Use of a Quality by Design Approach to Optimize Coating Process Parameters for Opadry® 200

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Purpose

This work describes a Quality by Design (QbD) approach to determine the optimal coating process conditions and robust process design space for Opadry 200, a fully formulated film coating system from Colorcon.

Methods

Through the use of prior knowledge, the critical quality attributes (CQAs) for the film coated product were identified as lack of coating defects (measured as % defect level), tablet disintegration time, and tablet appearance (color difference and gloss), while the critical process parameters (CPPs) were identified as dispersion spray rate, inlet air temperature, airflow, % solids and pan speed.

Study Design and Process Optimization

Minitab software (Minitab Inc., PA, USA) was used to develop a central composite - face centered response surface design for the study using five input factors (Resolution V). Thirty-two coating trials using a single batch of Opadry 200 were conducted to examine the impact of the CPPs on the CQAs. By defining goals for CQAs and their relative importance, a set of optimized coating process parameters were identified, and a coating process operating space developed for the Opadry 200 coating system. The coating process parameters evaluated in each trial are shown in Table 1.

All coating trials were conducted in a 24" fully perforated O'Hara Labcoat II coating pan. In each trial, 15 kg of biconvex placebo tablets (10mm) were coated to a 4% weight gain (WG) with the same lot of a blue Opadry 200 formulation.

Table 1. Coating Process Parameters

Trial No.	Spray Rate (g/minute)	Inlet Temp (°C)	Airflow Rate (CFM) / (m^3/hr)	% Solids	Pan Speed (rpm)
1	50	72.5	150 / 255	20	14
2	50	72.5	250 / 425	20	18
3	75	55.0	350 / 595	25	10
4	75	55.0	150 / 255	25	18
5	75	80.0	350 / 595	25	18
6	25	80.0	150 / 255	15	10
7	50	72.5	250 / 425	20	10
8	50	80.0	250 / 425	20	14
9	25	55.0	350 / 595	25	18
10	50	72.5	350 / 595	20	14
11	75	55.0	150 / 255	15	10
12	50	72.5	250 / 425	20	14
13	75	80.0	150 / 255	25	10
14	75	55.0	350 / 595	15	18
15	50	72.5	250 / 425	25	14
16	25	55.0	350 / 595	15	10
17	25	55.0	150 / 255	15	18
18	25	72.5	250 / 425	20	14
19	50	55.0	250 / 425	20	14
20	25	80.0	150 / 255	25	18
21	50	72.5	250 / 425	20	14
22	75	80.0	350 / 595	15	10
23	25	55.0	150 / 255	25	10
24	75	80.0	150 / 255	15	18
25	25	55.0	150 / 255	15	18
26	75	72.5	250 / 425	20	14
27	50	72.5	250 / 425	20	14
28	25	80.0	150 / 255	15	10
29	75	55.0	150 / 255	15	10
30	50	72.5	250 / 425	15	14
31	25	80.0	350 / 595	25	10
32	25	80.0	350 / 595	15	18

Coated tablets from each trial were visually evaluated for defects and tested for gloss, color difference and disintegration time (DT) in purified water using the following methods:

Defects

At the end of each coating trial, samples were collected and assessed for the percentage of tablets having defects. For the purposes of this evaluation, a defect was defined as any instance where the coating was not contiguous, and the tablet core was exposed. The number of defects in a batch was determined by visual observation of 100 tablets, repeated 4 times per trial, and the average result reported.

Disintegration Time

Disintegration time was tested following the standard USP method in deionized water at 37°C, and the average result was determined from 6 tablets per trial.

Color Development and Uniformity

Film coated tablets were sampled during each trial at theoretical 1, 2, 3, and 4% weight gains and tested for color development and uniformity using a reflectance spectrophotometer (Datacolor, NJ, USA).

Tablets with 4% coating weight gain were regarded as the target reference color for each trial. All other weight gain samples were measured using the 4% weight gain references to calculate color difference (ΔE). Twenty tablets were tested from each batch at each theoretical weight gain to determine the color development versus the standard and also color uniformity within the sample.

Gloss

40 film coated tablets with a 4% weight gain of Opadry 200 from each trial were analyzed for gloss using a gloss meter (Tricor, IL, USA). Results were reported in gloss units (GU).

Results

Table 2. Coating Defects Observed per Trial (Defect level > 0%)

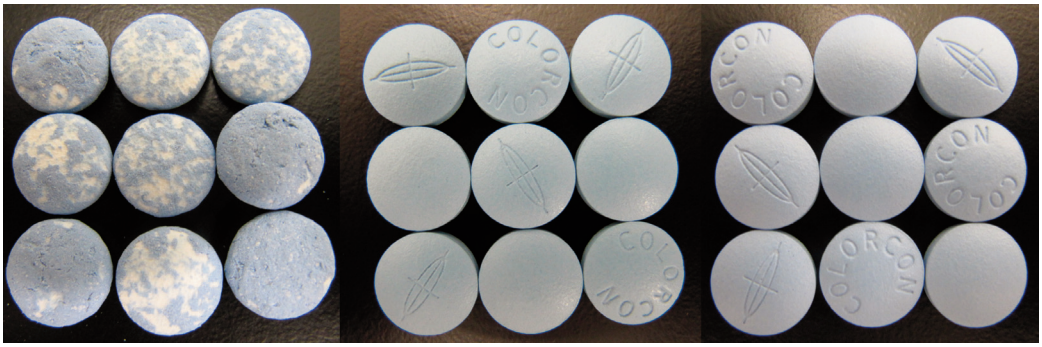
Trial Number	Mean Coating Defects (% of Tablets)
3	0.75
4	33
9	0.25
10	0.5
11	100
13	0.5
14	0.25
24	3.75
29	100

Defects

Coating trials that exhibited defects are shown in Table 2. Only 9 of 32 trials exhibited any defects, and of those, only 4 trials had mean defects values greater than 1%. These trials indicate that even when a wide range of coating parameters were employed, the number of defects observed with the Opadry 200 film coating was low.

Coating trials 11 and 29 exhibited 100% defects. These trials had low bed temperature coating conditions where significant overwetting of the tablet bed occurred, leading to poor coating uniformity and tablet appearance. This can be seen in Figure 1, which compares images of tablets from Trial 11 (bed temperature of 22°C) with those from Trial 19 (bed temperature of 33°C) and Trial 12 (bed temperature of 47°C). It can be seen that the tablets coated with the bed temperature of 33°C had no defects and equivalent visual appearance and color uniformity to that of the coating trial with a bed temperature of 47°C. This indicates the robust nature of the product performance across a broad range of coating temperatures.

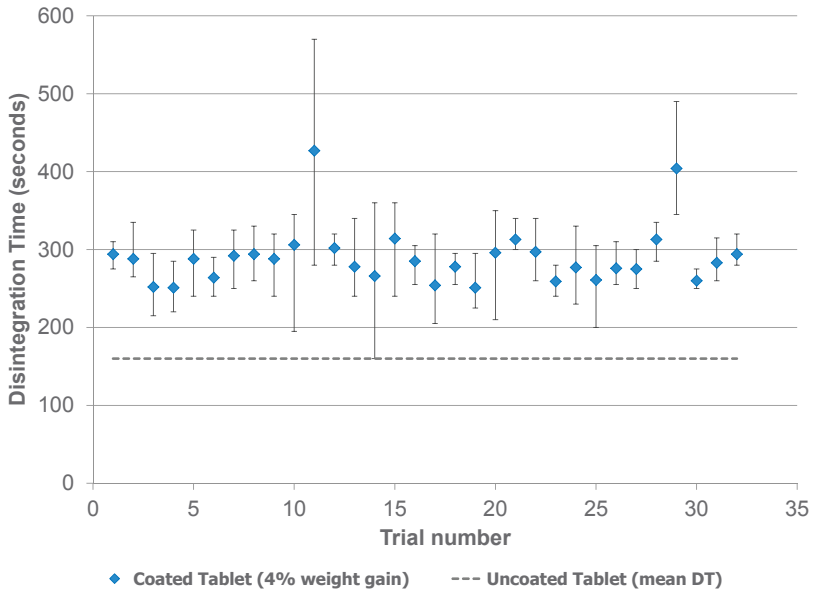
Figure 1. Coated Tablets from Trials 11 (left), 19(center) and 12 (right)



Disintegration Time

Tablet disintegration was consistent across all coating trials, except for trials 11 and 29, where thick accumulations of film coating material remained in the basket after the tablet had fully disintegrated. The film coating remnants for trials 11 and 29 were observed to dissolve after 570 and 492 seconds, respectively. Figure 2 shows that disintegration times for all coating trials, except 11 and 29 were less than 360 seconds, indicating that this CQA is largely independent of coating process parameters for Opadry 200.

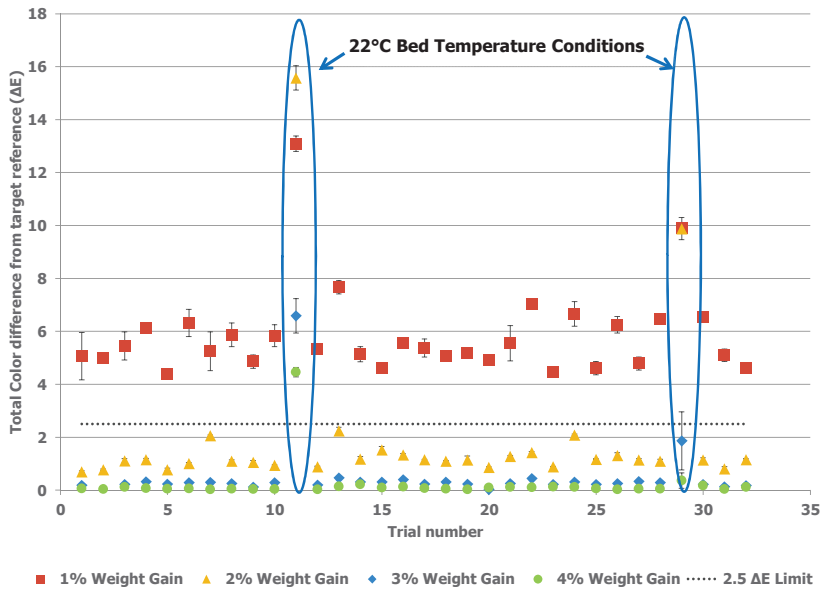
Figure 2. Average Coated Tablet Disintegration Time for Each Trial



Color Development and Uniformity

Color development and color consistency throughout the batch provides a visible indication of quality and uniformity of the applied coating. At 4% weight gain, all coating trials gave excellent color uniformity with the exception of trials 11 and 29. Figure 3 shows the tablet color development data for all coating trials, represented as color difference (ΔE) versus the reference at 4% weight gain and color uniformity between tablets in each sample set.

Figure 3. Color Difference from Target Reference ΔE for Each Trial

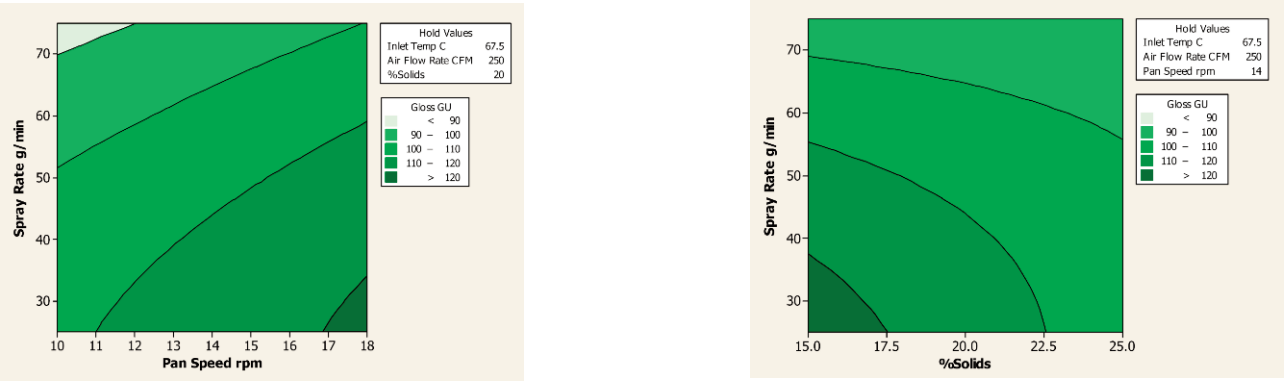


Aside from trials 11 and 29, all samples had a color difference less than 2.5 ΔE at 2% weight gain, which is not visually discernible. The color uniformity for each sample is indicated by the error bars, which shows that, after 1% weight gain, there is minimal variability in tablet color. From a product appearance perspective, all samples with greater than 2% coating weight gain were found to be visually equivalent.

Gloss

The gloss results indicated that all coating trials (except runs 11 and 29) produced tablets with gloss values greater than 81 gloss units. Gloss can be correlated to surface smoothness, so conditions which prolong or increase frictional forces tend to favor gloss development. This can be seen in Figure 4, where contour plots show that gloss increases under the influence of reduced spray rate, higher pan speed and lower % solids.

Figure 4. Contour Plots of Gloss versus Spray Rate, Pan Speed and % Solids



Coating Process Optimization and Confirmation

Based on the trial results, a multivariant model was developed to determine the optimized process parameters and operating space based on CQA goals. Selection of CQA goals and their relative importance plays a significant role in determining the optimized process parameters necessary to deliver enhanced appearance, productivity or functionality. In this case, the goals and importance factors selected for the CQAs were chosen to provide a product with good overall performance and minimal defects.

Table 3 describes the optimization goals, importance factors and predicted, as well as actual, CQA values obtained after a confirmation run at the optimized coating process parameters described in Table 4.

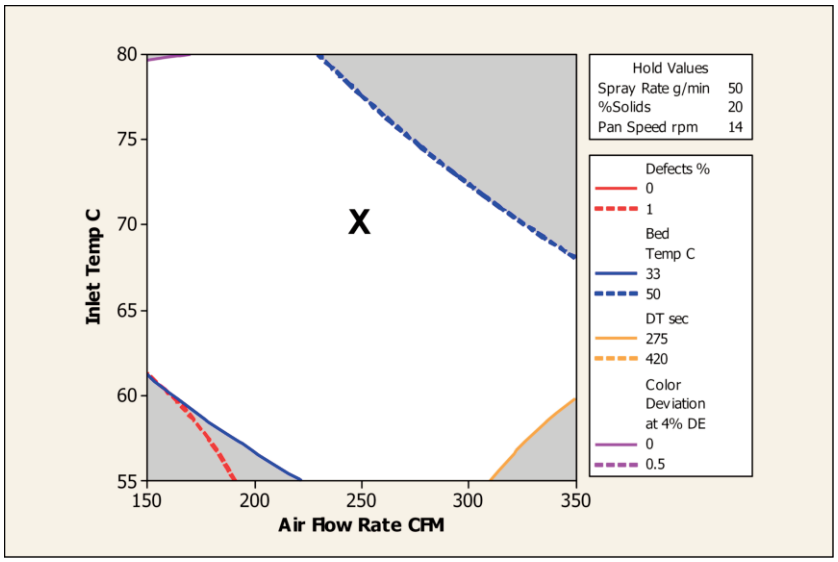
Table 3. Optimization Goals, Importance and Predicted / Actual CQAs

Critical Quality Attribute	Goal	Importance Factor (arbitrary 1-10 scale)	Predicted Results at Optimized Coating Conditions	Actual Results at Optimized Coating Conditions
Defects (%)	< 1	10	0	0
Disintegration Time (seconds)	< 420	10	268	241
Color Deviation at 4% WG (DE)	< 0.5	2.5	0.02	0.01
Gloss (GU)	> 90	2.0	107	101

Table 4. Optimized Coating Parameters

Coating Process Parameter	Optimized Value
Spray Rate (g/minute)	50
Inlet Temperature (°C)	70
Airflow Rate (CFM) / (m^3/hr)	250 / 425
% Solids	20
Pan Speed (rpm)	14
Total Coating Time (minutes)	46
Bed Temperature (°C)	45

Figure 5. Acceptable Operating Space



Once the goals and relative importance of CQAs were considered as a whole, proven, acceptable ranges for process parameters were identified for Opadry 200. Figure 5 shows a plot of the acceptable ranges for inlet temperature and airflow at set conditions of spray rate, solids and pan speed. The white space indicates the range of process parameters that meet all the CQA performance criteria outlined in Table 3. The 'X' in Figure 5 shows the location of optimum coating process parameters described in Table 4.

Conclusions

A QbD approach was used successfully to identify and characterize the impact of varying critical coating process parameters on critical quality attributes of Opadry 200 coated placebo tablets. Productivity, color uniformity and very low defect levels were obtained with Opadry 200 even when using a broad range of coating process conditions.

References

1. US Pharmacopeia, USP/NF General Chapter 701, Disintegration. Web site: http://www.uspnf.com/uspnf/pub/index?usp=35&nf=30&s=1&official On=August1,2012 Accessed August 31, 2012.

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