The Impact of Tablet Compression Parameters for a Directly Compressible Formulation Containing a Model Low Dose API

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Introduction

Direct compression is the simplest method for manufacturing tablet, involving blending the active with suitable excipients to achieve desired powder and tablet properties. When formulating low-dose drugs, achieving good content uniformity (CU) becomes a primary critical quality attribute (CQA) for the tablets

The objective of this work was to study the impact of critical process parameters (CPPs) for tablet compression on selected quality attributes for a directly compressible formulation using a low-dose model drug, glimepiride.

Methods

Glimepiride with 1 mg strength, was used as a model low-dose drug. Since glimepiride is poorly water-soluble, lactose monohydrate was selected as a diluent. A novel excipient, StarTab®, directly compressible starch was used to provide good flow, compressibility, and disintegration for the tablet.

Table 1. Composition of Glimepiride 1 mg Tablets

Ingredients	% w/w	Mg/tablet
Glimepiride	1.00	1.00
StarTab	25.00	25.00
Lactose monohydrate spray dried	73.75	73.75
Magnesium stearate	0.25	0.25
TOTAL	100.00	100.00

Tablet Manufacturing:

Glimepiride, StarTab and lactose monohydrate were passed through ASTM #40 mesh screen, mixed in a blender for 10 mins at 20 rpm followed by lubrication for 2 min with magnesium stearate after passing through ASTM #60 mesh screen. The powder blend was evaluated for bulk density, tap density, powder flow and drug uniformity (n=10) with samples taken from different positions within the blender. Tablets were compressed using Cadmach 26 stations compression machine (CTX-26D) using 6.00 mm standard concave tooling and tested for weight, hardness, thickness, friability, and disintegration time followed by determination of CU in individual tablets (n=10).

Compression Parameters:

A 3-factor 2-level study was used for manufacturing glimepiride tablets (1mg) using Placket Burman Design with Fusion Pro 9 software (Table 2). Twelve trials were conducted to study the impact of compression parameters such as turret speed, feeder speed and compression force (Table 3) on tablet hardness, friability, disintegration time, CU and dissolution (CQAs). Operating ranges of 12 to 70 rpm and 10 to 60 rpm for turret and feeder speed, were used for this study with 25 and 50 rpm selected as turret and feeder speed, respectively. The main compression forces of 2.5 and 6.5 kN were used.

Table 2. Variables and Levels

Critical Process Parameters	-1	-1
Turret speed (rpm)	25	50
Force Feeder speed (rpm)	25	50
Compression force (kN)	2.5	6.5

Table 3. Experimental Design Matrix

Run No.	Turret Speed (rpm)	Feeder Speed (rpm)	Compression Force (kN)
1	50	50	2.5
2	25	50	6.5
3	25	25	2.5
4	25	50	2.5
5	50	50	2.5
6	25	25	6.5
7	25	25	2.5
8	25	50	6.5
9	50	50	6.5
10	50	25	6.5
11	50	25	2.5
12	50	25	6.5

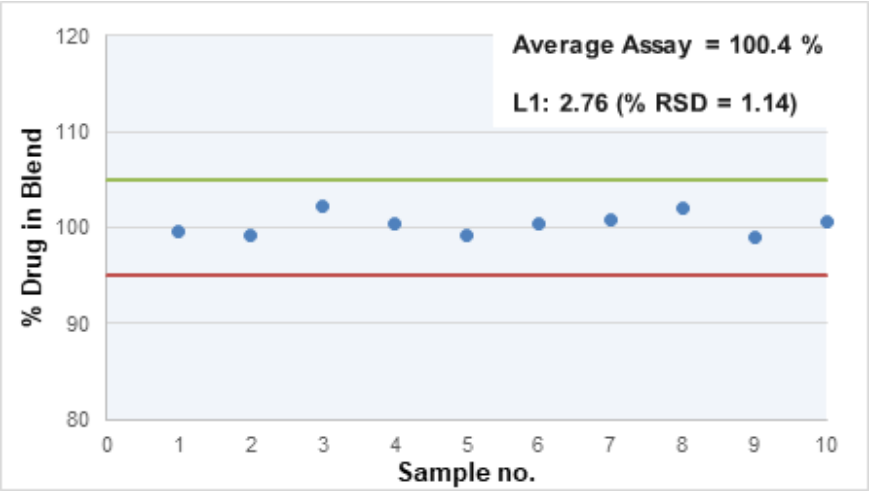
Table 4. Physical Properties of Powder Blend

Parameters	Glimepiride Blend
Bulk density (g/ml)	0.59
Tapped density (g/ml)	0.74
Compressibility index (%)	19.05
Hausner ratio	1.24
LOD (%)	3.45

Results

The powder blend showed satisfactory flow properties when compared with the API alone (Table 4) and the blend uniformity samples taken from 10 different positions within the blender (i.e., top, middle, and bottom) were found to be within an L1 value of 2.76 and % RSD of 1.14 (Figure 1).

Figure 1. Blend Uniformity from 10 Sample Locations



a. Tablet Physical Properties:

All tablets showed good hardness between 2.6 to 6.4 kP based on compression force in each run and low friability of 0.24-0.32% at 100 rotations. The disintegration time was from 20 seconds (compression force 2.5 kN) to 1.8 min (compression force 6.5 kN) and the overall tablet output of 640 to 650 units/ min and 1295 to 1310 units/ min was achieved at 25 and 50 rpm of turret speed, respectively.

b. Tablet Content Uniformity:

Drug content for 10 individual tablets from the 12 experimental runs was determined, and Acceptance Value (AV) was less than 6 in all compression trials suggesting very good drug uniformity in all tablets (Figure 2). The factors that influence the content uniformity along with their relative contribution are presented in the model term ranking Pareto chart (Figure 3) suggesting that feeder speed has a major impact. The effects plot and surface response curve for CU (Figure 4) confirmed that the AV decreased as the feeder speed decreased whereas the AV was slightly higher when the feeder speed was higher. The turret speed did not have much impact on AV, within the limits used in this study. The response surface is indicative of linear correlation, and the lowest AV was obtained at low feeder speed for all turret speeds and compression force values used in this study.

Figure 2. Acceptance Value (AV) for Glimepiride DOE Trials

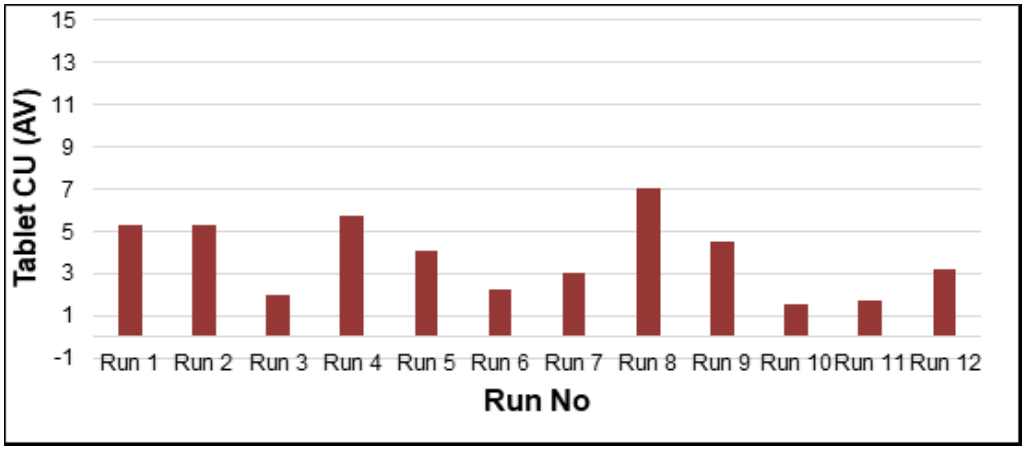
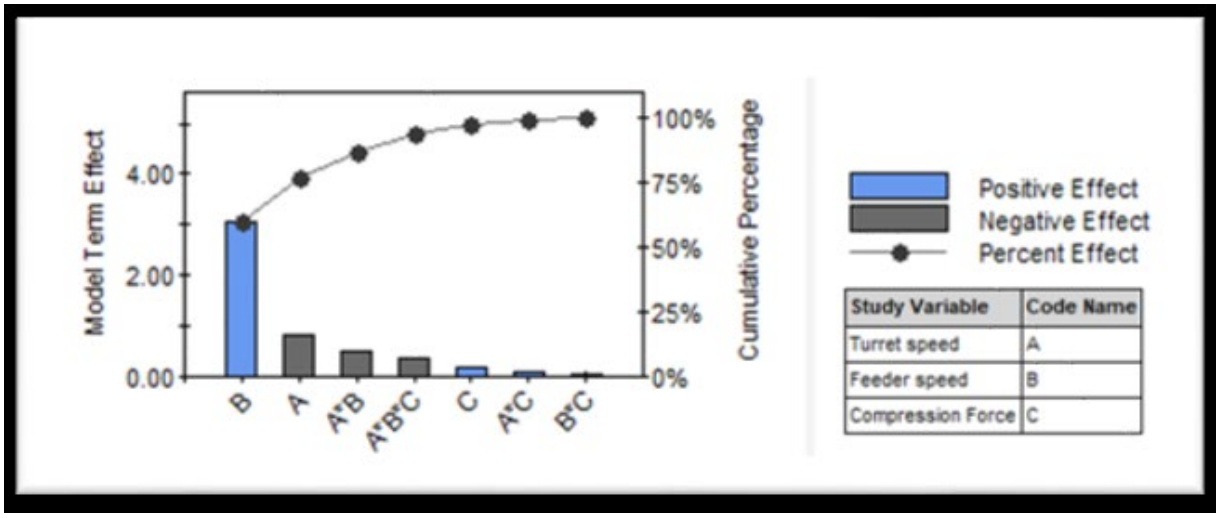


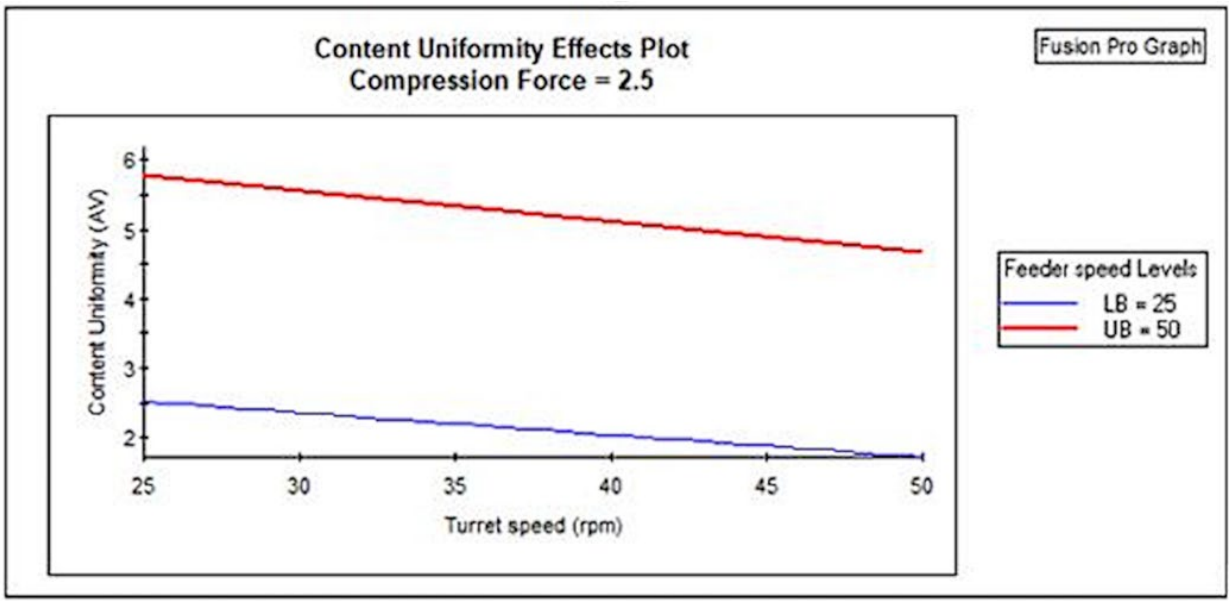
Figure 3. Model Term Ranking Pareto Chart

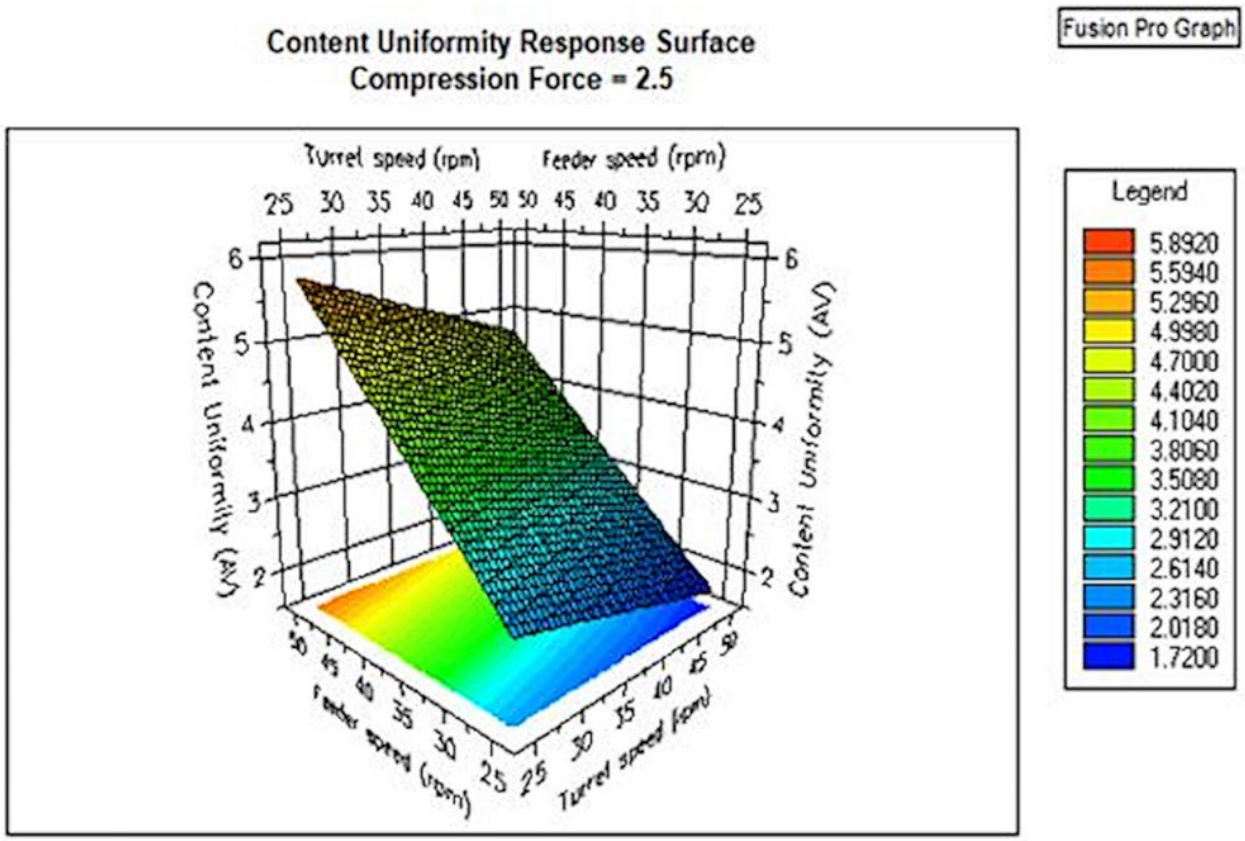


c. Drug Dissolution:

No significant difference in dissolution profiles was observed for all compression trials with more than 85% of drug release obtained within 20 mins (Figure 5).

Figure 4. Effects Plot and Response Surface





d. Optimized Trial:

The results confirmed that at lower turret to feeder speed ratios, 25:25 and 50:25, the AV is on the lower side 1.60 to 3.06 whereas at higher ratios, 25:50 and 50:50, the AV value is on the higher side 4.09 to 7.02. Thus, feeder speed had a significant impact whereas turret speed and compression force had a lesser impact on drug content uniformity. An optimized trial was conducted using a turret to feeder ratio of 25:25 and 4.5kN compression force with an output of 650 tablets/ min. Tablets were collected at the start, middle and end of the 4-hour tableting process. All the compressed tablets showed robust hardness between 4.0 to 4.5 kP, a DT of less than 1 min and achieved AV of 3.74, 4.64 and 2.97 for content uniformity of the tablets through the start, middle and end of the compression cycle, respectively (Figure 6).

The tablets were coated with Opadry® QX, quick and flexible coating, to achieve an elegant, finished appearance (Figure 7). The release profiles of glimepiride (Figure 8) remained unaffected by the coating process (f_2 = 69).

Figure 5. Release Profiles of Glimepiride Tablets

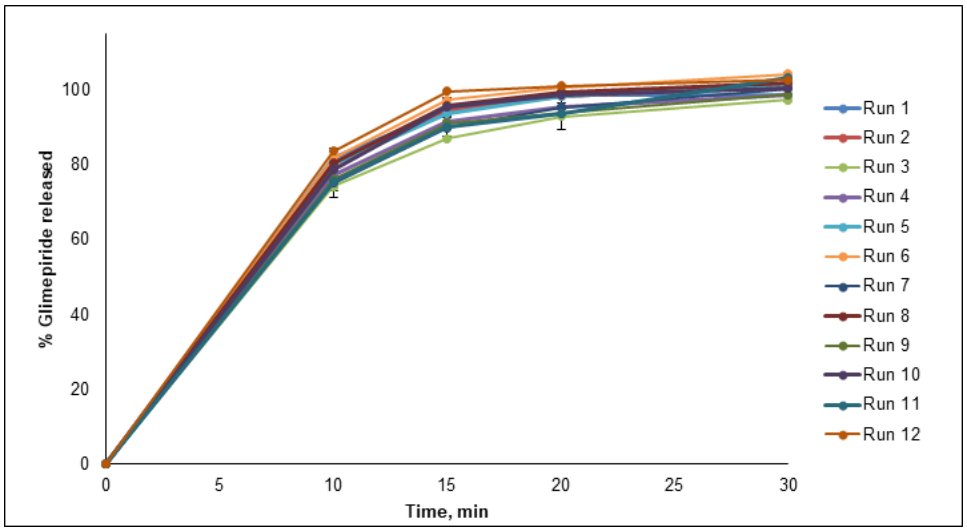


Figure 6. Content Uniformity of Start, Middle and End of Compression Cycle

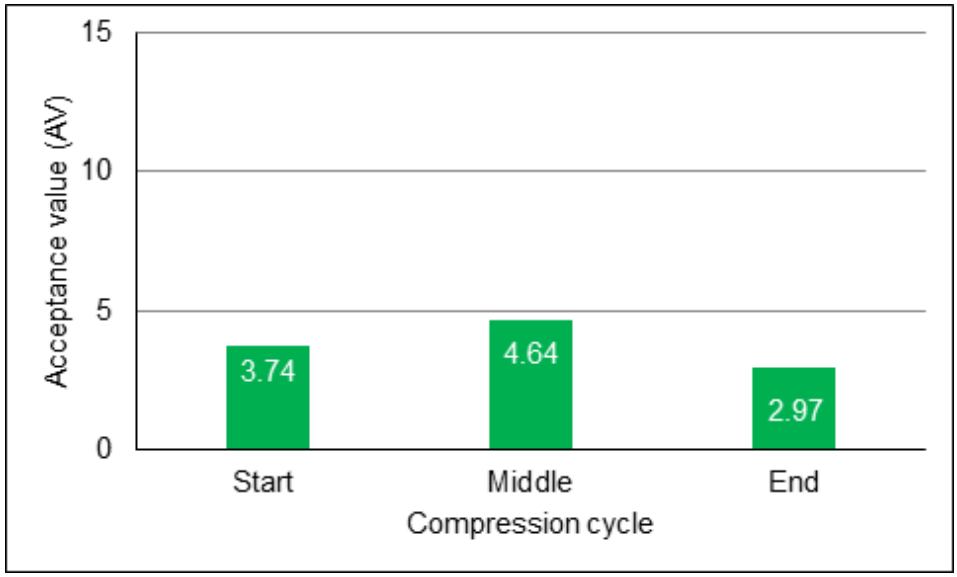
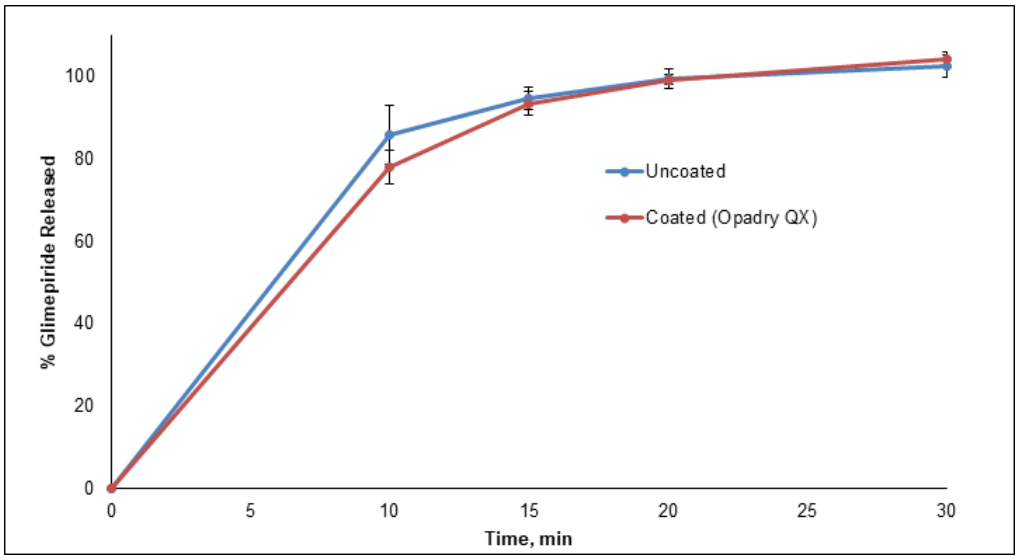


Figure 7.
Glimepiride Tablets, Uncoated Tablets

Tablets Coated with 3% Opadry QX

Figure 8. Release Profiles of Glimepiride from Uncoated and Coated Tablets



Conclusions

The impact of turret speed, feeder speed and compression force on the product critical quality attributes (CQAs) for tablet hardness, friability, disintegration time, content uniformity and dissolution for glimepiride tablets (1mg) were studied. All tablets showed good hardness, low friability, and acceptable content uniformity with more than 90% drug release in 20 min.

The results demonstrate that StarTab is a suitable direct compression excipient for low-dose formulations, enabling good blend homogeneity and content uniformity. The compression study indicated that low feeder speed improved the content uniformity of the tablets.

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