MgSt*MgSt[b] ($P = 0.1788$)		MgSt*MgSt ($P = 0.0506$)		
			Lubrication time *CSD ($P = 0.0521$)		MgSt*CSD ($P = 0.0949$)		
					Lubrication time* CSD ($P = 0.0417$)		

[a] Values of this response were transformed (nature of transformation discussed in Section 3.1).
[b] If this term is taken out of the model, all the remaining terms become insignificant. Thus, this term was kept in the model despite its high P-value.



Note:

Region D1: Robust Manufacturing Region - (Tablets Picked+0.01)^0.2 < 1.38, Toolings Picked < 5, Letters Picked < 5

Region D2: Letters Picked > 5

Region D3: Letters Picked > 5, Toolings Picked > 5

Region D4: Letters Picked > 5, Toolings Picked > 5, (Tablets Picked + 0.01)^0.2 > 1.38

Fig. 2. Contour plots of picking – original compression tooling.

3.2. Robust manufacturing process using original compression tooling (70° cut angle)

The graphical optimization procedure in DX-5 was used to predict a robust manufacturing region. This procedure allowed simultaneous optimization of a given set of responses subject to certain restrictions. These restrictions reflect the

values of the responses that are considered desirable. In realization of the variability associated with any statistical model, the restrictions on picking were relaxed from zero to a maximum of five. Five represents the upper limit from a 95% prediction interval at the optimum design conditions for the original and modified compression tooling. Therefore, the maximum allowable number of letters picked, tooling picked, and tablets picked were each restricted to less than or equal to five.

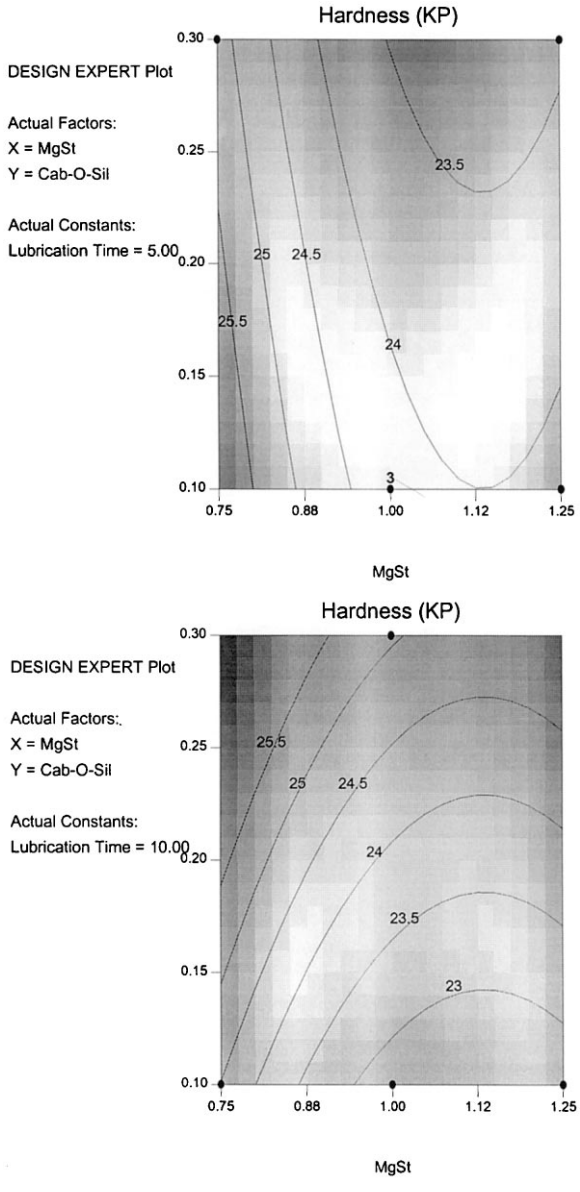


Fig. 3. Two-dimensional contour plots of tablet hardness.

Based on statistical analysis and the picking restrictions discussed earlier ($\leqslant 5$), the robust manufacturing region, as predicted for original compression tooling, is graphically presented by the lighter region (D1) in Fig. 2(D). The approximate factor levels needed to produce desirable tablets using original compression tooling are: (1) 0.1% w/w CSD, (2) 1.12–1.25% w/w magnesium stearate, and (3) a lubrication time of 5–8 min. Experimental run number 10 (0.1% w/w CSD, 1.25% w/w magnesium stearate, and a lubrication time of 5 min) had factor levels within these ranges. To achieve optimum tablet formulation, using original compression tooling, CSD must be kept at its lowest level (0.1% w/w). This robust region is very small and does not provide assurances of manufacturing process robustness.

3.3. Analysis of data – modified compression tooling (90° cut angle)

Since severe picking and a small robust manufacturing region was obtained using original compression tooling (70° cut angle, without any chrome plating), changes in the tooling design were made. The effect of modified compression tooling that had 90° cut angle in embossing with chrome plating was evaluated. Chromium plating of punch faces can produce a smooth and non-adherent face thereby reducing picking (Gunsel and Kanig, 1976). Runs 2, 3 and 7 which demonstrated the worst picking with original compression tooling were evaluated with modified compression tooling. Run 5, which did not show any picking with original compression tooling was selected as a control run. Results in Table 5 indicate that for these runs, the modified compression tooling performed significantly better than the original tooling in terms of picking. Due to this trend, the other batches that had shown minor or no picking with the original embossed tooling were not evaluated with the modified tooling. The assumption was made that if no picking was observed with a batch using original tooling

Table 5
Picking results using modified compression tooling

Run	MgSt (%)	Lubrication time (min)	CSD (%)	Letters picked	Tooling picked	Tablets picked
1	1	5	0.1	0	0	0
2	1	10	0.3	0	0	0
3	1.25	5	0.3	0	0	0
6	1.25	10	0.1	0	0	0
9	1	10	0.1	0	0	0
4	1	5	0.1	0	0	0
5	1	5	0.1	0	0	0
7	0.75	5	0.3	0	27	300
8	0.75	10	0.1	15	15	14
10	1.25	5	0.1	0	0	0

then it will also not pick with modified tooling. Hence of these runs (with the exception of run 8), the number of letters and toolings picked were assigned a value of zero. For run 8 that showed some picking with original compression tooling, the picking values with modified compression tooling were assigned based on scientific experience and trends seen with the original compression tooling.

The responses measured in these runs using modified compression tooling were the number of letters, tooling and tablets picked. During data analysis, a model was selected for each response using a backward elimination procedure and a cut-off P-value of 0.10. Table 6 shows the reduced model along with significance levels associated with each model term selected for each response. Because of the abundance of zeros in the data set, the models for letters picked, tooling picked and tablets picked did not fit the data exceptionally well in terms of the predicted R^2 values. However, the models are adequate to detect trends in the data and ultimately determine an approximate robust manufacturing region. This is evident upon comparing the robust manufacturing region (Fig. 4) to the raw data (Table 5).

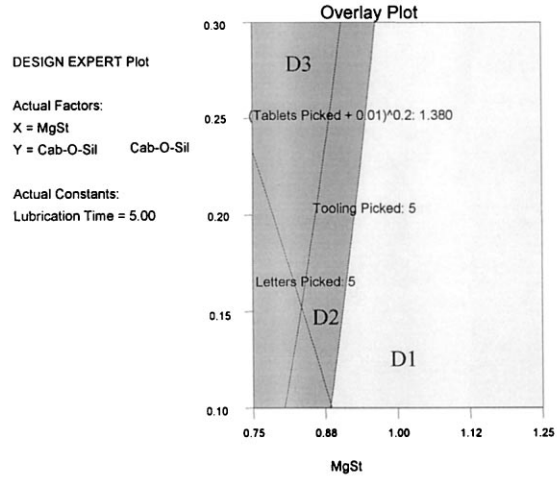
3.4. Robust manufacturing process using modified compression tooling (90° cut angle)

Based on the statistical analysis and the picking restrictions discussed earlier ($\leqslant 5$), the trends observed with the modified compression tooling indicate a larger region which will produce acceptable tablets. This region include 0.1–0.3% w/w CSD, 1.0–1.25% w/w magnesium stearate, and a lubrication time of 5–10 min using modified compression tooling. This region is represented as a robust manufacturing region D1 in Fig. 4. This region is large (approximately 25 times larger) compared to the region (D1) predicted for original compression tooling in Fig. 2(D) and provides greater assurances to the robustness of the process with respect to manufacturing region.

Table 6
Reduced statistical models selected for picking with modified compression tooling

Letters picked	Tooling picked	Tablets picked[a]
Intercept	Intercept	Intercept
MgSt ($P<0.0001$)	MgSt ($P<0.0001$)	MgSt ($P=0.0002$)
Lubrication time ($P<0.0001$)	CSD ($P=0.0442$)	CSD ($P=0.0442$)
CSD ($P<0.0001$)	MgSt*MgSt ($P=0.0006$)	MgSt*MgSt ($P=0.0020$)
MgSt*MgSt ($P<0.0001$)	MgSt*CSD ($P=0.0216$)	MgSt*CSD ($P=0.0216$)
MgSt*Lubrication time ($P<0.0001$)		
MgSt*CSD ($P<0.0001$)		
Lubrication time*CSD ($P<0.0001$)		

[a] Values of this response were transformed (nature of transformation discussed in text).



Note:
Region D1: Robust Manufacturing Region - (Tablets Picked+0.01)^0.2 < 1.38, Toolings Picked < 5, Letters Picked < 5
Region D2: Toolings Picked > 5, Letters Picked > 5
Region D3: Toolings Picked > 5, Letters Picked > 5, (Tablets Picked + 0.01)^0.2 > 1.38

Fig. 4. Overlay plot of robust manufacturing region using modified compression tooling.

These results highlight the importance of cut angles in embossed letters and numbers in the compression tooling in optimization of tablet formulation and process. The modified compression tooling provided a greater robust manufacturing process and region. This approach avoids the use of increasing concentration of magnesium stearate in the formulation that could impact tablet compression and may require additional stability data. The original compression tooling however, were more discriminatory in evaluating various formulations and allowed a greater understanding of the interaction between various factors and processes.

3.5. Effect of magnesium stearate level, colloidal silicon dioxide level, and lubrication time on the compression force versus tablet hardness profile

To better understand the interaction between lubricant/glidant levels and mixing times, the hardness versus compression force profiles were collected for various formulations using original compression tooling. The results indicated that hardness increased with an increase in the compression force. Satisfactory tablet hardness values, complying with the in-process control limits (21–29 kP), were achieved within a compression force range of 14–20 kN as shown in Fig. 5. The trends observed in the compression force profile indicated that the tablet hardness decreased as magnesium stearate level and lubrication times were increased. This can be attributed to reduction in interparticulate bonding upon increase in magnesium stearate concentration and in part due to extensive relaxation of the lubricated tablet (Zuurman et al., 1999).

For a fixed level of magnesium stearate, increase in lubrication time decreases tablet hardness. This has been attributed to the formation of lubricant film upon adhesion of magnesium stearate to the substrate surface and followed by gradual shearing off of the primary magnesium stearate particles from the distributed aggregates during the mixing process (Bolhuis et al., 1975; Kikuta and Kitamori, 1994). Although macroscopic uniformity during film formation has been suggested but microscopically the distribution of magnesium stearate may be non-uniform with preferential deposition in superficial cavities of the powder blend to smoothen surface irregularities

to be followed by formation of a peripheral layer of varying uniformity (Roblot-Treupel and Puisieux, 1986).

The data indicate that CSD interacts with magnesium stearate and affects lubrication efficiency of magnesium stearate. Lack of lubricity or lubrication efficiency is manifested as picking in the tablets. Magnesium stearate had higher lubrication efficiency when low amounts of CSD were present in the formulations as indicated by less picking but tablets had lower hardness values. Whereas at higher levels of CSD, lubrication efficiency of magnesium stearate is reduced resulting in more picking but tablet hardness was higher. Runs 2, 3, and 7 had higher levels of CSD and showed maximum picking. CSD influences the film formation by magnesium stearate during mixing, as has been reported (Lerk et al., 1977). CSD coats the particles of magnesium stearate and prevents the formation of lubricant film on the powder blend thereby resulting in the restoration of bonding properties and a higher tablet strength. The presence of CSD, therefore, suppresses the negative effect of magnesium stearate on the tablet bonding properties.

Johansson and Nicklasson (1987) have reported that CSD interacts primarily with the free fraction of the lubricant which is then not available for lubrication of the die wall or further coverage on the surface of the powder blend. In that study, when colloidal silica and magnesium stearate were added together during lubrication, the surface coverage was reduced and an increase in ejection force was observed (Johansson and Nicklasson, 1987). It appears that increase in levels of CSD reduces the free fraction of magnesium stearate available for lubrication thereby resulting in higher degree of picking.

Our results demonstrate a concentration dependent effect of CSD on lubrication efficiency of magnesium stearate. At high concentration (0.3% w/w), more CSD is available to interact with magnesium stearate and thus free magnesium stearate available for lubrication is reduced resulting in higher picking. The tablet hardness increases because of increased interparticle cohesive interactions between the powder. These effects are more pronounced when a plastically deforming excipient such as microcrystalline cellulose is used as is the case in the present study. The opposite

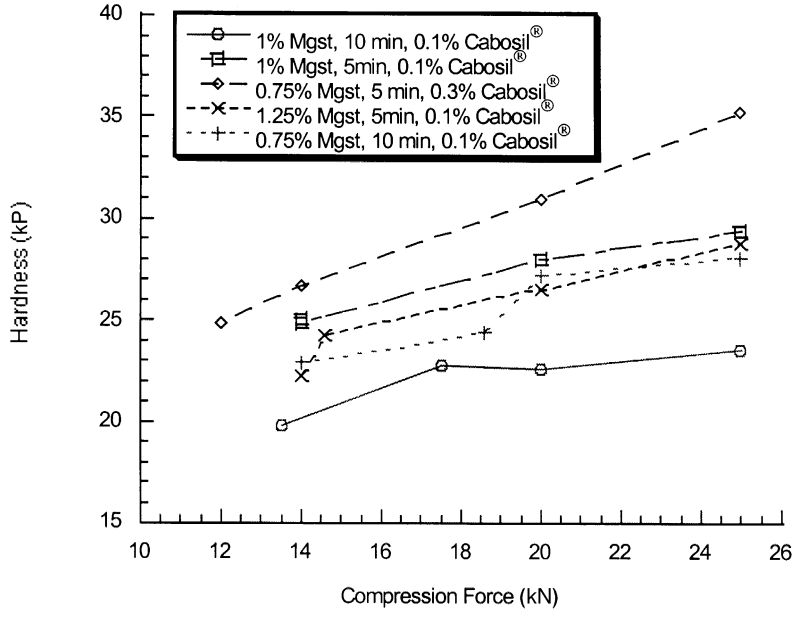


Fig. 5. Effect of compression force on tablet hardness.

effects were true at lower CSD concentrations of 0.1% w/w. These results emphasize the importance of cohesive and adhesive interactions in the ternary components powder systems (Rowe, 1988).

The order of mixing of CSD and magnesium stearate significantly effects the efficiency of lubrication. When CSD and magnesium stearate are added together during lubrication step: CSD coats magnesium stearate preferentially, resulting in less magnesium stearate being available for lubrication as manifested by increase in picking. However, interparticulate bonding or cohesive interactions between microcrystalline cellulose are higher and therefore tablet hardness is greater. When CSD is added during blending stage followed by magnesium stearate at the lubrication stage: CSD coats the blend particles preferentially, thereby, magnesium stearate is available for lubrication and hence picking is reduced. Premixing of CSD with powder blend followed by subsequent blending for a short period with magnesium stearate has been reported to reduce the deleterious effect of magnesium stearate on the binding properties of different excipients while still retaining its lubricating properties (Johansson and Nicklasson, 1987; Bolhuis and Holzer, 1996).

The learnings from interaction between CSD and magnesium stearate could be applied in different ways. Because of difficult material handling of CSD, formulation may be preferentially optimized without the use of CSD and with an optimum amount of lubricant, if required. If CSD is needed, lower amounts of CSD in formulations containing magnesium stearate and microcrystalline cellulose could be used to increase the lubricity of the magnesium stearate. CSD may be added to the formulations containing magnesium stearate and microcrystalline cellulose to increase interparticulate bonding and subsequently increase the hardness of the tablets. The mode of addition of CSD will dictate the magnitude of increase in hardness of tablets containing microcrystalline cellulose. These effects may be different for formulations where excipients used as filler/binder differ in deformation behavior from microcrystalline cellose.

4. Conclusions

Our results provide another approach in alleviating picking of powder during compression – by changing the cut angles in embossed letters and numbers in compression tooling. This study showed that by modifying the tooling and optimizing the process and formulation variables a robust manufacturing region could be identified where the manufacturing process reliably produces tablets of acceptable quality. This approach avoids the use of increasing concentration of magnesium stearate in formulation that could impact tablet compression and may require additional long-term stability data. This approach may also reduce the dependency of the compression process on the drug substance characteristics. The optimized process includes 0.1% w/w CSD (sieved through 20 mesh with a portion of microcrystalline cellulose) in the initial blend and 1.25% w/w magnesium stearate (sieved through 120 mesh) added for a lubrication time of 5 min, and utilized modified compression tooling. An increase in the cut angles of embossed letters/numbers from 70° to 90° in modified compression tooling significantly reduced the picking/filming. Interaction of CSD with magnesium stearate decreased the lubrication efficiency of magnesium stearate and increased the compactability of microcrystalline cellulose containing formulation. However, this effect was shown to be dependent upon the concentration of CSD. In addition, at a pilot scale, pre-blending of CSD with powder blend followed by lubrication with magnesium stearate maintained the lubrication efficiency of magnesium stearate while retaining the binding properties of plastically deforming excipients such as microcystalline cellulose.

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