Opadry®
Complete Film Coating System

Colorcon®

Influence of Coating Parameters on Uniformity and Yield of Immediate Release Coating Formulation of a Low Dose Drug (Linagliptin) onto Metformin HCl ER Tablets

Authors: P. Xia, J. Yang, C. Zhu, S. Missaghi, A. Rajabi-Siahboomi

Colorcon, Inc. Harleysville, PA 19438, USA

Introduction

Fixed dose combinations (FDC) of high dose/low dose active pharmaceutical ingredient (API) are often presented with high dose API in the core and low dose API in the coating. The main challenges of this type of dosage form are how to concurrently achieve content uniformity of the low dose drug and high yield.[1,2,3] Optimal coating parameters are key to improve the performance of these tablets. The purpose of this study was to investigate the effect of the critical coating parameters on the uniformity and yield of a film coating formulation containing linagliptin (5 mg) onto extended-release tablets of metformin HCl (1000 mg). Further, suitable processing conditions were investigated to provide adequate content uniformity and yield of linagliptin.

Methods

Design of Experiment (DoE) was used to carry out the random customized experimental design and 19 experiments were obtained (Table 1), including one central point. Process air flow, atomizing air pressure, weight gain and coating solids were fixed in the study. Variables included inlet air temperature (55-65°C), pan load (600-1000 g), pan speed (15-25 rpm), spray gun-to-tablet bed distance (5-10cm), pattern air pressure (1.0-2.0 bar), and spray rate (6-8 g/min).

All coating trials were performed in a 12'' fully perforated O'Hara Labcoat M coating pan (O'Hara Technologies, Canada). In each trial, the metformin tablets, seal coated with an HPMC-based film coating system, then coated to 8-9% weight gain of linagliptin suspended in an Opadry formulation (at 7% solids content). The compositions of extended release core, seal coating and API coating are shown in Table 2. Coated tablets from each trial were assayed using HPLC to evaluate the uniformity and yield of linagliptin coated tablets.

Results

The results of the statistical analysis of the data indicated that within the design space, there were significant relationships ($p<0.05$) between API uniformity and pan load, pan speed, and spray rate for the coated drug layer. Among them, pan load and spray rate had positive impacts, caused better API uniformity on the tablet, while the pan speed and the interaction between the pan load and gun-to-bed distance had negative impacts (Fig 1). Figure 2 shows the trend of the influence of each variable on uniformity.

Yield of linagliptin coated on the ER tablets was in the range of 54%-84% in all 19 coating trials. All parameters had significant impacts on yield except the pan speed. The pan load, its interactions with pattern air pressure, spray rate and inlet temperature had positive impacts on yield (Figure 3), its means with the parameters increase the yield will be higher. Figure 4 shows the trend of the influence of each variable on yield.

The operating range of parameters were identified according to the analytical result. In this case study, a relative standard deviation (RSD) of drug content less than 6% is considered acceptable. Figure 5 shows a plot of acceptable ranges of inlet temperature and gun-to-bed distance to achieve the drug content RSD below 6% and a yield higher than 70% at a constant pan load, pan speed, pattern air pressure and spray rate. The unshaded area of the graph shows the acceptable range of parameters.

Table 1. Coating Process Parameters of DoE

No.	Pan Load (g)	Pan Speed (rpm)	Gun-to-Bed Distance (cm)	Pattern Air Pressure (bar)	Spray Rate (g/min)	Inlet Air Temperature (°C)
1	600	15	10	2	8	55
2	600	25	10	2	6	65
3	600	15	5	2	6	65
4	1,000	15	10	1	6	65
5	1,000	15	5	2	8	65
6	1,000	15	5	1	8	55
7	1,000	25	5	2	6	55
8	1,000	25	10	1	8	55
9	800	20	7.5	1.5	7	60
10	800	20	7.5	1.5	7	60
11	1,000	25	10	2	8	65
12	600	25	10	1	6	55
13	1,000	25	5	1	6	65
14	600	25	5	1	8	65
15	600	25	5	2	8	55
16	800	20	7.5	1.5	7	60
17	600	15	10	1	8	65
18	600	15	5	1	6	55
19	1,000	15	10	2	6	55

Table 2. Composition of Extended Release Core, Seal-Coating and API Coating

1000 mg + 5 mg	Composition (% w/w)	mg/Tablet
Extended Release Core		
Metformin	70.5	1000
HPMC E5 (binder)	2.4	34
Polyox 303	26.1	370
Mg-st	1.1	15
Subtotal	100	1419
Seal-Coating		
Opadry 40F18389-CN	100	85
Subtotal	100	85
Solid	20	--
API Coating		
Opadry 00F19246	47.6	40
Linagliptin	6	5
L-Arginine	23.8	20
PEG 6000	11.9	10
Talc	10.7	9
Subtotal	100	84
Total		**1588**

Figure 1: Pareto Charts for Uniformity (A: Pan Load B: Pan Speed C: Gun-to-Bed Distance D: Pattern Air Pressure E: Spray Rate F: Inlet Temp.)

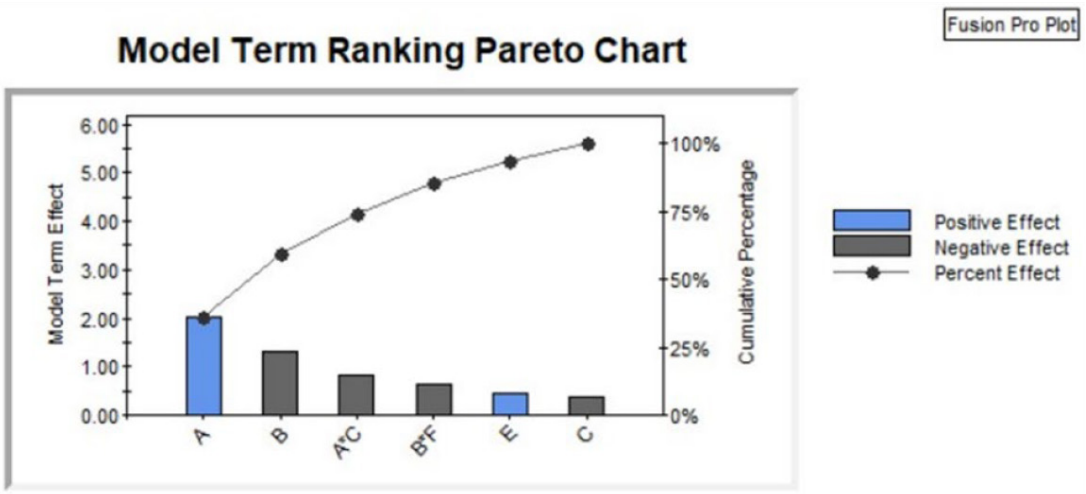


Figure 2: Influence of Coating Parameter on Uniformity

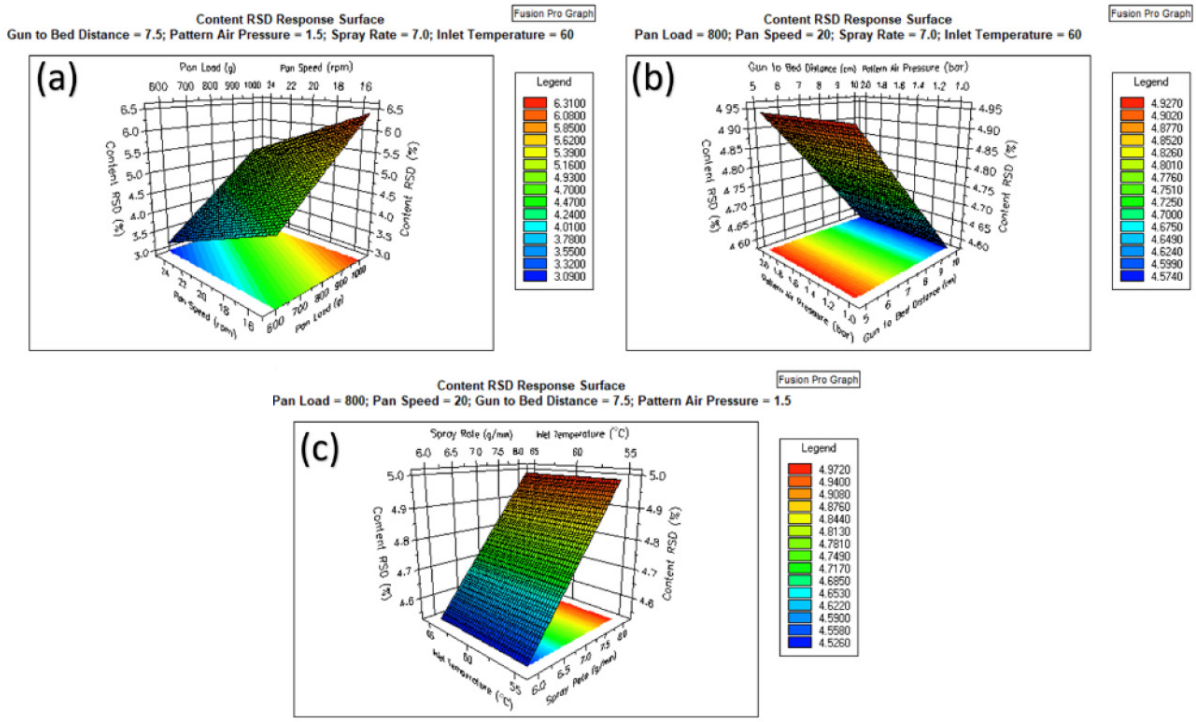


Figure 3: Pareto Charts for Yield (A: Pan Load B: Pan Speed C: Gun-to-Bed Distance D: Pattern Air Pressure E: Spray Rate F: Inlet Temp.)

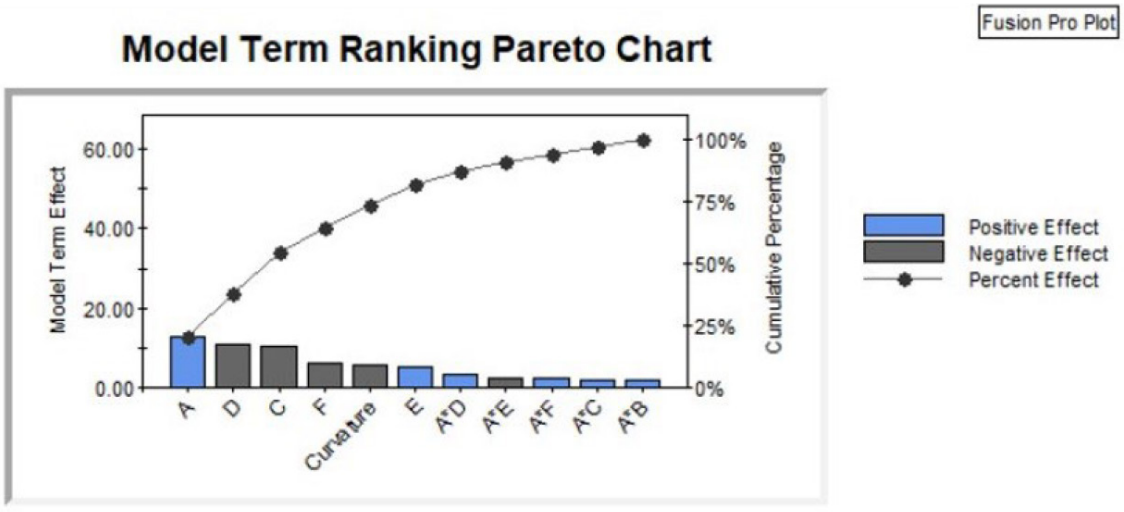


Figure 4: Influence of Coating Parameter on Yield

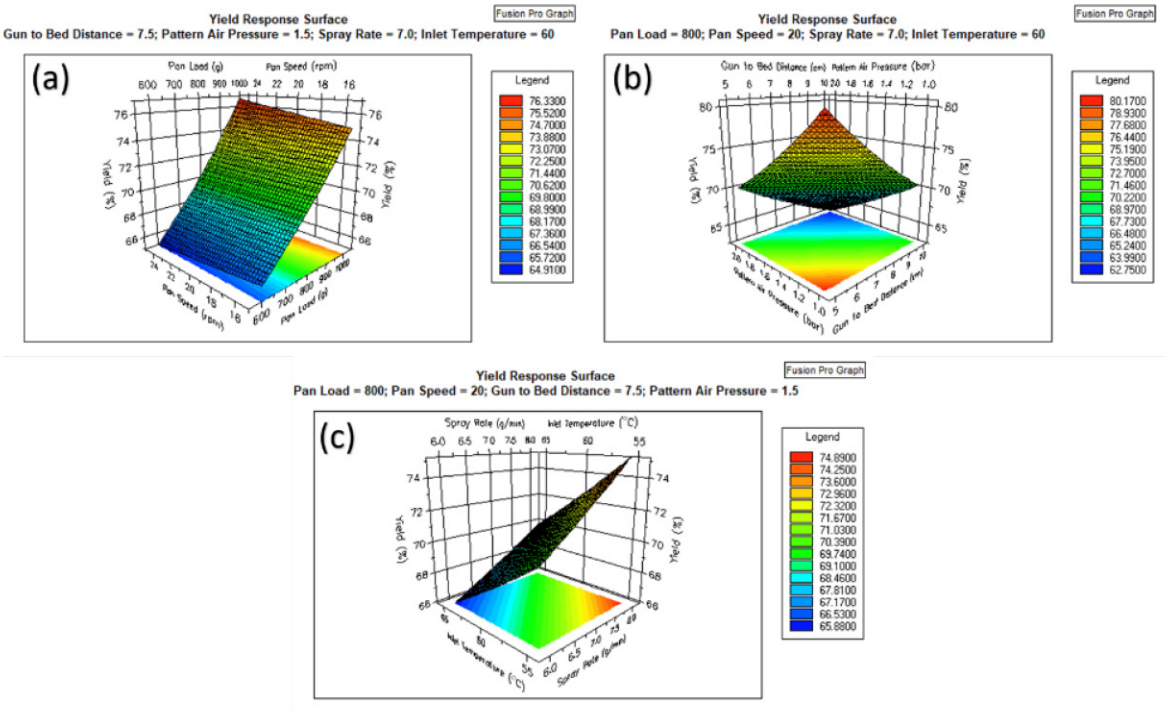
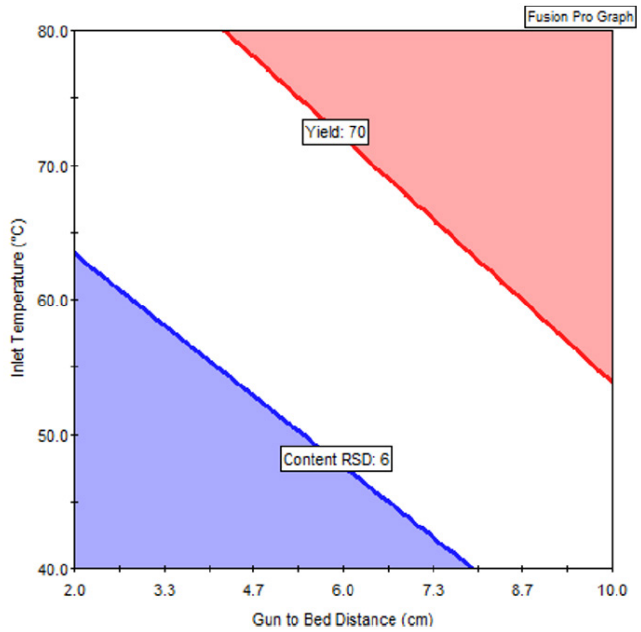


Figure 3: Pareto Charts for Yield (A: Pan Load B: Pan Speed C: Gun-to-Bed Distance D: Pattern Air Pressure E: Spray Rate F: Inlet Temp.)



Conclusions

DoE experiment was successfully used to identify and characterize the impact of critical variable parameters of a low dose drug coating on metformin HCl tablets. Through this study, an acceptable range of process parameters using a small-scale coating machine were obtained for a defined product performance with RSD < 6% and yield > 70%.

References

1. Uniformity of Dosage Units, Pharmacopoeia Europaea, seventh ed., vol. 7.6, 2013, pp. 4102–4103 (Chapter 2.9.40).
2. Uniformity of Dosage Units, United States Pharmacopoeia, thirty-first ed., vol. 31, Port City Press, Baltimore, 2008, pp. 363–369 (Chapter 905).
3. Uniformity of Dosage Units, Japanese Pharmacopoeia, vol. 16, 2011, pp. 127–129 (Chapter 6.02)