AAPS PharmSciTech, Vol. 14, No. 2, June 2013 (© 2013)
DOI: 10.1208/s12249-013-9935-3

Research Article

Process Optimization of a Novel Immediate Release Film Coating System using QbD Principles

Jason Teckoe,[1,2] Tracey Mascaro,[1] Thomas P. Farrell,[1] and Ali R. Rajabi-Siahboomi[1]

Received 5 October 2012; accepted 6 February 2013; published online 13 March 2013

Abstract. This work describes a quality-by-design (QbD) approach to determine the optimal coating process conditions and robust process operating space for an immediate release aqueous film coating system (Opadry® 200). Critical quality attributes (CQAs) or associated performance indicators of the coated tablets were measured while coating process parameters such as percent solids of the coating dispersion, coating spray rate, inlet air temperature, airflow rate and pan speed were varied, using a design of experiment protocol. The optimized process parameters were then confirmed by independent coating trials. Disintegration time of coated tablets was not affected by the coating process conditions used in this study, while tablet appearance, as determined by measurement of tablet color, coating defects and gloss was determined to be a CQA. Tablet gloss increased when low spray rate and low percent solids were used, as well as with increased coating pan speed. The study used QbD principles and experimental design models to provide a basis to identify ranges of coating process conditions which afford acceptable product quality. High productivity, color uniformity, and very low defect levels were obtained with Opadry 200 even when using a broad range of coating process conditions.

KEY WORDS: film coating; immediate release; Opadry 200; quality by design.

INTRODUCTION

Film coating of pharmaceutical solid dosage forms has been a common practice for many decades. The application of an immediate release film coating provides many significant advantages to the dosage form; it protects the drug from light and moisture and allows easy identification by healthcare professionals and consumers. Film coatings also improve swallowability, taste masking, mechanical strength, and improve safety and ease of handling. Coatings have also been used for market branding and anticounterfeiting purposes (1). Both film-coating formulations and coating process parameters are generally well understood. The ICH Pharmaceutical Development Q8 Guideline outlines the expectations of some regulatory agencies for the incorporation of quality-by-design (QbD) studies for new drug applications and abbreviated new drug applications. Here, a case study is used to illustrate the utilization of QbD principles to investigate the influence of film coating process parameters on some of the quality attributes of the coated tablet dosage form.

Considering that the critical quality attributes (CQAs) of a drug product are a function of both critical material attributes (CMAs) and critical process parameters (CPPs), film coatings can impact CQAs in two ways. First, the film coating formulation itself may have one or more CMAs. For immediate release, film-coated tablets (where no deliberate effort has been made to modify the API release rate), if the film coating color is carefully controlled by the manufacturer, and sound quality systems are in place to control the raw materials and manufacture of the coating formulations, then it is expected that the film coating formulation itself is low risk and does not represent any CMAs. The second way that a film coating may impact CQAs of the drug product is *via* the coating process, *i.e.*, it may have one or more CPPs that significantly influence CQAs. For example, coating color development and uniformity may be significantly affected by coating process parameters such as tablet bed temperature, pan speed, and spray rate. Different coating parameters may be required to provide optimal coating performance for different film coating products. When coating Opadry® amb, a lower spray rate is used compared to other polyvinyl alcohol (PVA)-based film coatings systems to avoid surface defects due to its relatively tacky nature. Opadry II

[1] Colorcon Inc. Global Headquarters, 275 Ruth Road, Harleysville, Pennsylvania 19438, USA.
[2] To whom correspondence should be addressed. (e-mail: jteckoe@colorcon.com)

1530-9932/13/0200-0531/0

Table I. Critical Quality Attributes and Performance Indicators

Product attributes	Process parameters
Critical quality attributes/ (performance indicators)	
	Spray rate
Appearance (coating defects, gloss, and color uniformity)	Inlet air temperature
Disintegration Time (dissolution of the film coating)	Air flow rate
Productivity[a] (coating time)	Solids level (%)
	Coating pan speed

[a] Productivity is typically part of the Target Product Profile (TPP) and is a key manufacturing parameter for the coating process

Table III. Experimental Design Process Parameters

Process parameter	Range
Spray rate (g/min)	25–75
Inlet temp (°C)	55–80
Air flow rate (CFM)	150–350
(m^3/h)	255–595
Solids level (%)	15–25
Pan speed (rpm)	10–18

CFM cubic feet/min, *rpm* revolutions per minute

(PVA based) formulations can be coated at double the coating rate of Opadry amb and exhibit minimal coating defects. Leading suppliers of film coating formulations conduct coating process design of experiments to support process robustness for users and minimize the need for subsequent optimization work. For scale-dependent process parameters, it is prudent to re-evaluate the DoE upon significant increases in coating scale or when changing coating equipment.

Several models have been evaluated to facilitate the coating scale up process. Ebey (2) developed a thermodynamic model for the film coating process that showed tablet coating quality can be maintained at a variety of coating conditions and scales, provided equivalent environmental coating conditions are used which maintain coating drying rates. Macleod (3) evaluated the impact of atomizing air pressure and spray gun selection on coating performance and concluded that careful consideration must be given to maintaining equivalent spray properties when products move from development to production scale manufacture. Mueller (4) evaluated the impact of pan speed on tablet velocity at a variety of scales and found that at larger-scale manufacture, the angle of repose and tablet velocity in the pan was higher than would be indicated by simply scaling the peripheral velocity of the pan based on rpm. More recently, Pirpich (5) used a QbD approach to determine scale-up process parameters between different types of coating pans. They found that by utilizing thermodynamic and atomization film coating models, they were able to predict coating parameters and successfully scale-up manufacture of a varenicline immediate release tablet, while, Dubey (6) used laser-induced breakdown spectroscopy and a QbD approach to model lot to lot coating uniformity across a variety of coating conditions and batch sizes. They found that the main source of tablet to tablet variability was linked to the mixing limitations of the coating pan.

The objective of this study was to use a QbD approach to determine the optimal coating process conditions and identify a robust process operating space for application of an immediate release aqueous film coating system, Opadry 200.

METHODS AND MATERIALS

Study Design

The product attributes which include CQAs and performance indicators, and process parameters that were evaluated in this study are shown in Table I. A prioritization matrix was used to determine the relative importance of these CQAs and to select the process parameters which would have the largest impact on the CQAs. The prioritization matrix is shown in Table II, where the ranking of CQAs is shown across the top of the table, and the correlation factors for each process parameter are shown beneath.

Coating defects, appearance/gloss, coating time, color uniformity, and disintegration time were identified, based on prior knowledge, as CQAs to be evaluated. The perceived importance of the CQAs was weighted according to their impact on product quality. A prioritization score was calculated by multiplying the average process parameter score by the average CQA importance. The sum total for each process parameter/CQA was

Table II. Prioritization Matrix

	Process parameter/CQA assessment					
Critical quality attribute	Coating defects	Appearance/gloss	Coating time	Color uniformity	Disintegration time	Prioritization score
Importance	5.8	5.4	5.2	2.0	2.0	
Process parameter						
Spray rate	5.8	5.8	5.8	3.4	3.8	110
Inlet temp.	4.6	5.4	6.0	4.2	4.4	104
Air flow	3.8	4.6	6.0	2.8	3.8	91
% Solids	3.0	5.6	3.0	3.0	1.8	73
Pan speed	4.6	3.8	1.8	1.8	1.2	63
Atomization air pressure	2.6	3.4	3.2	2.2	1.6	58
Pattern air pressure	2.4	2.6	2.8	2.0	1.4	49

Table IV. Experimental Design Matrix

Run no.	Spray rate (g/min)	Inlet temp (°C)	Air flow rate (CFM)/ (m^3/h)	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

rpm revolutions per minute

used to determine the prioritization score for each process parameter. The equation used to determine this is shown below:

$$Ps = (I_1)(O_1) + (I_2)(O_2) + (I_3)(O_3) + (I_4)(O_4) + (I_5)(O_5)$$

where Ps is the prioritization score, *I* is the average process parameter score, and *O* is the average CQA importance.

The prioritization score was used to determine the relative rank of the process parameters to be included in the experimental design. Based on the prioritization score and prior knowledge (7), spray rate, inlet air temperature, air flow rate, percent solids, and pan speed were selected as the coating process parameters that would have the greatest impact on the product quality. Therefore, one experimental study design encompassing these product attributes and process parameters was developed.

Quality target product profiles (QTPPs) were developed based on relative ranking of the product attributes. In the first case study, the product attributes considered as having greatest importance and risk were coating defects, product appearance and coating time (productivity). In the second study, tablet appearance (gloss) and coating defects were considered most important. While in the third study, coating time (productivity), and coating defects were the focus.

Minitab software (Version 16; Minitab Inc., State College, USA) was used to develop a central composite–face centered–response surface design for the study using five input factors (resolution V). The study included a total of 32 coating trials (27 trials with two center point replicates and three noncenter point replicates). This response surface design was chosen, as it is a three-level design capable of detecting curvature in the data. This attribute is important when several of the input parameters are predicted to have interactions such as the relationship between spray rate, inlet temperature, air flow volume, and solids content. Using prior knowledge of the typical operating parameters of the coating pan, the process ranges were selected to define the range of experimental parameters as shown in Table III and the actual trial parameters used are listed in the experimental design matrix in Table IV.

Materials

Each coating batch consisted of 15 kg of 10 mm, round, biconvex placebo tablets (345 mg), and 600 g of Opadry 200 (Colorcon, West Point, USA) dispersed in a sufficient amount of deionized water to obtain the target percent solids level for each trial. The primary film former in the Opadry 200 formula used in this study was polyvinyl alcohol. The pigments were titanium dioxide and FD&C Blue #2 lake. Polyethylene glycol 3350 and talc were included as a plasticizer and detackifier, respectively.

Film Coating

A 24-in, fully perforated coating pan (Labcoat II, O'Hara Technologies Inc., Toronto, Canada), equipped with two spray guns (VAU, Spraying Systems Inc., Wheaton, USA), was used for all trials. Tablets were coated with the Opadry 200 blue coating system to a theoretical 4% weight gain. Atomization and pattern air pressures were each held constant at 1.7 bar (24.7 psi). Gun-to-bed distance was held constant at 16 cm (6.3 in). Tablets were heated to 50°C (±5°C), prior to initiating the coating process. Bed temperature was recorded during each coating run using a handheld infrared gun (MiniTemp FS, Raytek Corporation, Santa Cruz, USA).

Product Attribute Testing

Defects

At the end of each 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. Defects could be related to edge chipping, peeling, sticking, picking, or pin holes in the coating. The number of defects in a batch was determined by visual observation of 100 tablets, repeated four times per trial, and the average result reported.

Color Development and Uniformity

Film coated tablets were sampled during each trial at a theoretical 1%, 2%, 3%, and 4% weight gain and tested for

Table V. Mean Coating Defects Observed per Trial (for trials wherein the defect level was >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

color development and uniformity using a reflectance spectrophotometer (Datacolor, Datacolor Inc., Lawrenceville, USA) employing the Commission Internationale de l'Eclairage (CIE) L* a* b* system. The total color difference (ΔE) from the target reference color was determined by calculating the distance between two points in the color space using the following equation:

$$\Delta E* = \left[(L*1 - \mathrm{L}*2)^2 + (a*1 - \mathrm{a}*2)^2 + (b*1 - \mathrm{b}*2)^2\right]^{1/2}$$

Tablets with 4% coating weight gain were regarded as a color standard for each trial, and all other weight gain samples were measured against this to calculate color difference ΔE and uniformity. Twenty tablets were tested from each batch for each theoretical weight gain to determine the color development *versus* the standard and also color uniformity within the sample.

Gloss

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

Disintegration Time

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

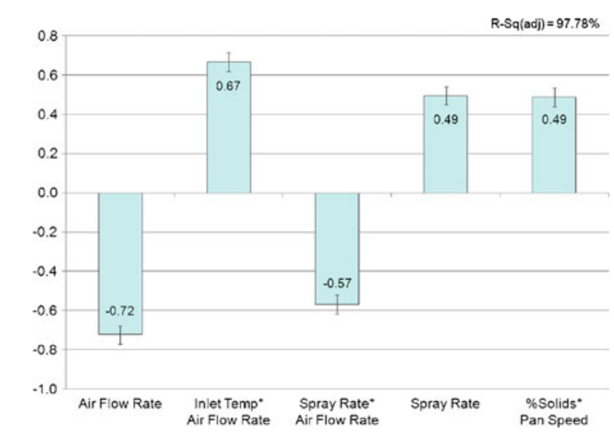

Fig. 1. Coefficient plot indicating process parameters and interactions that impacted percent defects

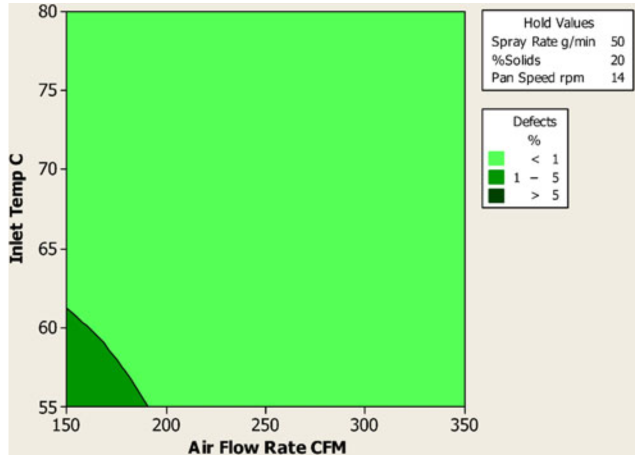

Fig. 2. Contour plot of percent defects *versus* inlet temperature and air flow

RESULTS AND DISCUSSION

Defects

Evaluation of defects indicated that only nine coating trials exhibited defects, and, of those nine, only four trials had a mean defects value of greater than 1% (Table V). The trials indicated that even when a wide range of coating parameters were applied, the number of defects observed with the film coating was minimal.

The model coefficients for the top five process parameters or parameter interactions that impacted defects are shown in Fig. 1. In general, it was determined that process conditions leading to overwetting or spray drying resulted in the most tablet defects. Increased spray rate, reduced air flow and decreasing inlet temperature all have the tendency to increase the likelihood of overwetting the tablet bed. Air flow had the largest model coefficient for defects, which, being negative

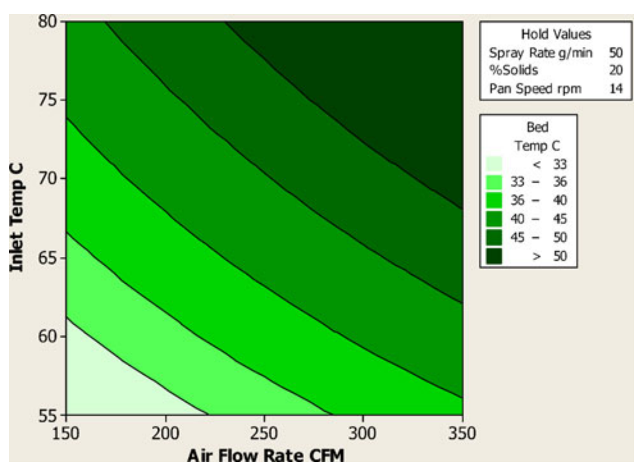

Fig. 3. Contour plot of bed temperature *versus* inlet temperature and air flow

Fig. 4. Coated tablets from trials 11 (*left*), 19 (*center*), and 12 (*right*)

indicated that as air flow increased, the number of defects was reduced. At low air flow rates, the tablet bed became wet leading to defects associated with sticking and picking. The interaction of air flow and inlet temperature had a positive coefficient indicating that the number of defects increased under the interaction of these parameters.

Tablet defects decreased when air flow rate was increased and when spray rate and air flow rate were simultaneously increased. Tablet defects increased when spray rate was increased and when either inlet temperature and air flow rate or percent solids and pan speed were increased simultaneously.

Coating trials 11 and 29 exhibited 100% defects. These trials were conducted under conditions where significant over-wetting of the tablet bed occurred due to a combination of low inlet air temperature, high spray rates and low air flow. Figure 2 shows that, under most coating conditions, less than 1% defects were observed. Figure 3 shows the relationship between inlet air temperature, airflow and tablet bed temperature. By comparing Figs. 2 and 3, it can be seen that coating with a bed temperature of less than 33°C corresponds to observation of greater than 1% defects.

In Fig. 4, tablets from Trial 11, coated at a bed temperature of 22°C, are compared to those from Trial 19, coated with a bed temperature of 33°C and Trial 12, which represents the center point of the experimental design with a bed temperature of 47°C. The tablets coated with a 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. The wide range of acceptable bed temperatures indicates the robust nature of the product.

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

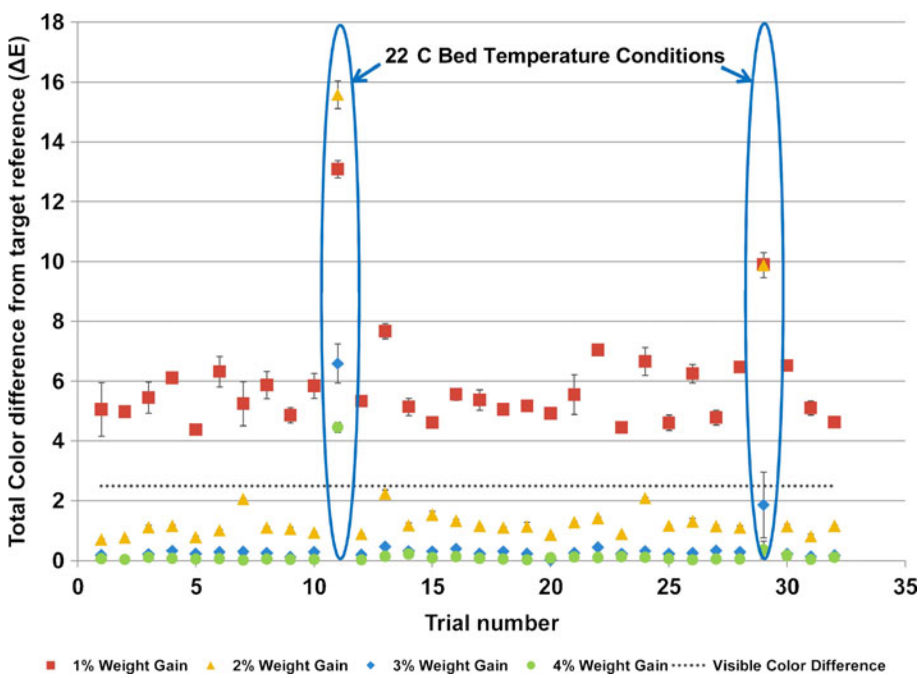

Fig. 5. Color difference from target reference ΔE for each trial

exception of trials 11 and 29, which as previously described, had a low bed temperature and led to tablet sticking and non-uniform tablet appearance. Figure 5 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.

The visible color difference limit in this study is specific to the blue color tablets used. The color uniformity for each sample is indicated by the error bars, which shows that, after a 1% weight gain, there is minimal variability in tablet color. From a product quality perspective, all samples (except 11 and 29) with greater than 2% coating weight gain were visually equivalent based on color, indicating that color development and uniformity is robust across a wide range of coating process parameters. However, it should be noted that other functional attributes such as moisture barrier performance may necessitate additional coating weight gain.

Gloss

Surface gloss is a key aesthetic product attribute. The gloss results indicated that all the coating trials (except runs 11 and 29) produced tablets with gloss values of greater than 81 gloss units. The top 5 process parameters and interactions within the model that impacted gloss are shown in Fig. 6. Gloss has been correlated to surface smoothness, so conditions which prolong or increase frictional forces tend to favor gloss development. Therefore, gloss increased when spray rate and percent solids were decreased. This combination of process parameters led to a wetter tablet bed which increased the surface tackiness of the coating and corresponding tablet to tablet friction. Gloss also increased when pan speed increased since tablet tumbling and cumulative tablet-to-tablet and tablet-to-pan contact increased under this condition. Gloss was further increased when air flow rate was increased, as a consequence of increased surface drying and the increased tendency for sliding of tablets in the coating pan.

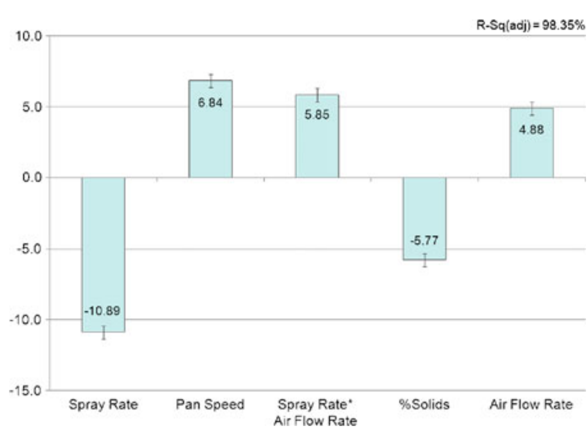

Fig. 6. Coefficient plot indicating process parameters and interactions that impacted gloss

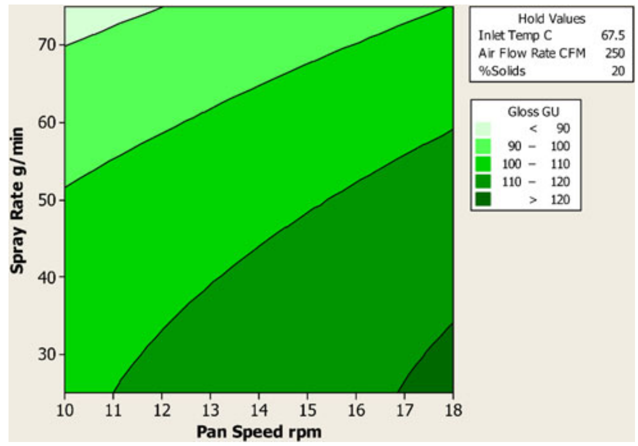

Fig. 7. Contour plot of gloss *versus* spray rate and pan speed

The relationship between gloss and process parameters can be further observed in Figs. 7 and 8, which show contour plots where gloss is shown to increase under the influence of slower spray rate, higher pan speed, and lower percent solids.

Disintegration Time

Tablet disintegration was consistent across all coating trials, except for 11 and 29, where significant overwetting occurred and inconsistent coating thickness resulted in thick accumulations of film coating material which 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 s, respectively. Disintegration times for all other coating trials were less than 360 s. Excluding these two trials, the disintegration time of all samples was very consistent, giving a mean increase in disintegration time *versus* the uncoated core of 120 s. This can be seen in Fig. 9. Therefore, unless extreme coating conditions were used, disintegration time was essentially equivalent regardless of variation in coating process parameters.

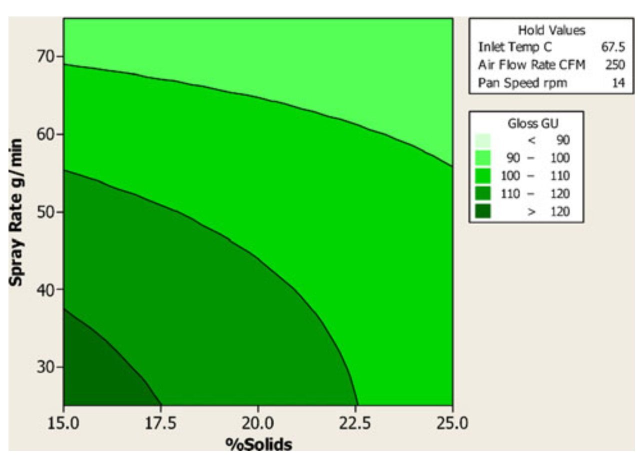

Fig. 8. Contour plot of gloss *versus* spray rate and percent solids

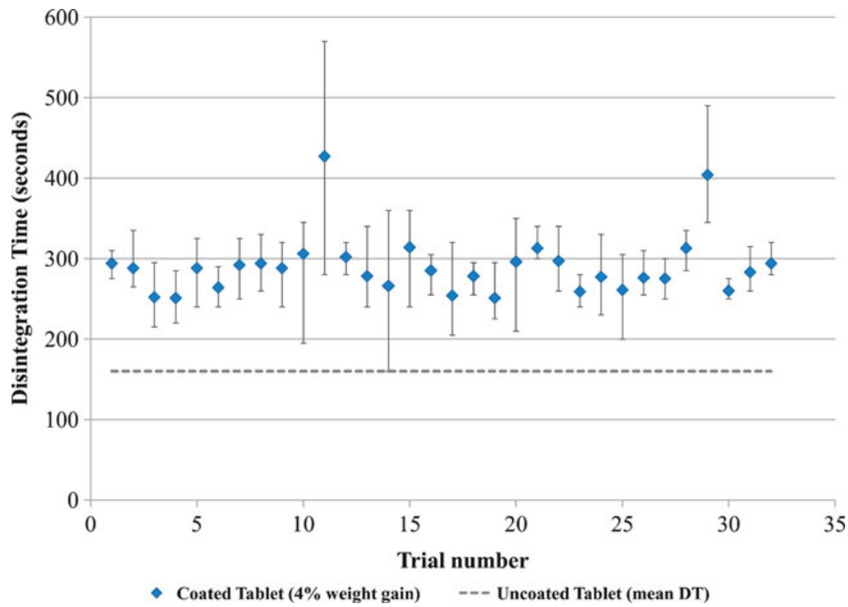

Fig. 9. Average coated tablet disintegration time for each trial

Case Studies

When developing the Quality Target Product Profile (QTPP) for a coated product, it is essential to identify and rank the relative risk associated with each product attribute on overall product suitability. The QTPP is then used to help identify the coating process parameters necessary to meet the product requirements and outline a robust operating space where minor changes in process parameters will have no significant impact on overall product quality. For each case study, a prioritization matrix approach was used to rank the relative importance of each product attribute and assign a risk factor.

Case Study 1—Overall Suitability

In this first case study, defects, disintegration time, and coating time were considered the most important product attributes. The optimization criteria and ranking of these product attributes based on risk are shown in Table VI.

Using the above criteria, the empirical data derived from the experimental design was interrogated to identify the process parameters required to meet the QTPP. The optimized process parameters and those used in a confirmation trial are shown in Table VII.

Using the process parameters from Table VII, the predicted and actual performance indicator values for the coated product were obtained and are shown in Table VIII. The predicted performance indicators and actual experimental values correspond well and support the use of the data to further predict the influence of process parameters on product attributes (Table VIII).

In addition to identifying the optimal process parameters, it is also possible to identify a process operating space where the ranges of process parameters yielding the desired product attributes are identified. The impact of varying inlet temperature and air flow within acceptable ranges on the product performance is shown in Fig. 10.

Table VI. Case Study 1—Response Optimization Criteria for Overall Product Suitability

Product attribute	Goal	Lower	Target	Upper	Risk factor
Defects (%)	Minimize	0	–	1	10
Disintegration time (s)	Minimize	275	–	420	10
Coating time (min)	Minimize	32	–	180	8.0
Color deviation at 4% weight gain (ΔE)	Minimize	0	–	0.5	2.5
Gloss (GU)	Maximize	70	–	130	2.0
Bed temp. (C)	Target	40	45	50	1.0

Table VII. Case Study 1: Optimized and Actual Process Parameters

Process parameter	Optimized value	Mean experimental value
Spray rate (g/min)	50	53
Inlet Temperature (°C)	70	69
Air Flow Rate (CFM)/(m^3/h)	250/425	265/450
% Solids	20	20
Pan speed (rpm)	14	14

rpm revolutions per minute

Table VIII. Case Study 1—Predicted and Experimental Performance Indicator Values and Desirability Factor

Product attribute	Predicted value	Experimental value	Desirability factor
Defects (%)	0	0	1.0000
Gloss (GU)	107	101	0.6229
DT (s)	269	241	0.9178
Bed temp (C)	44	42	0.8285
Coating time (min)	58	57	0.8239
Color deviation at 4% weight gain (ΔE)	0.0155	0	0.9691

Composite desirability=0.8975

Table IX. Case Study 2—Response Optimization Criteria for Maximum Gloss

Product attribute	Goal	Lower	Target	Upper	Risk factor
Gloss (GU)	Maximize	100	–	130	10
Defects (%)	Minimize	0	–	1	10
Disintegration time (s)	Minimize	275	–	420	5
Color deviation at 4% weight gain (ΔE)	Minimize	0	–	0.5	2.5
Coating time (min)	Minimize	32	–	160	1.0
Bed temp. (°C)	Target	40	45	50	1.0

The acceptable operating space where all critical quality attributes were met is shown as the white area in Fig. 10, while the location of the optimized process parameters from Table VII are indicated by an X. The spray rate, percent solids, and pan speed are fixed at center point values in Fig. 10, but a wide range of inlet and air flow values provided an acceptable quality product based on the QTPP criteria.

Case Study 2—Optimized Appearance

Based on the observation that disintegration time does not change significantly under different coating process conditions, a second case study was developed where the QTPP criteria were adjusted such that defects and tablet appearance (gloss) were considered most significant. The optimization criteria and ranking of product attributes are shown in Table IX.

Using the above criteria and empirical data derived from the experimental design, the process parameters that provided the optimal results were identified and are shown in Table X.

Using these process parameters, the predicted performance indicator values for the product are shown in Table XI. Changing the QTPP criteria clearly had a significant impact on the predicted, optimal process parameters compared to the previous case study. In this case, the requirement for high gloss led to optimized process parameters with reduced solids, higher pan speed and lower spray rates. The impact of varying inlet temperature and air flow within approved ranges on the product performance can be seen in Fig. 11.

A wide operating range of inlet temperatures and air flow was identified with only bed temperature defining the acceptable range, indicating a robust process under these coating conditions. While this set of coating conditions led to the glossiest tablets with no indication of defects in the operating space, the coating time to prepare these tablets was over double that employed in case study 1.

Case Study 3—Optimized Coating Productivity

In this third case study, the QTPP criteria were adjusted such that defects and coating productivity (*i.e.* coating time) were considered the highest risk product attributes. The

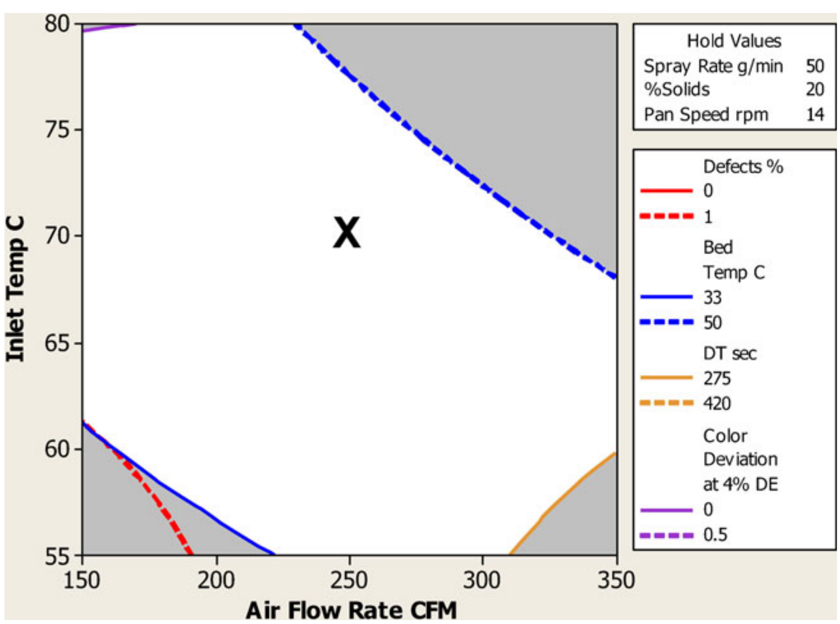

Fig. 10. Case study 1—acceptable operating space

optimization criteria and ranking of product attributes are shown in Table XII.

Using the above criteria and empirical data derived from the experimental design, the process parameters that were predicted to provide optimal results were identified and shown in Table XIII. Using these process parameters, the predicted product attribute values for the product are shown in Table XIV. The impact of varying inlet temperature and air flow within approved ranges on the product performance is shown in Fig. 12.

In this case study, the coating time was reduced to 34 min through the use of high solids, high spray rate, and high inlet temperature. While a large operating space was identified, it was noticeably shifted to higher inlet temperatures and air

Table XII. Case Study 3—Response Optimization Criteria for Maximum Productivity

Product attribute	Goal	Lower	Target	Upper	Risk factor
Coating time (min)	Minimize	32	–	180	10
Defects (%)	Minimize	0	–	1	10
Disintegration time (s)	Minimize	275	–	420	5
Color deviation at 4% weight gain (ΔE)	Minimize	0	–	0.5	2.5
Gloss (GU)	Maximize	70	–	130	1.0
Bed temp. (°C)	Target	40	45	50	1.0

Table X. Case Study 2—Process Parameter Optimization Results

Process parameter	Optimized value
Spray rate (g/min)	35
Inlet temperature (°C)	63
Air flow rate (CFM)/(m^3/h)	265/450
% Solids	15
Pan speed (rpm)	18

rpm revolutions per minute

Table XIII. Case Study 3—Process Parameter Optimization Results

Process parameter	Optimized value
Spray rate (g/min)	60
Inlet temperature (°C)	80
Air flow rate (CFM)/(m^3/h)	184/312
% Solids	25
Pan speed (rpm)	15

rpm revolutions per minute

Table XI. Case Study 2—Predicted Performance Indicator Values and Desirability Factor

Product attribute	Predicted value	Desirability factor
Defects (%)	0	1.0000
Gloss (GU)	130	0.9967
Disintegration time (s)	264	1.0000
Bed temperature (°C)	45	0.9643
Coating time (min)	143	0.1308
Color deviation at 4% weight gain (ΔE)	0.0075	0.9850

Composite desirability=0.9300

Table XIV. Case Study 3—Predicted Performance Indicator Values and Desirability Factor

Product attribute	Predicted value	Desirability factor
Defects (%)	0	1.0000
Gloss (GU)	100	0.4986
Disintegration time (s)	288	0.9150
Bed temperature (°C)	45	0.9977
Coating time (min)	34	0.9876
Color deviation at 4% weight gain (ΔE)	0	1.0000

Composite desirability=0.9452

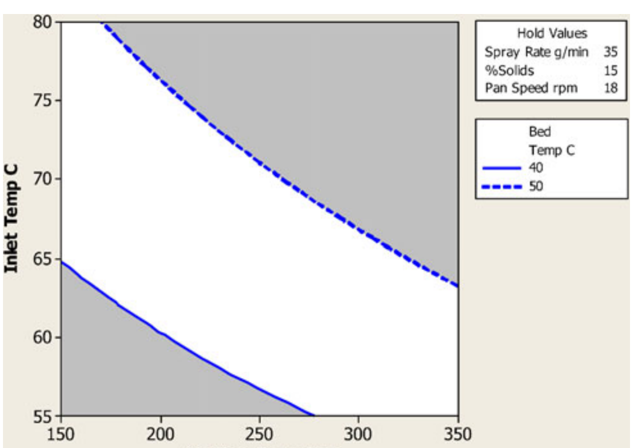

Fig. 11. Case study 2—acceptable operating space

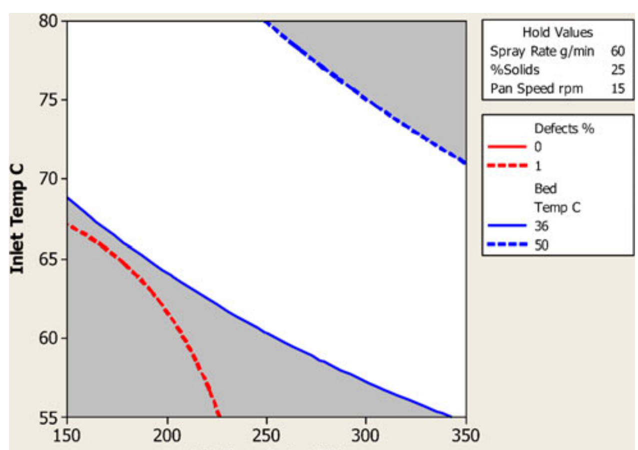

Fig. 12. Case study 3—acceptable operating space

flow rates to achieve the desired drying conditions under these higher spray rate conditions. This is reflected in the increase in the minimum acceptable bed temperature from 33°C in case study 1, to 36°C in this case. Gloss results were comparable to those obtained in case study 1 but were significantly lower than that achieved in case study 2, wherein gloss had the highest risk factor.

CONCLUSIONS

Quality by design principles were used to develop enhanced process knowledge of a fully formulated immediate release film coating system, Opadry 200. The work used prior knowledge and a systematic approach with predefined objectives to identify and interrogate the impact of variation in process parameters on product quality, a key driver of QbD. The case studies illustrated that process operating spaces can be defined that target specific product CQAs or performance indicators based on varying levels of risk (*e.g.*, defects and tablet gloss). These studies confirmed that robust performance was observed over a wide process operating range leading to high quality tablet appearance (low defects, color uniformity, tablet gloss), consistent film disintegration and high coating productivity.

REFERENCES

1. Rajabi-Siahboomi AR, Farrell TP. The applications of formulated systems for the aqueous film coating of pharmaceutical oral solid dosage forms. In: Felton L, McGinity J, editors. Aqueous polymeric coatings for pharmaceutical dosage forms. 3rd ed. New York: New York; 2008.
2. Ebey GC. A thermodynamic model for aqueous film-coating. Pharm Tech. 1987;4:1–6.
3. Macleod GS, Fell JT. Different spray guns used in pharmaceutical film coating. Pharm Tech Eur. 2002;14:25–33.
4. Mueller R, Kleinebudde P. Prediction of tablet velocity in pan coaters for scale-up. Powder Tech. 2007;173:51–8.
5. Pirpich A, Am Ende M, Katzschner T, Lubczyk V. Drug product modeling predictions for scale-up of tablet film coating—a quality by design approach. Comp and Chem Eng. 2010;34:1092–97.
6. Dubey A, Boukouvala F, Keyvan G, Hsia R, Saranteas K, Brone D, *et al*. Improvement of tablet coating uniformity using a quality by design approach. AAPS PharmSciTech. 2012;13(1):231–46.
7. Cunningham CR, Neely CR, Film coating process conditions for the application of high productivity, high solids concentration film coating formulations. AAPS Annual Meeting, Los Angeles, USA 2009