Quality by Design for ANDAs: An Example for Modified Release Dosage Forms

Introduction to the Example

This is an example pharmaceutical development report illustrating how ANDA applicants can move toward implementation of Quality by Design (QbD).

The purpose of the example is to illustrate the types of pharmaceutical development studies ANDA applicants may use as they implement QbD in their development process and to promote discussion on how OGD would use this information in review.

Although we have tried to make the example as realistic as possible, the development of a real product may differ from this example. The example is for illustrative purposes and, depending on applicants' experience and knowledge, the degree of experimentation for a particular product may vary. The impact of experience and knowledge should be thoroughly explained in the submission. The risk assessment process is one avenue for this explanation. At many places in this example alternative pharmaceutical development approaches would also be appropriate.

Notes to the reader are included in *italics* throughout the text. Questions and comments may be sent to GenericDrugs@fda.hhs.gov

Pharmaceutical Development Report
Example QbD for MR Generic Drugs

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1.1 Executive Summary

The following pharmaceutical development report summarizes the development of Example Modified Release (MR) Tablets, 10 mg, a generic version of the reference listed drug (RLD), Brand MR Tablets, 10 mg, indicated for therapeutic relief. We used a Quality by Design (QbD) approach to develop a tablet formulation and manufacturing process that ensures the quality, safety and efficacy of Example MR Tablets.

Initially, the quality target product profile (QTPP) was defined based on the properties of the drug substance, characterization of the RLD product, and consideration of the RLD label and intended patient population. Example MR Tablets were designed to achieve all of the attributes in the QTPP. However, our investigation during pharmaceutical development focused on those critical quality attributes (CQAs) that could be impacted by a realistic change to the drug product formulation or manufacturing process. For Example MR Tablets, these attributes included physical attributes (size and splitability), assay, content uniformity and drug release.

Example MR Tablets contain drug substance Z, a chemically stable BCS Class I compound. To match the RLD, Example MR Tablets were designed to have immediate release (IR) granules and extended release (ER) coated beads with extragranular cushioning agents and other excipients all compressed into scored tablets. ANDA aaaaaa documents the approved formulation and manufacturing process for the IR granules. Kollicoat SR 30 D was selected as the release rate controlling polymer and the formulation was optimized using design of experiments (DOE). Two grades of microcrystalline cellulose (MCC) were used in an optimized ratio to prevent segregation of the IR granules and ER coated beads. The appropriate levels of disintegrant (sodium starch glycolate) and lubricant (magnesium stearate) were also identified to produce a robust formulation.

A predictive dissolution method was a key element of our development program. We developed the method (USP apparatus 3 at 10 dpm in 250 mL of pH 6.8 phosphate buffer) by performing an extensive evaluation of dissolution conditions using our initial prototype formulation (F-1) that failed in our first pilot bioequivalence (BE) study. A subsequent BE study confirmed the theoretical polymer coating level needed to match the RLD performance. We utilized pharmacokinetic data collected from the BE studies to establish an *in vitro-in vivo* relationship (IVIVR). The predictive dissolution method will be used for quality control of the final drug product.

Risk assessment was used throughout development to identify potentially high risk formulation and process variables and to determine which studies were necessary to increase our knowledge. Each risk assessment was then updated to capture the reduced the level of risk based on our improved product and process understanding.

As the IR granulation process has been previously established, this development report focuses on four key steps for ER bead and final tablet process development: 1) drug layering, 2) ER polymer coating, 3) blending and lubrication, and 4) compression. We selected a bottom spray fluid bed process for both drug layering and polymer coating of the ER beads. We utilized diffusive mixing for the final blend before compressing the blend into scored tablets. For each

unit operation, we conducted a risk assessment and then utilized DOE to investigate the identified high risk variables to determine the critical material attributes (CMAs) and critical process parameters (CPPs). An inline NIR method was validated and implemented to monitor blend uniformity and to reduce the risk associated with the blending step. Our process optimization facilitated the creation of a design space at the pilot scale. A pivotal BE study conducted with the exhibit batch manufactured at pilot scale demonstrated equivalence between our product and the RLD.

Our first verification batch at commercial scale failed dissolution testing. Subsequent investigation showed that film coat thickness increased on the beads manufactured at commercial scale versus beads manufactured at pilot scale due to a difference in process efficiency. A second verification batch was manufactured by decreasing the theoretical polymer coating level from 30% to 28 % to account for improved processing efficiency at commercial scale. The formulation change resulted in drug product that met our predefined CQA targets.

We propose a control strategy that includes the input material attributes and process parameters identified as potentially high risk variables during the initial risk assessment. Our control strategy also includes in-process and finished product specifications. The process will be monitored during the lifecycle of the product and additional knowledge gained will be utilized to make adjustments to the control strategy as appropriate.

The development time line for Example MR is presented in Table 1.

Table 1. Development of Example MR Tablets, 10 mg, presented in chronological order

Study	Scale	Page
Analysis of the Reference Listed Drug product	N/A	7
Evaluation of drug substance properties	N/A	28
Excipient compatibility	N/A	33
Dissolution of IR granules compressed with placebo beads	Lab (1 kg)	42
Binder optimization and drug substance solid state stabilization	Lab (1 kg)	46
Drug layering process development – feasibility and optimization studies	Lab (4 kg)	88
Dissolution of drug-layered beads compressed with placebo granules	Lab (1 kg)	47
ER polymer coating formulation feasibility and optimization studies	Lab (1 kg)	54
ER polymer coating process development – feasibility, screening and optimization studies	Lab (4 kg)	105
NIR method for blending endpoint determination	N/A	122
Prototype tablet formulation studies – filler, disintegrant and lubricant optimization	Lab (4, 10 kg)	64
Development of formulation for first pilot BE study (prototype F-1)	Lab (4 kg)	70
First pilot BE study using prototype F-1	N/A	17
Development of formulation for second pilot BE study (F-2 and F-3)	Lab (4 kg)	71
Second pilot BE study using prototypes F-2 and F-3	N/A	25
Development of a predictive dissolution method and IVIVR	N/A	18
Drug layering process robustness study	Pilot (40 kg)	96
ER polymer coating process robustness study	Pilot (40 kg)	115
ER bead curing process confirmation study	N/A	118
Blending process study – segregation investigation and optimization of process parameters	Pilot (40 kg)	123
Tablet compression process development – optimization of process parameters	Pilot (40 kg)	133
Pivotal bioequivalence study	Exhibit (40 kg)	26
Exhibit batch	Exhibit (40 kg)	139
Scale-up to commercial scale	Commercial (180 kg)	141

1.2 Analysis of the Reference Listed Drug Product

1.2.1 Clinical

The reference listed drug (RLD) is Brand MR Tablets, 10 mg, and is a modified release (MR) formulation composed of both an immediate release (IR) and an extended release (ER) component. The RLD was approved in the United States in 2009 in NDA aaaaaa and is indicated for therapeutic relief. Tablets contain the active ingredient Z that acts through the CNS; however, its mechanism of action remains unknown. Brand MR Tablets, 10 mg, were developed based upon the corresponding IR formulation, Brand IR Tablets, 3 mg, approved in 2005 in NDA bbbbbb. The ANDA approval for Example IR Tablets (ANDA aaaaaa) was in 2010.

Brand MR Tablets are designed for once-a-day dosing to provide both immediate onset of therapeutic relief similar to the IR product as well as maintenance of the therapeutic effect. The label-recommended dosing is 10 mg once daily in adults; however, this dose may be titrated to a maximum daily dose of 20 mg. The tablet is scored to allow for 5 mg dosing, particularly for elderly patients or patients with hepatic insufficiency who do not clear the drug as rapidly as normal. The label warns of the potential risk of dose dumping that may occur with the co-ingestion of alcohol.

1.2.2 Pharmacokinetics

Z is metabolized to the corresponding Z* inactive metabolite and has a half-life of approximately 5 hours. In the original Brand IR formulation, the short half-life of Z limits its ability to maintain a therapeutic effect, requiring multiple dosing every 8 hours. The Brand MR formulation was designed to overcome this limitation by releasing the drug in two phases: an IR phase followed by an ER phase. According to the product label, the IR phase achieves plasma concentrations comparable to the IR product (3 mg) through the first two hours for rapid onset of the therapeutic effect. The ER phase sustains plasma concentrations of the drug through 24 hours for maintenance of the therapeutic effect. The product label indicates that the drug can be taken regardless of meals because there is no food effect. Based upon publically available information (under FOI) and applicable product literature, Figure 1 shows the PK profile of Brand MR.

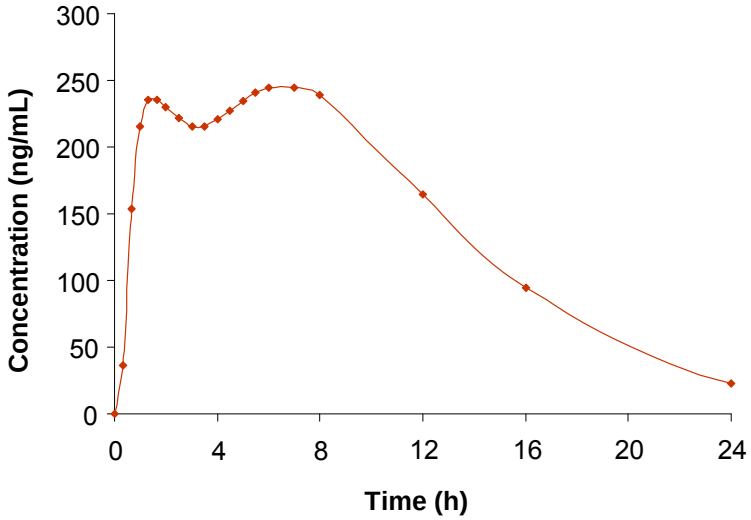

Figure 1. Plasma concentration of Brand MR Tablets, 10 mg, as a function of time

1.2.3 Drug Release

The drug release of the Brand MR Tablets was characterized using USP apparatus 2 at 50 rpm in 900 mL of various media including water, 0.1 N HCl, pH 4.5 phosphate buffer and pH 6.8 phosphate buffer as shown in Figure 2. The figure includes the drug release profiles for both whole and split tablets.

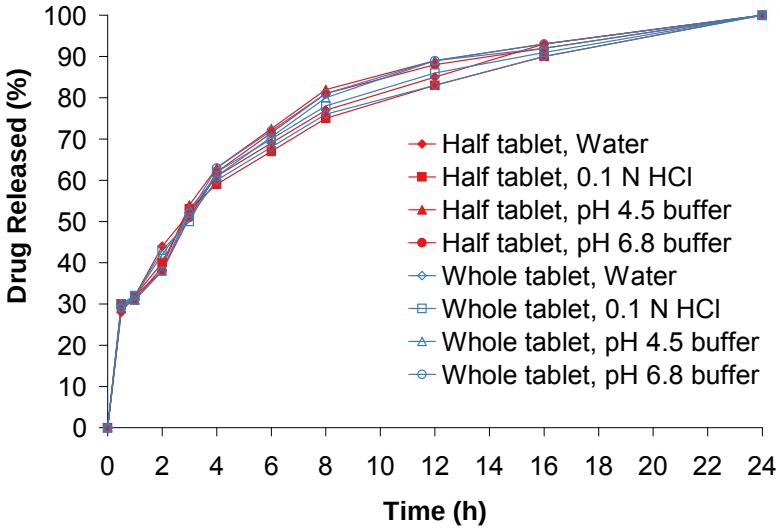

Figure 2. Drug release profiles for Brand MR whole and split tablets using USP apparatus 2 at 50 rpm in 900 mL of media

The drug release profiles convey three critical characteristics of the RLD:

1. Biphasic *in vitro* drug release suggests that the Brand MR Tablet design contains both IR (30% of the nominal dose) and ER (70% of the nominal dose) components. Primarily, the IR component provides the first plasma concentration peak shown in Figure 1 which is responsible for the initial onset of the effect. The ER component likely causes the second peak which provides the sustained release exposure to drug for maintenance of the effect.
2. Drug release occurs in a pH-independent manner.
3. Drug release characteristics of whole and split tablets are similar.

To provide a comparable release profile to the RLD, the target for drug release from Example MR Tablets, 10 mg, was based upon rapid release (NMT 30 minutes (min)) of the active ingredient (30% of the nominal dose) followed by extended release (from 30 min to 24 hours (h)) of the remaining ER component (70% of the nominal dose). The initial dissolution method utilized USP apparatus 2 at 50 rpm in 900 mL of pH 6.8 phosphate buffer.

1.2.4 Physicochemical Characterization

The physicochemical characterization of Brand MR Tablets is summarized in Table 2. Notably, the disintegration observation and cross-sectional examination via optical microscopy and SEM (Figures 3a, 3b, and 3c) are indicative of the Brand MR Tablet being composed of intact beads (~0.45 mm) having 2-3 layers of polymer coating.

Table 2. Physicochemical characterization of Brand MR Tablets, 10 mg

Description	White capsule-shaped tablet debossed with "XX" on one side of the break line and "234" on the other side
Batch No.	A0420B
Expiry date	June 2009
Strength (Label claim)	Each scored tablet contains 10 mg of Z
Average weight (mg)	250.70
Score	Yes, divides into two equal parts
Coating	Uncoated
Length (mm)	10.97 – 11.02
Width (mm)	5.48 – 5.53
Thickness (mm)	5.73 – 5.77
Volume (mm^3)	207.50 measured using image analysis
Hardness (kP)	10 – 12
Disintegration time	1 min 30 sec
Disintegration Observation	Beads are observed after tablet disintegration
Optical microscopy	Cross section of tablet reveals beads with a diameter of ~0.45 mm
SEM	Intact beads with 2-3 layers of polymer coating
Assay, % w/w of labeled amount	100.2
Highest Individual unknown	0.10

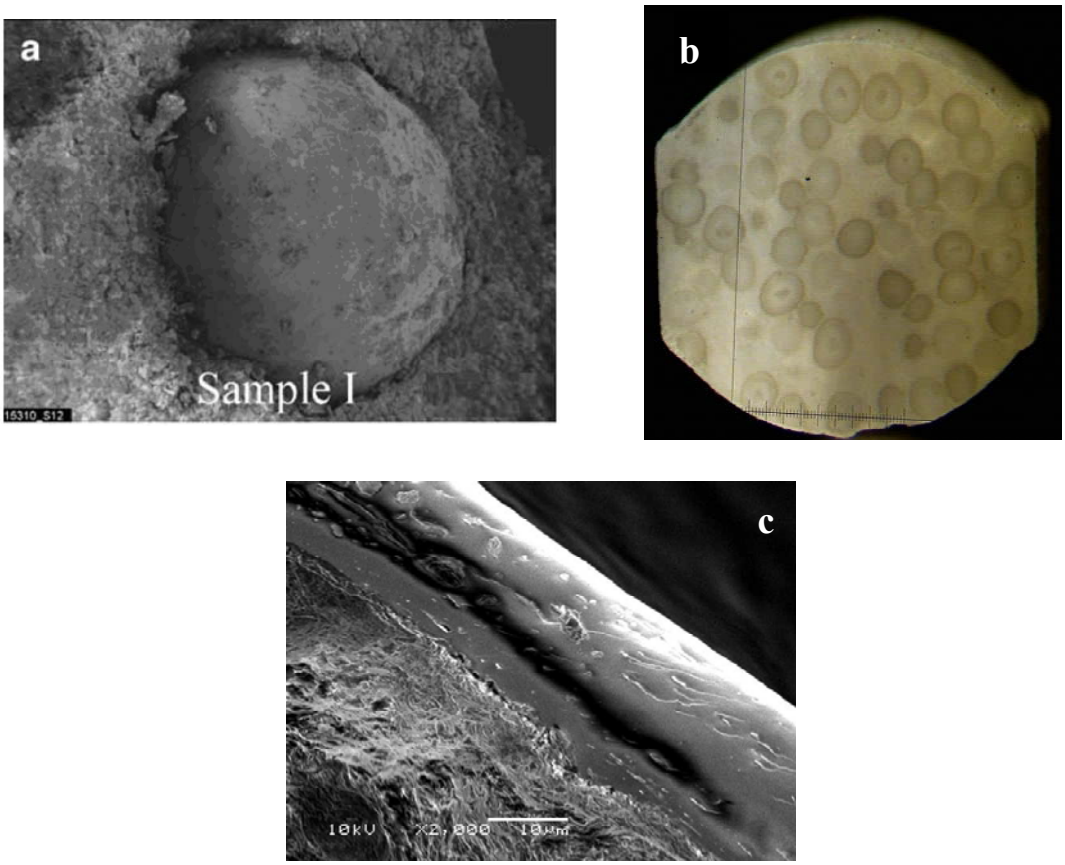

Figure 3. Images of a Brand MR Tablet, 10 mg: (a and b) Cross section of tablet; (c) Cross section of bead showing 2-3 layers of polymer coating

1.2.5 Composition

Based on the RLD labeling, patent literature, product features and reverse engineering, Table 3 lists the composition of Brand MR Tablets, 10 mg. The level provided for each excipient is consistent with previous experience and the IIG level previously FDA-approved for oral solid dosage forms.

Table 3. Composition of Brand MR Tablets, 10 mg

Components	Function	Unit (mg per tablet)	Unit (% w/w)
ER Coated Beads			
Z	Drug substance	7.0	2.8
Povidone (PVP)	Binder	2-4	0.8-1.6
Ethyl Cellulose	Coating polymer	3-5	1.2-2.0
Polyethylene Glycol (PEG)	Plasticizer	0.2-0.8	0.08-0.3
Sugar Sphere	Substrate	18-28	7.2-11.2
ER Coated Beads Subtotal		**40**	**16.0**
IR Granules and Final Blend (excluding beads)			
Z	Drug substance	3.0	1.2
Microcrystalline Cellulose (MCC)	Filler	100-140	40.0-56.0
Lactose Monohydrate	Filler	40-70	16.0-28.0
Sodium Starch Glycolate (SSG)	Disintegrant	10-20	4.0-8.0
Magnesium Stearate	Lubricant	1.5-3.5	0.6-1.4
Blend (excluding beads) Subtotal		**210**	**84.0**
Total tablet weight		**250**	**100.0**

1.3 Quality Target Product Profile for the ANDA Product

Note to Reader: The Quality Target Product Profile (QTPP) is "a prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product."[1] The QTPP is an essential element of a QbD approach and forms the basis of design for the development of the product. For ANDAs, the target should be defined early in development based on the properties of the drug substance (DS), characterization of the RLD product and consideration of the RLD label and intended patient population. By beginning with the end in mind, the result of development is a robust formulation and manufacturing process with an acceptable control strategy that ensures the performance of the drug product.

A critical quality attribute (CQA) is "a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality."[1] The identification of a CQA from the QTPP is based on the severity of harm to a patient should the product fall outside the acceptable range for that attribute.

All quality attributes are target elements of the drug product and should be achieved through a good quality management system, appropriate formulation/process design and development. From the perspective of pharmaceutical development, we only investigate the subset of CQAs of the drug product that also have a high potential to be impacted by the formulation or process variables. Our investigation culminates in an appropriate control strategy.

[1] ICH Harmonised Tripartite Guideline: Q8(R2) Pharmaceutical Development. August 2009.

Based on the clinical and pharmacokinetic characteristics of Brand MR Tablets given in the product label as well as the *in vitro* drug release and physicochemical characteristics of the branded drug, a QTPP was defined and justified as shown in Table 4 to guide the development of generic Example MR Tablets that are therapeutically equivalent to the RLD.

Table 4. Quality Target Product Profile (QTPP) for Example MR Tablets, 10 mg

QTPP Element	Target	Justification
Dosage form	MR Tablet	Pharmaceutical equivalence requirement: Same dosage form
Route of administration	Oral	Pharmaceutical equivalence requirement: Same route of administration
Dosage strength	10 mg	Pharmaceutical equivalence requirement: Same strength
Pharmacokinetics	Fasting Study and Fed Study 90 % confidence interval of the PK parameters, AUC_{0-2}, AUC_{2-24}, $AUC_{0-\infty}$ and C_{max}, should fall within bioequivalence limits	Bioequivalence requirement Initial plasma concentration through the first two hours that provides a clinically significant therapeutic effect followed by a sustained plasma concentration that maintains the therapeutic effect
Stability	At least 24-month shelf-life at room temperature	Equivalent to or better than RLD shelf-life
Drug product quality attributes	Physical Attributes	Pharmaceutical equivalence requirement: Meeting the same compendial or other applicable (quality) standards (i.e., identity, assay, purity, and quality)
	Identification	
	Assay	
	Content Uniformity	
	Degradation Products	
	Residual Solvents	
	Drug Release	
	Microbial Limits	
	Water Content	
Container Closure System	Suitable container closure system to achieve the target shelf-life and to ensure tablet integrity during shipping.	HDPE bottles with Child Resistant (CR) Caps are selected based on similarity to the RLD packaging. No further special protection is needed due to the stability of drug substance Z.
Administration/concurrence with labeling	A scored tablet can be divided into two 5 mg tablets.	Information is provided in the RLD labeling.
	The tablet can be taken without regard to food (no food effect).	
Alternative methods of administration	None	None are listed in the RLD labeling.

Table 5 summarizes the quality attributes of Example MR Tablets and indicates which attributes were classified as drug product CQAs. For this product, physical attributes (size and splitability), assay, content uniformity (whole and split tablets) and drug release (whole tablets, split tablets and alcohol-induced dose dumping) are investigated and discussed in detail in subsequent formulation and process development studies.

On the other hand, CQAs including identity, degradation products and microbial limits which are unlikely to be impacted by formulation and process variables will not be discussed in detail in the pharmaceutical development report. However, these CQAs are still target elements of the QTPP and are ensured through the product and process design and the control strategy

Table 5. Critical Quality Attributes (CQAs) of Example MR Tablets, 10 mg

Quality Attributes of the Drug Product		Target	Is it a CQA?	Justification
Physical Attributes	Appearance	Color and shape acceptable to the patient. No visual tablet defects observed.	No	Color, shape and appearance are not directly linked to safety and efficacy. Therefore, they are not critical. . The target is set to ensure patient acceptability.
	Odor	No unpleasant odor	No	In general, a noticeable odor is not directly linked to safety and efficacy, but odor can affect patient acceptability and lead to complaints. For this product, neither the drug substance nor the excipients have an unpleasant odor. No organic solvents will be used in the drug product manufacturing process.
	Size	Similar to RLD	Yes	Tablet size correlates to swallowability; therefore, it is critical. For comparable ease of swallowing as well as patient acceptance and compliance with treatment regimens, the target for tablet size and volume is set similar to the RLD.
	Score and Splitability	Scored and can be split for half-dosing	Yes	The RLD tablet is scored and labeled for half-dosing; thus, ease of splitting is critical for this drug product design.
	Friability (whole and split tablets)	Not more than 1.0% w/w	No	A target of NMT 1.0% mean weight loss is set according to the compendial requirement and to minimize post-marketing complaints regarding tablet appearance. This target friability will not impact patient safety or efficacy.
Identification		Positive for drug substance Z	Yes*	Though identification is critical for safety and efficacy, this CQA can be effectively controlled by the quality management system and will be monitored at drug product release. Formulation and process variables do not impact identity.
Assay (whole and split tablets)		100.0% of label claim	Yes	Variability in assay will affect safety and efficacy; therefore, assay is critical.
Content Uniformity	Whole tablets	Conforms to USP <905> Uniformity of Dosage Units	Yes	Variability in content uniformity will affect safety and efficacy. Content uniformity of whole and split tablets is critical.
	Split tablets			
Degradation Products		Individual unknown degradation product: NMT 0.2% Total degradation products: NMT 1.0%	Yes*	The limit of degradation products is critical to drug product safety. The limit for individual unknown degradation products complies with ICH Q3B. A limit for the total degradation products is set based on analysis of the RLD near expiry. The molecular structure of drug substance Z contains no functional groups with obvious sensitivities to oxidation, hydrolysis, acid, base, light or heat and its stability was confirmed in a forced degradation study. No chemical interactions were observed during the development of the IR tablet (ANDA aaaaaa, Section 3.2.P.2.1.2 and Section 3.2.P.8.3 (Appendix I)) or during the excipient compatibility studies performed as part of the development of the MR tablet. Therefore, formulation and process variables are unlikely to impact this CQA.

Quality Attributes of the Drug Product		Target	Is it a CQA?	Justification
Residual Solvents		Conforms to USP <467>	Yes*	The drug substance and excipients used in the drug product formulation contain residual solvents. The limit is critical to drug product safety. However, no organic solvent is used in the drug product manufacturing process and the drug product complies with USP <467> Option 1. This CQA will not be discussed in the pharmaceutical development report but will be considered when setting the raw material acceptance criteria.
Drug Release	Whole tablets	Similar drug release profile as RLD using a predictive dissolution method.	Yes	The drug release profile is important for bioavailability (BA) and bioequivalence (BE); therefore, it is critical. Since *in vitro* drug release is a surrogate for *in vivo* performance, a similar drug release profile to the RLD is targeted to ensure bioequivalence.
	Split tablets	Similar drug release to whole tablets: f2 > 50		For tablets containing a multi-particulate system, a non-uniform distribution of beads may cause different drug release profiles between whole and split tablets. Therefore, it is critical and the target is set in accordance with regulatory guidance.
	Alcohol-induced dose dumping	Comparable or lower drug release compared to the RLD in 5% (v/v), 20% (v/v), and 40% (v/v) Alcohol USP in 0.1 N HCl dissolution medium		The drug release profile in alcohol is critical to patient safety. The target is set to ensure that alcohol stress conditions do not alter bioavailability of the generic product and introduce additional risks to the patient.
Water Content		Not more than 2.0% w/w	No	Limited amounts of water in oral solid dosage forms will not impact patient safety or efficacy. Therefore, it is not critical.
Microbial Limits		Meets relevant pharmacopoeia criteria	Yes*	Non-compliance with microbial limits will impact patient safety. However, as long as raw materials comply with compendial microbial requirements, the formulation and process variables are unlikely to impact this CQA. Water activity will be tested on the final prototype formulation to confirm that the drug product does not support microbial growth.

*Formulation and process variables are unlikely to impact the CQA. Therefore, the CQA will not be investigated and discussed in detail in subsequent risk assessments and pharmaceutical development. However, the CQA remains a target element of the QTPP and is ensured through the product and process design and the control strategy.

Note to Reader: In order for accurate measurement of the product attributes at in-process and finished product stages, the analytical methodology should be evaluated for its capability of producing test data that are closely representative of the true attributes. Before a formulation or manufacturing process is studied for a given product, the analytical method should be assessed to determine the degree of variability in the test data imparted by the analytical method itself versus the degree of variability inherent to the product.

One such approach to conduct measurement system analysis is to use ANOVA-based statistical methods designed for this purpose. This allows quantitative discernment between different sources of variability including, but not limited to, the instrument, the operator and the sample. Analysis of the measurement system and assurance of its capability to produce representative data are even more important when changes in the values of the product attributes are studied as responses to controlled changes in the formulation and the process parameters in a design of experiments (DOE).

1.4 Dissolution Method Development and Bioequivalence Studies

It was important to understand the relationship between *in vitro* drug release and *in vivo* performance in order to 1) evaluate the impact of formulation and process variable changes on drug product quality during development; 2) predict the performance of the commercial batches based on the BE data from the exhibit batch manufactured at the pilot scale, and 3) facilitate the evaluation of post-approval changes. Therefore, we decided to develop a predictive dissolution method and establish an *in vitro-in vivo* relationship (IVIVR) between *in vitro* drug release and *in vivo* performance of the drug product. A predictive dissolution method should be able to predict *in vivo* performance of the drug product reasonably well and also discriminate between the formulations that perform differently.

The first prototype formulation F-1 (described in Section 2.2.1.4) contained the drug-layered beads coated with 25% theoretical polymer. A pilot BE study was conducted using prototype F-1. The study was a randomized single dose two-way crossover study comparing the prototype to the RLD in 12 healthy subjects. Table 6 shows the geometric mean ratios of pharmacokinetic parameters for prototype F-1 relative to the RLD.

Table 6. Summary of PK parameters from BE study comparing prototype F-1 to the RLD

Prototype/RLD Ratio				
	AUC_{0-2}	AUC_{2-24}	$AUC_{0-\infty}$	C_{max}
Prototype F-1	1.1	1.21	1.10	1.32

The plasma drug concentration obtained for prototype F-1 and the RLD are compared in Figure 4.

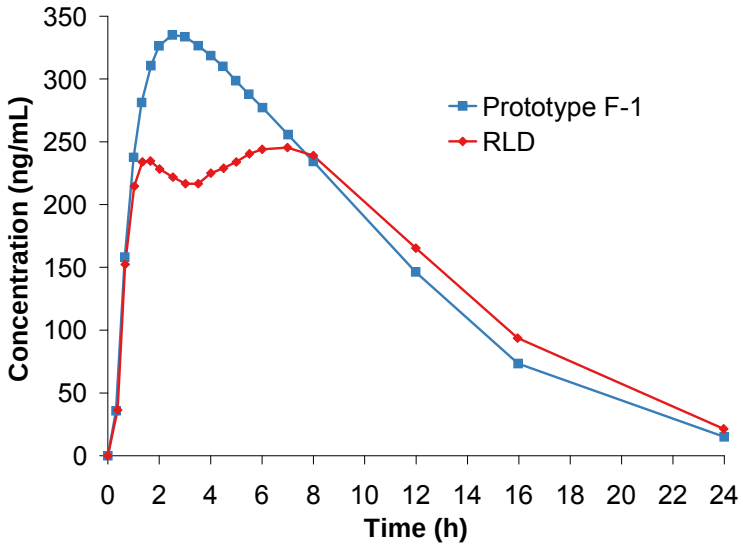

Figure 4. Comparative plasma drug concentrations after oral administration of prototype F-1 and the RLD

The RLD provided a biphasic profile representing the IR and ER portions of the formulation which was not observed for prototype F-1. The data suggested the need to slow the release rate from the ER coated beads in the prototype formulation in order to achieve bioequivalence to the RLD. Therefore, prototype F-1 was used to develop a predictive dissolution method.

1.4.1 Development of a Predictive Dissolution Method

The effects of dissolution medium pH, stirring speed or number of dips per minute (dpm) as applicable, and dissolution medium volume were systemically evaluated to develop the predictive dissolution method. The effect of ionic strength of the dissolution medium was considered but not evaluated because a predictive method could be developed using a standard USP buffer.

USP Apparatus 2 (Paddle)

An initial attempt at developing the discriminating dissolution method that would be predictive of *in vivo* performance was made using USP apparatus 2 because the RLD was extensively characterized as shown in Figure 2 using this apparatus early in the formulation development.

Effect of dissolution medium pH

Both prototype F-1 and the RLD were subjected to dissolution testing using USP apparatus 2 at 50 rpm in 900 mL of various media including water, 0.1 N HCl, pH 4.5 phosphate buffer, and pH 6.8 phosphate buffer. The drug release profiles obtained showed that *in vitro* drug release of prototype F-1 matched that of the RLD as shown in Figure 5.

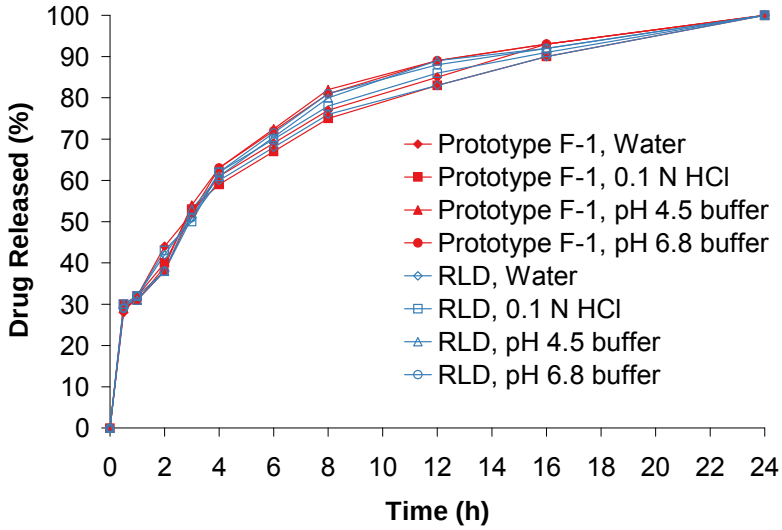

Figure 5. Comparative *in vitro* release characteristics of the prototype formulation (F-1) and the RLD using USP apparatus 2 at 50 rpm in 900 mL of various media

The drug release profile of prototype F-1 shows pH-independence similar to the RLD. This is not surprising considering that the drug substance is highly soluble (BCS Class I) and the ER polymer impacts drug release through a pH-independent mechanism. These results indicated that dissolution testing using USP apparatus 2 may not be predictive because prototype F-1 did not exhibit

bioequivalence to the RLD when dosed in healthy human volunteers despite giving almost identical drug release profiles under various pH conditions. Therefore, the effect of pH was not studied further during the development of a predictive dissolution method. The pH 6.8 phosphate buffer was selected as the dissolution medium since this medium is often used for modified release drug products.

Effect of dissolution medium volume

The drug release of prototype F-1 was evaluated using pH 6.8 phosphate buffer volumes of 900 mL, 500 mL and 250 mL. The stirring speed was 50 rpm in each case. Identical drug release profiles were obtained in all three volumes as is evident in Figure 6. The high solubility of drug substance Z provides sink condition in great excess even at 250 mL. Therefore, changing the dissolution medium volume does not improve the predictive power of the dissolution test using USP apparatus 2.

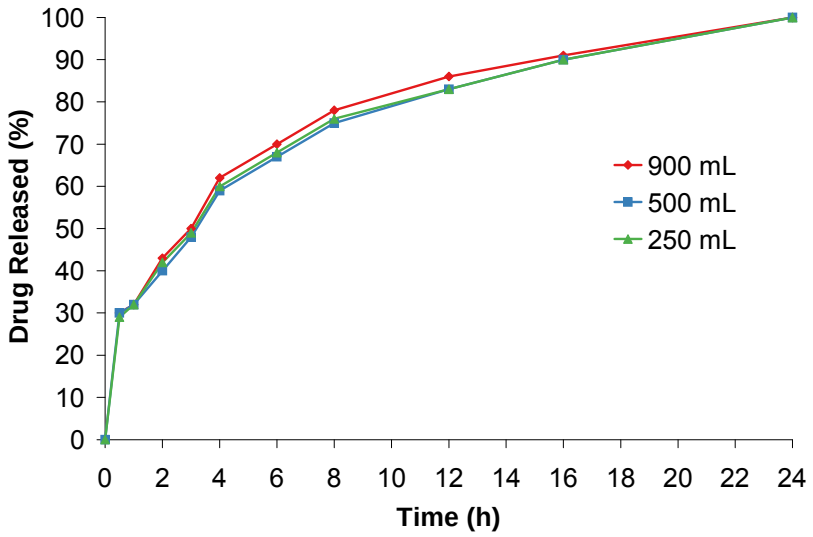

Figure 6. Comparative *in vitro* release characteristics of the prototype formulation (F-1) using USP apparatus 2 at 50 rpm in 900, 500 and 250 mL of dissolution medium

Effect of stirring speed

The drug release of prototype F-1 was also evaluated at 25 rpm in 900 mL of pH 6.8 phosphate buffer. Severe coning at the bottom of the vessel was observed during dissolution testing. This observation was reflected in extremely variable drug release profiles as shown in Figure 7. Therefore, 25 rpm could not be used as the stirring speed. A higher stirring speed (> 50 rpm) was not explored because 50 rpm itself failed to discriminate formulation F-1 and the RLD as shown earlier in Figure 5.

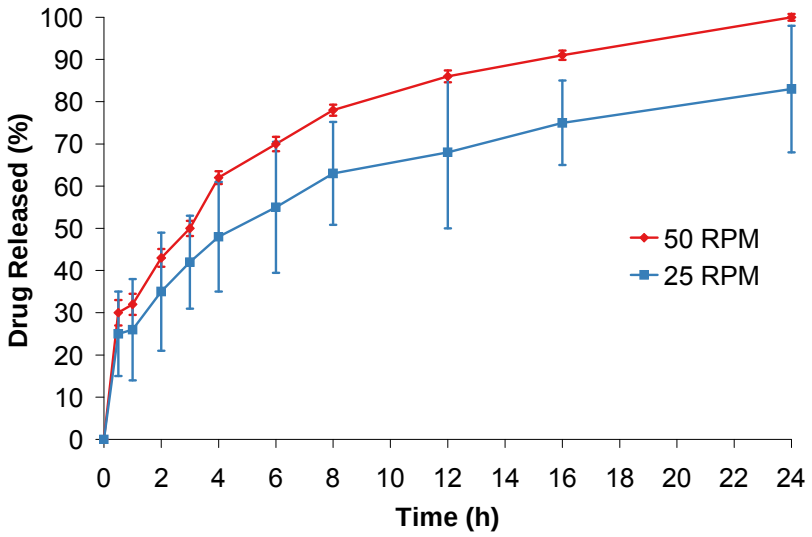

Figure 7. Comparative *in vitro* release characteristics of the prototype formulation (F-1) using USP apparatus 2 at 25 and 50 rpm in 900 mL of dissolution medium

Based on the extensive evaluation of USP apparatus 2, it was concluded that this apparatus does not provide predictive conditions for evaluation of *in vivo* performance of the drug product.

The evaluation of USP apparatus 1 and 3 was limited to stirring speed and the number of dips per minute, respectively. The pH and dissolution medium volume do not provide predictive conditions based on the results obtained during evaluation of USP apparatus 2.

USP Apparatus 1 (Basket)

Dissolution testing of both prototype F-1 and the RLD was conducted at 50, 75, and 100 rpm in 900 mL of pH 6.8 phosphate buffer. Severe coning was observed at 50 and 75 rpm resulting in extremely variable and incomplete drug release profiles after 24 hours for both prototype F-1 and the RLD as shown in Figure 8. At 100 rpm, the drug release profiles of both formulations were still incomplete after 24 hours but had similarly low variability. The results indicate that USP apparatus 1 does not provide discriminating conditions.

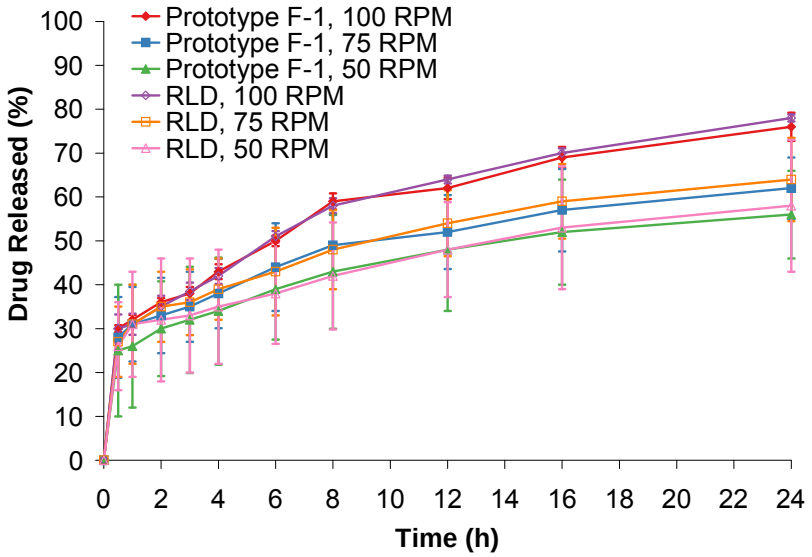

Figure 8. Comparative *in vitro* release characteristics of the prototype formulation (F-1) and the RLD using USP apparatus 1 at 100, 75 and 50 rpm in 900 mL of dissolution medium

USP Apparatus 3 (Reciprocating Cylinder)

The evaluation of USP apparatus 3 was limited to the number of dips per minute. Dissolution testing on both prototype F-1 and the RLD was conducted at 5 and 10 dpm in 250 mL of pH 6.8 phosphate buffer. Figure 9 shows the drug release profiles.

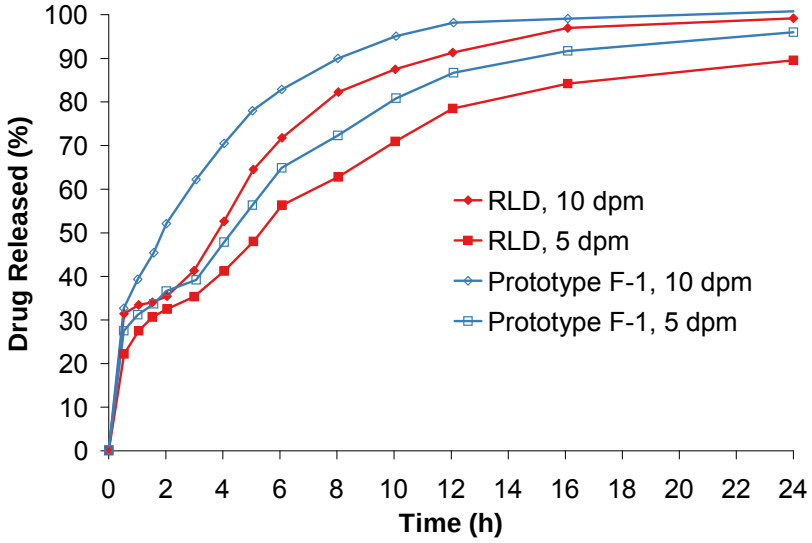

Figure 9. Comparative *in vitro* release characteristics of the prototype formulation (F-1) and the RLD using USP apparatus 3 at 5 and 10 dpm in 250 mL of dissolution medium

Based on these results, discriminating dissolution conditions were obtained at 5 and 10 dpm using USP apparatus 3. The next step was to evaluate if either of these conditions could reasonably predict the *in vivo* performance of the drug product.

1.4.2 Establishment of the IVIVR

The PK profile of prototype F-1 was deconvoluted to obtain the fraction of *in vivo* drug release. The fraction of *in vivo* drug release was plotted against the fraction of *in vitro* drug release using USP apparatus 3 at 5 and 10 dpm. Figures 10 and 11 show the IVIVR obtained at 5 and 10 dpm, respectively.

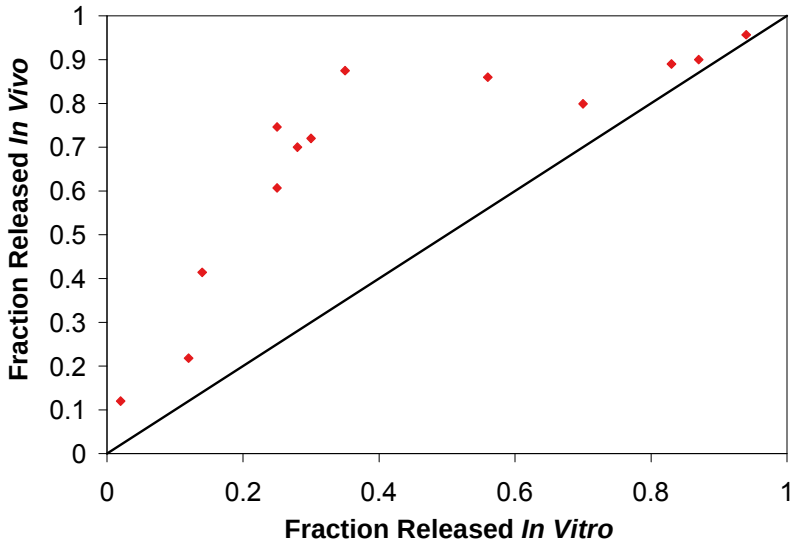

Figure 10. IVIVR using USP apparatus 3 at 5 dpm and the prototype formulation (F-1)

Figure 10 clearly indicates that the dissolution testing at 5 dpm under predicts *in vivo* performance of prototype F-1. The fraction of drug released *in vitro* is consistently lower than the fraction of drug released *in vivo* indicating over-discriminating dissolution conditions. The coefficient of determination (R^2) value of 0.65 also indicates poor predictive capability of the relationship. Similar results were obtained for the RLD formulation ($R^2 = 0.55$, data not shown).

Figure 11 gives a reasonably good relationship between the fractions of *in vivo* and *in vitro* drug release at 10 dpm with an R^2 value of 0.85.

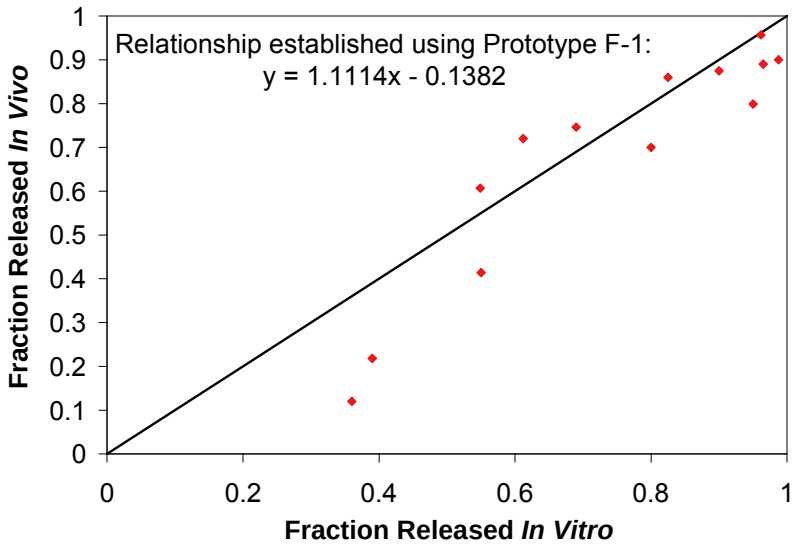

Figure 11. IVIVR using USP apparatus 3 at 10 dpm and the prototype formulation (F-1)

This relationship could be used to predict the *in vivo* performance of both the prototype and RLD formulations with prediction errors of approximately 10% for PK parameters such as C_{max}, $AUC_{0\text{-}2,}$ $AUC_{2\text{-}24}$ and $AUC_{0\text{-}\infty}$. Based on the results of the failed BE study using prototype F-1, the predictive dissolution method using USP apparatus 3 at 10 dpm in 250 mL of pH 6.8 phosphate buffer was developed and the IVIVR was established.

The drug release profiles for all of the batches from the ER polymer coating development work (Batch No. 1-12) were reevaluated using the new dissolution method. It was observed that the $T_{20\%}$, $T_{50\%}$ and $T_{80\%}$ values of prototype F-1 were considerably shorter when measured by the new dissolution method. Therefore, the formulation needed an adjustment in the theoretical polymer coating level to achieve the optimal release profile. Formulation of the ER coated beads was further modified to develop two new prototypes, F-2 and F-3, as described in Formulation Development 2.2.1.4. Prototypes F-2 and F-3 contained ER beads coated with 30% and 35% polymer levels, respectively.

In vitro drug release profiles were generated for prototypes F-2 and F-3 using the predictive USP apparatus 3 dissolution method and compared against the original non-discriminating USP apparatus 2 method in Figure 12. The increase in the theoretical polymer coating level from 25% (F-1) to 30% (F-2) led to a formulation exhibiting a drug release profile which was similar to the RLD drug release profile using USP apparatus 3. However, 35% theoretical polymer coating (F-3) showed a slower drug release profile.

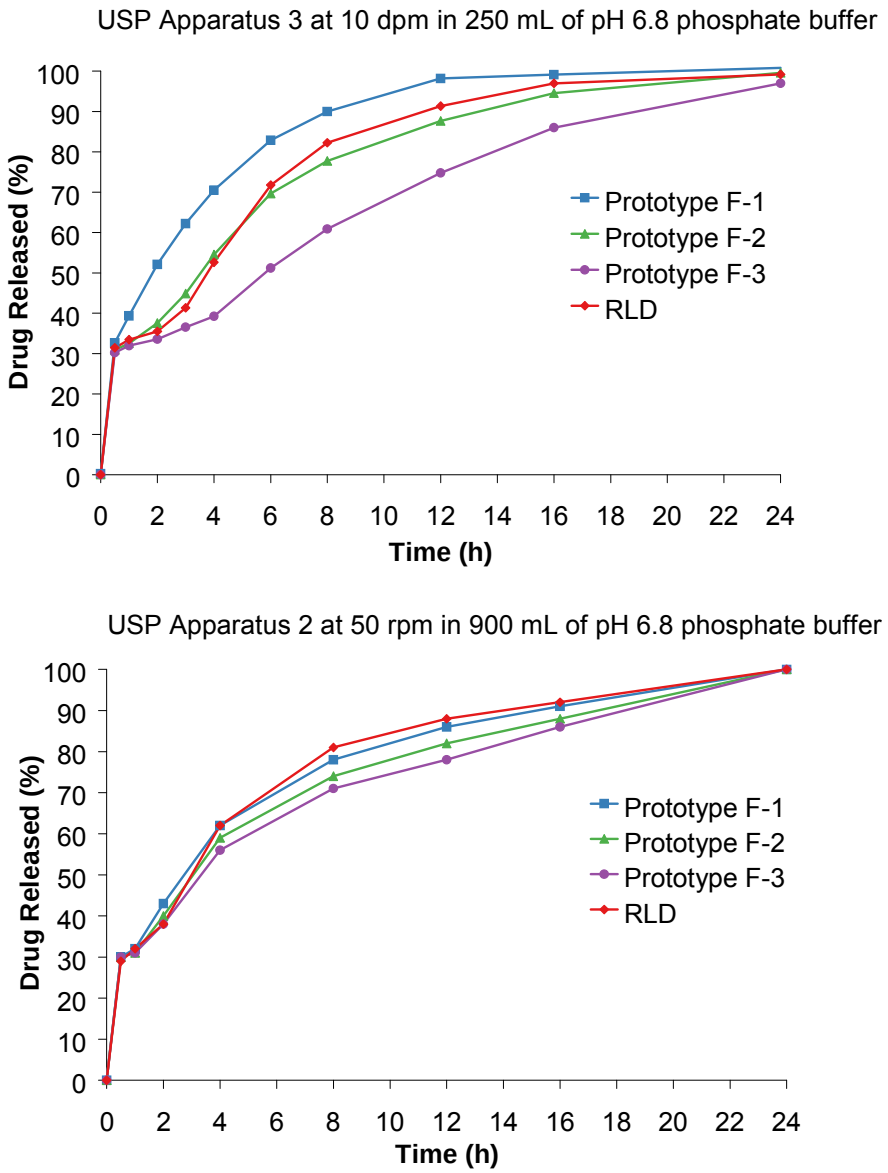

Figure 12. Comparative *in vitro* release characteristics of the prototype formulations (F-1, F-2 and F-3) and the RLD using the predictive method (top) and non-predictive method (bottom)

The drug release data of prototypes F-2 and F-3 were convoluted using the established IVIVR (y = 1.1114x - 0.1382) to predict mean plasma concentration-time profiles. Virtual trial simulations were conducted to assess the variability of the PK parameters before undertaking a second BE study. For virtual trial simulations, distributions for each parameter were pre-defined for previously fixed model parameters. In each simulation, a random number was generated from the pre-defined distribution and used as the model parameter. Thus, the *in vivo* performance of F-2 and F-3 were assessed in a virtual population. The mean plasma concentration-time profile and the 90% CI of mean plasma concentration for prototype F-2 are presented in Figure 13. These virtual simulation trials provided confidence that prototype F-2 had a strong likelihood of being equivalent to the RLD.

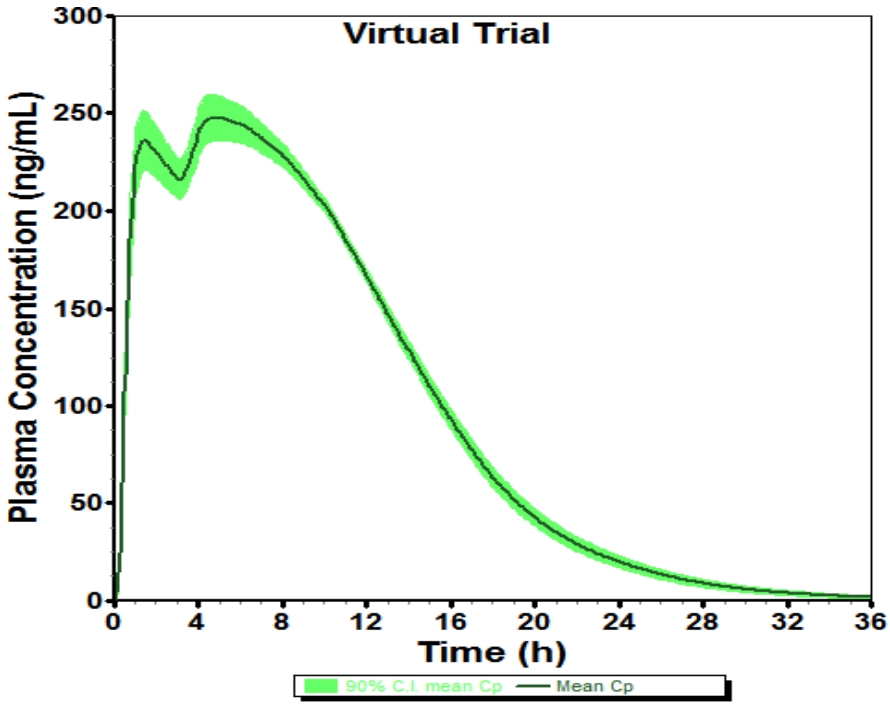

Figure 13. Predictive virtual trial generated using the test formulation (F-2) drug release data

A second pilot BE study was conducted comparing prototypes F-2 and F-3 to the RLD. The study consisted of a randomized single dose three-way crossover study in 12 healthy subjects. Table 7 shows the geometric mean ratios of pharmacokinetic parameters for prototypes F-1, F-2 and F-3 relevant to the RLD. While the C_{max} ratio for prototypes F-1 and F-3 did not meet the bioequivalence limit (0.8-1.25), all ratios were acceptable for prototype F-2.

Table 7. Summary of PK parameters from BE studies comparing the prototype formulations to the RLD

Prototype/RLD Ratio				
	AUC_{0-2}	**AUC_{2-24}**	**$AUC_{0-\infty}$**	**C_{max}**
Prototype F-1	1.1	1.21	1.10	1.32
Prototype F-2	0.97	0.98	0.96	1.03
Prototype F-3	0.81	0.95	0.95	0.75

A comparison of plasma concentration profiles for the RLD and the two prototypes, F-2 and F-3, is presented in Figure 14.

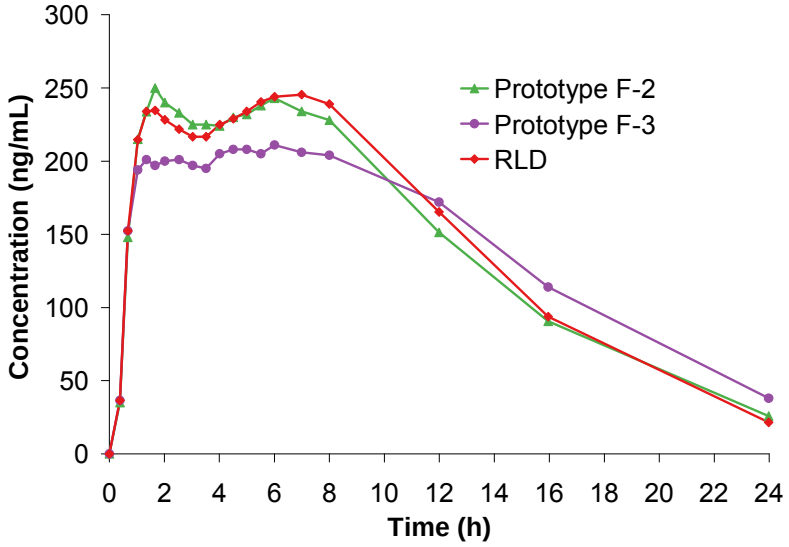

Figure 14. Comparison of plasma drug concentrations after oral administration of the prototype test formulations (F-2 and F-3) and the RLD

A final IVIVR was built ($y = 1.1131x - 0.1242$, $R^2 = 0.87$) using PK data obtained for the three prototypes F-1, F-2, and F-3 used in the two BE studies and the *in vitro* drug release data obtained using the predictive dissolution method. This final IVIVR could be used to perform convolution of the *in vitro* data for the prototypes and RLD formulations. This IVIVR could also predict the failed study outcome from the drug release data obtained for prototypes F-1 and F-3 using USP apparatus 3. In addition, this IVIVR can be used to establish the linkage between exhibit and commercial batches.

1.4.3 Pivotal Bioequivalence Study

Note to Reader: Several options are available to ensure that drug product lots manufactured at both the pilot and commercial scale (scaled-up batches) are bioequivalent to the RLD. A discussion of each option follows:

1. In Vivo – In Vitro Correlation (IVIVC)
Establishment of an IVIVC is one of the more robust options to assure continued BE of the commercial lots. It establishes a control for post-approval changes to the critical material attributes (CMAs) and critical process parameters (CPPs) and ensures continued product quality and BE. However, IVIVC is difficult to establish.

2. Predictive in vitro method (In Vivo – In Vitro Relationship (IVIVR))
A product designed and developed using QbD principles should lead to the establishment of a predictive in vitro dissolution method. Establishing an IVIVR, although less robust than an IVIVC, may be sufficient to assure product quality when combined with product and process understanding. Such an in vitro method will also be useful in assessing post-approval changes.

3. Bioequivalence study of commercial scale batches
It is well recognized that an ER product developed at pivotal batch scale may not always scale-up to commercial scale and yield a drug product that is BE to the RLD. Both fed and fasting bioequivalence studies may be necessary to assure that the commercial batches are BE to the RLD. It is also expected that the risk assessment of a product developed on QbD principles will identify all the CMAs and CPPs and include adequate controls; one of these controls will be a discriminating in vitro method. While the bioequivalence study of commercial batches will assure BE of the drug product, a discriminating in vitro method will assure product quality through its life-cycle (post-approval changes).

From the product and process understanding gained throughout pharmaceutical development and the established IVIVR, an exhibit batch based on the formulation of prototype F-2 (Batch No. ZAb041911) was manufactured and used for a randomized single dose two-way crossover pivotal fasting BE study conducted in 36 healthy subjects. The exhibit batch was found to be bioequivalent to the RLD. The 90% confidence interval meets the bioequivalence limit of 80-125% for C_{max}, AUC_{0-2}, AUC_{2-24}, and $AUC_{0-\infty}$, as shown in Table 8. Figure 15 shows the plasma concentration profiles under fasting conditions. A fed bioequivalence study was also conducted and passed (data not shown). Similar to the RLD, the proposed generic drug product showed no food effect on pharmacokinetic parameters.

Table 8. Pivotal Fasting BE Study No. 1234

Example MR Tablets Batch No. ZAb041911 Drug Substance: Z Dose: 10 mg				
	Test	**RLD**	**Test/RLD**	
Parameter	**Least Squares Geometric Mean (LSGM)**		**LSGM Ratio**	**90% Confidence Interval**
AUC_{0-2}	332.40	329.31	1.02	94-108
AUC_{2-24}	3308.88	3340.12	0.98	92-105
$AUC_{0-\infty}$	3316.86	3345.88	1.01	96-107
C_{max}	238.86	243.92	0.96	88-105
T_{max}	6	7	--	--

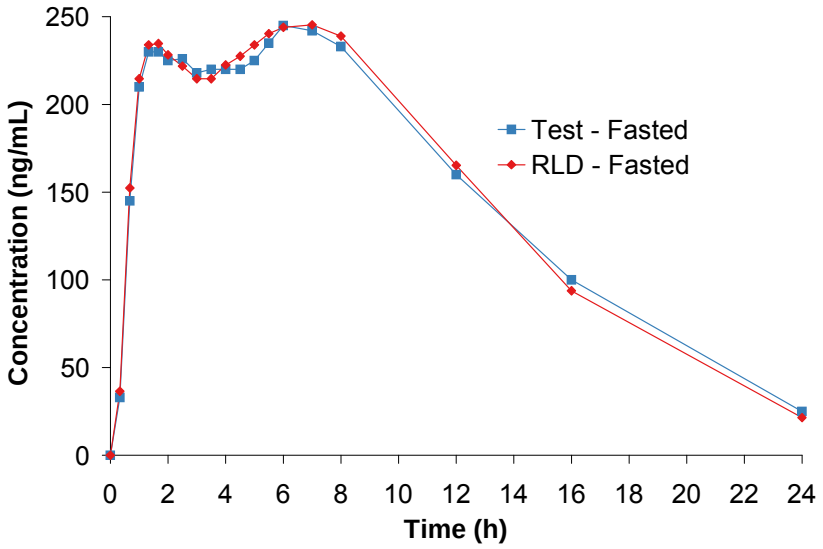

Figure 15. Plasma drug concentration of the test product versus the RLD

2.1 Components of Drug Product

2.1.1 Drug Substance

2.1.1.1 Physical Properties

Physical description:
Appearance: white to off white crystalline powder
Particle Morphology: irregular shaped crystals
Particle Size (ranges based on ten batches of drug substance used in Example IR Tablets; measured by Malvern Insitec X):

d_{10} - Observed 3-8 µm
d_{50} - Observed 20-25 µm
d_{90} - Observed 32-38 µm

Solid State Form:
Z is the free form (i.e. not a salt form) of the drug substance.

There is only one known crystalline form of Z. Supporting XRD and DSC data were submitted in ANDA aaaaaa (Appendix I). To date, no other crystalline forms have been identified in the literature. This is substantiated by a broad range of crystallization experiments using solvents of varying polarity at several temperatures each.

Drug substance Z can also exist as an amorphous form. Conditions that introduce mechanical stress and mimic the manufacture of oral solid dosage forms (e.g., during granulation, drying, and compression) were evaluated to determine if a form change of Z was induced. During the manufacture of Example IR Tablets, the crystalline form remains the same.

The physical stability of both the crystalline and amorphous form of Z under stress conditions is discussed further in 2.1.1.2 Chemical Properties.

Melting point: 246-251 °C

Aqueous solubility as a function of pH:
The aqueous solubility of the crystalline form of Z is high and constant across physiological pH as shown in Table 9 and Figure 16. The solubility and permeable nature of Z are consistent with BCS Class I compounds. The solubility of the amorphous form is approximately 10-fold that of the crystalline form.

Table 9. pH solubility profile of Z (crystalline)

pH	Solubility of Z (mg/mL)	Medium
1.2-1.4	124.0	0.1 N Hydrochloric Acid
4.5	124.0	Sodium Acetate buffer
6.8	124.0	Phosphate buffer
7.5	123.7	Phosphate buffer

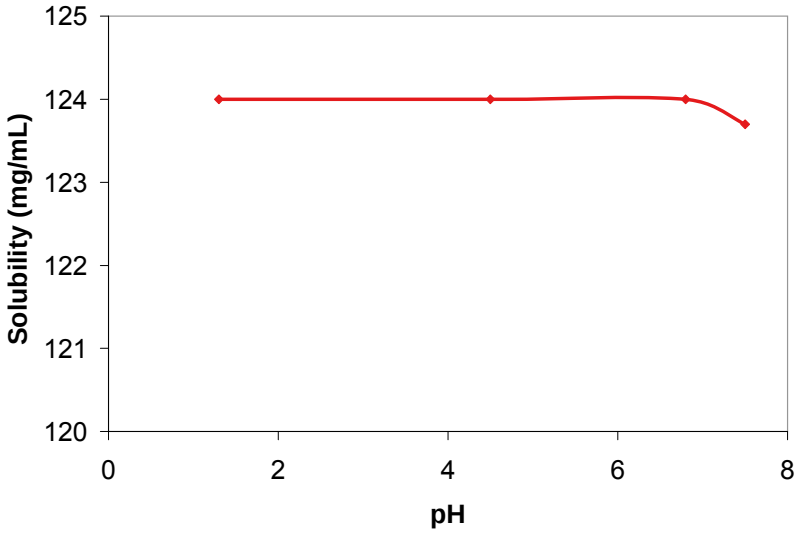

Figure 16. Aqueous solubility of drug substance Z as a function of pH

Hygroscopicity: not hygroscopic

Density (Bulk, Tapped, and True) and Flowability: ~0.22 g/cc (bulk), ~0.41 g/cc (tapped), and ~0.68 g/cc (true). The angle of repose is 75 degrees and the compressibility index is 46 suggesting very poor flow properties. The particle size distribution of the batch used for density measurements was as follows: d_{10} - 5 µm; d_{50} - 20 µm; d_{90} - 35 µm.

2.1.1.2 Chemical Properties

pKa: 7.0

Chemical stability in solid state (crystalline & amorphous) and in solution:
Stress testing of drug substance Z was conducted to gain insight into the intrinsic stability of the molecule, to identify any likely degradation products, and to facilitate the development of a stability-indicating analytical method. A more comprehensive overview of the forced degradation studies of Z is located in ANDA aaaaaa, Section 3.2.S.4.3 (Appendix I). Table 10 summarizes the results of the stress testing.

Table 10. Stability of drug substance Z under stress conditions

Stress Conditions	Assay	Impurities	Solid State Form
	(% w/w)	(% w/w)	
Untreated	99.6	ND	Crystalline
In Solution			
1% solution (Purified Water, RT, 14 days)	99.3	ND	N/A
Acid (0.1% solution, 1.0 N HCl, RT, 14 days)	99.5	ND	N/A
Base (0.1% solution, 1.0 N NaOH, RT, 14 days)	99.2	ND	N/A
Peroxide (0.1% solution, 3% H_2O_2, RT, 7 days)	99.1	ND	N/A
Crystalline Material			
Humidity and heat (open container, 90% RH, 40 °C, 7 days)	99.6	ND	Crystalline
Dry heat (105 °C, 96 hrs)	99.5	ND	Crystalline
Photostability according to ICH Q1B Option 1	99.6	ND	Crystalline
Amorphous Material			
Humidity and heat (open container, 90% RH, 25 °C, 7 days)	99.5	ND	Amorphous
Humidity and heat (open container, 90% RH, 40 °C, 7 days)	99.5	ND	Crystallization observed
Humidity and heat (open container, 90% RH, 60 °C, 7 days)	99.3	ND	Crystallization observed
Photostability according to ICH Q1B Option 1	99.6	ND	Amorphous
Dry heat (105 °C, 96 hrs)	99.4	ND	Amorphous

Overall, Z is chemically stable and insensitive to light, oxidation, and heat. A 1% solution was stable at room temperature for two weeks. The amorphous form of Z crystallizes under combined conditions of high humidity and temperature greater than 40 ºC. No degradation products were identified. These results concur with information provided by the DMF holder.

2.1.1.3 Biological Properties

Partition Coefficient: log P 0.5 (25 °C, pH 6.8)

Biopharmaceutics Classification: BCS Class I (See ANDA aaaaaa, 3.2.P.2.1 (Appendix I))

2.1.1.4 Risk Assessment of Drug Substance Attributes

A risk assessment of the drug substance attributes was performed to evaluate the impact that each attribute could have on the drug product CQAs. The outcome of the assessment and the accompanying justification is provided as a summary in the pharmaceutical development report. The relative risk that each drug substance attribute presents was ranked as high, medium, or low. Those attributes that could have a high impact on the drug product CQAs warranted further investigation whereas those attributes that had low impact on the drug product CQAs required no further investigation. The same relative risk ranking system was used throughout the pharmaceutical development and is summarized in Table 11. For each risk assessment performed, the rationale for the risk assessment tool selection and the details of the risk identification, analysis, and evaluation are available to the FDA Reviewer upon request.

Table 11. Overview of relative risk ranking system

Low	Broadly acceptable risk. No further investigation is needed.
Medium	Risk is accepted. Further investigation may be needed in order to reduce the risk.
High	Risk is unacceptable. Further investigation is needed to reduce the risk.

Note to Reader: According to ICH Q9 Quality Risk Management, it is important to note that "it is neither always appropriate nor always necessary to use a formal risk management process (using recognized tools and/or internal procedures e.g. standard operating procedures). The use of informal risk management processes (using empirical tools and/or internal procedures) can also be considered acceptable. Appropriate use of quality risk management can facilitate but does not obviate industry's obligation to comply with regulatory requirements and does not replace appropriate communications between industry and regulators."

The two primary principles that should be considered when implementing quality risk management:

- *The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient; and*

- *The level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk.*

Risk assessment of the drug substance attributes on the drug product CQAs is presented in Table 12 and Table 13 provides the justification for the level of risk that was assigned to each attribute. Both solid state form and solubility were identified as high risks and need to be further investigated.

Table 12. Risk assessment of the drug substance attributes

Drug Product CQAs	Drug Substance Attributes						
	Solid State Form	Particle Size/ Bulk Density	Hygroscopicity	Solubility	Residual Solvents	Process Impurities	Chemical Stability
Physical Attributes (size and splitability)	Low	Low	Low	Low	Low	Low	Low
Assay	Low	Low	Low	Low	Low	Low	Low
Content Uniformity	Low	Low	Low	Low	Low	Low	Low
Drug Release	High	Low	Low	High	Low	Low	Low

Table 13. Justification for the risk assessment of the drug substance attributes

Drug Substance Attributes	Drug Product CQAs	Justification
Solid State Form	Physical Attributes (size and splitability)	Solid state form does not affect tablet physical attributes (size and splitability), assay or content uniformity (CU).
	Assay	
	Content Uniformity	
	Drug Release	Example IR Tablets contain crystalline drug substance Z and no solid state form transformation occurs during manufacture. However, the drug substance may convert to its amorphous state during the drug layering process used to manufacture Example MR Tablets. This transformation may impact drug release. Furthermore, if Example MR Tablets contain amorphous drug substance that crystallizes during storage of the finished product, the drug release profile may change. The risk of solid state form to impact drug release from the tablets is high.
Particle Size/Bulk Density	Physical Attributes (size and splitability)	As discussed in ANDA aaaaaa, drug substance Z has poor flow characteristics. Particle size distribution (PSD) was optimized (d_{10}: 1-10 µm; d_{50}: 10-30 µm; d_{90}: 25-50 µm) during the IR granulation development. The risk of starting PSD and bulk density to impact the IR granules is low. The drug substance Z is dissolved in the drug layering solution used to manufacture the drug-layered beads. The risk of starting PSD and bulk density to impact the ER coated beads is low. Therefore, the risk of PSD or bulk density to impact the drug product CQAs is also low.
	Assay	
	Content Uniformity	
	Drug Release	
Hygroscopicity	Physical Attributes (size and splitability)	Because the drug substance is not hygroscopic, the risk of sorbed water to impact tablet physical attributes (size and splitability), assay, CU or drug release is low.
	Assay	
	Content Uniformity	
	Drug Release	
Solubility	Physical Attributes (size and splitability)	Drug substance solubility has no impact on tablet physical attributes (size and splitability), assay, or CU. The risk is low.
	Assay	
	Content Uniformity	
	Drug Release	Drug substance Z has a high intrinsic dissolution rate and a high solubility. It may migrate into the ER polymer film and potentially impact the drug release profile. The risk is high.

Drug Substance Attributes	Drug Product CQAs	Justification
Residual Solvents	**Physical Attributes (size and splitability)**	The residual solvents in the drug substance are well below the ICH Q3C levels (based on ten commercial batches). As such, the risk of drug substance residual solvents to impact the drug product CQAs is low.
	Assay	
	Content Uniformity	
	Drug Release	
Process Impurities	**Physical Attributes (size and splitability)**	The drug substance supplied by the vendor is consistently pure with total impurities < 0.05% (based on ten commercial batches). The risk of process impurities in drug substance Z to impact the drug product CQAs is low.
	Assay	
	Content Uniformity	
	Drug Release	
Chemical Stability	**Physical Attributes (size and splitability)**	Both crystalline and amorphous forms of the drug substance are stable both in the solid state and in solution. The risk of the drug substance chemical stability to impact the drug product CQAs is low.
	Assay	
	Content Uniformity	
	Drug Release	

2.1.2 Excipients

The choice of excipients for the formulation of Example MR Tablets, 10 mg, was based on the intent to combine the IR granules used in Example IR Tablets, 3 mg, (ANDA aaaaaa) with ER coated beads to provide a drug product with an extended release profile of Z.

2.1.2.1 Excipients in the IR Granules

Excipients used in the IR portion of the formulation for Example MR Tablets are the same as the excipients used in the formulation for Z granules in ANDA aaaaaa (Appendix I). The drug substance Z was demonstrated to be compatible with MCC, lactose, PVP, sodium starch glycolate (SSG), and magnesium stearate. Table 14 lists the excipients used in the IR portion of Example MR Tablets.

Table 14. Composition of the IR portion of Example MR Tablets, 10 mg

Components	Function	Compendial Reference	mg per tablet	% w/w
IR Granules				
Z	Drug substance	In-house	3.00	4.8
Microcrystalline Cellulose (MCC), Grade 200	Filler	NF	32.62	52.2
Lactose Monohydrate	Filler	NF	21.88	35.0
Povidone (PVP), K30	Binder	USP	2.50	4.0
Sodium Starch Glycolate (SSG), Type A	Disintegrant	NF	2.50	4.0
Purified Water	Solvent	USP	--	
IR Granules Subtotal			**62.50**	**100.0**

No additional formulation work for the IR granules was performed during development of Example MR Tablets. The excipient compatibility studies performed in ANDA aaaaaa have been reproduced below for ease of review.

The excipient compatibility was assessed through HPLC analysis of binary mixtures of excipient and drug substance Z at a 1:1 ratio in the solid state except for the lubricants where the ratio was 1:10. Samples were stored at 25 °C/60 % RH and 40 °C/75 % RH in both open and closed containers for 1 month. Common excipients functioning as fillers, disintegrants, and lubricants were evaluated in the excipient compatibility study. Table 15 summarizes the results for the samples stored at the most aggressive condition (40 °C/75 % RH, open container).

Table 15. Excipient compatibility (Binary Mixtures)

Binary Mixture Condition: 40 °C/75 % RH, open container, 1 month	Assay (% w/w)	Degradants (% w/w)
Lactose Monohydrate/DS (1:1)	99.6	ND
Microcrystalline Cellulose (MCC), Grade 200/DS (1:1)	99.2	ND
Dibasic calcium phosphate/DS (1:1)	100.2	ND
Mannitol/DS (1:1)	99.8	ND
Povidone (PVP), K30/DS (1:1)	99.6	ND
HPMC 2910 6 cP/DS (1:1)	100.4	ND
HPC-EF/DS (1:1)	100.1	ND
Pregelatinized Starch/DS (1:1)	99.1	ND
Croscarmellose Sodium/DS (1:1)	100.5	ND
Crospovidone/DS (1:1)	99.2	ND
Sodium starch glycolate (SSG), Type A/DS (1:1)	99.1	ND
Talc/DS (1:10)	99.7	ND
Magnesium Stearate/DS (1:10)	100.1	ND

No loss of assay was observed in any of the binary mixtures at 40 °C/75% RH in open containers. In addition, no degradants were observed indicating that the excipients investigated were compatible with the drug substance in the respective binary mixtures.

An additional study was conducted to investigate the potential for drug degradation due to interaction between several excipients and the drug. In this experiment, several different mixtures of drug and excipients were prepared. The first mixture consisted of drug and all excipients in the ratio representative of the proposed finished product formulation. In subsequent sets, one excipient was removed at a time. These mixtures were stored at 25 °C/60 % RH and 40 °C/75 % RH in both open and closed containers for 1 month. The results of the study are presented in Table 16.

Table 16. Excipient compatibility (Interaction Study)

Mixture Condition: 40 °C/75 % RH, open container, 1 month	Assay (% w/w)	Degradants (% w/w)
All excipients	99.8	ND
All excipients except Lactose Monohydrate	99.6	ND
All excipients except Microcrystalline Cellulose (MCC), Grade 200	100.3	ND
All excipients except Povidone (PVP), K30	100.2	ND
All excipients except Sodium Starch Glycolate (SSG), Type A	100.8	ND
All excipients except Talc	99.9	ND
All excipients except Magnesium Stearate	100.5	ND

The results indicate that there are no interactions between the excipients and the drug substance that can cause drug degradation.

2.1.2.2 Excipients in the ER Coated Beads

The ER coated beads consist of a substrate for drug layering, binder, ER polymer, plasticizer and an anti-tacking agent as listed in Table 17.

Table 17. Composition of the ER portion of Example MR Tablets, 10 mg

Components	Function	Compendial Reference	mg per tablet	% w/w	Comments
ER Beads					
Z	Drug substance	In-house	7.00	18.6	
Microcrystalline Cellulose (MCC) Beads	Substrate	NF	19.98	53.0	
Povidone (PVP), K30	Binder	USP	1.24	3.3	
Purified Water	Solvent	USP	--	--	Evaporates during processing
Drug-layered Beads Subtotal			**28.22**	**74.9**	
Kollicoat SR 30 D*	Coating polymer	NF	7.90	20.9	28% theoretical polymer coating based on drug-layered bead weight
Triethyl Citrate (TEC)	Plasticizer	NF	0.40	1.1	5% of dry polymer
Talc	Anti-tacking agent	USP	1.19	3.2	15% of dry polymer
Purified Water	Solvent	USP	--	--	Evaporates during processing
ER Polymer Coating Subtotal			**9.49**	**25.2**	
ER Coated Beads Subtotal			**37.71**	**≈ 100.0**	

*Kollicoat SR 30 D contains 27% Polyvinyl Acetate (PVAc), 2.7% Povidone (PVP) and 0.3% Sodium Lauryl Sulfate (SLS) as per vendor's product technical data sheet.

Povidone (PVP) K30 was selected as the binder because it was used as such in the IR tablets described in ANDA aaaaaa. Likewise, as microcrystalline cellulose (MCC) was used as the filler in the IR tablet, MCC beads were chosen as the substrate for drug layering. The compatibility of PVP and MCC with crystalline drug substance Z was demonstrated during the formulation of the IR

tablet. However, further testing was conducted to demonstrate the compatibility of these excipients with the amorphous form of drug substance Z resulting from the drug layering process.

Drug substance Z and PVP were dissolved in water at the target drug concentrations. The MCC beads were crushed using a mortar and pestle and added to the drug/PVP solution to form a suspension. An aliquot of this suspension was allowed to air dry. Drug substance (control) and the dried residue from the drug substance/PVP/MCC suspension were exposed to 40 °C/75% RH for 4 weeks. Drug substance stability was monitored using HPLC for the drug substance and impurities.

The drug substance assay and impurities were unchanged (compared to the drug substance control) throughout the test period, indicating that the drug substance was chemically compatible with PVP and MCC under the conditions that approximate those encountered during processing. The XRPD scans confirmed the amorphous nature of the drug substance in the dried residue throughout the duration of the compatibility study. This observation was also verified in binder optimization studies conducted during formulation development as described in Section 2.2.1.3 *Binder Optimization and Drug Substance Solid State Stabilization*.

As discussed in Section 2.2.1.3 *Selection of Coating Polymer*, Kollicoat SR 30 D was selected as the ER polymer based on favorable physico-mechanical properties that can withstand downstream compression conditions. Triethyl citrate (TEC) and talc were chosen as the plasticizer and anti-tacking agent, respectively. For the compatibility study, 1% drug substance Z was spiked into a prototype coating dispersion containing 82.8% Kollicoat 30 SR D, 4% TEC and 12.2% Talc. An aliquot of the spiked coating dispersion was allowed to air dry. Drug substance Z (control) and the spiked dispersion were exposed to 60 °C/75% RH for 1, 7 and 14 days and to 40 °C/75% RH for 1, 2 and 4 weeks. Drug substance stability was monitored using HPLC for drug substance Z and impurities.

Drug substance assay and impurities were unchanged (compared to the drug substance control) throughout the test period. This demonstrated that the prototype coating dispersion was chemically compatible with drug substance Z under conditions which mimicked those expected during the ER polymer coating and curing (if needed) processes.

2.1.2.3 Excipients in Example MR Tablets, 10 mg

It was important to choose a formulation that would maintain bead structural integrity during compression while exhibiting consistent, optimal drug release. Premature crushing or damage to the beads would alter the drug release profile leading to an inconsistent pharmacokinetic profile of the extended release portion of the drug product. The components in the final formulation of the Example MR Tablets are listed in Table 18. Because the compatibility of the excipients used in the extragranular matrix was already demonstrated during the IR tablet development, no additional compatibility study was conducted.

Table 18. Composition of Example MR Tablets, 10 mg

Components	Function	Compendial Reference	mg per tablet	% w/w
IR granules	Drug substance-IR portion	In-house	62.50	23.8
ER coated beads	Drug substance-ER portion	In-house	37.71	14.4
Microcrystalline Cellulose (MCC), Grade 200	Filler	NF	97.50	37.1
Microcrystalline Cellulose (MCC), Grade 101	Filler	NF	52.50	20.0
Sodium Starch Glycolate (SSG), Type A	Disintegrant	NF	10.47	4.0
Magnesium Stearate	Lubricant	NF	2.09	0.8
Total tablet weight			**262.77**	**≈ 100.0**

Table 19 compares the excipients used in the generic product to those used in the innovator product.

Table 19. Comparison of excipients used in the generic and brand drug product

Excipient	Function	Example MR Tablets, 10 mg (Generic)	Brand MR Tablets, 10 mg (Brand)
Z	Drug substance	✓	✓
Microcrystalline Cellulose (MCC)	Filler	✓	✓
Lactose Monohydrate	Filler	✓	✓
Povidone (PVP)	Binder	✓	✓
Sodium Starch Glycolate (SSG)	Disintegrant	✓	✓
Magnesium Stearate	Lubricant	✓	✓
Microcrystalline Cellulose (MCC) Beads	Substrate	✓	×
Sugar Spheres	Substrate	×	✓
Kollicoat SR 30 D*	Coating polymer	✓	×
Ethyl Cellulose	Coating polymer	×	✓
Triethyl Citrate (TEC)	Plasticizer	✓	×
Polyethylene Glycol (PEG)	Plasticizer	×	✓
Talc	Anti-tacking agent	✓	×

*Kollicoat SR 30 D contains 27% PVAc, 2.7% PVP and 0.3% SLS as per vendor's product technical data sheet.
Key: ✓ Present; × Absent

2.2 Drug Product

2.2.1 Formulation Development

Note to Reader: This section discusses formulation design and understanding. Steps to basic product understanding are as follows:

- *Identify all possible drug substance attributes as well as excipient attributes and levels that could impact the performance of the product.*
- *Use risk assessment and scientific knowledge to identify potentially high risk drug substance attributes as well as excipient attributes and levels.*
- *Identify levels or ranges of these high risk formulation variables.*
- *Design and conduct experiments, using DOE when appropriate.*
- *Analyze the experimental data to determine if a formulation variable is critical.*
  - *An input material attribute is critical when a realistic change in that material attribute can significantly impact the quality of the output material.*
- *Develop a control strategy.*
  - *For critical material attributes (CMAs), define acceptable ranges. For non-critical material attributes, the acceptable range is the range investigated.*

The proposed generic formulation for Brand MR Tablets, 10 mg, was developed for once-a-day dosing. Based upon the clinical, pharmacokinetic and physicochemical characterization of the RLD product (see details in Section 1.2), the initial formulation strategy was defined and justified as follows:

- Design a tablet formulation that provides biphasic release of drug with initial rapid release followed by sustained release.
- Exclude non-disintegrating ER matrix tablets due to the rapid disintegration of the RLD tablet and the immediate drug release from the beads.
- Exclude ER polymer coating on a compressed tablet core or osmotic pump due to: 1) the scored configuration of the RLD; and 2) RLD whole and split tablets showing similar drug release profiles.
- Formulate a multi-particulate delivery system comprised of IR granules, ER coated beads, and extragranular excipients all compressed into scored tablets. Such a system is similar to the RLD and minimizes any food effect or variability in GI transit among individuals.
- Obtain similar alcohol-induced dose dumping profile as RLD tablet because the RLD label warns that dose dumping due to alcohol co-ingestion is possible. Select a suitable ER polymer coating system to reduce the potential risk.

Figure 17 shows a flow diagram of the manufacturing steps used during formulation development studies to manufacture the multi-particulate deliver system comprised of IR granules, ER coated beads, and extragranular excipients all compressed into scored tablets. .

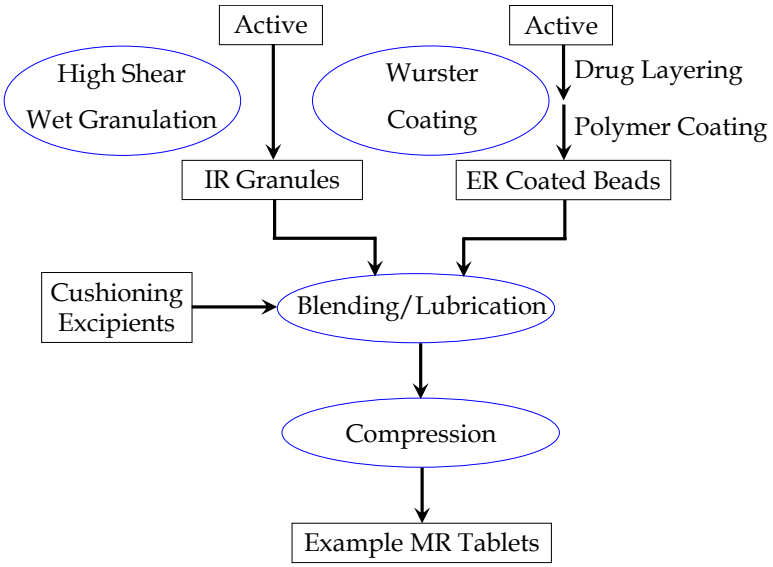

Figure 17. Flow diagram of the manufacturing steps used during formulation development

2.2.1.1 Initial Risk Assessment of the Formulation Components

Note to Reader: At the time of the risk assessment of formulation development, the detailed manufacturing process was not yet established. Thus, risks were analyzed and evaluated assuming that for each formulation attribute studied, an optimized manufacturing process would be established.

An overall risk assessment of the drug product formulation components was performed to determine which formulation components have a high risk of impacting the drug product CQAs. The results of the initial formulation risk assessment are presented in Table 20 and the justification for the risk prioritization is presented in Table 21. Each formulation component that has a high risk to impact the drug product CQAs is further evaluated in subsequent risk assessments to determine which formulation variables need to be studied to reduce the risk.

Table 20. Initial risk assessment of the formulation components

Drug Product CQAs	Formulation Components			
	IR Granules	ER Beads: layered beads	ER Beads: coated beads	Extragranular Excipients
Physical Attributes (size and splitability)	Low	Low	Low	High
Assay	Low	High	Low	Medium
Content Uniformity	Low	Medium	Low	High
Drug Release – whole tablets	Medium	High	High	High
Drug Release – split tablets	Medium	High	High	High
Drug Release – alcohol-induced dose dumping	N/A	N/A	High	Medium

Table 21. Justification for the initial risk assessment of the formulation components

Formulation Components	Drug Product CQAs	Justification
IR Granules	**Physical Attributes (size and splitability)**	The IR granule component in Example MR Tablets, 10 mg, is the same as the IR granules used in Example IR Tablets, 3 mg (ANDA aaaaaa). As a result, the formulation and manufacturing process was previously optimized and is fixed. IR granules exhibit good compressibility and compactability; therefore, the risk of the IR granules to impact tablet physical attributes (splitability) is low. The amount of IR granules per tablet is fixed (62.5 mg). The risk of IR granules to impact tablet physical attributes (size) is also low.
	Assay	The variability of IR granule assay is low based on Example IR Tablets (ANDA aaaaaa) commercial batch data. The risk of impact on tablet assay is low.
	Content Uniformity	The variability of IR granule CU is low based on Example IR Tablets (ANDA aaaaaa) commercial batch data. IR granules also have good flowability. The risk of impact on tablet CU is low.
	Drug Release – whole tablets	Optimal dissolution of IR granules was achieved through Example IR development. However, the desired immediate release may change when the IR granules are compressed with ER beads and extragranular excipients. The risk of impact on whole tablet drug release is medium.
	Drug Release – split tablets	The variability of IR granule CU is low and the risk of a non-uniform tablet due to IR granule variability is low. However, since the risk of IR granules to impact whole tablet drug release is medium, the risk of impact on split tablet drug release is also medium.
	Drug Release – alcohol-induced dose dumping	Alcohol-induced dose dumping is primarily controlled by the ER polymer coating formulation and the amount of coating applied and is not related to the IR granules.
ER Beads: drug-layered beads	**Physical Attributes (size and splitability)**	The weight gain of the drug layer is low and the impact of drug layer on bead size is minimal. Therefore, the risk of drug-layered beads to impact tablet physical attributes (size and splitability) is low.
	Assay	Binder type and level as well as viscosity of the drug layering solution will impact the adhesion of drug to the beads. The risk of impact on tablet assay is high.

Formulation Components	Drug Product CQAs	Justification
	Content Uniformity	Significant PSD and bulk density differences between ER beads and IR granules may cause segregation of the blend. Thus, selection of beads and the extent of drug layering may impact blend uniformity (BU) and, ultimately, tablet CU. The IR granule material attributes are well characterized and controlled, and it is feasible to find commercial beads with a comparable PSD and bulk density. The risk of the drug-layered beads to impact tablet CU is medium.
	Drug Release – whole tablets	More than an optimal amount of binder in the drug layer may delay the drug release. Beads with high friability tend to break and lead to high variability in the drug release profile. The highly soluble drug substance in drug layer may diffuse into certain type of cores or outer ER polymer coatings and impact the drug release profile. Binder/stabilizer type may impact the physical stability (solid state form) of the drug substance and the dissolution rate of the resultant drug-layered beads. The risk of the drug-layered beads to impact whole tablet drug release is high.
	Drug Release – split tablets	For tablets with poor CU, the drug release rate from split tablets will be different from that of whole tablets. The risk of drug-layered beads to impact tablet CU is medium and to impact whole tablet drug release is high. Therefore, the risk of impact on split tablet drug release is high.
	Drug Release – alcohol-induced dose dumping	Alcohol-induced dose dumping is primarily controlled by the ER polymer coating formulation and the amount of coating applied and is not related to drug-layered beads.
ER Beads: coated beads	**Physical Attributes (size and splitability)**	The ER polymer coating layer thickness is expected to be ~50 µm. The impact of the ER polymer coating layer on bead size and density is minimal. The risk of the ER coated beads to impact physical attributes of the tablet (size and splitability) is low.
	Assay	Assay is mainly determined during the drug layering step. Although attrition of the drug-layered beads may occur during initial ER polymer coating, the risk of the ER coated beads to impact tablet assay is low.
	Content Uniformity	Relative to the drug-layered bead size, the ER polymer coating layer does not significantly increase the bead size since the polymer film thickness is only ~50 µm. The Wurster coating usually results in good coating uniformity. Though some beads may receive slightly more or less coating than other beads, the overall population can be controlled within a narrow distribution to minimize variability. The risk of the ER coated beads to impact tablet CU is relatively low.
	Drug Release – whole tablets	Inadequate ER polymer coating and/or excessive pore former in the coating formulation may cause dose dumping and significantly increase the immediate release of drug. ER polymer type and level, pore former type and level, plasticizer type and level and polymer material attributes and level can impact the extended release of drug. The risk of the ER coated beads to impact drug release from whole tablets is high.
	Drug Release – split tablets	The risk of the ER coated beads to impact tablet CU is low. However, since the risk of the ER coated beads to impact drug release from whole tablets is high, the risk of impact on drug release from split tablets is also high.
	Drug Release – alcohol-induced dose dumping	Both ER polymer type and theoretical coating level have a direct impact on alcohol-induced dose dumping. The amount of plasticizer and pore former may also impact alcohol-induced dose dumping. The risk of the ER coated beads to impact alcohol-induced dose dumping is high.

Formulation Components	Drug Product CQAs	Justification
Extragranular Excipients	**Physical Attributes (size and splitability)**	The amount of extragranular excipients used in the formulation has a significant impact on the tablet size, compressibility and compactability which impact tablet splitability. The risk of extragranular excipients to impact tablet physical attributes (size and splitability) is high.
	Assay	Flowability of the final blend may impact die filling during tablet compression. However, extragranular excipients with good flow properties can be selected. The risk of extragranular excipients to impact tablet assay is medium
	Content Uniformity	Both the type and level of extragranular excipients can impact BU. The risk of impact on tablet CU is high.
	Drug Release – whole tablets	The type and level of extragranular disintegrant and lubricant will impact the disintegration of the whole tablet. As a result, it can change the rapid release of the IR portion of the tablet. The type and amount of extragranular cushioning agent will impact the integrity of the ER polymer film during compression. Therefore, it can change the extended release profile of the tablet. The risk of extragranular excipients to impact whole tablet drug release is high.
	Drug Release – split tablets	Because the risk of extragranular excipients to impact both CU and drug release from whole tablets is high, the risk of impact on drug release from split tablets is also high.
	Drug Release – alcohol-induced dose dumping	Insufficient extragranular cushioning agent may cause micro level structural changes in the ER film. It is possible to observe an altered alcohol-induced dumping profile due to the alcohol stress condition even though there is no noticeable drug release change under normal dissolution conditions. The risk is medium.

2.2.1.2 IR Granule Formulation Development

The IR portion was adopted from the granulation process for the production of Example IR Tablets approved in ANDA aaaaaa, Section 3.2.P.2.2.1 (Appendix I). No additional formulation or process development for the IR granules was conducted. The components of the IR granules are listed in Table 14. The manufacturing process involves granulating Z with lactose, MCC, PVP and SSG by high shear mixing with water. The granules are then dried and milled. The mean IR granular size is controlled within the range of 250-350 µm by the existing manufacturing process. In addition to the mean granule size, the control strategy also defines the target granule size distribution.

Dissolution of IR Granules Compressed with Placebo Beads

Several small batches were prepared and dissolution studies were performed to determine if the expected dissolution (NLT 80% in 30 min) is met when IR granules are compressed with placebo ER coated beads under increasing compression force. Figure 18 shows the results. Based upon these studies, it was concluded that the formulation of IR granules used in the manufacture of Example IR Tablets could be incorporated into the MR tablet formulation without any further formulation adjustment.

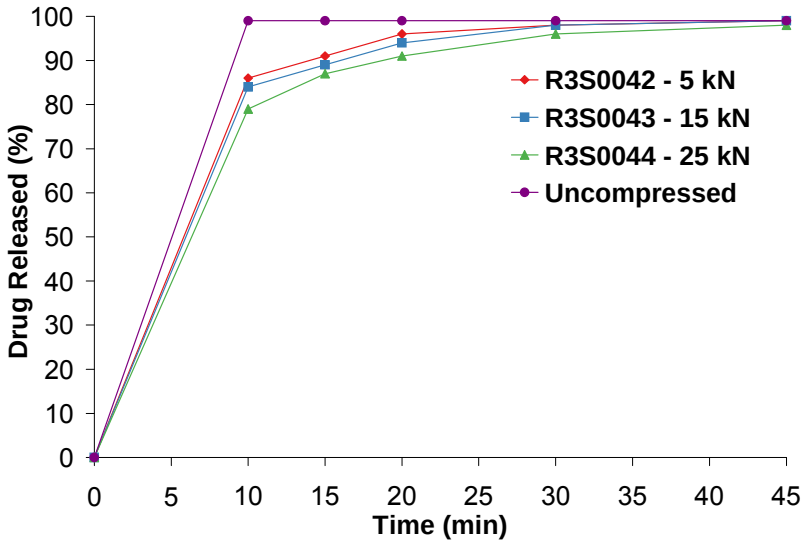

Figure 18. Dissolution profiles of IR granules compressed with placebo ER beads

2.2.1.3 ER Bead Formulation Development

Drug-Layered Beads

A drug layering approach was selected over extrusion-spheronization because drug-layered beads typically have smoother surfaces and a narrower particle size distribution. These attributes are important for the subsequent ER bead coating and tablet compression steps. The drug substance was dissolved in purified water and sprayed onto the selected beads using a bottom-spray fluid bed (Wurster) coating process to produce the drug-layered beads. The drug substance had a low intrinsic binding property so the addition of a binder to the aqueous coating was considered necessary to maintain the physical integrity of the drug-layered bead during subsequent processing.

Initial Risk Assessment of the Drug Layer Formulation Variables

The initial risk assessment of the formulation components shown in Table 20 identified assay and drug release from whole tablets to be at high risk of failure due to the variability of the drug-layered beads quality attributes. Subsequently, assay and drug release from the layered beads were identified as the CQAs of the drug layer. The formulation variables that could directly impact assay and drug release from the beads were assessed to identify which of the variables could have the highest potential to cause an assay or drug release failure of the beads. This method of identifying formulation and/or process variables for further study is illustrated in Figure 19 and is applied in all risk assessments of formulation components and process steps.

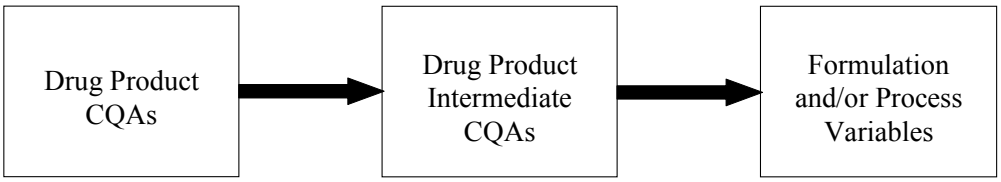

Figure 19. Schematic of method used to identify formulation and process variables for further study

The initial risk assessment of the drug layer formulation variables is shown in Table 22 and the justification for the initial risk assessment is presented in Table 23.

Table 22. Initial risk assessment of the drug layer formulation variables

Drug-layered beads CQAs	Drug Layer Formulation Variables					
	Bead selection (type/size)	**DS particle size**	**Binder type/grade**	**Binder lot-to-lot variability**	**DS/Binder ratio**	**Viscosity of drug layering solution**
Assay	Low	Low	High	Medium	High	Medium
Drug Release	Medium	Low	Medium	Low	High	Low

Table 23. Justification for the initial risk assessment of the drug layer formulation variables

Formulation Variables	Drug-layered beads CQAs	Justification
Bead selection (type/size)	**Assay**	The beads are the substrate for drug layering but have no impact on assay because assay only depends on the amount of drug layered onto the beads. Thus, the risk of bead size and type to impact drug-layered bead assay is low.
	Drug Release	Beads with high friability tend to break and lead to high variability in the drug release profile. In addition, the highly soluble drug substance may diffuse into certain type of cores which may affect the drug release profile of the beads. The risk of bead selection to impact drug release from the drug-layered beads is medium.
DS particle size	**Assay**	Within the specified particle size distribution, the drug substance is readily dissolved in water and then sprayed onto beads. Since the drug substance is used in solution, particle size has no impact on the assay of the beads. Therefore, the risk of drug substance particle size to impact assay is low.
	Drug Release	After the drug substance is dissolved, the starting drug substance particle size is irrelevant to drug release. Therefore, the risk of impact on drug release from the layered beads is low.
Binder type/grade	**Assay**	Binder type and grade selection will impact the adhesion of the drug substance to the beads. The risk of binder type and grade to impact drug-layered bead assay is high.
	Drug Release	Binder type and grade may impact the solid state physical stability of the drug substance and, therefore, the dissolution rate of the drug substance in the drug layer. However, the solubility and intrinsic dissolution rate of the drug substance is high. The risk of impact on drug release from the layered beads is medium.

Formulation Variables	Drug-layered beads CQAs	Justification
Binder lot-to-lot variability	**Assay**	Binder lot-to-lot variability may impact the adhesion of the drug substance to the beads. However, binder lot-to-lot variability can be controlled through tighter internal specifications. The risk of binder variability to impact drug-layered bead assay is medium.
	Drug Release	Once the drug layer formulation is optimized, the impact of binder lot-to-lot variability on drug layer dissolution is low for a highly soluble drug substance. The risk of impact on drug release from the layered beads is low.
DS/Binder ratio	**Assay**	The drug substance to binder ratio will impact the adhesion of the drug substance to the beads. The risk of the ratio to impact drug-layered bead assay is high.
	Drug Release	The ratio of drug substance to binder may impact the physical stability of the amorphous form in the drug-layered beads and excessive binder may retard the release of drug substance from the drug layer. The risk of impact on drug release from the layered beads is high.
Viscosity of drug layering solution	**Assay**	A highly viscous drug layering solution can not be effectively atomized and the assay of the drug-layered beads may be adversely affected. Since the viscosity of the drug layering solution is kept low (< 5 mPa•s), the risk of the solution viscosity to impact drug-layered bead assay is medium.
	Drug Release	The drug release from the drug layer is mainly controlled by the binder type and grade as well as the drug substance to binder ratio. The risk of the drug layering solution viscosity to impact drug release from the layered beads is low.

Selection of Beads

The diameter of the final ER coated beads was proposed to be ~450 µm. This size was selected to be similar to the size of the IR granules to minimize segregation. In addition, beads less than 1 mm in size show a less significant food effect.[2]

A bead size of 250-350 µm was selected for drug layering. Initially, MCC, sugar, calcium carbonate and other commercially available beads with a mean diameter of 250-350 µm were considered for evaluation. Beads made from calcium carbonate were eliminated due to the higher bulk density and the increased potential for segregation in the final blend. Sugar spheres tend to have greater attrition and agglomeration during the production process. On the other hand, MCC beads are insoluble in most organic solvents and in water, offering the advantage of aqueous-based drug layering. The low friability of MCC beads combined with the high solubility of Z, the drug substance, facilitates an efficient drug layering process. In addition, MCC beads do not normally require a seal coat to smooth out the irregular crystalline surface that is normally associated with other commercial beads. The extreme hardness of the MCC beads make them the best choice for ER polymer coating and downstream manufacturing processes including tableting. Therefore, MCC beads of 250-350 µm were selected for this drug product.

Commercially available MCC beads are provided with ≥ 85% of the beads meeting the particle size distribution (PSD) criterion of 250-350 µm. Furthermore, batch-to-batch or vendor-to-vendor PSD variability for commercial MCC beads was not found to be significant. The narrow PSD and sphericity enable a Wurster coating process to provide drug product with consistent content

[2] "Physiological Pharmaceutics – Biological Barriers to Drug Absorption", C.G. Wilson and N. Washington. Ellis Horwood Ltd, John Wiley & sons, chapter 5, pp 73.

uniformity and drug release profile. Physical parameters for commercially available MCC beads with a 250-350 μm PSD are listed below:

- PSD: 250-350 μm with ≥ 85% of beads meeting criterion
- Loss on Drying (LOD): ≤ 7.0%
- Bulk density: ~ 0.80 ± 5% g/cc
- Sphericity degree: 0.90 ± 0.05
- Friability: < 0.1%
- Swelling index: ≤ 2 mL/g

Prior to drug layering, the MCC beads received from the vendor are sieved and only the fraction that falls within the desired PSD of 250-350 μm is used for processing.

Binder Optimization and Drug Substance Solid State Stabilization

A lab scale formulation development study was performed on a 1 kg batch. Aqueous solution of drug substance and binder was coated onto beads and the effect of each binder on drug substance physical stability and drug release profile was investigated.

Binders are selected based on their spreading coefficients. For a binder to be effective, it is vital that it is able to form a film on the particle surface. If binders are added in a higher than optimal concentration, films can form viscous gels on the bead's surface, thereby retarding the dissolution properties of the drug.

PVP was selected because it was used as the binder in IR granules and is known to be compatible with both MCC and drug substance Z. In addition, PVP was shown to provide good adhesion of the drug layer to MCC beads and the layer displays satisfactory uniformity, porosity and LOD values.

The solution of drug substance and binder in water has to be neither too viscous nor too tacky to ensure successful drug layering. The following studies were performed to optimize the drug substance to binder ratio and to assess its effect on drug substance physical stability and drug layering efficiency. Results are summarized in Table 24.

Table 24. Drug substance to binder ratio optimization studies for drug layering

Experiment	DS:Binder Ratio	Release in 15 min	HPLC Assay	LOD	Amount of crystalline DS*
		(%)	(% w/w)	(%)	(%)
No binder	100:0	89	99.9	0.1	80
With PVP K30	95:5	89	99.8	0.2	20
With PVP K30	90:10	96	99.7	0.2	ND
With PVP K30	85:15	97	99.6	0.3	ND
With PVP K30	80:20	92	99.4	0.2	ND
With PVP K30	75:25	85	99.5	0.2	ND

*Amorphous-crystalline ratio as determined by XRPD after 6 months storage at 40 °C/75% RH.

The output characteristics measured include rate of release, assay (HPLC), LOD and solid state characterization (Table 24). Each drug substance to binder ratio investigated gave a clear solution of low viscosity and resulted in drug-layered beads that met the predefined release and assay targets of not less than 85% in 15 minutes and 95.0 – 105.0%, respectively. At ratios of 90:10, 85:15 and

80:20, the release at 15 minutes increased due to the absence of crystalline material. However, even though the drug was also amorphous at a ratio of 75:25, release was retarded due to the presence of too much binder. A ratio of 85:15 was selected.

Stress testing of the drug-layered beads at 40°C/75% RH was performed to probe the physical stability of amorphous material formed during the drug layering process. The normalized XRPD data presented in Figure 20 confirms the absence of crystalline drug substance for the 85:15 drug substance to binder formulation. Additionally, DSC showed the absence of an endothermic transition at the melting point of Z, suggesting that the drug substance is amorphous. This contrasted with the baseline formulation without binder which exhibited a sharp drug melt associated with crystalline drug. Without binder, transformation of the amorphous drug substance to the crystalline form occurred following storage for 6 hours at 40 °C/75% RH. With an 85:15 drug substance to binder ratio, no transformation was observed for the lab batch (6 months at 40 °C/75% RH). Physical stability of the amorphous form was subsequently confirmed on drug-layered beads stored up to two years at 25 °C/60% RH (data not shown).

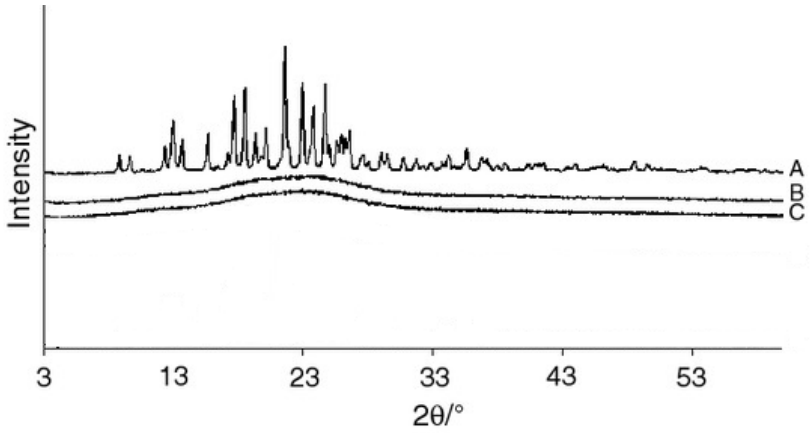

Figure 20. XRPD Analysis: (A) Drug substance crystals; (B) Binder; and (C) Amorphous drug substance with an 85:15 DS:Binder ratio

Dissolution of Drug Layered Beads Compressed with Placebo Granules

Several small batches of drug-layered beads formulated with an 85:15 drug substance to binder ratio were prepared and compressed with placebo granules under increasing compression force. The dissolution studies showed that the expected rapid dissolution (NLT 85% in 15 min) was met and there was no significant retarding effect due to binder addition.

Final Formulation of the Drug-Layered Beads

Based on these studies, the final formulation for drug-layered beads was selected for the pilot scale batch as shown in Table 25.

Table 25. Composition of the drug-layered beads

Components	Function	mg per tablet	Comments
ER Beads			
Z	Drug substance	7.00	DS: Binder ratio = 85:15
Povidone (PVP), K30	Binder	1.24	
Microcrystalline Cellulose (MCC)	Substrate	19.98	
Purified Water		--	
Drug-Layered Beads Subtotal		**28.22**	

Updated Risk Assessment of the Drug Layer Formulation Variables

These formulation development studies for drug-layered beads addressed the identified high risks. Table 26 shows the updated risk assessment and Table 27 provides the justification for the risk reduction.

Table 26. Updated risk assessment of the drug layer formulation variables

	Drug Layer Formulation Variables					
Drug-layered beads CQAs	**Bead selection (type/size)**	**DS particle size**	**Binder type/grade**	**Binder lot-to-lot variability**	**DS/Binder ratio**	**Viscosity of drug layering solution**
Assay	Low*	Low*	Low	Low	Low	Low
Drug Release	Low	Low*	Low	Low*	Low	Low*

*The level of risk is not reduced from the initial risk assessment.

Table 27. Justification for the reduced risks of the drug layer formulation variables

Formulation Variables	Drug-layered beads CQAs	Justification
Bead selection (type/size)	**Drug Release**	MCC beads with a size of 250-350 µm were selected. MCC beads show low friability (< 0.1%) and tend not to break. The MCC beads are insoluble in water. The drug substance did not diffuse into this kind of bead. The risk of the selected MCC beads to impact drug release from the layered beads is reduced from medium to low.
Binder type/grade	**Assay**	PVP K30 was selected as a binder based on previous experience. No other type or grade of binder was evaluated. PVP K30 provided good adhesion of the drug layer to MCC beads. The risk of binder type and grade to impact drug-layered bead assay is reduced from high to low.
	Drug Release	PVP K30 used at 15% in the layering solution kept the drug substance amorphous in the drug layer for up to 2 years at room temperature based on stability results. The drug-layered beads demonstrated rapid release when compressed with placebo granules. Therefore, the risk of binder type and grade to impact drug release from the layered beads is reduced from medium to low.
Binder lot-to-lot variability	**Assay**	Binder lot-to-lot variability is controlled through in-house specifications. In the range studied, no impact on assay of the drug-layered beads was observed. Therefore, the risk of impact on drug-layered bead assay is reduced from medium to low.

Formulation Variables	Drug-layered beads CQAs	Justification
DS/Binder ratio	**Assay**	At a ratio of 85:15, the drug substance can be uniformly applied onto the MCC beads without adhesion issues. The risk of the drug substance to binder ratio to impact drug-layered bead assay is reduced from high to low.
	Drug Release	Using a drug substance to binder ratio of 90:10, 85:15 or 80:20 stabilized the amorphous form in the drug-layered beads. A drug substance to binder ratio of 85:15 was selected and the beads showed rapid dissolution when compressed with placebo IR granules. The risk of the ratio to impact drug release from the layered beads is reduced from high to low.
Viscosity of drug layering solution	**Assay**	The viscosity of the drug layering solution is very low (< 5 mPa•s) and the drug layering solution can be effectively atomized. Therefore, the risk of solution viscosity to impact assay is reduced from medium to low.

ER Coated Beads

Figure 21 illustrates the design of the ER coated beads which possess an inert core loaded with 7.0 mg of Z per unit dose. The beads are further coated with a rate controlling polymer to mimic the RLD release profile. The ER beads, IR granules and extragranular excipients will be compressed into scored tablets.

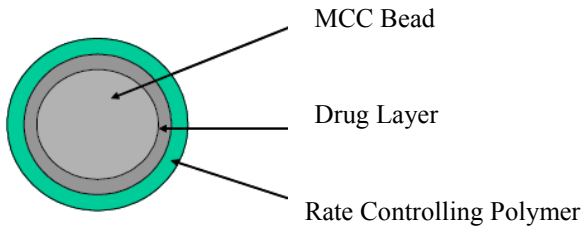

Figure 21. Structural representation of ER beads

Initial Risk Assessment of the ER Polymer Coating Formulation Variables

Multi-particulate ER portion performance depends on the choice of excipients such as the coating polymer, plasticizer and anti-tacking agent. Initial selection of polyvinyl acetate (PVAc) as the coating polymer, TEC as the plasticizer, and talc as the anti-tacking agent in the formulation was based on process requirements, a literature survey and previous experience. In the initial risk assessment of the ER polymer coating formulation variables shown in Table 28, ER excipient type, level and material attributes were evaluated in order to identify formulation variables with high risk. Justification for the risk ranking is presented in Table 29. All the formulation variables identified as high risk were further studied to reduce the level of risk to an acceptable level.

Table 28. Initial risk assessment of the ER polymer coating formulation variables*

ER coated beads CQAs	ER Polymer Coating Formulation Variables						
	Theoretical polymer coating level**	Polymer aging	Polymer lot-to-lot variability	Additional pore former level	Plasticizer level	Anti-tacking agent level	Viscosity of coating dispersion
Drug release	High	High	Medium	High	High	Medium	Medium
Drug release – alcohol-induced dose dumping	High	High	Medium	High	High	Low	Medium

*The type of ER polymer, pore former, plasticizer and anti-tacking agent was selected based on process requirements, a literature survey and previous experience.
**The percentage of theoretical polymer coating is calculated using total weight of polymer sprayed into the fluid bed divided by the total weight of drug-layered beads.

Table 29. Justification for the initial risk assessment of the ER polymer coating formulation variables

Formulation Variables	ER coated beads CQAs	Justification
Theoretical polymer coating level	**Drug release**	If the theoretical polymer coating level is suboptimal, the ER coated beads will not have the desired extended drug release profile. The risk of the polymer coating level to impact drug release from the ER coated beads is high.
	Drug release – alcohol-induced dose dumping	Although PVAc is insoluble in water, it is soluble in alcohol and dose dumping may occur. The risk of theoretical polymer coating level to impact alcohol-induced dose dumping is high.
Polymer aging	**Drug release**	Polymer aging or degradation may alter the polymer properties and affect drug release from the ER coated beads. The drug release profile under both normal and alcohol stress conditions could be impacted. The risk is high.
	Drug release – alcohol-induced dose dumping	
Polymer lot-to-lot variability	**Drug release**	Lot-to-lot variability could affect the drug release profile under both normal and alcohol stress conditions. However, the polymer will be sourced from a single supplier and, if necessary, controlled by tighter internal specifications beyond those of the vendor. Therefore, the risk of polymer variability to impact drug release is medium.
	Drug release – alcohol-induced dose dumping	
Additional pore former level	**Drug release**	A pore former in the film will dissolve upon contact with aqueous medium and form diffusion channels for the release of the drug substance. Additional pore former may need to be included in the formulation to optimize drug release from the ER coated beads. The concentration of PVP may impact drug release under both normal and alcohol stress conditions. The risk is high.
	Drug release – alcohol-induced dose dumping	
Plasticizer level	**Drug release**	Plasticizers play an important role in controlling film quality and permeability and, therefore, the drug release profile. The risk of TEC concentration to impact drug release from the ER coated beads is high.
	Drug release – alcohol-induced dose dumping	TEC is more soluble in alcohol than in water. Thus, the concentration of TEC may affect alcohol-induced dose dumping. The risk is high.
Anti-tacking agent level	**Drug release**	An anti-tacking agent is used to minimize stickiness during coating. It has a tendency to change the drug release profile because it increases the hydrophobicity of the film. The risk of impact on drug release is medium.
	Drug release – alcohol-induced dose dumping	Talc concentration will not alter susceptibility to alcohol-induced dose dumping because talc is not soluble in water or alcohol. The risk is low.

Formulation Variables	ER coated beads CQAs	Justification
Viscosity of coating dispersion	**Drug release**	If the coating dispersion is highly viscous, then the dispersion cannot be effectively atomized and the quality of the ER polymer film may be adversely affected. This could affect drug release under both normal and alcohol stress conditions. Since the viscosity of an aqueous-based latex coating dispersion can be kept low (< 100 mPa•s), the risk of the dispersion viscosity to impact drug release from the ER coated beads is medium.
	Drug release – alcohol-induced dose dumping	

Selection of Coating Polymer

An aqueous coating process was selected in this application as it is environmentally friendly, less toxic, and economically advantageous. Commercially available sustained release coating polymers of cellulosic and acrylic monomers as well as other newly developed vinyl acetate-based materials were evaluated for pH independent and sustained release drug delivery.

Common polymers used in aqueous dispersions include ethyl cellulose (Aquacoat ECD), Eudragit (RS 30D, RL 30D, NE 30D) and PVAc (Kollicoat SR 30 D). Important parameters to be further evaluated during polymer coating selection include 1) mechanical strength properties and 2) film formation temperature.

The coating polymer should be able to generate reliable films that achieve reproducible drug release characteristics. The polymer should also impart mechanical properties that allow beads to be compressed without compromising the drug release profile. In addition, high elasticity of the film prevents the initiation and propagation of cracks during subsequent processing and reduces the potential for dose dumping. For these reasons, the percent elongation of the film needs characterization under dry and wet conditions. A journal article published by N. Langly and Y. Lan described a study conducted on the polymers represented in Figure 22. Highest elongations were observed in both dry and wet states for Eudragit RS 30D, Eudragit RL 30D, and Kollicoat SR 30 D.[3] Therefore, these polymers were considered for further development.

[3] N. Langly and Y. Lan. How to make oral dosage coatings count. *PFQ*, June 2009, (http://www.pharmaquality.com).

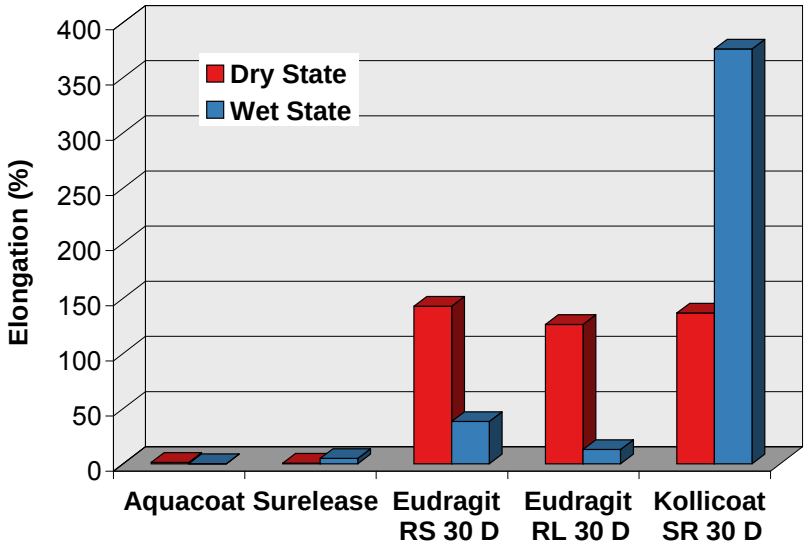

Figure 22. Elongation (%) of polymer film (Kollicoat SR 30 D film with 10% TEC, other polymer films with 20% TEC)[3]

A fundamental property of any polymer is its glass transition temperature (Tg). In evaluating various polymers, a useful parameter to consider is the minimum film-forming temperature (MFT). The MFT is positively correlated to Tg and the usual correlation reported in literature is between 0.9 - 1.1. The MFT of a given coating polymer determines the process temperature above which a continuous polymer film is formed. Previous formulation experience suggests that during manufacturing, the process temperature needs to be set at least 10 °C above the MFT to achieve good film quality. The process temperature can also be manipulated by choosing an appropriate plasticizer to lower the Tg and hence the MFT.

Eudragit NE 30 D and Kollicoat SR 30 D have MFTs below room temperature, while ethyl cellulose (Aquacoat and Surelease) and other methacrylate polymers (Eudragit RS 30 D and RL 30 D) have MFTs above room temperature. As noted previously, the manufacturing process involves compression of the ER coated beads so it is critical that the coating is sufficiently flexible to withstand the compression force. The high elongation percentage at break coupled with the low MFT of Kollicoat SR 30 D substantiated its use in the ER polymer coating process. In addition, the literature reported that films using Kollicoat SR 30 D may not need to undergo a curing process which is an additional processing advantage.[4] Therefore, Kollicoat SR 30 D was pursued as the coating polymer during development.

Kollicoat SR 30 D is commercially available as a 30% w/w aqueous dispersion of polyvinyl acetate (PVAc, 27%) stabilized with polyvinylpyrrolidine (PVP, Povidone, 2.7%) and sodium lauryl sulfate (SLS, 0.3%). Only one grade of the polymer dispersion is available. Polyvinyl acetate is water insoluble and forms the barrier while PVP acts as a pore former. As PVAc does not possess ionic functional groups, drug release is not affected by pH.

[4] Dashevsky, *et al.* Physicochemical and release properties of beads coated with Kollicoat SR 30 D, a new aqueous polyvinyl acetate dispersion for extended release. *International Journal of Pharmaceutics*, 2005, 290: 15-23.

Based on vendor recommendation, the starting level of Kollicoat SR 30 D needed to achieve the desired film thickness was 20% theoretical polymer coating relative to the drug-layered bead weight. To understand the impact of additional pore former on the drug release profile, additional PVP was added to the aqueous dispersion of the commercial polymer to adjust the membrane to pore former ratio during the optimization studies (see ER Polymer Coating Optimization Studies).

The extent of polymer aging and its impact on coating performance was also considered during optimization. Acetic acid is a degradation product of Kollicoat SR 30 D and may be present at different levels depending on the age of the polymer. Three commercial lots of Kollicoat SR 30 D aqueous dispersion, each with a different amount of acetic acid present as a degradant, were evaluated.

Another important property of a polymer is its molecular weight distribution. Kollicoat SR 30 D is a synthetic polymer and was sourced from one manufacturer that tightly controls the mean molecular weight distribution in the range of 420-480 KDa. Thus, the impact of molecular weight variability on drug release from the ER coated beads was not investigated further.

The impact of Kollicoat SR 30 D aqueous dispersion lot-to-lot variability (PVAc content ranging from 25 – 29 g/100g and apparent viscosity ranging from 50 – 90 mPa•s in) on drug release from the ER coated beads was studied subsequent to formulation optimization.

Selection of Plasticizer

Plasticizers are used in polymeric coating dispersions to optimize properties of the film such as permeability, hydrophobicity, adhesiveness, flexibility and brittleness. Three commonly used plasticizer types are polyethylene glycols (PEGs), fixed oils (e.g.: Castor oil, Oleic acid) and organic esters (e.g.: Triacetin, Tributyl citrate). Plasticizers are known to affect the Tg of the polymer. Some plasticizers such as glycerin or PEG 400 are water soluble while others are not.

The reported MFT for Kollicoat SR 30 D is 18 °C on the product technical data sheet. This temperature is close to room temperature and the polymer can become brittle during handling, processing and even storage. It is possible to reduce the MFT with the addition of a plasticizer. Several plasticizers such as PEG 400, tributyl citrate (TBC), propylene glycol (PG) and triethyl citrate (TEC) were evaluated.

Polyethylene glycol 400 and PG are more soluble than TBC and TEC and will increase pore formation when mixed with the polymer. Thus, release from an ER polymer coating formulated with PEG 400 or PG would be faster than release from an ER polymer coating formulated with TBC or TEC. In addition, pH-dependent release has been reported from PEG 400, PG and TBC.[5] Finally, distribution behavior using TEC is not affected by the mixing time or the degree of agitation due to adequate water solubility. Therefore, TEC was selected for the coating process.

[5] Okarter, *et al.* The Effects of Plasticizers on the Release of Metoprolol Tartrate from Granules Coated with Polymethacrylate Films. *Drug Development and Industrial Pharmacy* 2000; 26(3): 323-329.

Selection of Anti-tacking Agent

As a result of low MFT, polymer-coated beads may be sticky. Therefore, the addition of an anti-tacking agent is often necessary. The commonly used anti-tacking agent, talc, was selected.

ER Polymer Coating Formulation Feasibility Study

A preliminary feasibility study was performed to test the pre-selected excipients and to direct the scope of future studies. The composition of the initial coating dispersion shown in Table 30 was set based on information published in the vendor's product technical data sheet. The suggested amount of anti-tacking agent (talc) and plasticizer (TEC) was 15% – 50% and 5% – 10% of dry polymer, respectively.

Table 30. Initial composition of the ER polymer coating dispersion

Components	Weight (% w/w)	Solids Content (% w/w)	Comments
Kollicoat SR 30 D	50.00	15.0	Kollicoat SR 30 D contains 30% solids content, which is referred to as dry polymer
Triethyl Citrate (TEC)	1.50	1.50	10% of dry polymer
Talc	2.25	2.25	15% of dry polymer
Purified Water	46.25		
Total	100.00	18.75	Overall, the solids content is 18.75%

Initial formulation development was done on a 1 kg scale and took place in a Glatt GPCG-1 fluid bed coater with a 6″ Wurster insert. All process parameters except product temperature were selected based on previous experience. The product temperature range was selected based on the vendor's recommendation for Kollicoat SR 30 D. Coating process parameters are listed in Table 31.

Table 31. Equipment and process parameters for lab scale formulation development batches

Formulation Development	Lab Scale
Equipment model	Glatt GPCG-1
Batch size	1 kg
Fluid bed insert	6″ Wurster
Partition height	15 mm
Distribution plate	Fixed
Nozzle tip diameter	1.0 mm
Nozzle tip/air cap position	Flush
Inlet temperature	50-60 ºC
Product temperature	30-40 ºC
Spray rate	6-8 g/min
Atomization air pressure	1.5 bar
Air volume	Approx. 40% of flap setting

Samples were pulled at different theoretical polymer coating levels: 10%, 20%, 30%, 40%, and 50%. These samples were dried until the LOD was less than 2% and evaluated for drug release by dissolution testing. The drug release profile was too fast at 10% theoretical polymer coating, and too slow at 50% theoretical polymer coating. Future optimization studies focused on 20% to 40% theoretical polymer coating. The amount of talc used was sufficient to prevent sticking during the

coating process. Therefore, no further study was performed to optimize the amount of talc. Some tackiness was observed when product temperature approached 40 °C. Therefore, the amount of TEC was further investigated in the optimization studies.

Although the vendor states that curing for this polymer is not required, published scientific literature[4] found that curing may impact drug release for certain drug substances. A study was performed to verify if curing would be required for this drug product. The results showed that there was no difference in drug release profile between the uncured beads and the beads cured at 60 °C for 24 hours (data not shown). Curing was found unnecessary at the 1 kg scale and was not performed on subsequent development batches. However, a curing confirmation study was conducted at pilot scale to evaluate if high attrition at larger scale had any impact on the polymer film which rendered curing necessary (see ER Beads Curing Process Confirmation Study).

ER Polymer Coating Formulation Optimization Studies

Based on the initial risk assessment and the preliminary feasibility study, a 2^{4-1} fractional factorial DOE with three center points was performed to optimize the formulation. Drug release was identified as a CQA of the ER coated beads in Table 28. The objective of this study was to evaluate the effect of the theoretical polymer coating level applied based on drug-layered bead weight[6], additional pore former (PVP) level, plasticizer (TEC) level, and extent of polymer aging (% Acetic Acid as degradant) on drug release from the ER coated beads. The responses studied were the times at which 20%, 50% and 80% of drug in the ER portion was released ($T_{20\%}$, $T_{50\%}$ and $T_{80\%}$) using USP apparatus 2 at 50 rpm in pH 6.8 phosphate buffer. The initial target ranges for the responses were based on the drug release profile obtained for the RLD. Table 32 summarizes the study design and acceptance criteria. Table 33 presents the experimental results.

Table 32. Design of the 2^{4-1} study to optimize the ER polymer coating formulation

Defining Relation		I = ABCD	
Resolution		IV	
Factors: Formulation Variables		Levels	
		-1	+1
A	Theoretical polymer coating level applied based on drug-layered bead weight (%)	20	40
B	Additional PVP level (% of the dry polymer)	0	10
C	TEC level (% of the dry polymer)	2	10
D	Polymer aging (% of Acetic Acid as degradant)	0.5	1.5
Responses		Target Ranges	
Y_1	$T_{20\%}$ (h)	0	3
Y_2	$T_{50\%}$ (h)	3.5	5.5
Y_3	$T_{80\%}$ (h)	10	13

[6] Theoretical polymer coating level (%) was calculated using total weight of polymer sprayed into the fluid bed divided by the total weight of drug-layered beads. The actual % weight gain of the beads will vary based on process efficiency.

Table 33. Effect of ER polymer coating formulation variables on ER coated bead characteristics

Std. Code	Batch No.	Factors: Formulation Variables				Responses			
		A: Theoretical polymer coating level	B: Additional PVP level	C: TEC level	D: Polymer aging	Y_1: $T_{20\%}$	Y_2: $T_{50\%}$	Y_3: $T_{80\%}$	Comments
		(%)	(%)	(%)	(% Acetic Acid)	(h)	(h)	(h)	
1	6	20	0	2	0.5	1.29	3.37	8.67	
2	3	40	0	2	1.5	2.92	6.71	17.74	
3	1	20	10	2	1.5	0.81	2.79	5.98	
4	5	40	10	2	0.5	2.39	5.81	16.04	
5	10	20	0	10	1.5	1.48	4.15	9.12	Some tackiness due to excessive TEC was observed
6	8	40	0	10	0.5	3.07	7.54	19.18	
7	2	20	10	10	0.5	1.08	3.27	7.42	
8	7	40	10	10	1.5	2.69	6.33	16.48	
9	11	30	5	6	1.0	2.12	5.12	13.07	
10	9	30	5	6	1.0	2.02	4.98	12.61	
11	4	30	5	6	1.0	1.91	4.83	12.27	

Note to Reader: When center points are included in the factorial DOE, it is possible to test if the curvature effect is significant. The data analysis is done by separating the curvature term from the regression model in an adjusted model. This approach provides the factorial model coefficients as if there were no center points. If the curvature is significant, the design should be augmented to add runs that can estimate the quadratic terms. On the other hand, if the curvature is not significant, the adjusted model and unadjusted model will be similar.

In this mock example, we have not included ANOVA results for each DOE. In practice, please be advised that ANOVA results should accompany all DOE data analysis, especially if conclusions concerning the significance of the model terms are discussed.

For all DOE data analysis, the commonly used alpha of 0.05 was chosen to differentiate between significant and not significant factors.

Significant factors for $T_{50\%}$ of ER coated beads

Since center points were included in the ER polymer coating optimization DOE, the significance of the curvature effect was tested using an adjusted model. The Analysis of Variance (ANOVA) results are presented in Table 34.

Table 34. ANOVA results for the model adjusted for curvature effect

Source	Sum of Squares	df*	Mean Square	F Value	p-value Probability > F	Comments
Model	22.96	3	7.65	322.39	< 0.0001	significant
A-Theoretical polymer coating level (%)	20.51	1	20.51	864.17	< 0.0001	
B-Additional PVP level (%)	1.59	1	1.59	67.12	0.0002	
C-TEC level (%)	0.85	1	0.85	35.87	0.0010	
Curvature	8.37E-04	1	8.37E-04	0.04	0.8573	not significant
Residual	0.14	6	0.02			
Lack of Fit	0.10	4	0.02	1.19	0.5035	not significant
Pure Error	0.042	2	0.02			
Total	23.10	10				

*df: degrees of freedom

Because the curvature effect is not significant for $T_{50\%}$, the center points were included for model fitting. As shown in the following half-normal plot (Figure 23) and ANOVA results for the unadjusted model (Table 35), the significant factors affecting $T_{50\%}$ of ER coated beads were A (theoretical polymer coating level), B (additional PVP level) and C (TEC level).

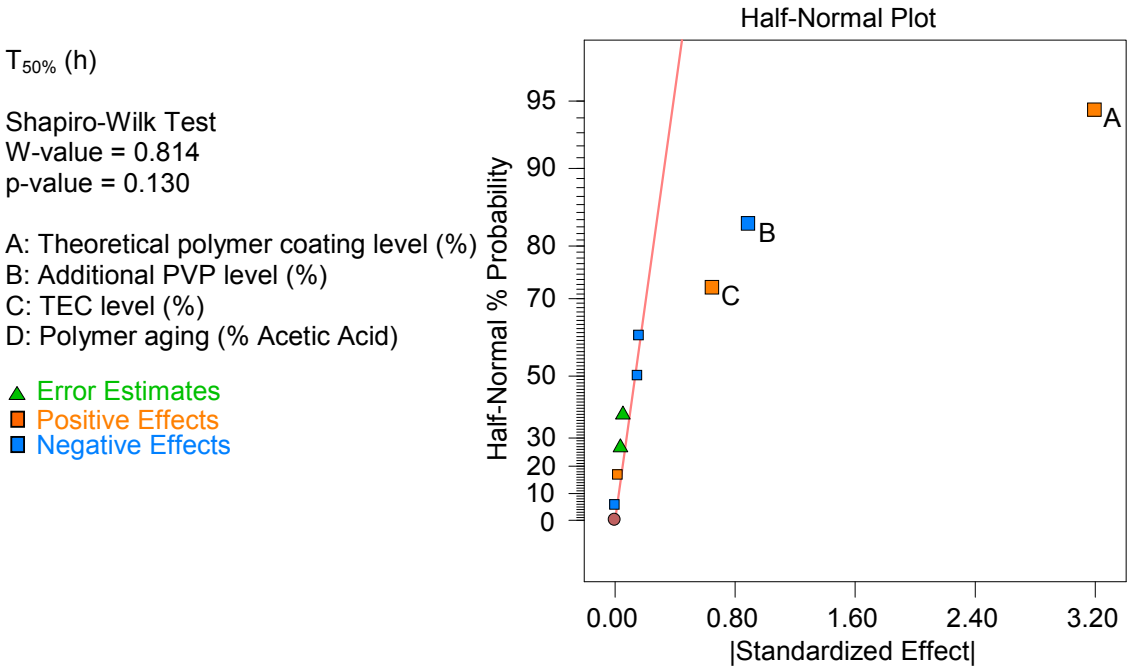

Figure 23. Half-normal plot of the formulation variable effects on $T_{50\%}$ of ER coated beads

Table 35. ANOVA results for the unadjusted model

Source	Sum of Squares	df*	Mean Square	F Value	p-value Probability > F	Comments
Model	22.96	3	7.65	373.92	< 0.0001	significant
A-Theoretical polymer coating level (%)	20.51	1	20.51	1002.31	< 0.0001	
B-Additional PVP level (%)	1.59	1	1.59	77.85	< 0.0001	
C-TEC level (%)	0.85	1	0.85	41.61	0.0004	
Residual	0.14	7	0.02			
Lack of Fit	0.10	5	0.02	0.96	0.5807	not significant
Pure Error	0.042	2	0.02			
Total	23.10	10				

*df: degrees of freedom

Factor A (theoretical polymer coating level) was the dominating factor affecting the drug release, followed by B (additional PVP level) and C (TEC level). The remaining four model terms had no significant impact because they came from the normally distributed population as pure error based on Shapiro-Wilk hypothesis test results.

The effect of additional pore former on ER $T_{50\%}$ is presented in Figure 24. The $T_{50\%}$ decreased with increasing amounts of pore former (i.e. the more pore former added, the faster the drug release). In addition, the initial part of the drug release profile differed significantly from the target drug release profile of the RLD. Therefore, the commercial product of Kollicoat SR 30 D was used in the formulation as is with no additional pore former.

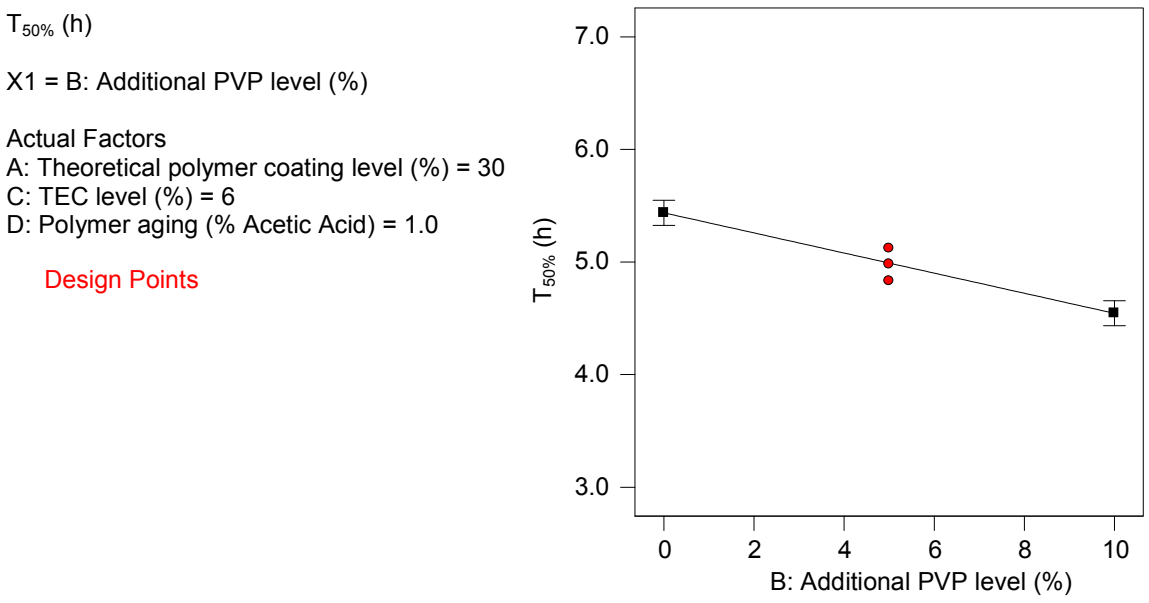

Figure 24. Main effect of additional pore former (% PVP) on $T_{50\%}$ of ER coated beads

The effect of theoretical polymer coating level and TEC level (with 0 % additional PVP) on $T_{50\%}$ of ER coated beads is presented in Figure 25. The $T_{50\%}$ increased (i.e. slower drug release) as theoretical polymer coating level and TEC level increased.

Some agglomeration due to film tackiness was observed for batches with 10% TEC as plasticizer. Therefore, the amount of TEC was reduced to 5 % for the final formulation.

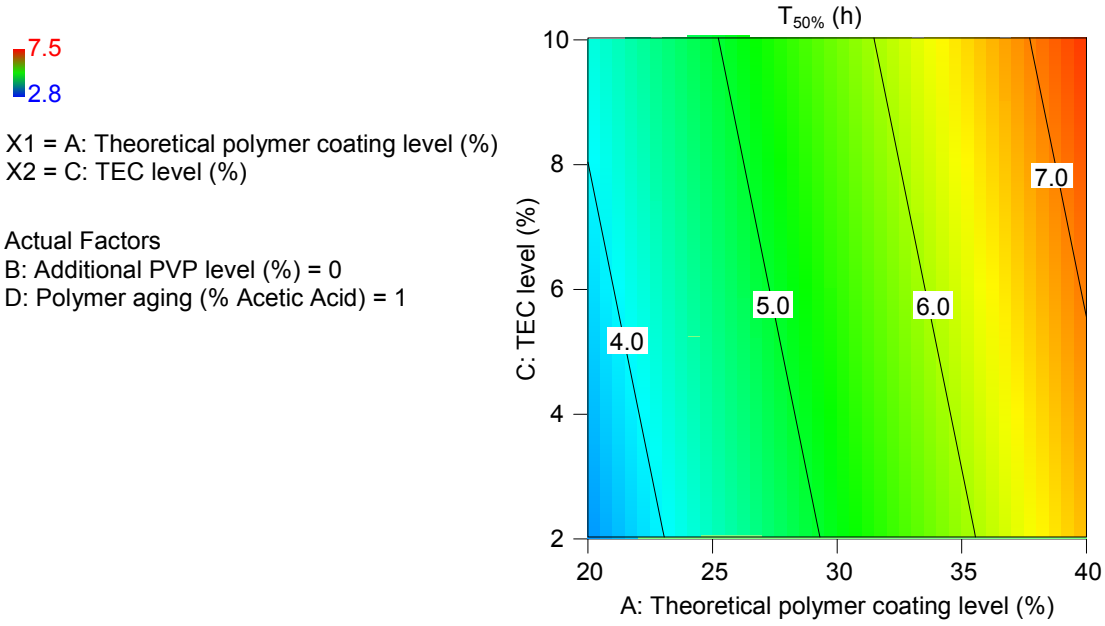

Figure 25. Effect of theoretical polymer coating level and TEC level on $T_{50\%}$ of ER coated beads

Similar cause and effect relationships were observed for $T_{20\%}$ and $T_{80\%}$ of ER coated beads (data not shown). There were no interaction terms or curvature effects for any of the factors on the responses studied. Therefore, further optimization was not necessary.

The DOE studies showed that the formulation with 25% theoretical polymer coating, 5% TEC and 15% Talc (both of the dry polymer) had optimal performance characteristics when compared to the drug release characteristics of the RLD using USP apparatus 2 at 50 rpm in 900 mL of pH 6.8 phosphate buffer. The viscosity of the coating dispersion caused no concerns during atomization. The amount of acetic acid present as a degradant in the commercial polymer had no impact on the ER coated bead drug release when present in the range of 0.5 – 1.5%. The drug release profile of the coated beads was not affected under accelerated storage conditions (6 months at 40 °C/75% RH, data not shown).

The commercial product of Kollicoat SR 30 D aqueous dispersion lot-to-lot variability (PVAc content ranging from 25 – 29 g/100g and apparent viscosity ranging from 50 – 90 mPa•s) was studied and no impact on the drug release profile of ER coated beads was observed.

Formulation of the ER Coated Beads

Based on these studies, the formulation of the ER coated beads was selected for the pilot scale batch as shown in Table 36.

Table 36. Composition of the ER coated beads

Components	Function	mg per tablet	Comments
ER Beads			
Z	Drug substance	7.00	
Microcrystalline Cellulose (MCC) Beads	Substrate	19.98	
Povidone (PVP), K30	Binder	1.24	
Purified Water	Solvent	--	
Drug-layered Beads Subtotal		**28.22**	
Kollicoat SR 30 D*	Coating polymer	7.06	25% theoretical polymer coating based on drug-layered bead weight
Triethyl Citrate (TEC)	Plasticizer	0.35	5% of the dry polymer
Talc	Anti-tacking agent	1.06	15% of the dry polymer
Purified Water	Solvent	--	
ER Polymer Coating Subtotal		**8.47**	
ER Coated Beads Subtotal		**36.69**	14.0%

*Kollicoat SR 30 D contains 27% PVAc, 2.7% PVP and 0.3% SLS as per product technical data sheet.

Effect of Compression on Drug Release from ER Coated Beads

Since it is desirable that the drug release from ER coated beads remain unaltered after compression into tablets, a compression study was conducted on ER coated beads from the DOE study in the previous section (Batch No. 1 with 2% TEC and 15% Talc) with placebo IR granules. The relationship between drug release and compression force was investigated. Significantly faster drug release from ER coated beads was observed and it indicated the existence of damaged beads. Therefore, cushioning from the IR granules alone was not sufficient. One way to eliminate the damage is to add additional cushioning agents. MCC was selected initially as the cushioning agent based on its use as such in the scientific literature.[7] The formulation of the final blend is discussed in Section 2.2.1.4.

Alcohol-induced Dose Dumping Study

An *in vitro* alcohol-induced dose dumping study was conducted using 0.1 N HCl with 5%, 20% and 40% (v/v) of Alcohol USP. Data was collected every 15 minutes for a total of two hours. The ER coated beads performed similarly to the RLD tablets under each condition (data included in Module 5). The study also investigated if Kollicoat SR 30 D aging or lot-to-lot variability impacted alcohol-induced dose dumping and concluded that, for this formulation, these variables played an insignificant role in susceptibility to alcohol-induced dose dumping.

Updated Risk Assessment of the ER Polymer Coating Formulation Variables

These formulation development studies addressed the identified high risks. The updated risk assessment is presented in Table 37 followed by the justification for the reduced risks in Table 38.

[7] Mount, DL. and Schwartz, JB. Formulation and Compaction of Nonfracturing Deformable Coated Beads. *Drug Development and Industrial Pharmacy,* 1996, 22(7): 609-621.

Table 37. Updated risk assessment of the ER polymer coating formulation variables

ER coated beads CQAs	ER Polymer Coating Formulation Variables						
	Theoretical polymer coating level**	Polymer aging	Polymer lot to lot variability	Additional pore former level	Plasticizer level	Anti-tacking agent level	Viscosity of coating dispersion
Drug release	Medium	Low	Low	N/A	Low	Low	Low
Drug release – alcohol-induced dose dumping	Medium	Low	Low	N/A	Low	Low*	Low

*The level of risk is not reduced from the initial risk assessment.
**The percentage of theoretical polymer coating is calculated using total weight of polymer sprayed into the fluid bed divided by the total weight of drug-layered beads.

Table 38. Justification for the reduced risks of the ER polymer coating formulation variables

Formulation Variables	ER coated beads CQAs	Justification
Theoretical polymer coating level	**Drug release**	The theoretical polymer coating level (based on drug-layered bead weight) was identified as 25% because this coating level resulted in comparable drug release to the RLD using USP apparatus 2. A trial BE study will be conducted to verify that the dissolution method is predictive. Therefore, the risk of theoretical polymer coating level to impact drug release from the ER coated beads is reduced from high to medium.
	Drug release – alcohol-induced dose dumping	The alcohol-induced dose dumping study showed that the ER coated beads and RLD tablets had comparable *in vitro* drug release profiles. However, drug release is sensitive to polymer coating level. If the theoretical polymer coating level is adjusted based on the results of the trial BE study, then alcohol-induced dose dumping may be impacted. The risk is reduced from high to medium.
Polymer aging	**Drug release**	Polymer aging was studied and found to have no impact on *in vitro* drug release. The risk of polymer aging to impact drug release from ER coated beads is reduced from high to low.
	Drug release – alcohol-induced dose dumping	
Polymer lot-to-lot variability	**Drug release**	Polymer lot-to-lot variability did not show any significant impact on drug release from ER coated beads within the range investigated. The risk is reduced from high to low.
	Drug release – alcohol-induced dose dumping	
Additional pore former level	**Drug release**	The concentration of pore former is no longer considered a risk to drug release from ER coated beads because optimal release was achieved without adding additional pore former to the formulation.
	Drug release – alcohol-induced dose dumping	
Plasticizer level	**Drug release**	Plasticizer concentration was optimized at 5% of the dry polymer. This level resulted in adequate film quality. The risk of plasticizer concentration to impact drug release from the ER coated beads is reduced from high to low.
	Drug release – alcohol-induced dose dumping	*In vitro* drug release studies demonstrated comparable alcohol-induced dose dumping to the RLD. The risk is reduced from high to low.
Anti-tacking agent level	**Drug release**	Talc is used to minimize stickiness during coating. Its concentration was adequate at 15% of the dry polymer. The risk of anti-tacking agent concentration to impact drug release from the ER coated beads is reduced from medium to low.

Formulation Variables	ER coated beads CQAs	Justification
Viscosity of coating dispersion	**Drug release**	The viscosity of the selected coating dispersion can be effectively atomized. The risk of dispersion viscosity to impact drug release from ER coated beads under both normal and alcohol stress conditions is reduced from medium to low.
	Drug release – alcohol-induced dose dumping	

2.2.1.4 Prototype Tablet Formulation Development

The objectives of the prototype tablet formulation development were to 1) prevent segregation of the blend, and 2) ensure an adequate cushioning effect to maintain ER bead integrity during tablet compression. A validated NIR spectroscopic method was used to determine the blending endpoint in the development studies (see Section 2.3.4 for details). Studies to optimize the filler and disintegrant levels in the prototype formulation used a 4 kg batch size. To optimize the lubricant, the batch size was increased to 10 kg for the compression unit operation.

Initial Risk Assessment of the Extragranular Excipients in the Prototype Tablet Formulation

The IR granules and ER coated beads are both components of the prototype tablet formulation that have been previously optimized, and the associated risk of these components on drug product CQAs has been reduced to acceptable levels. In addition to the IR granules and the ER coated beads, the prototype formulation was designed to contain cushioning agent, disintegrant and lubricant.

As discussed previously, MCC was selected as a cushioning agent based on scientific literature.[7] After consideration of the PSD and bulk density of both the IR granules and ER coated beads, MCC grade 200 was chosen as a starting point. The choice of disintegrant was made with respect to its effect on disintegration and dissolution. Crospovidone and SSG were initially evaluated as potential disintegrants in the formulation and preliminary studies showed that both excipients performed similarly in promoting tablet disintegration. Therefore, SSG was selected for further development because it was used in approved ANDA aaaaaa for Example IR Tablets and demonstrated good compatibility with drug substance Z. Magnesium stearate was selected as the lubricant based on its use in the RLD and its compatibility with drug substance Z.

To identify formulation variables for further study, an initial risk assessment of the extragranular excipients was conducted. Differences in particle size and other physiochemical characteristics such as bulk density, morphology between the IR granules, ER coated beads and extragranular excipients may cause blend uniformity and tablet content uniformity failure due to segregation during downstream processing after blending. All the excipients used in the prototype formulation were evaluated in order to identify formulation variables with high risk as shown in Table 39. In Table 40, the justification for the risk prioritization is provided.

Table 39. Initial risk assessment of the extragranular excipients in the prototype tablet formulation

Prototype Tablet Formulation CQAs	Extragranular Excipients in the Prototype Tablet Formulation		
	Filler (Cushioning Agent)	Disintegrant	Lubricant
Physical Attributes (size and splitability)	High	Low	Medium
Content Uniformity	High	Low	Medium
Drug Release – whole tablets	High	High	High
Drug Release – split tablets	High	High	High

Table 40. Justification for the initial risk assessment of the extragranular excipients in the prototype tablet formulation

Formulation Variables	Prototype Tablet Formulation CQAs	Justification
Filler (Cushioning Agent)	**Physical Attributes (size and splitability)**	MCC was selected as the extragranular cushioning agent. A lower than optimal amount of MCC may lead to ER polymer film rupture or bead fusion during compression and could facilitate segregation. Furthermore, the compressibility and compactability of the formulation may be poor. However, a greater than optimal amount of MCC may significantly impact the size of the tablets. Additionally, if the final formulation is overly compactable, high tablets that are difficult to split may result. The risk of extragranular filler level to impact the tablet physical attributes (size and splitability) is high.
	Content Uniformity	PSD and bulk density differences between IR granules, ER coated beads and extragranular excipients can cause segregation. The MCC comprises the greatest percentage of the prototype formulation; thus, the risk of the MCC 200 PSD and bulk density to impact the tablet CU is high.
	Drug Release – whole tablets	Insufficient extragranular cushioning agent may cause ER film rupture or fusion during compression. The risk of the extragranular filler level to impact whole tablet drug release is high.
	Drug Release – split tablets	The risk of MCC 200 to impact both tablet CU and whole tablet drug release is high. Therefore, the risk of impact on split tablet drug release is also high.
Disintegrant	**Physical Attributes (size and splitability)**	SSG is a super-disintegrant. Since this super-disintegrant is used at low levels (< 5%), it will not significantly impact flowability, compressibility, compactability or tablet size. The risk of SSG to impact the tablet physical attributes (size and splitability) is low.
	Content Uniformity	Because SSG is used at low levels (< 5%), its PSD will have a minimal impact on segregation. The risk of SSG to impact tablet CU is low.
	Drug Release – whole tablets	Insufficient extragranular super-disintegrant will delay the disintegration of the tablet as well as the desired immediate release of drug substance from the IR granules. The degree of substitution for SSG Type A may also affect drug release. The risk of SSG to impact drug release from whole tablets is high.
	Drug Release – split tablets	Although the risk of SSG to impact tablet CU is low, the risk of impact on drug release from whole tablets is high. Therefore, the risk of impact on drug release from split tablets is also high.

Lubricant	**Physical Attributes (size and splitability)**	The amount of lubricant used in the formulation may impact the appearance of the tablets. If the amount is lower than optimal, picking may occur. If the amount is higher than optimal, it may adversely affect compressibility and compactability of the formulation. The risk of magnesium stearate to impact tablet physical attributes (size and splitability) is medium.
	Content Uniformity	Because magnesium stearate reduces the friction between particles and may impact the flowability of the tablet formulation, the risk of impact on tablet CU is medium.
	Drug Release – whole tablets	If the prototype formulation contains more than the optimal level of magnesium stearate or if the magnesium stearate specific surface area is not optimal, the powder particles may be over coated, leading to a delayed drug release profile. The risk of the lubricant to impact drug release from whole tablets is high.
	Drug Release – split tablets	The risk of the lubricant to impact tablet CU is medium and the risk of impact on whole tablet drug release is high. For these reasons, the risk of the lubricant to impact split tablet drug release is high.

Optimizing the Ratio of Filler to ER Coated Beads

Previous experience with multi-particulate systems compressed into tablets suggests that, as a starting point, the drug product formulation should contain not more than 25% w/w of coated beads per tablet to ensure sufficient ER bead cushioning during compression.[7] Cushioning prevents the polymer film on the beads from rupturing. It also prevents beads from fusing together during compression. Table 41 lists the weight ratios of extragranular filler to ER coated beads that were considered in prototype tablet formulations. For these batches, the quantity of disintegrant and lubricant in the formulation was held constant for simplicity and the corresponding percentages used were kept within the ranges recommended in the Handbook of Pharmaceutical Excipients.[8] Lubricant and disintegrant levels will be optimized in subsequent experiments.

Table 41. Prototype tablet formulations with different ratios of extragranular MCC 200 to ER coated beads

Batch No.	IR Granules	ER Beads	MCC 200	SSG	Magnesium Stearate	Tablet Weight	Beads	Weight Ratio Filler:Beads
	(mg)	(mg)	(mg)	(mg)	(mg)	(mg)	(% w/w)	
RD-22	62.50	36.69	50.00	10.00	2.50	161.69	22.69	1.36
RD-23	62.50	36.69	75.00	10.00	2.50	186.69	19.65	2.04
RD-24	62.50	36.69	100.00	10.00	2.50	211.69	17.33	2.73
RD-25	62.50	36.69	150.00	10.00	2.50	261.69	14.02	4.09
RD-26	62.50	36.69	200.00	10.00	2.50	311.69	11.77	5.45

All five batches were compressed into tablets with a target hardness of 8 kP and the drug release profiles were compared with the drug release profile of active components (IR granules and ER coated beads) in a capsule. The results are graphed in Figure 26.

[8] Rowe, RC., PJ Sheskey and ME Quinn. Handbook of Pharmaceutical Excipients, 6th Edition. Grayslake, IL: RPS Publishing, 2009.

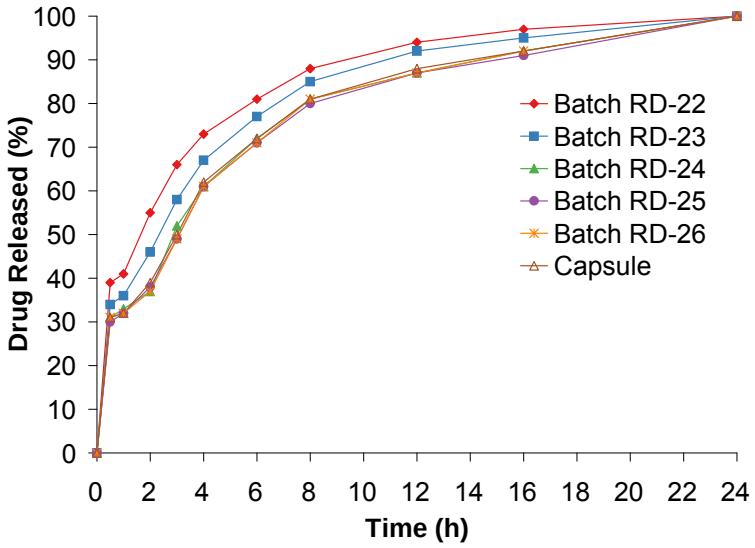

Figure 26. Drug release profile comparison of batches made with different ratios of filler to ER coated beads

Batches RD-22 and RD-23 showed significantly faster drug release compared to drug filled capsules which suggested that the higher ratio of extragranular excipients to ER coated beads is essential to provide enough cushioning to avert bead rupture. The drug release profiles for batches RD-24, RD-25 and RD-26 are very similar to the release profile for the drug filled capsules. Based on this data, 150 mg of extragranular filler per tablet was selected for the final MR tablet formulation, which would yield a tablet with a similar size and total weight as the RLD.

Subsequent to optimizing the ratio of filler to ER coated beads, a predictive dissolution method was developed. The drug release study was repeated and once again, a level of 150 mg of extragranular filler per tablet provided adequate cushioning to protect ER coated beads from rupture during compression.

Segregation was observed during manufacturing (see detail in Section 2.3.4 *Blending and Lubrication Process Development*). To address the issue of segregation in the prototype formulation and to reduce the risk of poor content uniformity, the following approaches were considered: 1) keep the bulk density and the particle size of most materials as close as possible while filling voids with small particles, 2) roller compaction, and 3) multiple layer tableting. Approach 1 is discussed in the following section. As roller compaction may damage the membrane of the coated beads, this approach was ruled out. Multiple-layer tableting increases development complexity, especially when developing scored tablets; therefore, it was also ruled out.

Optimizing the Ratio of Different Grades of Extragranular Filler to Minimize Segregation

To minimize segregation, the prototype formulation had to be optimized such that the bulk density and the particle size of most materials were similar and any voids were filled with small particles. Various combinations of excipients having 1) bulk density and particle sizes as close as possible to the ER beads, and 2) particle sizes sufficiently small to fill the void volume were considered.

Multiple excipients were selected to be evaluated in trial batches to test blend uniformity and the cushioning effect on beads.

From previous experience, differences in bulk density and PSD among excipients can lead to segregation in a blend. In order to maintain the cushioning effect required to prevent ER bead damage during tablet compression and to minimize blend segregation, a combination of MCC fillers with different PSDs was investigated. The rationale is that two distinctly different grades of filler are more likely to fill large and small spaces in the formulation microenvironment than a single grade, thereby producing a more uniform and compressible prototype formulation. A variety of MCC grades are commercially available. After an extensive review of vendor technical data sheets, two MCC grades were selected based on bulk density and particle size distribution. MCC Filler 1 (Grade 200, bulk density: 0.32 g/cm^3, d_{50}: 180 µm) and Filler 2 (Grade 101, bulk density: 0.28 g/cm^3, d_{50}: 50 µm) were chosen for further optimization.

A series of trial lab batches were made with different ratios of the two fillers mixed with ER beads and IR granules. These prototype formulations were tested for blend uniformity (after discharging into drums). The results for blend uniformity measured by the assay percent relative standard deviation (RSD) are summarized in Table 42.

Table 42. Selection of filler ratio based on blend uniformity (optimal ratios highlighted)

Trial Batch No.	Filler 1: Filler 2 Ratio	Label Claim	RSD
		(% w/w)	(%)
RD-41	10:90	95.8	5.6
RD-42	20:80	96.5	4.6
RD-43	30:70	96.8	4.5
RD-44	40:60	98.6	2.6
RD-45	50:50	99.9	2.2
RD-46	60:40	100.3	1.3
RD-47	70:30	100.2	1.5
RD-48	80:20	96.4	4.3
RD-49	90:10	96.3	4.1

From the above experiment, Filler 1 and Filler 2 best prevent segregation and provide good blend uniformity when used in the ratios of 60:40 and 70:30.

Both trial batches RD-46 and RD-47 were compressed into tablets with a target hardness of 8.0 kP and drug release profiles were compared to that of the reference tablet as shown in Figure 27.

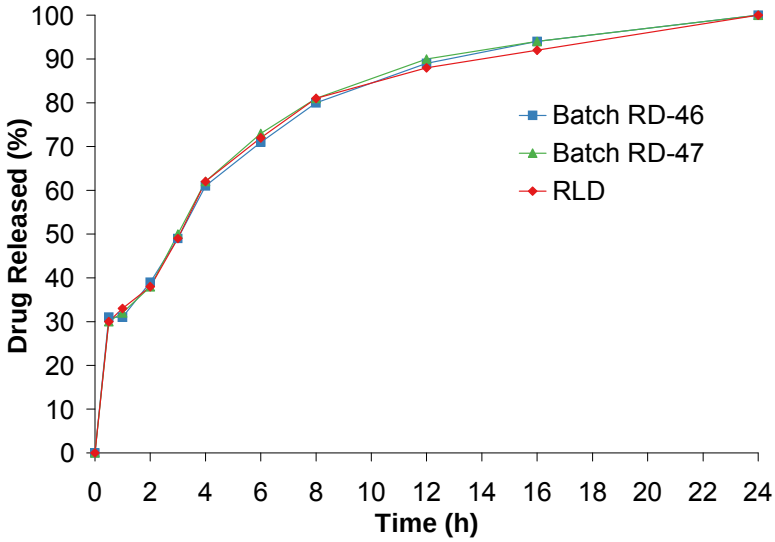

Figure 27. Drug release profiles of trial batches RD-46 and RD-47 and RLD tablets

Compressed tablets from both trial batches RD-46 and RD-47 showed comparable drug release profiles, indicting that Filler 1 and Filler 2 used in a ratio of 60:40 to 70:30 can prevent ER membrane rupture. A Filler 1 to Filler 2 ratio of 65:35 was selected for the final formulation.

Optimizing the Level of Disintegrant

The quantity of SSG Type A was varied (2 – 5%) within the range recommended in the Handbook of Pharmaceutical Excipients to evaluate its influence on product performance.[8] Compressed tablets containing both IR granules, ER coated beads, MCC 200, MCC 101 and magnesium stearate were used. The results are provided in Table 43.

Table 43. Optimization of the sodium starch glycolate level

Batch No.	RD-56	RD-57	RD-58	RD-59	RLD
SSG (%)	2	3	4	5	Unknown
Disintegration	6 min	2.5 min	1.5 min	1.5 min	1.5 min
Drug Release	% Drug dissolved in 900 mL of pH 6.8 phosphate buffer using USP Apparatus 2 at 50 rpm				
10 min	5	12	11	11	11
20 min	10	12	14	13	16
30 min	18	32	33	33	33

The dissolution profiles of the formulations containing 3 – 5% SSG were comparable to the RLD sample. Thus, 4% SSG was selected in the final formulation. A subsequent study using 4% SSG Type A in the formulation demonstrated that the degree of substitution investigated (0.25 – 0.35) had no impact on disintegration or drug release of the tablets.

Optimizing the Level of Lubricant

The goal of this study was to find the minimum level of magnesium stearate needed to provide adequate lubrication for tableting. The range of lubricant studied (0.2 – 1.2%) was within the range

recommended in the Handbook of Pharmaceutical Excipients.[8] Four batches (10 kg each) of prototype formulation were manufactured with the following quantities of lubricant: 0.2%, 0.4%, 0.8%, and 1.2%. The lubrication was carried out in a 1 cu ft V-blender at 15 rpm. The sensitivity of the responses to the number of revolutions (N_{rev}) was also investigated. Samples (500 g) were withdrawn at 60, 90, and 120 revolutions. These samples were compressed at 8 kN. The responses measured were:

- Tablet appearance
- Tablet tooling appearance
- Hardness
- Friability
- Ejection force
- Disintegration
- Drug Release

The study results are summarized in Table 44.

Table 44. Effect of lubricant and lubrication parameters on tablet properties

Batch No.	**RD-60**			**RLD**
Lubricant (%)	0.2			-
N_{rev}	60	90	120	-
Tablet appearance	Unclear score, uneven tablet surface and striations on the side			-
Tablet tooling appearance	Visible indication of sticking on punches and binding in the die			-
Ejection force (N)	650	500	450	
The remaining responses were not evaluated based on the results of tablet and tooling appearance.				
Batch No.	**RD-61**			**RLD**
Lubricant (%)	0.4			-
N_{rev}	60	90	120	-
Tablet appearance	Slightly rough surfaces but no visible picking/sticking			-
Tablet tooling appearance	Slight hazing of the punch surfaces but no evidence of binding in the die			-
Ejection force (N)	350	325	275	-
Hardness (kP)	10	9.5	9.5	-
Friability (%)	0.1	0.12	0.1	-
Disintegration time (min)	1.5	1.5	2	-
Drug release	% Drug dissolved in 900 mL of pH 6.8 phosphate buffer using USP Apparatus 2 at 50 rpm			
0.25 h	11	9	10	11
0.5 h	34	32	31	33
3 h	41	43	42	42
6 h	67	64	66	65
12 h	86	89	86	87

Batch No.	RD-62			RLD
Lubricant (%)	0.8			-
N_{rev}	60	90	120	-
Tablet appearance	Shiny appearance with smooth surface			-
Tablet tooling appearance	Shiny appearance with no evidence of picking and sticking			-
Ejection force (N)	150	100	125	-
Hardness (kP)	8.9	8.4	8.6	-
Friability (%)	0.08	0.07	0.07	-
Disintegration time (min)	2	1.5	2.5	-
Drug release	% Drug dissolved in 900 mL of pH 6.8 phosphate buffer using USP Apparatus 2 at 50 rpm			
0.25 h	11	10	11	11
0.5 h	31	33	32	33
3 h	38	39	40	42
6 h	66	67	65	65
12 h	90	86	88	87
Batch No.	**RD-63**			**RLD**
Lubricant (%)	1.2			-
N_{rev}	60	90	120	-
Tablet appearance	Shiny appearance with smooth surface			-
Tablet tooling appearance	Shiny appearance with no evidence of picking and sticking			-
Ejection force (N)	130	115	100	-
Hardness (kP)	8.0	8.2	8.3	-
Friability (%)	0.11	0.09	0.06	-
Disintegration time (min)	2.5	2	2	-
Drug release	% Drug dissolved in 900 mL of pH 6.8 phosphate buffer using USP Apparatus 2 at 50 rpm			
0.25 h	13	10	12	11
0.5 h	32	33	31	33
3 h	39	40	44	42
6 h	68	65	66	65
12 h	87	87	89	87

The results indicated that 0.2% and 0.4% magnesium stearate provide sub-optimal lubrication based on the appearance of the tablets. The 0.8% and 1.2% lubricant levels gave the desired drug release profile without significant compression-related issues such as tablet picking and sticking. In addition, none of the responses studied were sensitive to the number of revolutions. Based on these results, 0.8% magnesium stearate was used in the final formulation and 60-120 revolutions results in adequate lubrication.

Furthermore, the impact of magnesium stearate specific surface area on the responses listed above was studied using a level of 0.8% magnesium stearate in the formulation. Within the range investigated (6-10 m^2/g), the impact on the responses was not significant (data not shown).

The tablets compressed during Batch No. RD-62 (150 mg of cushioning agent, 4% SSG, and 0.8% magnesium stearate) were split either with a tablet splitter or by hand and were then evaluated for weight loss. For both splitting methods, the split tablets had a loss of mass less than 1.5% indicating that either method could be used. Regardless of splitting method, whole and hand-split tablets

performed similarly and met the drug product specifications for friability, assay and drug release (similarity factor (f2) > 80). Both whole and split tablets demonstrated content uniformity (AV< 5).

Updated Risk Assessment of the Extragranular Excipients in the Prototype Tablet Formulation

The prototype formulation development studies addressed the identified risks. The updated risk assessment is presented in Table 45 followed by the justification for the reduced risks in Table 46.

Table 45. Updated risk assessment of the extragranular excipients in the prototype tablet formulation

Prototype Tablet Formulation CQAs	Extragranular Excipients in the Prototype Tablet Formulation		
	Filler	Disintegrant	Lubricant
Physical Attributes (size and splitability)	Low	Low*	Low
Content Uniformity	Low	Low*	Low
Drug Release – whole tablets	Low	Low	Low
Drug Release – split tablets	Low	Low	Low

*The level of risk is not reduced from the initial risk assessment.

Table 46. Justification for the reduced risks of the extragranular excipients in the prototype tablet formulation

Formulation Variables	Prototype Tablet Formulation CQAs	Justification
Filler (Cushioning Agent)	**Physical Attributes (size and splitability)**	The level of filler required to cushion the ER coated beads was optimized to control the size of the tablet. The tablet size is similar to the RLD. The formulation demonstrated good compressibility and compactability. Therefore, the risk of extragranular filler level to impact physical attributes (size and splitability) is reduced from high to low.
	Content Uniformity	MCC 200 (d_{50}: 150 -250 µm) and MCC 101 (d_{50}: 30-80 µm) are fixed in the ratio 65:35 to prevent segregation. The flow of the prototype formulation was adequate based on a minimum orifice diameter of 20 mm as determined by Flowdex. Tablets demonstrated acceptable CU per USP <905>. The risk of extragranular filler level and grade to impact tablet CU is reduced from high to low.
	Drug Release – whole tablets	The level and grades of MCC were optimized to prevent segregation and to protect the ER coated beads from damage during compression. Therefore, the risk of MCC to impact drug release from whole tablets is reduced from high to low.
	Drug Release – split tablets	Both whole and split tablets demonstrated CU as per USP <905>. The drug release from whole and split tablets was comparable. The risk of extragranular filler to impact drug release from split tablets is reduced from high to low.

Disintegrant	**Drug Release – whole tablets**	The level of SSG Type A was optimized to achieve the desired drug release profile. The degree of substitution showed no effect on release. Thus, the risk of disintegrant to impact drug release from whole tablets is reduced from high to low.
	Drug Release – split tablets	The drug release from whole and split tablets was comparable. The risk of impact on drug release from split tablets is reduced from high to low.
Lubricant	**Physical Attributes (size and splitability)**	The level of magnesium stearate used in the prototype formulation (0.8%) did not cause any tablet appearance issues during compression. Thus, the risk of lubricant to impact tablet physical attributes (size and splitability) is reduced from medium to low.
	Content Uniformity	Tablets compressed with the selected level of magnesium stearate achieved acceptable tablet CU as per USP <905>. The risk of lubricant to impact tablet CU is reduced from medium to low.
	Drug Release – whole tablets	The impact of the magnesium stearate level and specific surface area on the drug release profile is not significant. The risk of impact on whole tablet drug release is reduced from high to low.
	Drug Release – split tablets	Both whole and split prototype tablets demonstrated good CU. The drug release from whole and split tablets was comparable. Thus, the risk of lubricant to impact drug release from split tablets is reduced from high to low.

2.2.1.5 Prototype Tablet Formulations and Trial BE Studies

The conclusions from the formulation development work supported the manufacture of a 4 kg lab scale batch of ER coated beads. The beads were blended with IR granules and extragranular excipients, and the blend was compressed into tablets for further evaluation. The formulation of prototype F-1, Lot No. ZAp030110, is summarized in Table 47.

Table 47. Formulation of prototype F-1

Components	Function	Compendial Reference	mg per tablet	Comments
IR Granules				
Z	Drug substance	In-house	3.00	
Microcrystalline Cellulose (MCC), Grade 200	Filler	NF	32.62	
Lactose Monohydrate	Filler	NF	21.88	
Povidone (PVP), K30	Binder	USP	2.50	
Sodium Starch Glycolate (SSG), Type A	Disintegrant	NF	2.50	
Purified Water	Solvent	USP	--	
IR Granules Subtotal			**62.50**	
ER Beads				
Z	Drug substance	In-house	7.00	
Microcrystalline Cellulose (MCC) Beads	Substrate	NF	19.98	
Povidone (PVP), K30	Binder	USP	1.24	
Purified Water	Solvent	USP	--	
Drug-layered Beads Subtotal			**28.22**	
Kollicoat SR 30 D*	Coating polymer	NF	7.06	25% theoretical polymer coating based on drug-layered bead weight
Triethyl Citrate (TEC)	Plasticizer	NF	0.35	5% of the dry polymer
Talc	Anti-tacking agent	USP	1.06	15% of the dry polymer
Purified Water	Solvent	USP	--	
ER Polymer Coating Subtotal			**8.47**	
ER Coated Beads Subtotal			**36.69**	
Extragranular Excipients				
Microcrystalline Cellulose (MCC), Grade 200	Filler	NF	97.50	
Microcrystalline Cellulose (MCC), Grade 101	Filler	NF	52.50	
Sodium Starch Glycolate (SSG), Type A	Disintegrant	NF	10.47	
Magnesium Stearate	Lubricant	NF	2.09	
Total tablet weight			**261.75**	

*Kollicoat SR 30 D contains 90% PVAc, 9% PVP and 1% SLS calculated on a solids basis.

The drug release profiles of prototype F-1 were obtained using USP apparatus 2 at 50 rpm in various media and the data showed that the *in vitro* drug release of this formulation matched the RLD profile (see Section 1.4.1 Figure 5). The drug release of the prototype showed pH-independence. In addition, *in vitro* alcohol-induced dose dumping studies were conducted in 5%, 20% and 40% v/v Alcohol USP in 0.1 N HCl medium. The drug release profile for the prototype did not indicate any increased alcohol-induced dose dumping potential for whole or split tablets as both the RLD and prototype performed comparably under each condition (data included in Section 5.3).

A pilot BE study was conducted using prototype F-1. The RLD provided a biphasic profile representing the IR and ER portions which was not observed for prototype F-1 (see Section 1.4.1 Figure 4). The data suggested the need to slow the release rate from the ER beads in the prototype formulation.

The BE study results also suggested that the *in vitro* dissolution method was not predictive of the *in vivo* performance of the prototype formulation. Although multimedia dissolution testing using USP apparatus 2 provided similar drug release profiles for the RLD and prototype F-1, the prototype released drug at a much faster rate *in vivo*.

Based on the results of the failed BE study, a more predictive dissolution method using USP apparatus 3 at 10 dpm in 250 mL of pH 6.8 phosphate buffer was developed and an IVIVR was established (see sections 1.4.1 and 1.4.2). The dissolution test on the first prototype formulation (F-1) was rerun using the new predictive dissolution method. It was evident that the *in vitro* drug release rate was much faster when measured by the new dissolution method (see Section 1.4.1 Figure 9).

Therefore, the formulation needed an adjustment in the theoretical polymer coating level to achieve the optimal release profile. The formulation of the ER coated beads was further modified to develop two new prototypes F-2 and F-3 as shown in Table 48.

Table 48. Formulation of prototypes F-2 and F-3

Components	Function	Compendial Reference	mg per tablet		Comments
			F-2	F-3	
IR Granules					
Z	Drug substance	In-house	3.00	3.00	
Microcrystalline Cellulose (MCC), Grade 200	Filler	NF	32.62	32.62	
Lactose Monohydrate	Filler	NF	21.88	21.88	
Povidone (PVP), K30	Binder	USP	2.50	2.50	
Sodium Starch Glycolate (SSG), Type A	Disintegrant	NF	2.50	2.50	
Purified Water	Solvent	USP	--	--	
IR Granules Subtotal			**62.50**	**62.50**	
ER Beads					
Z	Drug substance	In-house	7.00	7.00	
Microcrystalline Cellulose (MCC) Beads	Bead	NF	19.98	19.98	
Povidone (PVP), K30	Binder	USP	1.24	1.24	
Purified Water	Solvent	USP	--	--	
Drug-layered Beads Subtotal			**28.22**	**28.22**	
Kollicoat SR 30 D*	Coating polymer	NF	8.47	9.88	30% (F-2) and 35% (F-3) theoretical polymer coating based on drug-layered bead weight
Triethyl Citrate (TEC)	Plasticizer	NF	0.42	0.49	5% of dry polymer
Talc	Anti-tacking agent	USP	1.27	1.48	15% of dry polymer
Purified Water	Solvent	USP	--	--	
ER Polymer Coating Subtotal			**10.16**	**11.85**	
ER Coated Beads Subtotal			**38.38**	**40.07**	
Extragranular Excipients					
Microcrystalline Cellulose (MCC), Grade 200	Filler	NF	97.50	97.50	
Microcrystalline Cellulose (MCC), Grade 101	Filler	NF	52.50	52.50	
Sodium Starch Glycolate (SSG), Type A	Disintegrant	NF	10.47	10.47	
Magnesium Stearate	Lubricant	NF	2.09	2.09	
Total tablet weight			**263.44**	**265.13**	

*Kollicoat SR 30 D contains 90% PVAc, 9% PVP and 1% SLS calculated on a solids basis.

In vitro drug release profiles were generated for prototypes F-2 and F-3 using the predictive dissolution method (see Section 1.4.2 Figure 12). The increase in the theoretical polymer coating level from 25% (F-1) to 30% (F-2) led to a formulation exhibiting a drug release profile which was similar to the RLD drug release profile. However, a 35% theoretical polymer coating (F-3) showed a slower drug release profile.

A second pilot BE study was conducted comparing prototypes F-2 and F-3 to the RLD (see Section 1.4.2 Table 7 and Figure 14). Only prototype F-2 exhibited bioequivalence to the RLD. Based on the results, prototype F-2 with 30% theoretical polymer coating was selected and used in the subsequent development. Table 48 lists the composition of prototype F-2.

Accelerated stability data (6 months at 40 °C/75% RH) for prototype F-2 confirmed that the selected drug product formulation is stable and meets all quality attributes defined in the QTPP.

Water activity was measured and shown to be below 0.4, demonstrating that Example MR Tablets do not support survival or proliferation of microorganisms. An in-use stability study (3 months at 25 °C/60% RH) conducted on split tablets stored in the proposed packaging demonstrated that the split tablets also meet the established stability requirements. Detailed stability data for both studies can be found in Section 3.2.P.8.

A study comparing the drug release profiles of whole and split tablets was conducted using prototype F-2 tablets and the predictive dissolution method. Whole and split tablets demonstrated comparable drug release (f2 = 80). Prototype F-2 tablets were also tested in the indicated patient population to ensure that the patients could split the tablet correctly. The patient population found the tablet splitability to be acceptable whether tablets were split by hand or with a tablet splitter.

2.2.1.6 Updated Risk Assessment of the Formulation Components

During formulation development, the high risks for each component of the overall drug product formulation were addressed. Experimental studies were defined and executed to develop additional scientific knowledge and understanding and to reduce the risk to an acceptable level. After detailed experimentation, the initial overall risk assessment of the formulation components was updated in-line with the current product understanding. Tables 49 and 50 provide the updated risk assessment of the formulation of Example MR Tablets, 10 mg, and the justification for the reduced risk following formulation development, respectively.

Table 49. Updated risk assessment of the formulation components

Drug Product CQAs	Formulation Components			
	IR Granules	**ER Beads: drug-layered beads**	**ER Beads: coated beads**	**Extragranular Excipients**
Physical Attributes (size and splitability)	Low*	Low*	Low*	Low
Assay	Low*	Low	Low*	Low
Content Uniformity	Low*	Low	Low*	Low
Drug Release – whole tablets	Low	Low	Medium	Low
Drug Release – split tablets	Low	Low	Medium	Low
Drug Release – alcohol-induced dose dumping	N/A*	N/A*	Medium	Low

*The level of risk is not reduced from the initial risk assessment.

Table 50. Justification for the reduced risks of the formulation components

Formulation Components	Drug Product CQAs	Justification
IR Granules	**Drug Release – whole tablets**	The target drug release from the IR granules (NLT 80% in 30 min) can be met when IR granules are compressed with placebo beads. Therefore, the risk of the IR granules to impact drug release from whole tablets is reduced from medium to low.
	Drug Release – split tablets	Split tablets had adequate CU with an AV < 5 as per USP <905> and comparable drug release to whole tablets (f2 = 80). The risk of the IR granules to impact drug release from split tablets is reduced from medium to low.
ER Beads: drug-layered beads	**Assay**	The drug substance to binder ratio of 85:15 was selected and provided adequate adhesion of the drug substance to the beads. The risk of the drug-layered beads to impact tablet assay is reduced from high to low.
	Content Uniformity	In order to prevent segregation, MCC beads with a comparable PSD and bulk density to the IR granules were selected as the cores for drug layering. The tablets had acceptable CU with an AV < 5. Thus, the risk of the drug-layered beads to impact tablet CU is reduced from medium to low.
	Drug Release – whole tablets	MCC beads are insoluble and it is unlikely that the drug substance diffuses into the core. MCC beads have very low friability (< 0.1%) and the drug-layered beads showed rapid dissolution with low variability. An 85:15 drug substance to binder ratio produced uniform drug-layered beads. Drug substance was stabilized in an amorphous state in the drug layer, and no form conversion was observed at room temperature for up to two years. Thus, the risk of the drug-layered beads to impact drug release from whole tablets is reduced from high to low.
	Drug Release – split tablets	Split tablets had adequate CU with an AV < 5 and comparable drug release to whole tablets (f2 = 80). The risk of drug-layered beads to impact drug release from split tablets is reduced from high to low.
ER Beads: coated beads	**Drug Release – whole tablets**	The theoretical polymer coating level needed to match the RLD performance was identified as 30%. However, drug release is sensitive to polymer coating level based on the BE studies. Further evaluation during process development and scale-up is needed since process variables may affect the actual coating level achieved. The risk of the ER coated beads to impact drug release from whole tablets is reduced from high to medium.
	Drug Release – split tablets	Split tablets had adequate CU with an AV < 5 and comparable drug release to whole tablets (f2 = 80). The risk is reduced because there was no evidence that tablet splitting damaged the integrity of the ER coated beads. However, drug release is sensitive to polymer coating level based on the BE studies. Further evaluation during process development and scale-up is needed since process variables may affect the actual coating level achieved. Therefore, the risk of the ER coated beads to impact split tablet drug release is medium.
	Drug Release – alcohol-induced dose dumping	Alcohol-induced dose dumping was evaluated and found to be comparable to the RLD. However, this study will need to be repeated to confirm that tablets made at commercial scale also perform comparably to the RLD. Thus, the risk of the ER coated beads to impact alcohol-induced dose dumping is reduced from high to medium.

Formulation Components	Drug Product CQAs	Justification
Extragranular Excipients	**Physical Attributes (size and splitability)**	The type and level of cushioning agent, disintegrant and lubricant used in the prototype formulation was identified and the tablet size is similar to that of the RLD. Tablets could be split by the intended patient population and splitting resulted in less than 2% mass loss. Therefore, the risk of extragranular excipients to impact tablet physical attributes (size and splitability) is reduced from high to low.
	Assay	The flow of the prototype formulation was good based on a minimum orifice diameter of 20 mm as determined by Flowdex. The risk of the extragranular excipients to impact tablet assay is reduced from medium to low.
	Content Uniformity	The risk of segregation and poor BU was reduced using two grades of MCC with complementary PSDs (one similar to the IR granules and ER coated beads and one smaller to fill void space). Both whole and split prototype tablets demonstrated acceptable CU with an AV < 5. Therefore, the risk of extragranular excipients to impact tablet CU is reduced from high to low.
	Drug Release – whole tablets	MCC used as a cushioning agent in the prototype formulation prevented the ER polymer film from rupturing and from fusing during compression, and it reduced variability in the overall drug release profile. The level of SSG Type A was optimized to achieve the desired initial rapid drug release from the IR granules. The impact of the magnesium stearate amount and specific surface area on the drug release profile was not significant. The risk of extragranular excipients to impact whole tablet drug release is reduced from high to low.
	Drug Release – split tablets	Development studied showed that split tablets had adequate CU as per USP <905> and comparable drug release to whole tablets (f2 = 80). The risk of extragranular excipients to impact split tablet drug release is reduced from high to low.
	Drug Release – alcohol-induced dose dumping	The level of extragranular cushioning agent was optimized and the tablets performed comparably to the RLD under alcohol stress conditions. The risk is reduced from medium to low.

2.2.2 Overages

There are no overages used in the formulation of Example MR Tablets, 10 mg.

2.2.3 Physicochemical and Biological Properties

Please refer to Section 1.4 *Dissolution Method Development and Bioequivalence Studies* for a discussion of the development of a predictive dissolution method, the results of bioequivalence studies, and the establishment of an IVIVR.

2.3 Manufacturing Process Development

Note to Reader: This section involves process development and understanding. Steps to establish process understanding are as follows:

- *Identify all possible known material attributes and process parameters that could impact the performance of the process.*
- *Use risk assessment and scientific knowledge to identify potentially high risk attributes and/or parameters.*
- *Identify levels or ranges of these potentially high risk attributes and/or parameters.*
- *Design and conduct experiments, using DOE when appropriate.*
- *Analyze the experimental data to determine if a material attribute or process parameter is critical.*
  - *A material attribute or process parameter is critical when a realistic change in that attribute or parameter can significantly impact the quality of the output material.*
- *Develop a control strategy.*
  - *For CMAs and CPPs, define acceptable ranges. For non-critical attributes and parameters, the acceptable range is the range investigated.*

The process map for Example MR Tablets, 10 mg, is presented in Figure 28. This process map lists all of the unit operations in the manufacturing process for Example MR Tablets in the sequence of occurrence. It also presents how input material attributes and manufacturing process parameters can potentially impact intermediate and finished product quality attributes. The attributes of incoming raw materials and the process parameters used at the very first unit operation determine the quality attributes of the output material (intermediate) produced at this step. Attributes of the intermediate and processing parameters of the subsequent unit operations in the manufacturing scheme will determine quality attributes of the next intermediate and, eventually, those of the finished drug product. This cycle repeats until the final unit operation where finished product is manufactured and the finished product quality attributes are evaluated. Note that this process map excludes the quantities of raw materials (i.e. binder, coating agent, plasticizer, pore former, anti-tacking agent and extragranular excipients) from the material attributes column because these are evaluated as part of formulation development.

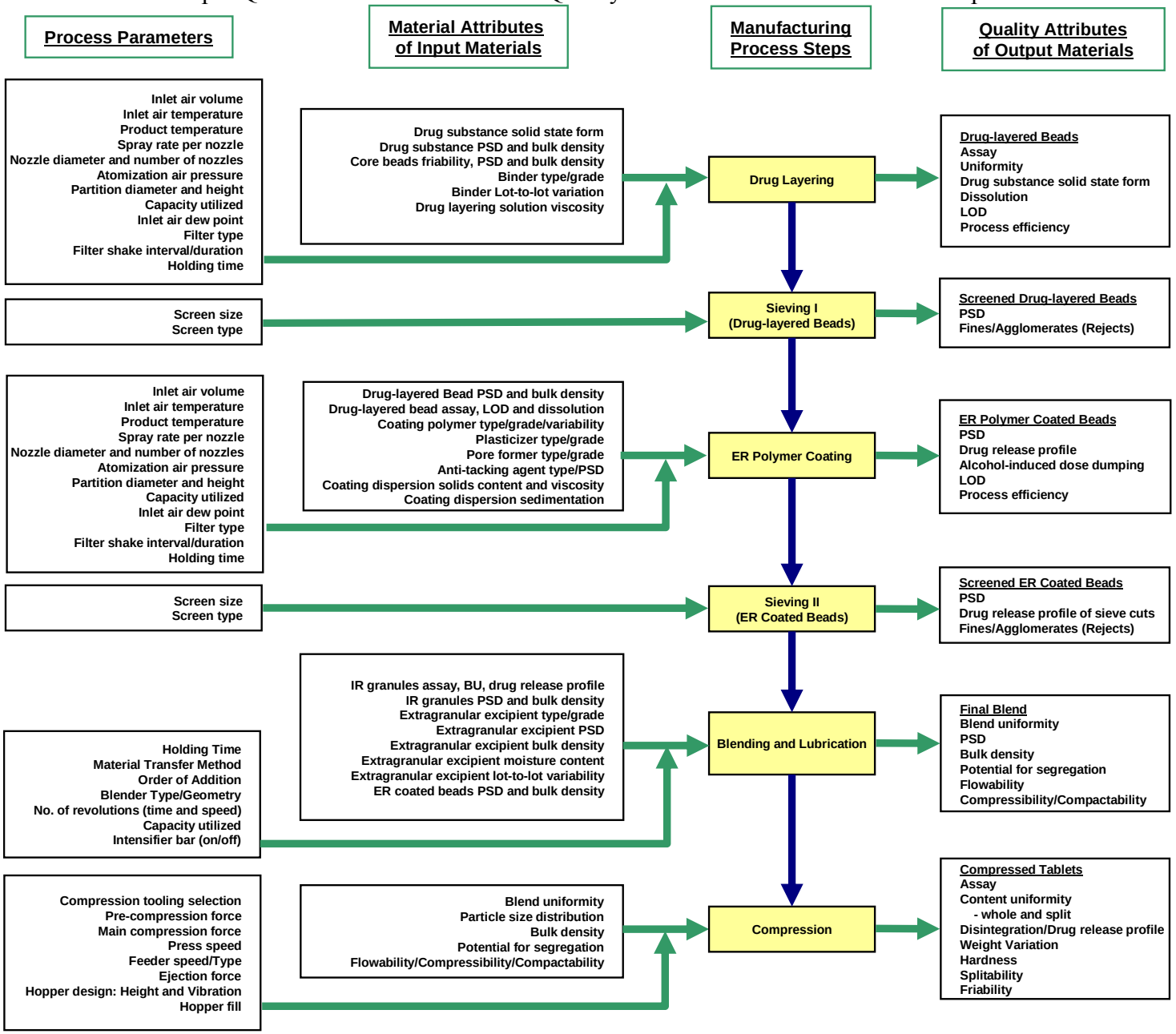

Figure 28. Process map for Example MR Tablets, 10 mg

2.3.1 Initial Risk Assessment of the Drug Product Manufacturing Process

A risk assessment of the overall drug product manufacturing process was performed to identify the high risk steps that could affect the final drug product CQAs. Subsequently, the drug product intermediate CQAs that are directly linked to the identified final drug product CQAs were identified. The process variables that could impact the identified drug product intermediate CQAs became the focus of the risk assessment to determine which variables have the highest potential to cause a CQA failure. These variables then needed to be investigated in order to optimize the drug product manufacturing process and reduce the risk of failure. For example, the overall risk assessment of the manufacturing process found assay of the tablets to be at high risk of failure due to the drug layering step. Subsequently, assay of the layered beads is directly linked to final tablet assay and was identified as the CQA of the drug-layered beads. Process variables that could directly impact the assay of the drug-layered beads were assessed to identify which of the variables could have the highest potential to cause a bead assay failure. This method of identifying process variables for further study was also illustrated previously in Figure 19.

In the initial risk assessment of the overall manufacturing process shown in Table 51, drug layering, ER polymer coating, blending and lubrication, and compression were identified as high risk steps that could affect the quality of the final product. Justification for each risk assignment is presented in Table 52.

Table 51. Initial risk assessment of the manufacturing process for Example MR Tablets, 10 mg

Drug Product CQAs	Process Steps						
	IR granulation	ER beads: drug layering	Sieving I	ER beads: polymer coating	Sieving II	Blending and Lubrication	Compression
Physical Attributes (size and splitability)	Low	Low	Low	Low	Low	Low	High
Assay	Low	High	Low	Low	Low	Medium	High
Content Uniformity	Low	Medium	Low	Low	Low	High	High
Drug Release – whole tablets	Low	Low	Low	High	Medium	Medium	High
Drug Release – split tablets	Low	Medium	Low	High	Medium	High	High
Drug Release – alcohol-induced dose dumping	N/A	N/A	N/A	Low	Low	Low	Low

Table 52. Justification for the initial risk assessment of the manufacturing process for Example MR Tablets, 10 mg

Process Steps	Drug Product CQAs	Justification
IR granulation	**Physical Attributes (size and splitability)**	The IR granules in Example MR Tablets are prepared the same as the IR granules in Example IR Tablets (ANDA aaaaaa(Appendix I)). The manufacturing process has been optimized previously and low variability of granule PSD and bulk density between commercial batches were observed. The risk of the IR granulation process variables to impact the tablet size and splitability is low.

Process Steps	Drug Product CQAs	Justification
	Assay	The approved commercial IR granulation routinely delivers granules with an assay of 95 – 105%. The risk is low.
	Content Uniformity	On the commercial scale, the IR granules routinely demonstrate good blend uniformity and Example IR Tablets show acceptable CU. The risk of the IR granulation process variables to impact Example MR Tablet CU is low.
	Drug Release – whole tablets	Example IR Tablets manufactured using the approved IR granulation process consistently demonstrate rapid drug release. During formulation development, the drug release from IR granules compressed with placebo beads was unaffected. Therefore, the risk of the IR granulation process variables to impact drug release from the IR portion of Example MR Tablets is low.
	Drug Release – split tablets	The commercial IR granulation delivers granules with acceptable BU and the Example IR Tablets have acceptable CU. Additionally, rapid drug release from Example IR Tablets is achieved. Thus, the risk of the IR granulation process variables to impact drug release from split tablets is low.
	Drug Release – alcohol-induced dose dumping	Alcohol-induced dose dumping is determined by the ER polymer coating formulation and the ER polymer coating step and is not related to the IR granulation.
ER beads: drug layering	**Physical Attributes (size and splitability)**	The impact of drug layering on the size of beads is low due to the low dose (7 mg) in the drug layer. The weight gain is low. Process variables may cause some variability in the coating efficiency; however, the impact on bead size is minimal and the risk of the drug layering process variables to impact tablet physical attributes is low.
	Assay	Poor adhesion and/or spray drying can have an impact on the potency of the drug-layered beads. The risk of impact on tablet assay is high.
	Content Uniformity	Drug substance and binder are uniformly dissolved and the resulting solution is sprayed onto beads in a fluid bed coater. Suboptimal fluidization may lead to some beads receiving more layering than others. The risk of the drug layering process variables to impact the uniformity of the beads, and therefore the tablet CU, is medium.
	Drug Release – whole tablets	Rapid dissolution of the drug-layered beads was achieved during formulation development. The risk of the drug layering process variables to impact drug release from whole tablets is low.
	Drug Release – split tablets	Although the risk of the drug layering step to impact whole tablet drug release is low, the risk of the step to impact tablet CU is medium. Therefore, the risk of the layering process variables to impact split tablet drug release is also medium.
	Drug Release – alcohol-induced dose dumping	Alcohol-induced dose dumping is determined by the ER polymer coating formulation and the ER polymer coating step and is not related to the drug layering step.
Sieving I	**Physical Attributes (size and splitability)**	The main purpose of the sieving I step is to screen out agglomerates and fines produced during the drug layering process. The risk of this separation procedure to impact the drug product CQAs is low.
	Assay	
	Content Uniformity	
	Drug Release – whole tablets	
	Drug Release – split tablets	
	Drug Release – alcohol-induced dose dumping	Alcohol-induced dose dumping is determined by ER polymer coating formulation and the ER polymer coating step and is not related to sieving I.

Process Steps	Drug Product CQAs	Justification
ER beads: polymer coating	**Physical Attributes (size and splitability)**	The ER polymer coating formulation is optimized and the ER polymer coating thickness is ~ 50 µm. The impact of the ER polymer coating process variables on bead size is minimal. The risk of the ER polymer coating process variables to impact the tablet physical attributes (size and splitability) is low.
	Assay	Assay is mainly determined by the drug layering step. Although attrition of the drug-layered beads may occur during initial ER polymer coating, the risk of the ER polymer coating process variables to impact tablet assay is low.
	Content Uniformity	Drug uniformity of the beads is mainly determined by the drug layering process step and is unaffected by the ER polymer coating process variables. The risk of the ER polymer coating process variables to impact tablet CU is low.
	Drug Release – whole tablets	ER polymer coating is the drug release rate controlling step for the ER coated beads. The risk of the ER polymer coating process variables to impact drug release from whole tablets is high.
	Drug Release – split tablets	Despite the fact that the ER polymer coating process has minimal impact on the drug uniformity of the beads, the process has a high potential to impact whole tablet drug release. For this reason, the risk of the ER polymer coating process variables to impact split tablet drug release is high.
	Drug Release – alcohol-induced dose dumping	Alcohol-induced dose dumping is determined by the ER polymer coating formulation which was optimized during development and shown to perform comparably to the RLD. Therefore, the risk of the coating process variability to alter susceptibility to alcohol-induced dose dumping is low.
Sieving II	**Physical Attributes (size and splitability)**	The main purpose of the sieving II step is to screen out agglomerates and fines produced during the ER polymer coating step. The risk of this separation procedure to impact physical attributes, assay, or content uniformity of the tablets is low.
	Assay	
	Content Uniformity	
	Drug Release – whole tablets	There is a chance that the polymer film on the ER coated beads may be damaged if excessive force is used during sieving II. This may change the drug release profile. The risk of sieving II to impact the drug release from whole tablets is medium.
	Drug Release – split tablets	Although the risk of sieving II to impact tablet CU is low, the risk of impact on drug release from whole tablets is medium. As such, the risk of sieving II to impact drug release from split tablets is also medium.
	Drug Release – alcohol-induced dose dumping	Alcohol-induced dose dumping is determined by the ER polymer coating formulation and the ER polymer coating step. Prototype tablets were shown to perform comparably to the RLD during formulation development. Therefore, the risk of sieving II to alter susceptibility to alcohol-induced dose dumping is low.
Blending and Lubrication	**Physical Attributes (size and splitability)**	Suboptimal blending may impact the distribution of magnesium stearate in the final blend. However, the risk of blending and lubrication process variables to impact tablet physical attributes (size and splitability) is considered low.
	Assay	Blending process variables will impact BU. However, good flowability of the final blend was achieved during formulation development which will facilitate BU if process variables are optimized. The risk of blending and lubrication to impact tablet assay is medium.
	Content Uniformity	Segregation is possible during the blending and lubrication step, during holding in the blender and during blender discharge. If segregation occurs, the CU of the final drug product will be impacted. The risk of impact on tablet CU is high.

Process Steps	Drug Product CQAs	Justification
	Drug Release – whole tablets	Blending process variables may impact the distribution of the extragranular disintegrant and lubricant. The risk of impact on whole tablet drug release is medium.
	Drug Release – split tablets	The risk of blending and lubrication to impact whole tablet drug release is medium. However, for a tablet with poor CU, the drug release profile of split tablets may differ from that of whole tablets. Since the risk of the blending and lubrication process variables to impact tablet CU is high, the risk of the step to impact split tablet drug release is also high.
	Drug Release – alcohol-induced dose dumping	The ER polymer coating formulation and the ER polymer coating step control alcohol-induced dose dumping. Prototype tablets performed comparably to the RLD. Therefore, the risk of blending and lubrication process variables to impact alcohol-induced dose dumping is low.
Compression	**Physical Attributes (size and splitability)**	Through tooling design, the shape and score configuration of the tablets are defined. Compression force may impact the splitability of the scored tablets. The risk of the compression process variables to impact the tablet physical attributes (size and splitability) is high.
	Assay	Segregation may occur when the final blend is transferred from the drum into the hopper or when the blend flows from the hopper to the feed frame and into the die cavity. In addition, tablet press speed and feeder speed may impact the flow of the blend into the die cavity. Although good flowability was achieved during optimization of the prototype formulation, the risk of compression process variables to impact tablet assay is high.
	Content Uniformity	Segregation may occur during compression due to vibration as well as poor flow from the hopper to feeder frame and, ultimately, into the die cavity. The risk of compression process variables to impact tablet CU is high.
	Drug Release – whole tablets	Excessive compression force may damage the integrity of the ER polymer coating and impact the drug release profile. As such, dose dumping may be a concern and needs to be evaluated. The risk of compression process variables to impact whole tablet drug release is high.
	Drug Release – split tablets	Because the risk of compression to impact both tablet CU and whole tablet drug release is high, the risk of this step to impact split tablet drug release is also high.
	Drug Release – alcohol-induced dose dumping	Alcohol-induced dose dumping is determined by the ER polymer coating formulation and the ER polymer coating step. Excessive compression force may cause dose dumping but not alcohol-induced dose dumping. The risk of compression process variables to impact alcohol induced dose dumping is low.

2.3.2 IR Granule Process Development

For complete details of the IR granule development, refer to ANDA aaaaaa (Appendix I). In brief, the granulation process involves dry mixing followed by the addition of granulating fluid, purified water. After wet granulation and milling, the wet mass is transferred to the fluid bed dryer. Granules are then dried to a target product bed temperature of 52 °C, corresponding to a LOD of < 2.0%. Dried granules are passed through a mill where the granule particle size is controlled to have a d_{50} between 250-350 µm. Batches were scaled-up by maintaining impeller tip speed. Assay of pilot batches was maintained between 95% and 105% and the acceptance value for content uniformity was less than 5. The critical operating parameters are summarized in Table 53.

Table 53. Critical operating parameters for IR granules based on ANDA aaaaaa

Process Parameters	Lab Scale	Pilot Scale
Active Powder Mixing		
Equipment model	Collette Gral 10	Collette Gral 300
Impeller speed	Low (285 rpm)	Low (125 rpm)
Mixing time	5 min	5 min
Granulation using Purified Water		
Equipment model	Collette Gral 10	Collette Gral 300
Impeller speed	Low (285 rpm)	Low (125 rpm)
Chopper speed	Low	Off
Solution addition rate	60 g/min	1.28 kg/min
Mixing time	12 min	12 min
Drying		
Equipment	Fluid Bed Dryer	Fluid Bed Dryer
Bed air temperature	52 ºC (50 – 55 °C)	52 ºC (50 – 55 °C)
Milling		
Equipment model	Fitzmill L1A	Fitzmill DA6
Screening mill	Screen size: 20 mesh	Screen size: 20 mesh
	Speed: 4740 ± 20 rpm	Speed: 2500 ± 20 rpm

2.3.3 ER Bead Process Development

This section addresses the potentially critical material attributes and process parameters involved in the fluid bed drug layering and ER polymer coating process development.

Figure 29 shows the functional components of bottom spray fluid bed equipment for the pilot scale drug layering operation. Important equipment parameters in the Wurster coating process include the insert diameter, nozzle diameter, and distribution plate and partition gap (distance between distribution plate and the bottom of partition column, also referred to as partition height). These parameters can affect the dynamics of air flow, fluidization pattern, heat transfer and moisture content which are all directly related to the quality of the layered product. Settings for these equipment parameters need to be determined in concert with operating conditions and scale of operation, but can usually remain fixed after optimization if the scale and equipment do not change.

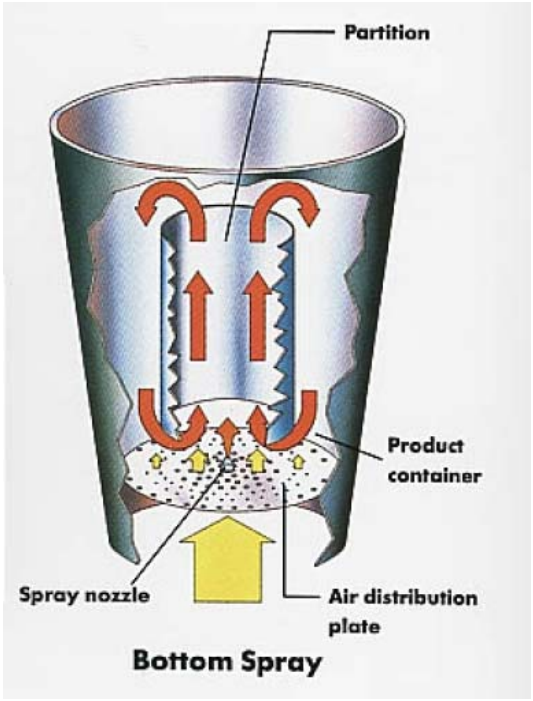

Figure 29. Schematic diagram of the bottom spray fluid bed coating equipment

2.3.3.1 Drug Layering Process Development

Initial Risk Assessment of the Drug Layering Process Variables

The initial risk assessment of the overall manufacturing process presented in Table 51 identified the risk of the drug layering step to impact assay of the drug product as high. Subsequently, assay of the drug-layered beads was identified as a CQA for the drug layering step. Process variables that could potentially impact assay of the drug-layered beads were identified and their associated risk was evaluated. Conducting DOEs to evaluate all the variables is not feasible. Therefore, variables ranked as low to medium risk during the assessment were set constant based on feasibility studies and previous experience. The variables ranked as high risk were evaluated by conducting DOE studies to gain process understanding.

Assay of the drug-layered beads will be controlled in the range of 95.0 – 105.0% of label claim. A suboptimal process may generate excessive fines or agglomerates which could adversely affect the drug-layered bead assay. Table 54 summarizes the initial risk assessment of the identified drug layering process variables that may impact the drug-layered bead assay.

Table 54. Initial risk assessment of the drug layering process variables

Unit Operation: Drug Layering		
Output Material CQA: Assay of the drug-layered beads		
Variables	**Risk Assessment**	**Justification and Initial Strategy**
Input Material Attributes		
Drug substance PSD	Low	The drug substance is dissolved and then sprayed. Its PSD has no impact on the assay of the beads.
Drug substance solid state form	Low	The drug substance is dissolved and is amorphous after drying on the bead surface. The initial solid state form of the drug substance has no impact on the drug-layered bead assay.
MCC beads PSD	Low	MCC beads are sieved and only the fraction between 250-350 µm is used for the layering process. Within this tight control, the risk of MCC PSD to impact drug-layered bead assay is low.
MCC beads friability	Low	MCC beads have low friability (< 0.1%). As such, the risk of friability to impact drug-layered bead assay is low.
PVP K30 K-value	Low	PVP K-30 is supplied with a K-value in the range of 29-32. This variability should not impact drug-layered bead assay.
Drug layering solution viscosity	Low	The drug layering solution viscosity is low (< 5 mPa•s) and can be effectively atomized.
Equipment Variables		
Equipment	Low	Glatt GPCG-5 selected based on availability.
Wurster insert diameter	Low	7″ Wurster HS insert is selected based on its capacity, 8.3 L, and the planned batch size.
Partition column diameter	Low	Fixed by equipment design: 89 mm in diameter.
Air distribution plate	Low	The air distribution plate can impact the fluidization pattern of beads passing through the partition column. C plate is selected based on the size of the beads and previous experience.

Unit Operation: Drug Layering		
Output Material CQA: Assay of the drug-layered beads		
Variables	**Risk Assessment**	**Justification and Initial Strategy**
Partition height (gap)	Medium	Partition gap can impact the circulation rate of beads passing through the coating zone. When the gap is more than optimal, insufficient differential pressure to draw beads into and up the partition column can be generated. Spraying cannot commence. When the gap is less than optimal, the circulation rate of beads increases, but the mass flow of beads is limited. Beads will be lost to the filter or the bed will collapse. This can be observed and remedied before spraying commences. Thus, the risk of impact on drug-layered bead assay is medium. The initial gap is set to 25 mm based on bed fill level and previous experience and may need adjustment for proper fluidization.
Nozzle tip diameter	Medium	Improper selection of nozzle tip size may impact atomization and spray rate capability and, ultimately, drug-layered bead assay. Based on the planned spray rate, a nozzle with a 1.0 mm orifice diameter is selected.
Nozzle tip/air cap position	Low	If the nozzle tip and air cap are kept flush, the impact on atomization is minimized. The risk of impact on drug-layered bead assay is low.
No. of nozzles	Low	Fixed by equipment design: one nozzle.
Filter type	Medium	A filter bag is used to prevent loss of material and to allow air to pass through. If the porosity is higher than optimal, the loss of material will be high. If the porosity is lower than optimal, the filter will clog and processing will be interrupted. The risk of impact on drug-layered bead assay is medium. A filter porosity of 10 µm is selected based on previous experience and differential pressure will be monitored.
Solution Preparation Variables		
Drug substance concentration	Low	The drug substance concentration of the layering solution is just below the solubility limit of the drug substance and is chosen to maintain a solution. The viscosity of the drug layering solution is low (< 5 mPa•s) and can be effectively atomized so the risk of impact on drug-layered bead assay is low.
Solution viscosity	Low	High viscosity may impact the droplet size of the atomized solution. The viscosity is low (< 5 mPa•s) and can be effectively atomized.
Delivery pump	Low	A peristaltic pump is selected to transfer the drug-layering solution to the column based upon availability and reliability to deliver consistent flow. The risk of impact on drug-layered bead assay is low.
Holding time	Low	The microbial limit of the drug layering solution needs to be controlled for patient safety; however, the risk of holding time to impact assay is low. Drug solution is used within 36 hours based on microbial test results.
Preheating Variables		
Inlet air dew point	Medium	Dew point needs to be controlled to minimize the static charge on the beads which may cause agglomeration. A dew point of 5-15 ºC is selected based on previous experience.
Shaking interval/duration	Low	Shaking prevents beads from being trapped in the filter bag. The risk of shaking to impact assay is low during preheating. Initial setting is 60 sec/5sec based on previous experience.

Unit Operation: Drug Layering		
Output Material CQA: Assay of the drug-layered beads		
Variables	**Risk Assessment**	**Justification and Initial Strategy**
Inlet air temperature	Medium	Higher than optimal temperature may lead to excessive static charge and processing difficulties. Equipment warm up: 50-60 ºC.
Product temperature	Medium	Higher than optimal temperature may lead to excessive static charge and processing difficulties. Equipment warm up: 40-50 ºC.
Air volume	Medium	Higher than optimal air volume may trap MCC beads in the filter bag. If these beads are shaken loose once spraying starts, it may result in variable drug-layered bead assay. Lower than optimal air volume may cause suboptimal bead fluidization and uneven heating. Drug-layered bead assay may be affected. The air volume range of 70 – 110 cfm was selected based on visual observation and previous experience.
Atomization air pressure	Low	Set at the minimum to prevent nozzle clog: 0.5 bar.
Preheat time	Low	Assay may be affected if the target bead temperature is not reached or if the bead population temperature is not uniform. Heat until target product temperature is reached.
Spraying Variables		
Inlet air dew point	Medium	Dew point affects droplet evaporation. If it is not controlled, the drying may be variable and assay may be impacted. A set point of 5-15 ºC is selected based on previous experience.
Shaking interval/duration	Low	Shaking prevents beads from being trapped in the filter bag. An appropriate interval is necessary to avoid high differential pressure and processing interruptions. Initial setting is 60 sec/5sec based on previous experience.
Inlet air temperature	Medium	Inlet temperature will be adjusted to reach the desired product temperature. If it is set higher than optimal, spray drying may occur and if it is set lower than optimal, agglomeration may occur. The range of 50-70 ºC is selected based on trial batches in a Glatt GPCG-1.
Product temperature	High	Product temperature is a function of inlet air temperature, air volume, and spray rate. If product temperature is higher than optimal, spray drying may occur resulting in a large amount of fines. If product temperature is lower than optimal, agglomeration may occur. Investigate with DOE to optimize and reduce risk.
Air volume	High	If air volume is higher than optimal, spray drying may occur. Product may also be blown into the filter. If air volume is lower than optimal, suboptimal fluidization may result and agglomeration may occur. Investigate with DOE to optimize and reduce risk.
Spray rate per nozzle	High	If spray rate is higher than optimal, agglomeration may occur. If spray rate is lower than optimal, spraying time may be long and spray drying may occur. Investigate with DOE to optimize and reduce risk.

Unit Operation: Drug Layering		
Output Material CQA: Assay of the drug-layered beads		
Variables	**Risk Assessment**	**Justification and Initial Strategy**
Atomization air pressure	High	If atomization air pressure is higher than optimal, attrition of the beads may occur. If atomization air pressure is lower than optimal, agglomeration may occur. Investigate with DOE to optimize and reduce risk.
Drying Variables		
Inlet air dew point	Medium	Dew point needs to be controlled to achieve consistent drying. A dew point of 5-15 ºC is selected based on previous experience.
Inlet air temperature	Medium	A lower than optimal temperature will increase the drying time. A higher than optimal temperature may speed up surface drying but will increase the product temperature before diffusion-limited water has evaporated, resulting in a false endpoint determination. Range of 50-60 ºC was selected based on desired product temperature.
Inlet air volume	Medium	A lower than optimal air volume will not maintain adequate fluidization to facilitate drying. A higher than optimal air volume may cause attrition of the drug layer which may impact assay. The air volume range of 70 – 110 cfm was selected based on visual observation and previous experience.
Exhaust temperature	Low	Exhaust temperature cannot be controlled directly but is an indicator of the drying endpoint and will be monitored.
Atomization air pressure	Low	Minimum setting to prevent nozzle clog: 0.5 bar.
Drying time	Medium	Water content is controlled to prevent microbial growth. However, unnecessary over-drying may cause attrition of the drug layer and statically charge the beads The LOD target is 2% based on previous experience.

Drug Layering Process Feasibility Study

A feasibility study was performed to test the initial parameters selected based on scientific literature and previous experience and to set the scope for future studies. The optimized formulation for the drug-layered beads shown in Table 25 was used for this study. Drug substance and binder were dissolved in purified water. The solids content of the drug layering solution is 12.4% as calculated in Table 55. During the process feasibility study, the dew point was initially set at 5 ± 2 ºC. At this temperature, the beads became statically charged; thus, the dew point was increased to 10 ± 2 ºC. The spray rate was initially 15 g/min and was incrementally ramped up during the course of the feasibility batch. At 50 g/min, agglomeration was observed, suggesting that the spray rate should not exceed the upper limit of 50 g/min. All the process parameters used in the feasibility study are summarized in Table 56.

Table 55. Composition of the drug layering solution

Components	Function	Concentration	Solids Content	Comments
		(mg/g of solution)	(% w/w)	
Z	Drug substance	105.2	10.5	
Povidone (PVP), K30	Binder	18.6	1.9	
Purified Water	Solvent	876.3		removed during drying process
Total		~1000	12.4	

Table 56. Equipment and process parameters for the lab scale layering feasibility batch

Drug Layering	Lab Scale
Equipment model	Glatt GPCG-5
Batch size	4 kg
Fluid bed insert	7″ Wurster
Partition height	25 mm
Distribution plate	C plate
Nozzle tip diameter	1.0 mm
Dew point	10 ± 2 ºC
Inlet temperature	50 – 60 ºC
Product temperature	45ºC
Spray rate	15 – 50 g/min
Atomization air pressure	1.5 bar
Air volume	~100 cfm

In order to optimize the drug layering process, gain insight on how process variables interact and identify potential boundary limits for acceptable operating ranges at full scale operation, a DOE was performed. All parameters were targeted at steady state.

Drug Layering Optimization Studies at Lab Scale (4 kg)

The rate of aqueous vehicle evaporation plays a critical role during the drug layering process. An overly wet environment can lead to bead agglomeration whereas an overly dry environment can impact adherence of the drug to the MCC beads and lead to spray drying (fine particles). Input variables such as air volume, spray rate, atomization pressure[9] and product temperature (as well as equipment design and scale) contribute interactively to the equilibrium between deposition on MCC beads and coating solution evaporation. These potential high risk process variables identified from initial risk assessment were investigated. All other process parameters were set the same as in the feasibility study (Table 56).

All of the formulation development for drug-layered beads was performed in a Glatt GPCG-1 using a 1 kg batch size. However, the drug layering process development batches were 4 kg in size and were manufactured using a Glatt GPCG-5 equipped with a 7″ Wurster HS insert because this equipment is more predictive of the pilot batch equipment. A 2^{4-1} fractional factorial DOE study

[9] Atomization air pressure is generally recognized as an easily adjustable variable for a given application depending on a company's level of prior experience using a Wurster column coating process. However, this variable may pose a serious impact on the coating process and, therefore, on product performance. Atomization air pressure in this example is studied with the assumption that prior knowledge about such a coating process either does not exist or is very minimal or not applicable.

with three center points was performed. Table 57 summarizes the study design and acceptance criteria for the responses. Upon completion of spraying the drug solution, the product was dried until the bed temperature reached 55 °C. Moisture content of the drug-layered beads was controlled to be less than 2.0% for each batch (actual LOD ranging from 0.5 – 1.2%). The responses studied were fine particles (< 250 µm), agglomerates (> 420 µm), and assay of drug-layered beads. Other physical properties of the drug-layered beads that were evaluated (data not shown) include bead surface roughness, film thickness (by SEM) and bead size distribution (by sieve analysis). Table 58 presents the experimental results.

Table 57. Design of the 2^{4-1} drug layering optimization study

Defining Relation	**I = ABCD**		
Resolution	**IV**		
Factors: Process Parameters		**Levels**	
		-1	**+1**
A	Air volume (cfm)	80	120
B	Spray rate (g/min)	25	45
C	Atomization pressure (bar)	1.2	2.0
D	Product temperature (°C)	42	50
Responses		**Target Ranges**	
Y_1	Fines < 250 µm (%)	≤ 5	
Y_2	Agglomerates > 420 µm (%)	≤ 5	
Y_3	Assay (HPLC method) (% w/w)	95.0	105.0

Table 58. Results of the drug layering optimization study (Glatt GPCG-5, 4 kg batch size)

Std. Code	**Batch No.**	**Factors: Process Parameters**				**Responses**		
		A: Air volume	**B: Spray rate**	**C: Atomization pressure**	**D: Product temperature***	**Y_1: Fines < 250 µm**	**Y_2: Agglomerates > 420 µm**	**Y_3: HPLC Assay**
		(cfm)	**(g/min)**	**(bar)**	**(°C)**	**(%)**	**(%)**	**(% w/w)**
1	22	80	25	1.2	42	0.4	8.0	99.7
2	18	120	25	1.2	50	6.3	0.5	94.5
3	19	80	45	1.2	50	2.8	3.9	97.9
4	15	120	45	1.2	42	0.8	6.4	99.4
5	17	80	25	2.0	50	3.5	1.9	97.5
6	16	120	25	2.0	42	0.9	3.4	99.4
7	21	80	45	2.0	42	0.5	11.0	99.6
8	13	120	45	2.0	50	5.5	0.8	96.0
9	12	100	35	1.6	46	2.2	4.1	98.4
10	20	100	35	1.6	46	1.8	3.8	98.7
11	14	100	35	1.6	46	2.5	4.4	98.2

*Inlet temperature was adjusted during the process to maintain the desired product temperature.

Note to Reader: For all drug layering process DOE studies in this example, the process parameter settings were targeted at steady state. During the drug layering process, the spray rate was ramped up from the low to the steady state value in the first two hours and the air volume was adjusted accordingly to maintain the desired product temperature and optimum fluidization pattern.

Significant factors for fines (< 250µm) generated during the drug layering step

As shown in the following half-normal plot (Figure 30), the significant factors affecting fines (< 250 µm) of drug-layered beads were D (product temperature) and A (air volume). These two process variables also showed strong interaction (AD). The remaining four model terms had no significant impact on fines (< 250 µm) based on Shapiro-Wilk hypothesis test results. As shown in the contour plot (Figure 31), % fines (< 250 µm) of the drug-layered beads increased with increasing product temperature and air volume. Air volume showed a more pronounced impact on % fines when coating at high product temperature.

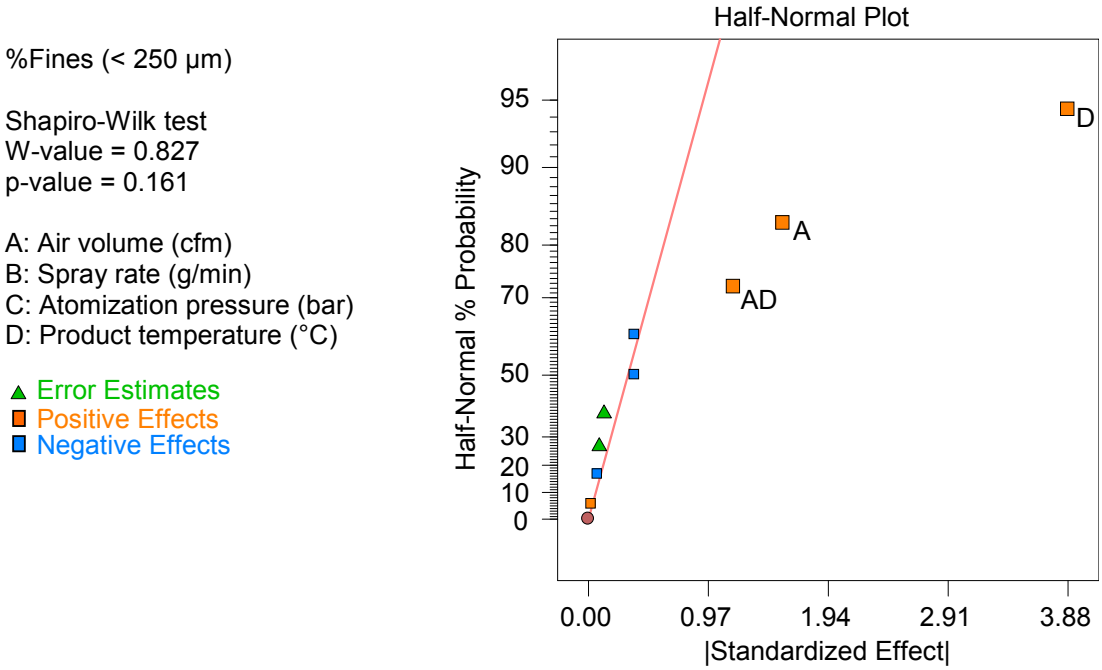

Figure 30. Half-normal plot of the process parameter effects on fines (< 250 µm) generated during the drug layering step

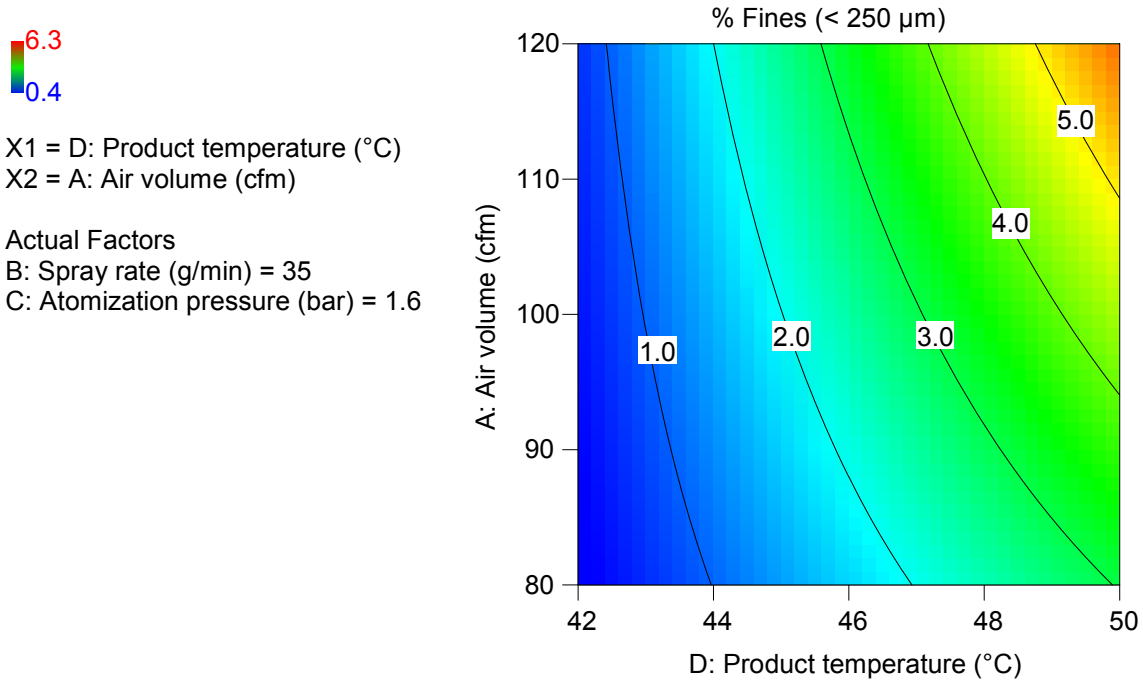

Figure 31. Effect of product temperature and air volume on fines (< 250 µm) generated during the drug layering step

Significant factors for agglomerates (> 420 µm) generated during the drug layering step

As shown in the following half-normal plot (Figure 32), the significant factors affecting agglomerates (> 420 µm) of drug-layered beads were D (product temperature), A (air volume), and B (spray rate). The remaining four model terms had no significant impact on agglomerates (> 420 µm) based on Shapiro-Wilk hypothesis test results. The effect of product temperature and air volume on agglomerates (> 420 µm) of drug-layered beads is presented in Figure 33. The percent of agglomerates decreased with increasing product temperature and air volume.

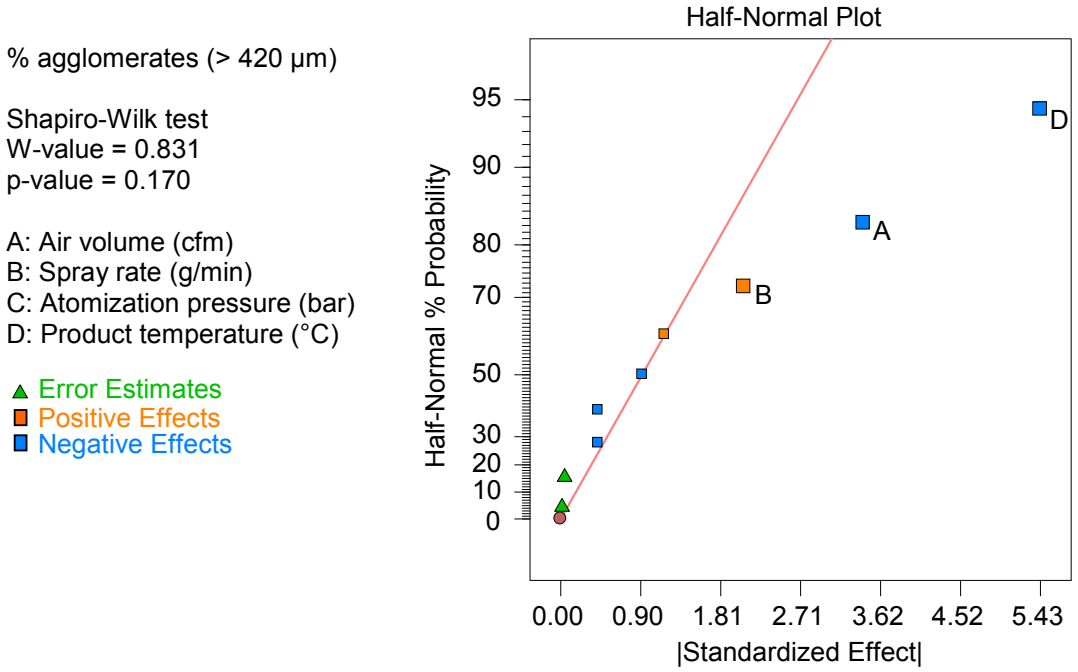

Figure 32. Half-normal plot of the process parameter effects on agglomerates (> 420 µm) generated during the drug layering step

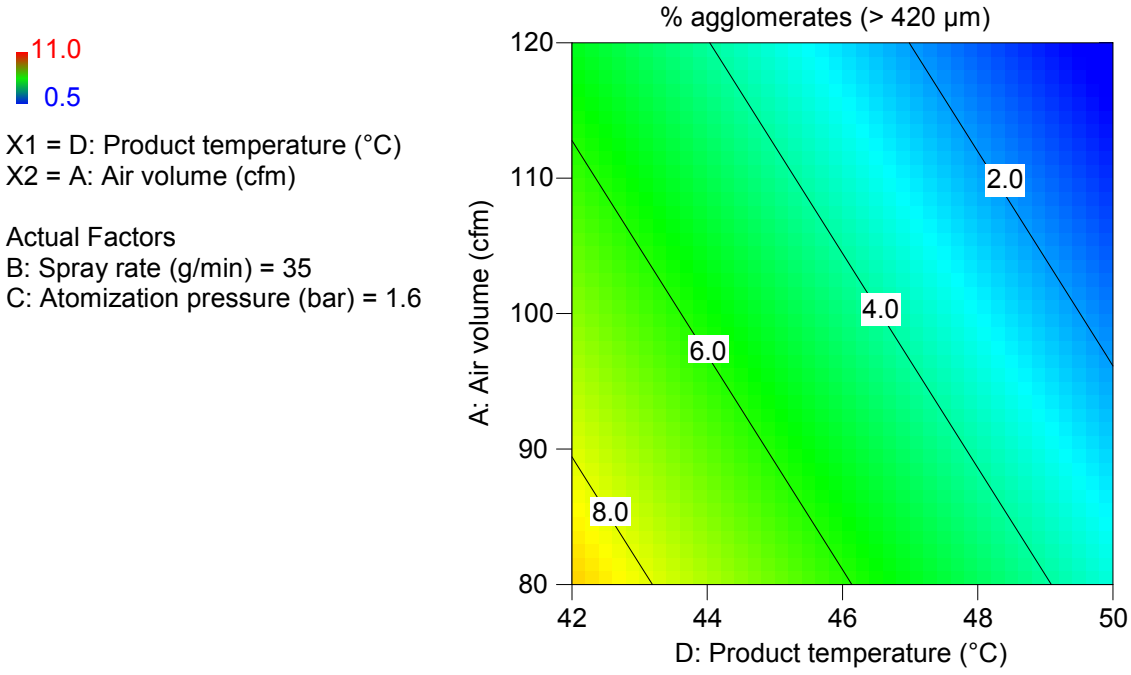

Figure 33. Effect of product temperature and air volume on agglomerates (> 420 µm) generated during the drug layering step

Significant factors for assay of the drug-layered beads

As shown in the following half-normal plot (Figure 34), the significant factors affecting the assay of drug-layered beads were D (product temperature) and A (air volume). These two process variables showed a significant interaction (AD). The remaining four model terms had no significant impact on assay based on Shapiro-Wilk hypothesis test results. The effect of product temperature and air volume on assay is presented in Figure 35. Assay decreased with increasing product temperature and air volume.

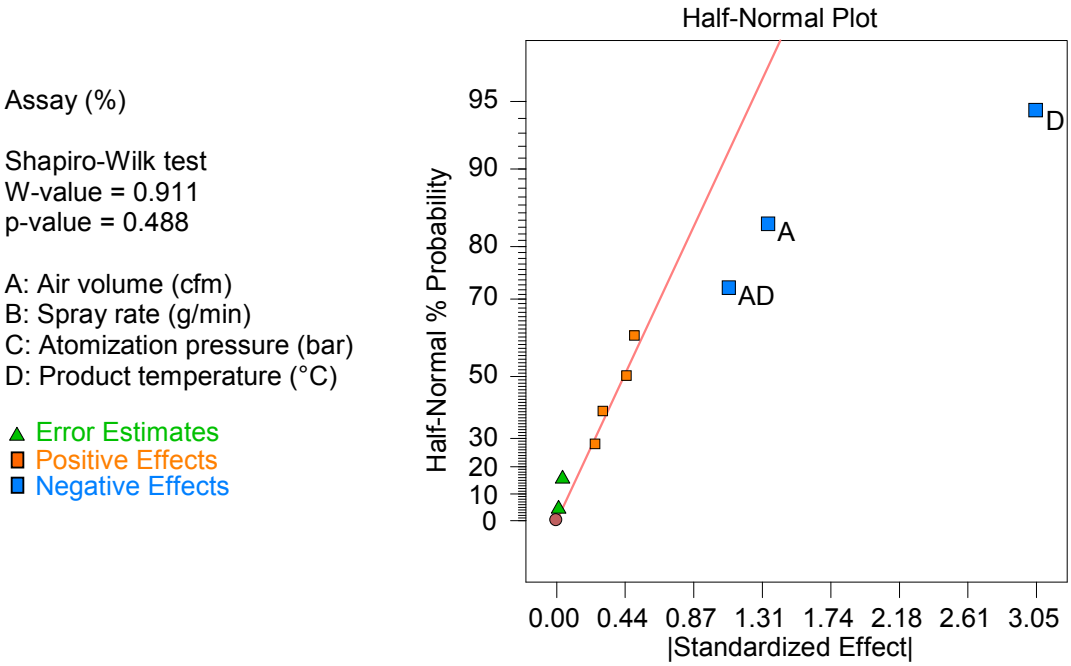

Figure 34. Half-normal plot of the process parameter effects on assay of drug-layered beads

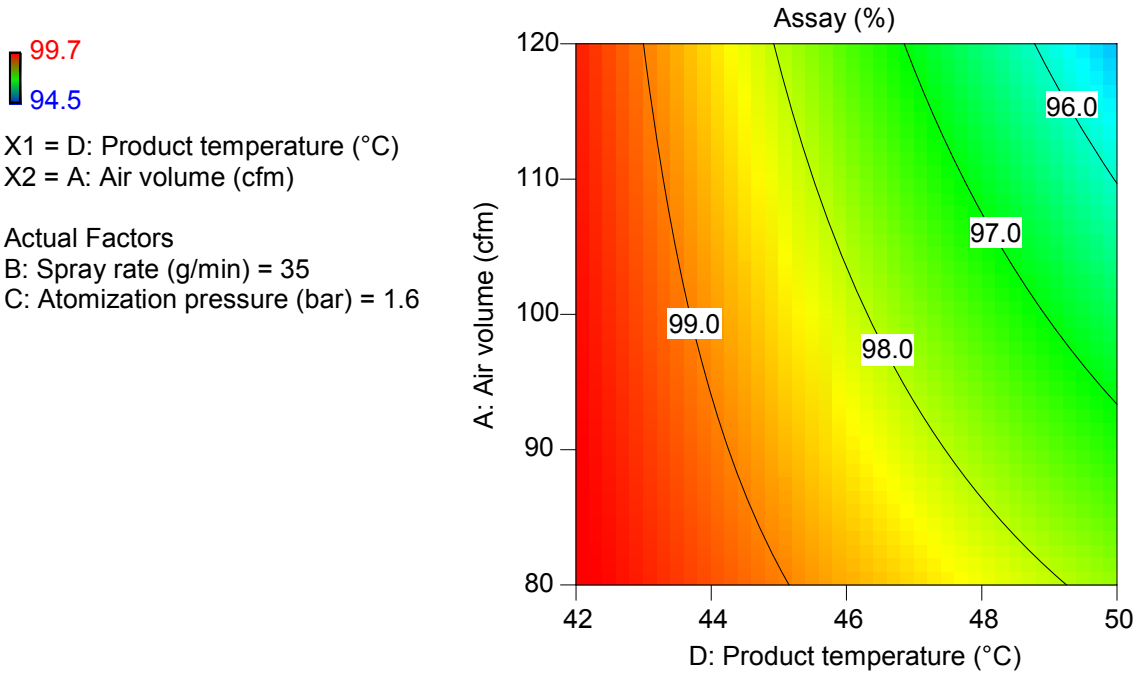

Figure 35. Effect of product temperature and air volume on assay of drug-layered beads

This process optimization study showed that at the 4 kg scale:

- Product temperature, air volume and spray rate were identified as CPPs for drug layering. Change of atomization air pressure within the study range (1.2 – 2.0 bar) had no significant impact on the three responses studied.
- Higher product temperature and higher air volume generally resulted in higher levels of fines. These two process variables also showed a significant interaction.
- Conversely, there was slightly greater agglomeration at lower product temperature and air volume. Spray rate also impacted agglomeration, but to a lesser extent within the study range (25 – 45 g/min).
- Higher product temperature and higher air volume generally resulted in lower assay of drug-layered beads.

To achieve the target assay level and to avoid excessive fines and particle agglomeration, the ranges for these three CPPs were proposed as shown in Table 59. Atomization pressure was found not critical within the range studied at this scale. Therefore, the studied range of 1.6 ± 0.4 bar was recommended for this scale. These critical factors will be further confirmed during scale-up.

Table 59. Optimum CPPs for Glatt GPCG-5 with a 7″ Wurster HS insert

Process Parameters	Ranges	Rationale
Product temperature	45 ± 3°C	Lower than optimum led to agglomeration. Higher than optimum increased the amount of fines. Scale independent.
Air volume	100 ± 20 cfm	Range set based on studies at the laboratory scale. Scale dependent.
Spray rate	35 ± 10 g/min	Ranges studied produced uniform distribution of drug substance on the MCC core without issues of product agglomeration. Scale dependent.

Drug Layering Process Robustness Study at Pilot Scale (40 kg)

A Glatt GPCG-60 with an 18″ Wurster HS insert (partition column diameter of 219 mm) was selected for the pilot scale batch because the chamber design and the distribution plate are geometrically similar to the intended commercial scale equipment (Glatt GPCG-120 with a 32″ Wurster HS insert). A comparison between lab scale and pilot scale equipment for the drug layering process is presented in Table 60.

Table 60. Comparison between lab scale and pilot scale equipment for the drug layering process

Drug Layering	Lab Scale	Pilot Scale
Equipment model	Glatt GPCG-5	Glatt GPCG-60
Fluid bed insert	7″ Wurster	18″ Wurster
Equipment capacity*	8.3 L	102 L
Partition column diameter	89 mm	219 mm
Starting batch size	4 kg	40 kg
Theoretical ending batch size (~41% weight gain based on substrate weight)	5.6 kg	56 kg
Estimated use of capacity**	79%	65%
Number of partition(s)	1	1
Partition height (gap)	25 mm	45 ± 3 mm
Nozzle diameter	1.0 mm	1.2 mm

*Volume outside of the partition column at rest on the orifice plate

**Calculated based on the bulk density of the ER coated beads = 0.85 g/cc

Linear scale-up from lab scale to pilot scale assumes that the bed fill levels are the same and the distribution plate in each piece of equipment is geometrically similar. Additionally, the ratios of air volume to plate area and of spray rate to air volume should be maintained. The scale-up factor from a 7″ Wurster to an 18″ Wurster is approximately 6-fold.

Even though atomization pressure in the studied range (1.6 ± 0.4 bar) was not critical at lab scale, it will be further evaluated at pilot scale due to the significant increase in spray rate and change in nozzle diameter. During scale-up, it is essential to keep the droplet size unchanged. However, since we don't have the capability to measure droplets less than 30 μm, atomization air pressure will be included as a factor in the pilot scale process understanding study. Based on the manufacturer's recommendation, the atomization pressure should range from 2.0 – 3.0 bar at pilot scale based on the intended increase in spray rate and nozzle diameter.

Product temperature is a critical process parameter. However, it is a scale independent parameter. Therefore, it was maintained in the recommend range (45 ± 3°C) during scale-up and was not

purposely varied for further investigation. The risk of extended processing at this temperature to drug product stability is low based on the results of the drug substance forced degradation studies.

A 2^{3-1} factorial DOE study with one center point was performed on the pilot batch scale (40 kg) to confirm process knowledge gained from the lab scale (4 kg). The study design and acceptance criteria for the responses are presented in Table 61 and experimental results are reported in Table 62.

Table 61. Design of the 2^{3-1} drug layering confirmation study

Defining Relation	I = ABC		
Resolution	III		
Factors: Process Parameters		**Levels**	
		-1	**+1**
A	Air volume (cfm)	510	690
B	Spray rate (g/min)	180	240
C	Atomization pressure (bar)	2.0	3.0
Responses		**Target Ranges**	
Y_1	Fines < 250 µm (%)	≤ 5	
Y_2	Agglomerates > 420 µm (%)	≤ 5	
Y_3	Assay (HPLC method) (% w/w)	95.0	105.0
Y_4	LOD (%)	≤ 2	
Y_5	Process Efficiency (%)	≥ 90	

Table 62. Results of the drug layering process confirmation study (Glatt GPCG-60, 40 kg batch size)

Std. Code	**Batch No.**	**Factors: Process Parameters**			**Responses**				
		A: Air volume	**B: Spray rate**	**C: Atomization pressure**	**Y_1: Fines (< 250 µm)**	**Y_2: Agglomerates (> 420 µm)**	**Y_3: Assay HPLC**	**Y_4: LOD**	**Y_5: Process Efficiency[10]**
		(cfm)	**(g/min)**	**(bar)**	**(%)**	**(%)**	**(% w/w)**	**(%)**	**(%)**
1	26	510	180	3.0	2.4	1.5	98.1	0.6	98
2	25	690	180	2.0	2.0	2.2	98.4	0.5	96
3	24	510	240	2.0	2.5	2.9	98.2	0.6	94
4	27	690	240	3.0	1.8	1.8	98.9	0.5	96
5	23	600	210	2.5	2.4	1.6	99.5	0.5	95

The data in Table 62 indicate that the various processing conditions employed for drug layering provided satisfactory drug-layered beads at the 40 kg scale. DOE statistical analysis also demonstrated that the impact of all factors (in the range studied) on the responses was not significant ($\alpha = 0.05$) since all the factor effects lie on the pure error line. See the half-normal plot of the process parameter effects on agglomerates (d_{50} > 420 µm) in Figure 36 as a representative example. Similar plots were obtained for all other responses studied (figures not shown). The study confirmed that when the CPPs are set within the optimized range, drug-layered beads that meet the

[10] Process Efficiency was defined as the ratio of the actual final weight of coated beads (W_f) to the theoretical final weight of coated beads (W_t) expressed as a percentage. Weight was corrected for moisture content.

$$Process\ Efficiency\ (\%) = \frac{W_f}{W_t} \times 100$$

predefined targets are produced. Based on the results of the confirmation study, a 40 kg scale design space for the drug layering unit operation was defined as shown in Table 63. The drug-layered beads were sieved to remove the agglomerates (> 420 µm) and fines (< 250 µm). Only the beads between 250 µm and 420 µm were used for subsequent processing.

Note to Reader: The design space for the drug layering unit operation is for the 40 kg scale only and the use of linear scale-up principles needs to be further verified at commercial scale (180 kg).

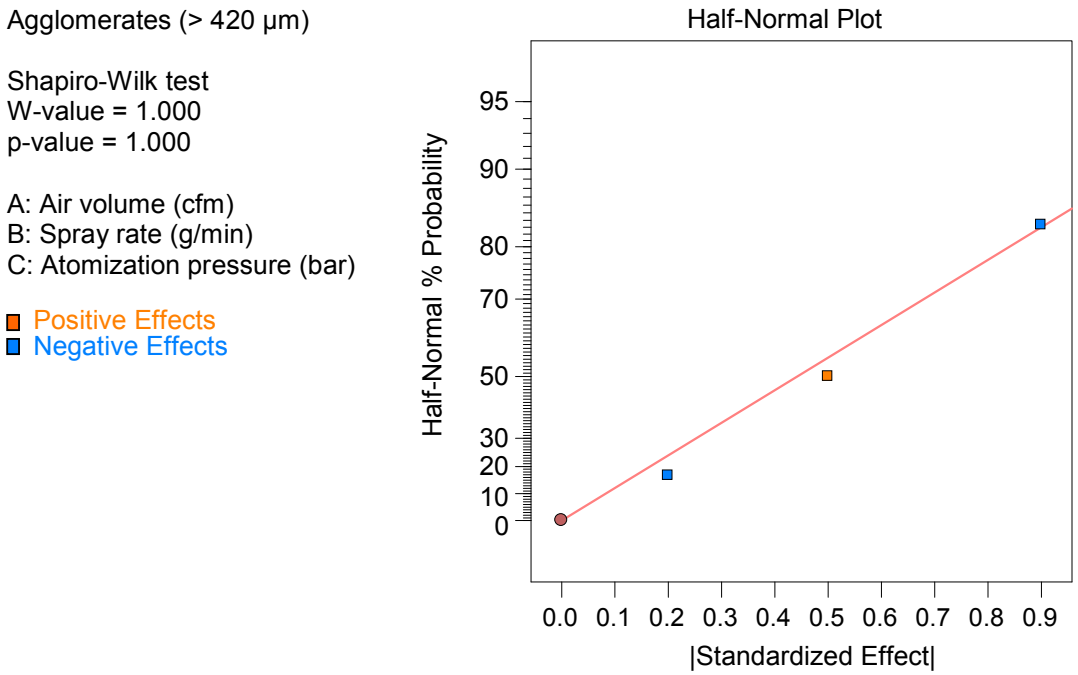

Figure 36. Half-normal plot of the process parameter effects on agglomerates (> 420µm) generated during the drug layering step

Table 63. Design space at 40 kg scale for the drug layering unit operation (Glatt GPCG-60 with an 18″ Wurster HS insert)

Process Parameters	Ranges
Product temperature	45 ± 3 °C
Atomization pressure	2.5 ± 0.5 bar
Air volume	600 ± 90 cfm
Spray rate	210 ± 30 g/min

Updated Risk Assessment of the Drug Layering Process Variables

Table 64 presents the risk reduction for the drug layering process as a result of the development work. Only the spraying process variables that were initially identified as high risk to the assay of drug-layered beads are shown.

Table 64. Updated risk assessment of the drug layering process variables

Unit Operation: Drug Layering		
Output Material CQA: Assay of the drug-layered beads		
Spraying Variables	**Risk Assessment**	**Justification for the Reduced Risks**
Product temperature	Low	An acceptable product temperature range was identified. In the studied range, drug-layered beads with consistent quality were produced at the 40 kg scale. Spray drying and agglomeration were minimized. Product temperature is a scale-independent parameter and will be applied to other scales. The risk of product temperature to impact the assay of the drug-layered beads is reduced from high to low.
Air volume	Low	Air volume range was identified and an optimal fluidization pattern was achieved. In the studied range, drug-layered beads with consistent quality were produced at the 40 kg scale. Air volume is a scale-dependent parameter. However, processing equipment change from an 18″ to a 32″ Wurster is a scale-out process instead of a scale-up process. For commercial scale, air volume will be increased 3-fold. The risk of air volume to impact drug-layered bead assay is reduced from high to low.
Spray rate	Low	Spray rate range was identified. In the studied range, drug-layered beads with consistent quality were produced at the 40 kg scale. Spray rate is a scale-dependent parameter. However, a processing equipment change from an 18″ to a 32″ Wurster is a scale-out process and each of the three nozzles used in the 32″ Wurster are identical to the one used in the 18″ Wurster. The spray rate per nozzle will be kept the same. The total spray rate will be increased 3-fold. The risk of spray rate to impact drug-layered bead assay is reduced from high to low.
Atomization air pressure	Low	Atomization air pressure was identified. In the studied range, drug-layered beads with consistent quality were produced at the 40 kg scale. Attrition was minimized. Atomization air pressure is an equipment-dependent parameter. As this is a scale-out process and each of the three nozzles used in the 32″ Wurster are identical to the one used in the 18″ Wurster, the atomization air pressure for each nozzle will be kept the same. The risk of atomization air pressure to impact drug-layered bead assay is reduced from high to low.

2.3.3.2 ER Polymer Coating Process Development

Based on the choice of a multi-particulate delivery system and an aqueous ER layer coating, bottom spray fluid bed coating and drying was selected as an appropriate manufacturing process. Input variables such as air volume, spray rate, atomization pressure and product temperature (as well as equipment design and scale) contribute interactively to the film quality and film thickness. A laboratory scale process (1 kg) was implemented in formulation development while a larger scale (4 kg) was implemented in process development. On the basis of prior experience and availability of equipment, all process development studies were conducted in a Glatt GPCG-5 with a 7″ Wurster HS insert (89 mm diameter partition) which was more predictive of the pilot batch equipment.

Initial Risk Assessment of the ER Polymer Coating Process Variables

The initial risk assessment of the overall manufacturing process presented in Table 51 identified the risk of the ER polymer coating step to impact drug release from the drug product as high. Subsequently, drug release from the ER coated beads was identified as a CQA for the ER polymer coating step. Process variables that could potentially impact drug release from the ER coated beads were identified and their associated risk was evaluated. Conducting DOEs to evaluate all the

variables involved in a Wurster coating process is not feasible. Therefore, variables ranked as low to medium risk during the assessment were set constant based on feasibility studies and previous experience. The variables ranked as high risk were evaluated by conducting DOE studies to gain process understanding. Table 65 summarizes the initial risk assessment of the ER polymer coating step.

Table 65. Initial risk assessment of the ER polymer coating process variables

Unit Operation: ER polymer coating			
Output Material CQA: Drug release from the ER coated beads			
Variables		**Risk Assessment**	**Justification and Initial Strategy**
Input Material Attributes			
Drug-layered beads assay		Low	Assay of drug-layered beads within 95-105% was achieved during the layering step. The risk of drug-layered bead assay to impact the drug release from ER coated beads is low.
Drug substance solid state form in the drug layer		Low	Drug substance Z was shown to remain amorphous on drug-layered beads stored up to 6 months at 40 °C/75% RH. The risk of form conversion resulting in altered drug release from the ER coated beads is low.
Drug-layered beads size distribution		Low	The drug-layered beads are sieved and only the fraction between 250-420 µm is used for the ER polymer coating step. The risk of this tight size distribution to impact the uniformity of the coating applied by a Wurster process and the resultant drug release profile of the ER coated beads is low.
Drug-layered beads LOD		Low	If the LOD of the drug-layered beads higher than optimal, it may impact film formation and drying of the ER coated beads. The LOD of the drug-layered beads is controlled to < 2% so the risk of drug-layered bead LOD to impact drug release from the ER coated beads is low.
Drug-layered beads release profile		Low	Rapid drug release from the drug-layered beads was achieved during formulation development. The risk of drug release from the layered beads to impact release from the ER coated beads is low.
Kollicoat SR 30 D	**Acetic Acid content**	Low	Kollicoat SR 30 D supplied with an acetic acid content of NMT 1.5% was shown to have no impact on drug release from the ER coated beads. Therefore, the risk is low.
	PVAc content	Low	A PVAc content of 25-29 g/100g was shown to have no impact on drug release. The risk is low.
	PVP content	Low	Based on the variability of the raw material observed during formulation development, an in-house specification was established to control the PVP content between 2.5-2.9% (target 2.7%) which is tighter than the vendor's specification of NMT 4%. Within this established range, PVP content variability did not have any impact on drug release from the ER coated beads. The risk is low.
	Apparent viscosity	Low	The apparent viscosity range of 50-90 mPa•s was shown to have no impact on drug release from the ER coated beads. The risk is low.
Talc PSD		Low	Used material within in-house spec (d_{50}: 2-8 µm NLT 99% passing 325 mesh (44 µm)) to reduce the risk of clogging the nozzle or tubing. The risk of talc PSD to impact drug release from the ER coated beads is low.
Equipment Variables			
Equipment		Low	Glatt GPCG-5 selected based on equipment availability.
Wurster insert diameter		Low	7″ Wurster HS insert is selected based on its capacity, 8.3 L, and the planned batch size.
Partition column diameter		Low	Fixed by equipment design: 89 mm in diameter.

Unit Operation: ER polymer coating		
Output Material CQA: Drug release from the ER coated beads		
Variables	**Risk Assessment**	**Justification and Initial Strategy**
Air distribution plate	Medium	The air distribution plate can impact the fluidization pattern of beads passing through the partition column. C plate is selected based on the size of the beads and previous experience.
Partition height (gap)	Medium	Partition gap can impact the circulation rate of beads passing through the coating zone. When the gap is more than optimal, insufficient differential pressure to draw beads up the partition column can be generated. Spraying cannot commence. When the gap is less than optimal, the circulation rate of beads increases, but the mass flow of beads is limited. Beads will be lost to the filter or the bed will collapse due to over-wetting. This can be observed and remedied before spraying commences. Thus, the risk of partition height (gap) to impact drug release from the ER coated beads is medium. The initial gap is set to 25 mm based on bed fill level and previous experience and may need adjustment for proper fluidization during the coating process.
Nozzle tip diameter	Medium	Improper selection of nozzle tip size may impact atomization and spray rate capability and, ultimately, drug release from the ER coated beads. The risk is medium. Based on potential spray rate, a nozzle with a 1.0 mm orifice diameter is selected for the planned batch size.
Nozzle tip/air cap position	Low	If the nozzle tip and air cap are kept flush, the impact on atomization is minimized. The risk is low.
No. of nozzles	Low	Fixed by equipment design: one nozzle. The risk is low.
Filter type	Medium	A filter bonnet is used to prevent loss of material and to allow air to pass through. If the porosity is higher than optimal, the loss of material will be high. If the porosity is lower than optimal, the filter will clog and processing will be interrupted. The risk of filter type to impact drug release from ER coated beads is medium. A filter porosity of 200 µm is selected based on previous experience.
Coating Dispersion Variables		
Solids content	Medium	The solids content of the coating dispersion was approximately 18%. This level was selected based on formulation design, supplier recommendation and previous experience. If the solids content is higher than optimal, it may not be effectively atomized. If the solids content is lower than optimal, total coating time will be long. The risk of coating dispersion solids content to impact drug release from the ER coated beads is medium.
Viscosity	Low	High viscosity may impact droplet size of the atomized dispersion. The viscosity of the coating dispersion is low (50 – 90 mPa•s) and did not show an impact on drug release from the ER coated beads during formulation development (Section 2.2.1.3). The risk of dispersion viscosity to impact drug release is low.

Unit Operation: ER polymer coating		
Output Material CQA: Drug release from the ER coated beads		
Variables	**Risk Assessment**	**Justification and Initial Strategy**
Sedimentation	Medium	Talc may settle during the coating process and subsequently change the dispersion composition. If the talc concentration is suboptimal, the ER polymer coating may become sticky and cause agglomeration. The risk is medium. The coating dispersion should be stirred continuously during the coating process.
Mixer type/mixing speed	Medium	The mixer is used to prepare the coating dispersion. An improper mixer type or speed selection may impact the coating dispersion shear stability. The risk of impact on drug release is medium. Proper mixer selection is based on previous experience. A shear stability test will be conducted.
Delivery pump	Low	The pump is used to deliver the coating dispersion to the column. The risk of the pump selection to impact drug release from the ER coated beads is low. A peristaltic pump is selected based upon availability and reliability to deliver consistent flow.
Holding time	Low	The microbial limit of the coating dispersion needs to be controlled for patient safety; however, the risk of holding time to impact drug release of the ER coated beads is low. The coating dispersion is used within 36 hours based on microbial test results.
Pre-heating Variables		
Inlet air dew point	Medium	Dew point needs to be controlled to minimize the static charge on the drug-layered beads which may cause agglomeration. The risk of impact on the drug release from ER coated beads is medium. A dew point of 5-15º C is selected based on previous experience.
Shaking interval/duration	Low	Shaking prevents beads from being trapped in the filter bag. The risk of shaking to impact drug release is low during preheating. Initial setting is 60 sec/5sec based on previous experience.
Inlet air temperature	Medium	Higher than optimal temperature may cause excessive static charge and lead to processing difficulties. Equipment warm up: 40-50ºC.
Product temperature	Medium	Higher than optimal temperature may cause excessive static charge and lead to processing difficulties. Equipment warm up: 30-40ºC.
Exhaust temperature	Low	Exhaust temperature is determined by a combination of inlet air temperature, air volume and humidity. It is an indicator of drying and it is monitored. The risk is low.

Unit Operation: ER polymer coating		
Output Material CQA: Drug release from the ER coated beads		
Variables	**Risk Assessment**	**Justification and Initial Strategy**
Air volume	Medium	If the air volume is higher than optimal, attrition to the drug-layered beads may occur. Lower than optimal air volume may cause poor bead fluidization and uneven heating. Drug release from ER beads may be affected. The risk is medium. The air volume range of 80 -120 cfm is selected based on the optimization result of the drug layering process.
Atomization air pressure	Low	Set at the minimum to prevent nozzle clog: 0.5 bar.
Preheat time	Low	Film formation may be affected if the target bead temperature is not reached or if the bead population temperature is not uniform. The risk of preheat time to impact drug release from the ER coated beads is low. Heat until the target product temperature is reached.
Spraying Variables		
Inlet air dew point	Medium	Variation of inlet air humidity may have an impact on droplet evaporation and the quality of the polymer film. The risk of inlet air dew point to impact drug release from ER beads is medium and needs to be evaluated. A set point of 5-15 ºC is selected based on previous experience.
Shaking interval/duration	Low	Shaking prevents beads from trapping the filter bonnet. The risk is low. Based on previous experience, 60 sec/5 sec is selected.
Inlet air temperature	Medium	Inlet temperature will be adjusted to reach the desired product temperature. If it is set higher than optimal, spray drying may occur and if it is set lower than optimal, agglomeration may occur. The product temperature will be monitored and optimized. Therefore, the risk of inlet air temperature to impact drug release from the ER coated beads is medium. The range of 40-60ºC is selected based on trial batches in a Glatt GPCG-1.
Product temperature	High	Product temperature is a function of inlet air temperature, air volume, and spray rate. If product temperature is higher than optimal, spray drying may occur and a large amount of fines may be generated. If product temperature is lower than optimal, agglomeration may occur. The risk of product temperature to impact drug release from the ER coated beads is high. Investigate with DOE to optimize and reduce the risk.
Air volume	High	If air volume is higher than optimal, spray drying may occur. Product may also be blown into the filter. If air volume is lower than optimal, suboptimal fluidization may result and agglomeration may occur. The risk of air volume to impact drug release from the ER coated beads is high. Investigate with DOE to optimize and reduce the risk.

Unit Operation: ER polymer coating		
Output Material CQA: Drug release from the ER coated beads		
Variables	**Risk Assessment**	**Justification and Initial Strategy**
Spray rate/nozzle	High	If spray rate is higher than optimal, agglomeration may occur. If spray rate is lower than optimal, spraying time may be long and spray drying may occur. The risk of spray rate to impact drug release from the ER coated beads is high. Investigate with DOE to optimize and reduce the risk.
Atomization air pressure	High	If atomization air pressure is higher than optimal, attrition to the beads may occur. If atomization air pressure is lower than optimal, agglomeration may occur. The risk of atomization air pressure to impact drug release from the ER coated beads is high. Investigate with DOE to optimize and reduce the risk.
Coating time	Medium	The coating dispersion may settle because the coating time is long. This may impact the homogeneity of the coating dispersion. The risk is medium.
Drying Variables		
Inlet air dew point	Medium	Variation of inlet air humidity may have an impact on drying and the quality of the polymer film. Dew point needs to be controlled to achieve consistent drying. The risk of inlet air dew point to impact drug release from ER coated beads is medium. A dew point of 5-15 ºC is selected based on previous experience.
Inlet air temperature	Medium	A lower than optimal temperature will increase the drying time. A higher than optimal temperature may cause agglomeration of the ER coated beads. The risk is medium. A range of 40-50 ºC is selected based on the desired product temperature.
Air volume	Medium	A lower than optimal air volume will not maintain adequate fluidization to facilitate drying. A higher than optimal air volume may cause attrition. The risk is medium. The air volume range of 80-120 cfm is selected based on the optimized drug layering process.
Atomization air pressure	Low	Set at the minimum to prevent nozzle clog: 0.5 bar.
Drying time	Medium	Water content is controlled to prevent microbial growth. However, unnecessary over-drying may increase the processing time. The risk is medium. The LOD target is 2% based on previous experience.

The following DOE studies were performed to identify and optimize critical process parameters and their ranges:

- A laboratory scale screening DOE study was conducted to assess the effect of process parameters on the drug release and to identify the CPPs.
- A laboratory scale optimization DOE study was conducted to optimize CPP ranges.
- A pilot scale robustness DOE study was conducted to confirm the knowledge gained from lab scale.

In the formulation studies, the theoretical polymer coating level had a significant impact on the drug release profile of the ER coated beads. During the ER polymer coating process, the theoretical polymer coating level was kept the same as formulation F-2 (30%) and the amount to be sprayed into the fluid bed was calculated based on the weight of the beads for each batch. The actual polymer weight gain on the beads will vary based on the process efficiency. Therefore, it is important to optimize the process to obtain high and consistent process efficiency.

Coating Dispersion Evaluation

The coating dispersion was prepared in two stages. Initially, an aqueous dispersion of TEC and Talc was prepared and homogenized using a corundum mill. The final coating material was prepared by slowly adding the TEC and Talc aqueous dispersion to the Kollicoat SR 30 D aqueous dispersion while stirring. A shear stability test was conducted on the coating dispersion by stirring at 2000 rpm for 15 minutes as suggested by the Kollicoat SR 30 D supplier. Afterward, the dispersion was passed through a 125 μm sieve and exhibited minimum coagulation.

The dispersion is continuously stirred during the application of the ER polymer coating to the drug-layered beads. A study was conducted to demonstrate that the viscosity of the coating dispersion retains its homogeneity during the spraying process. The coating material was prepared as previously described and was stirred continuously at 250 rpm for 48 hours. Samples were pulled periodically to evaluate the viscosity. Table 66 summarizes the results.

Table 66. Effect of continuous stirring on viscosity of the ER polymer coating dispersion

Holding time	Viscosity at 25 °C
(h)	(mPa•s)
0	58
3	58
6	55
24	57
48	57

The ER polymer coating dispersion retained its viscosity under continuous shear conditions for 48 hours. Therefore, a hold time of 48 hours will be included in the batch manufacturing records.

ER Polymer Coating Process Feasibility Study

A feasibility study was performed to test the initial process parameters selected based on scientific literature and previous experience and to set the scope of future studies. The optimized ER coated beads formulation (prototype F-2 in Table 48) was used for this study. Table 67 shows the composition of the ER polymer coating dispersion. After preparation, the coating dispersion was

mixed for at least one hour prior to the commencement of spraying. The coating dispersion was continuously stirred during the coating process. The solids content of the coating dispersion was 18%. During the process feasibility study, the dew point was initially set at 5 ± 2 ºC. At this point, the beads became very statically charged; thus, the dew point temperature was increased to 10 ± 2 ºC. The spray rate was initially 5 g/min and was incrementally ramped up during the course of the feasibility batch. At 35 g/min, agglomeration was observed, suggesting that the spray rate should not exceed 35 g/min. All process parameters for the lab scale coating feasibility study are summarized in Table 68.

Table 67. Composition of the ER polymer coating dispersion

Components	Function	Weight	Solids Content	Comments
		(% w/w)	(% w/w)	
Kollicoat SR 30 D	Coating polymer	50.00	15.00	30% solids content based on vendor COA
Triethyl Citrate (TEC)	Plasticizer	0.75	0.75	5% of dry polymer
Talc	Anti-tacking agent	2.25	2.25	15% of dry polymer
Purified Water	Solvent	47.00	--	removed during drying
Total		100.00	18.00	

Table 68. Equipment and process parameters for the lab scale coating feasibility study

ER Polymer Coating	Lab Scale
Equipment model	Glatt GPCG-5
Batch size	4 kg
Fluid bed insert	7″ Wurster
Partition height	25 mm
Distribution plate	C plate
Nozzle diameter	1.0 mm
Dew point	10 ± 2 ºC
Inlet temperature	40 – 50 ºC
Product temperature	30 ºC
Spray rate	5 – 35 g/min
Atomization air pressure	1.5 bar
Air volume	~100 cfm

In order to optimize the ER polymer coating process, gain insight on how process variables interact and identify CPPs and operating ranges, DOE studies were performed.

ER Polymer Coating Process Screening Study

The process parameters and ranges were selected based on the knowledge gained from the drug layering section and the ER polymer coating process feasibility study. A 2^{4-1} fractional factorial design with three center points was performed to screen the effect of process parameters on the drug release profile of ER coated beads ($T_{20\%}$, $T_{50\%}$ and $T_{80\%}$), the amount of fines and agglomerates generated and the process efficiency. Moisture content for ER coated beads was controlled to not more than 2.0%. The ER coated beads were sieved to remove the agglomerates (> 590 µm) and fines (< 350 µm). Only the beads between 350 µm and 590 µm will be used for subsequent processing. Other physical properties of the beads were evaluated (data not shown) including bead

surface roughness, film thickness (by SEM), and friability. Yield was also calculated. Table 69 summarizes the study design and acceptance criteria. Experimental results (Y_1 and Y_4, other responses not shown) are presented in Table 70.

Table 69. Design of the 2^{4-1} ER polymer coating process screening study

Defining Relation	I = ABCD		
Resolution	IV		
Factors: Process Parameters		**Levels**	
		-1	**+1**
A	Air volume (cfm)	70	170
B	Atomization pressure (bar)	1.2	2.0
C	Spray rate (g/min)	10	30
D	Product temperature (°C)	25	39
Responses		**Target Ranges**	
Y_1	$T_{20\%}$ (h)	2.5	2.9
Y_2	$T_{50\%}$ (h)	4.5	6.5
Y_3	$T_{80\%}$ (h)	8	12
Y_4	Process Efficiency (%)	≥ 90.0	
Y_5	Fines < 350 µm (%)	≤ 5	
Y_6	Agglomerates > 590 µm (%)	≤ 5	

Table 70. Results of the ER polymer coating process screening study

Std. Code	**Batch No.**	**Factors: Process Parameters**				**Responses**	
		A: Air volume	**B: Atomization pressure**	**C: Spray rate**	**D: Product temperature***	**Y_1: $T_{20\%}$**	**Y_4: Process Efficiency**
		(cfm)	**(bar)**	**(g/min)**	**(°C)**	**(h)**	**(%)**
1	30	70	1.2	10	25	2.8	90
2	31	170	1.2	10	39	2.0	86
3	38	70	2.0	10	39	2.2	87
4	36	170	2.0	10	25	2.7	90
5	34	70	1.2	30	39	2.7	82
6	29	170	1.2	30	25	3.0	85
7	35	70	2.0	30	25	3.1	85
8	28	170	2.0	30	39	2.4	82
9	32	120	1.6	20	32	2.6	92
10	33	120	1.6	20	32	2.7	93
11	37	120	1.6	20	32	2.8	91

*The inlet temperature was adjusted during the process to maintain the desired product temperature.

Note to Reader: For all coating process DOE studies in this example, the process parameter settings were targeted at steady state. During the coating process, the spray rate was ramped up from low to the steady state value in the first two hours and air volume was adjusted accordingly to maintain the desired product temperature and optimum fluidization pattern.

Significant factors for $T_{20\%}$ of the ER coated beads

As shown in the following half-normal plot (Figure 37), the most significant factors affecting $T_{20\%}$ of ER coated beads were D (product temperature), followed by C (spray rate), and A (air volume). The remaining three model terms ranked had no significant impact on $T_{20\%}$ based on Shapiro-Wilk hypothesis test results. The effect of product temperature and spray rate on $T_{20\%}$ of ER coated beads is presented in Figure 38. $T_{20\%}$ decreased with increasing product temperature and decreasing spray rate. Air volume showed a negative effect on $T_{20\%}$ but to a lesser extent than product temperature and spray rate.

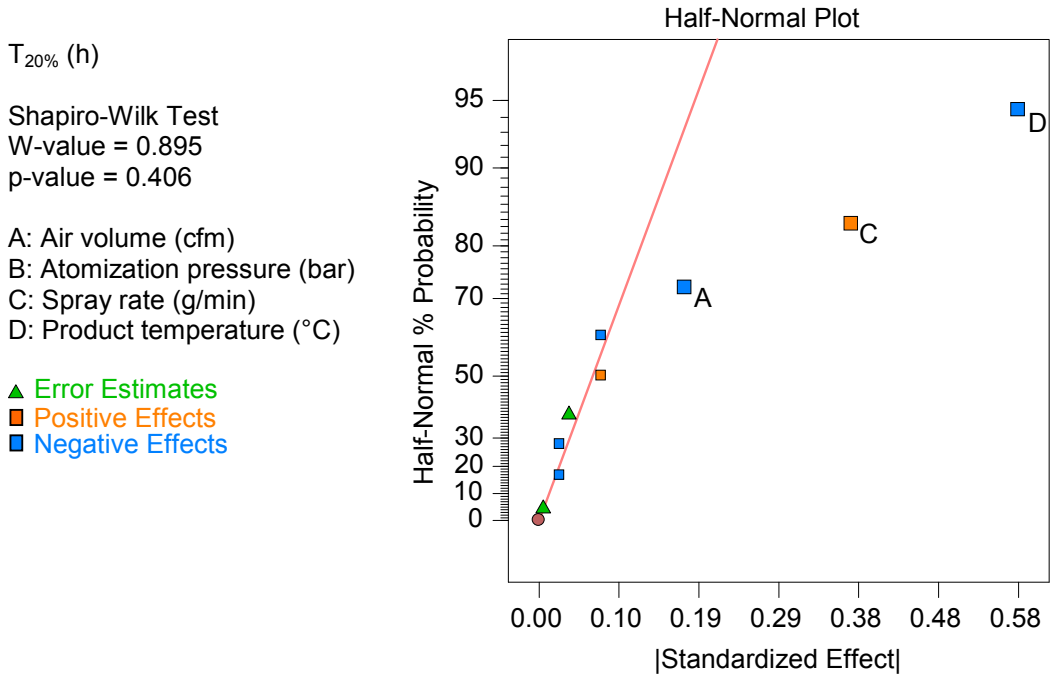

Figure 37. Half-normal plot of the process parameter effects on $T_{20\%}$ of ER coated beads

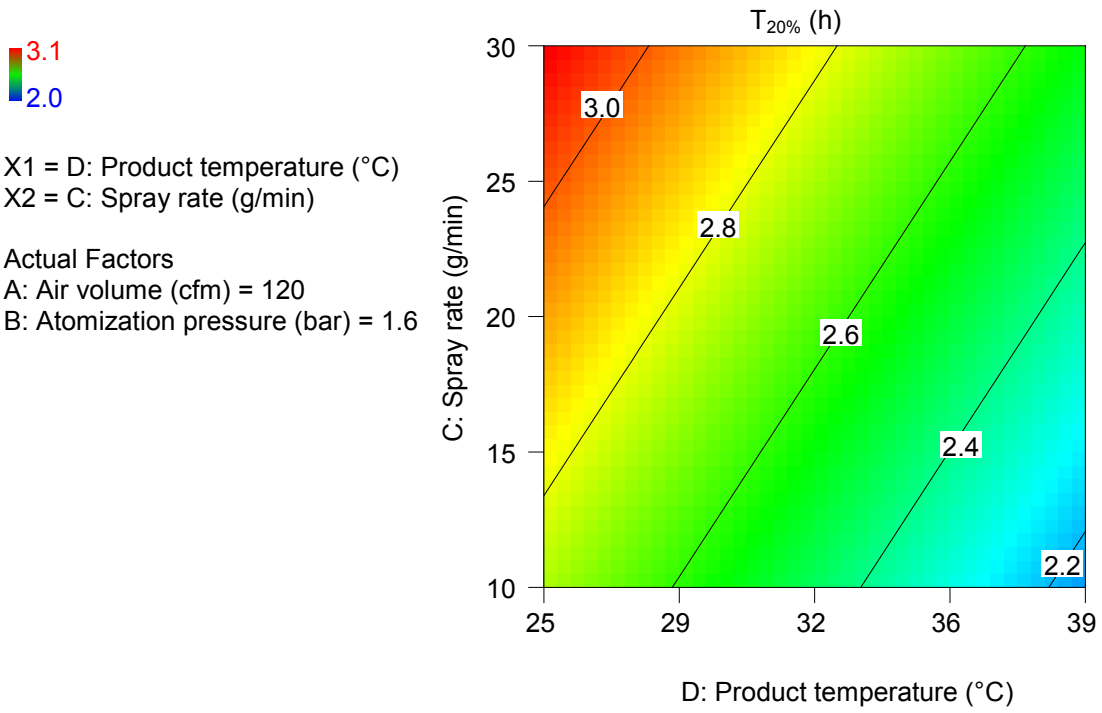

Figure 38. Effect of product temperature and spray rate on $T_{20\%}$ of ER coated beads

Similar cause and effect relationships were observed for $T_{50\%}$ and $T_{80\%}$ of ER coated beads (data not shown).

Significant factors for process efficiency of the ER polymer coating step

As shown in the following half-normal plot (Figure 39), the most significant factors affecting the process efficiency of the ER polymer coating step were C (spray rate) and D (product temperature). However, the p-value is less than 0.05 which indicates that the non-selected effects deviate from the Shapiro-Wilk test assumption of normalcy. Based on the ANOVA results presented in Table 71, the curvature effect was significant. Figure 40 shows the impact that product temperature has on process efficiency. Further optimization was necessary to gain more understanding of this curvature effect.

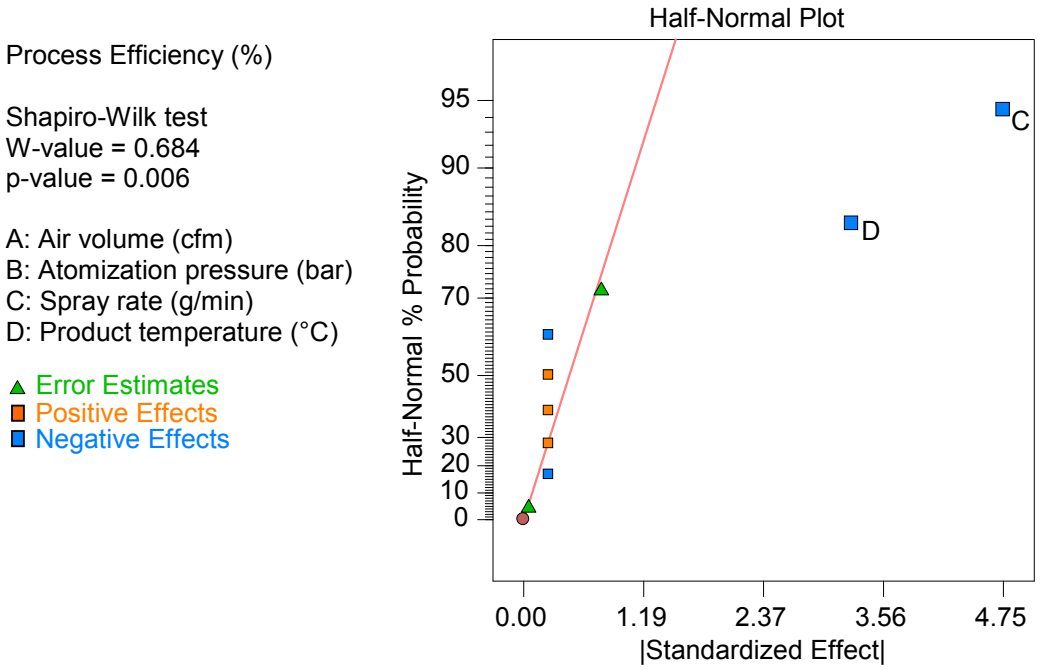

Figure 39. Half-normal plot of the process parameter effects on efficiency of the ER polymer coating process

Table 71. ANOVA results for the ER polymer coating process efficiency

Source	Sum of Squares	df*	Mean Square	F Value	p-value Probability > F	Comments
Model	66.25	2	33.13	88.33	< 0.0001	Significant
C-Spray rate (g/min)	45.13	1	45.13	120.33	< 0.0001	
D-Product temp (°C)	21.13	1	21.13	56.33	0.0001	
Curvature	**81.85**	**1**	**81.85**	**218.27**	**< 0.0001**	**Significant**
Residual	2.62	7	0.37			
Lack of Fit	0.62	5	0.12	0.125	0.9723	not significant
Pure Error	2	2	1			
Total	150.73	10				

*df: degree of freedom

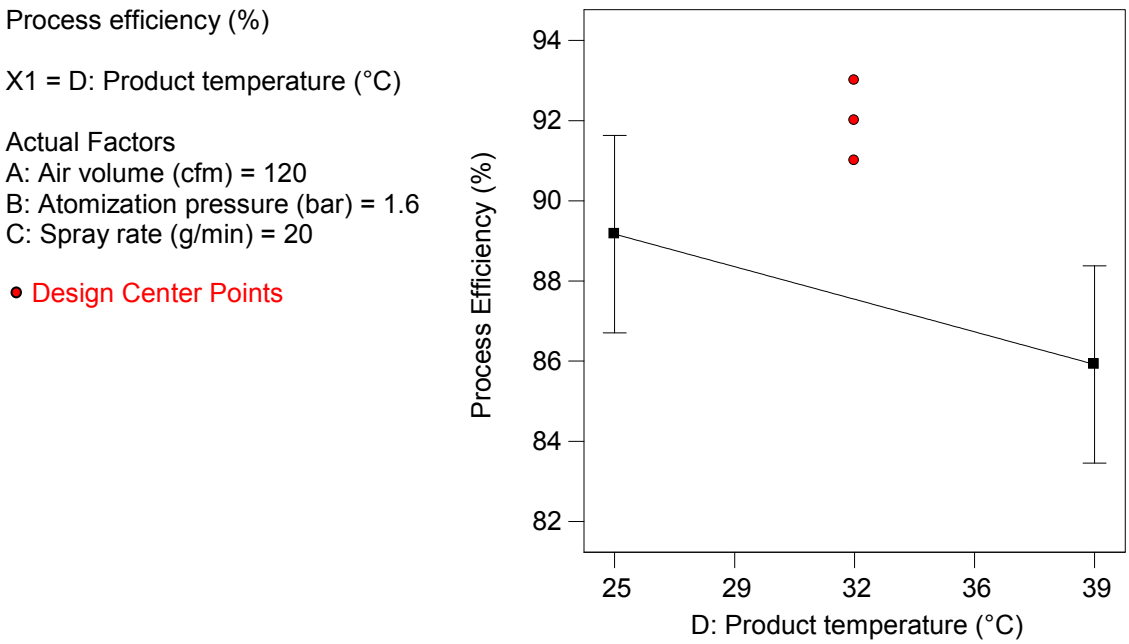

Figure 40. Main effect of product temperature on efficiency of the ER polymer coating process

Results from the screening DOE study demonstrated that product temperature, spray rate and air volume are the CPPs for the ER polymer coating process. Within the range studied, the impact of a change in atomization air pressure on the responses measured was not significant ($\alpha = 0.05$). Although the risk of atomization air pressure to impact the drug release profile of the ER coated beads was considered high during the initial assessment, atomization air pressure was not found to be a critical process parameter at lab scale.

ER Polymer Coating Process Optimization Study at Lab Scale (4 kg)

An optimization study was performed to optimize the three CPPs (product temperature, spray rate and air volume) identified in the previous screening and feasibility studies. The same equipment (Glatt GPCG-5 with a 7″ Wurster insert) was used as in the process screening study. Since the impact of atomization air pressure was not significant ($\alpha = 0.05$) in the screening study, it was kept constant at 1.6 bar for the optimization study.

In a full factorial design for three factors at three levels including six center point replicates, the total number of experiments needed would be 33. Though a full factorial design offers maximum resolution, a Central Composite Face-centered (CCF) design was chosen to reduce the number of runs and allow a quadratic model fit while evaluating three levels for each factor. The design had one center point, no replicates, $\alpha = 1.0$ and 15 runs total. Table 72 shows the study design and acceptance criteria. The measured responses were the drug release profiles ($T_{20\%}$, $T_{50\%}$ and $T_{80\%}$), the amount of fines and agglomerates generated and process efficiency. Table 73 summarizes experimental results (Y_1 and Y_4, other responses not shown).

Table 72. Design of the CCF study to optimize the ER polymer coating process

Factors: Process Parameters		Levels		
		-1	0	+1
A	Air volume (cfm)	80	110	140
B	Product temperature (°C)	28	32	36
C	Spray rate (g/min)	10	20	30
Responses		**Target Ranges**		
Y_1	$T_{20\%}$ (h)	2.5	2.7	2.9
Y_2	$T_{50\%}$ (h)	4.5	5.5	6.5
Y_3	$T_{80\%}$ (h)	8	10	12
Y_4	Process Efficiency (%)	≥ 90		
Y_5	Fines < 350 μm (%)	≤ 5		
Y_6	Agglomerates > 590 μm (%)	≤ 5		

Table 73. Results of the ER polymer coating process optimization study

Std. Code	Batch No.	Factors: Process Parameters			Responses	
		A: Air volume	B: Product temperature	C: Spray rate	Y_1: $T_{20\%}$	Y_4: Process Efficiency
		(cfm)	(°C)	(g/min)	(h)	(%)
1	51	80	28	10	2.8	94
2	40	140	28	10	2.6	95
3	53	80	36	10	2.5	93
4	48	140	36	10	2.4	93
5	42	80	28	30	3.1	90
6	44	140	28	30	3.0	90
7	41	80	36	30	2.7	88
8	50	140	36	30	2.6	88
9	47	80	32	20	2.7	93
10	45	140	32	20	2.6	93
11	46	110	28	20	2.7	92
12	43	110	36	20	2.5	91
13	49	110	32	10	2.6	96
14	52	110	32	30	2.7	91
15	39	110	32	20	2.6	93

Based on the sum of squares of sequential models (i.e. linear, 2 factor interaction, quadratic and cubic), the highest order polynomial model was selected where the additional terms were significant and the model was not aliased. The model terms were further reduced based on the significance level ($\alpha = 0.05$) using the backward model selection method.

Significant factors for $T_{20\%}$ of the ER coated beads

Based on ANOVA results, the significant factors affecting $T_{20\%}$ of ER coated beads were B (product temperature), C (spray rate), and A (air volume). The effect of product temperature and spray rate on $T_{20\%}$ of ER coated beads is presented in Figure 41. The $T_{20\%}$ decreased with increasing product temperature but increased with increasing spray rate. Air volume showed a negative effect

on $T_{20\%}$, but to a lesser extent than product temperature. Similar cause and effect relationships were observed for $T_{50\%}$ and $T_{80\%}$ of ER coated beads (data not shown).

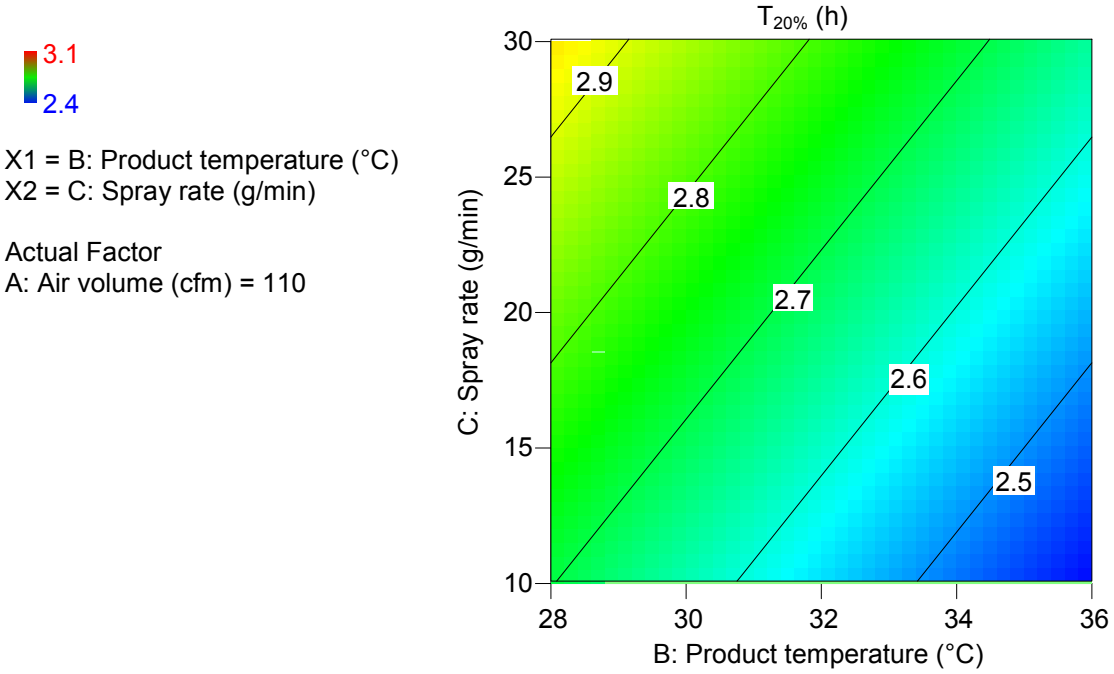

Figure 41. Effect of product temperature and spray rate on $T_{20\%}$ of ER coated beads

Significant factors for the process efficiency of the ER polymer coating step

Based on ANOVA results, the significant factors affecting the process efficiency of the ER polymer coating step were B (product temperature) and C (spray rate). The curvature effect identified in the screening DOE was well modeled by the square term of product temperature as illustrated in Figure 42.

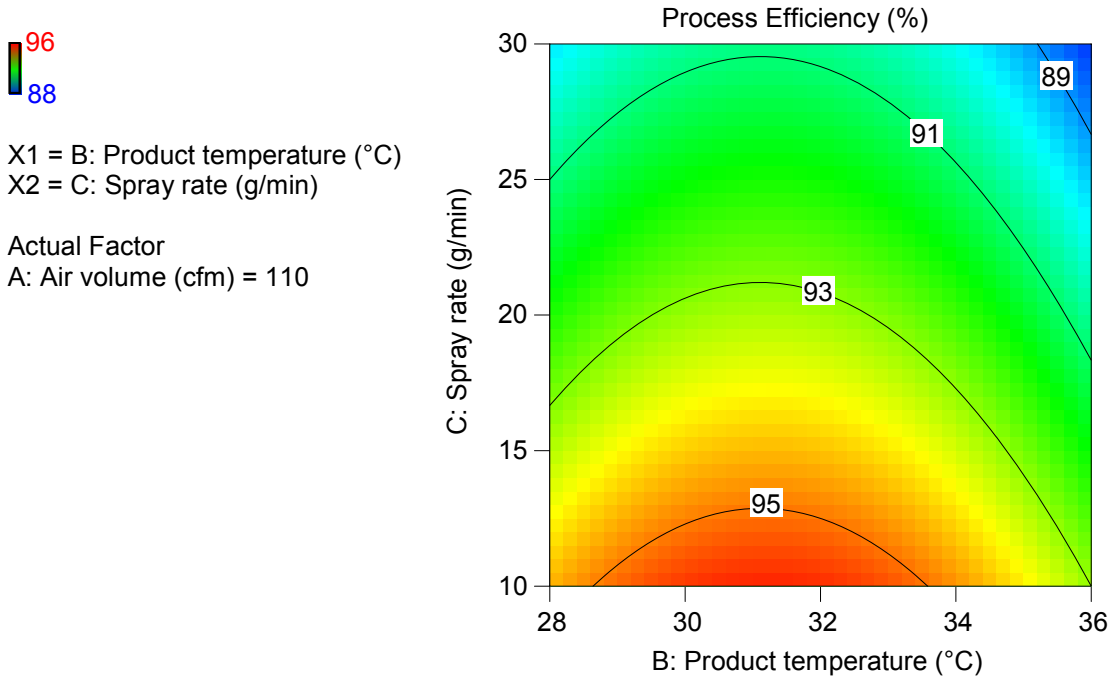

Figure 42. Effect of product temperature and spray rate on efficiency of the ER polymer coating process

Based on the results from the screening and optimization DOE studies, product temperature, spray rate and air volume were identified as CPPs. The design space (green zone in Figure 43) was determined from the common region of successful operating ranges for multiple CQAs for the ER polymer coating unit operation at the 4 kg scale using the Glatt GPCG-5 equipped with a 7″ Wurster insert. In this case, the overlap region is comprised of the ranges for $T_{20\%}$ and process efficiency.[11] The acceptable ranges for these three CPPs were proposed as shown in Table 74. Note that in this table, the acceptable range of one process parameter is dependent on the value of the other. This approach allows the maximum range of operation to achieve the desired quality attributes. Atomization pressure was found not critical within the range studied. Therefore, the studied range of 1.2 – 2.0 bar was recommended for this scale. The relevance of the proposed 4 kg scale design space for this unit operation will be verified when scaling up to pilot scale and, ultimately, to commercial scale.

[11] This is for concept demonstration only. All identified CQAs should be studied and included for a real drug product.

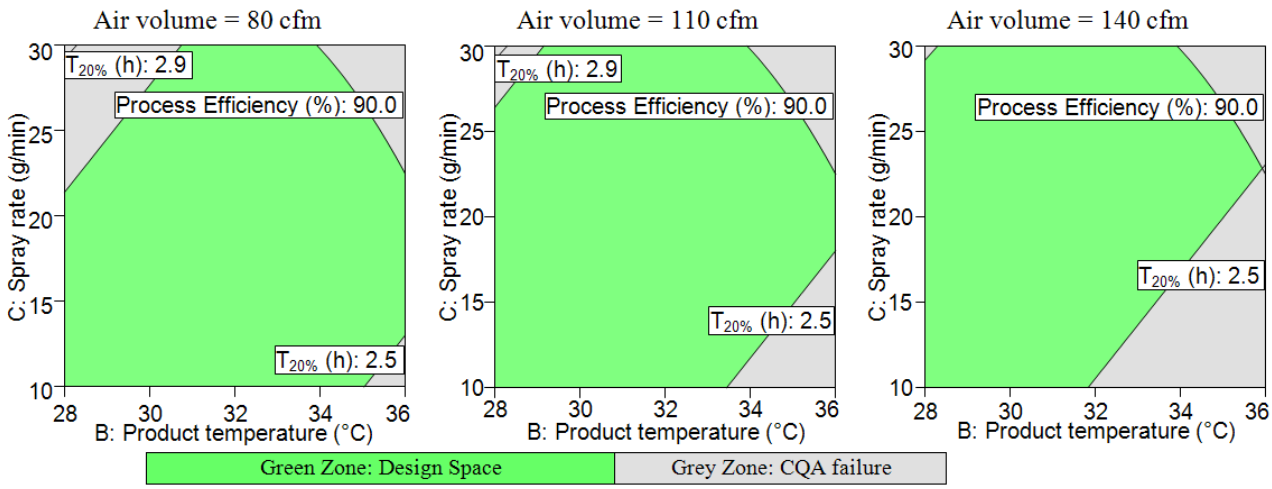

Figure 43. Overlay plots of the ER polymer coating unit operation at 4 kg scale (Glatt GPCG-5 with a 7″ Wurster HS insert)

Note to Reader: At this scale, the edge of failure for process parameters was determined because the CQAs cannot be met beyond a certain range. However, determining the edge of failure or demonstrating failure modes are not essential parts of establishing a design space.

Table 74. Acceptable ranges for the ER polymer coating process parameters at 4 kg scale (Glatt GPCG-5 with a 7″ Wurster HS insert)

Process Parameters	Ranges	Rationale
Product temperature	31 ± 3 °C	Lower than optimum led to agglomeration. Higher than optimum increased the amount of fines. Scale-independent parameter.
Air volume	110 ± 30 cfm	Range set based on studies on the laboratory scale. Scale-dependent parameter
Spray rate	20 ± 10 g/min	Ranges studied produced acceptable ER bead with desired release profile. Scale-dependent parameter.

ER Polymer Coating Process Robustness Study at Pilot Scale (40 kg)

To minimize the scale-up risk from lab scale (4 kg) to commercial scale (180 kg), a robustness study was performed to evaluate the CPPs at pilot scale (40 kg). A Glatt GPCG-60 with an 18″ Wurster HS insert (partition column diameter of 219 mm) was selected for the pilot scale batch because the chamber design and the distribution plate are geometrically similar to the intended commercial scale equipment (Glatt GPCG-120 with a 32″ Wurster HS insert). A comparison between lab scale and pilot scale equipment for the ER polymer coating process is presented in Table 75.

Table 75. Comparison between lab scale and pilot scale equipment for the ER polymer coating process

ER Polymer Coating	Lab Scale	Pilot Scale
Equipment model	Glatt GPCG-5	Glatt GPCG-60
Fluid bed insert	7″ Wurster	18″ Wurster
Equipment capacity*	8.3 L	102 L
Partition column diameter	89 mm	219 mm
Starting batch size	4 kg	40 kg
Theoretical ending batch size (~36% weight gain based on drug-layered bead weight)	5.4 kg	54 kg
Estimated use of capacity**	77%	62%
Number of partition(s)	1	1
Partition height (gap)	25 mm	45 ± 3 mm
Nozzle diameter	1.0 mm	1.2 mm

*Volume outside of the partition column at rest on the orifice plate

**Calculated based on the bulk density of the ER coated beads = 0.85 g/cc

Linear scale-up from lab scale to pilot scale assumes that the bed fill levels are the same and the distribution plate in each piece of equipment is geometrically similar. Additionally, ratios of air volume to plate area and spray rate to air volume should be maintained. The scale-up factor from a 7″ Wurster to an 18″ Wurster is approximately 6-fold based on vendor recommendation.

Even though atomization pressure was not critical within the studied range (1.2-2.0 bar) at lab scale, it will be further evaluated at pilot scale due to the significant increase in spray rate and change in nozzle diameter. During scale-up, it is essential that the atomization air pressure selected is capable of efficiently atomizing the coating dispersion at increased spray rate and nozzle diameter. An excessively high atomization air pressure generates smaller droplets which have a greater surface area. Thus, these smaller droplets evaporate faster while in the air making them susceptible to spray drying. On the contrary, when the atomization pressure is suboptimal, the nozzle can not develop a full spray pattern and may result in larger droplets which can potentially cause agglomeration. Based on the intended spray rate and air volume for pilot scale, the manufacturer recommended an atomization pressure range of 2.0 – 3.0 bar. By a visual check, the coating dispersion spray pattern was acceptable in this range.

Although product temperature is a CPP, it is a scale independent parameter; therefore, product temperature will be tightly controlled to 31 ± 3 °C based on the lab scale optimization and will be monitored during scale-up. The study design and acceptance criteria at pilot scale are given in Table 76. To reduce the number of runs, a 2^{3-1} fractional factorial DOE with one center point was performed instead of a full factorial design. The experimental runs and results (Y_1 and Y_4, other responses not shown) are summarized in Table 77.

Table 76. Design of the 2^{3-1} ER polymer coating process robustness study

Defining Relation	I = ABC		
Resolution	III		
Factors: Process Parameters		**Levels**	
		-1	+1
A	Air volume (cfm)	600	720
B	Atomization pressure (bar)	2.0	3.0
C	Spray rate (g/min)	100	140
Responses		**Target Ranges**	
Y_1	$T_{20\%}$ (h)	2.5	2.9
Y_2	$T_{50\%}$ (h)	4.5	6.5
Y_3	$T_{80\%}$ (h)	8	12
Y_4	Process Efficiency (%)	≥ 90%	
Y_5	Fines < 350 μm (%)	≤ 5	
Y_6	Agglomerates > 590 μm (%)	≤ 5	

Table 77. Results of the ER polymer coating process robustness study

Std. Code	**Batch No.**	**Factors: Process Parameters**			**Responses**	
		A: Air volume	**B: Atomization pressure**	**C: Spray rate**	**Y_1: $T_{20\%}$**	**Y_4: Process Efficiency**
		(cfm)	**(bar)**	**(g/min)**	**(h)**	**(%)**
1	57	600	2.0	140	2.8	94
2	55	720	2.0	100	2.6	93
3	59	600	3.0	100	2.7	95
4	58	720	3.0	140	2.9	92
5	56	660	2.5	120	2.7	94

The data in Table 77 indicate that the various processing conditions investigated for the ER polymer coating step provided satisfactory ER coated beads at the 40 kg scale. DOE statistical analysis also demonstrated that the impact of all factors (in the range studied) on the responses studied was not significant ($\alpha = 0.05$) since all the factor effects lie on the pure error line. See the half-normal plot of the process parameter effects on $T_{20\%}$ in Figure 44 as a representative example. Similar plots were obtained for all other responses studied (figures not shown). Based on the results of the confirmation study, a 40 kg scale design space for the ER polymer coating unit operation was defined as shown in Table 78. Operation within the design space resulted in a product meeting all predefined CQAs. Again, because air volume and spray rate are scale dependent variables, the 40 kg scale design space needs to be verified at commercial scale (180 kg). Atomization air pressure is an equipment-dependent parameter. However, scaling the coating unit operation from an 18″ Wurster to a 32″ Wurster is a scale-out instead of a scale-up. The three nozzles used in the 32″ Wurster are identical to the one used in the 18″ Wurster. The atomization air pressure is kept the same per nozzle.

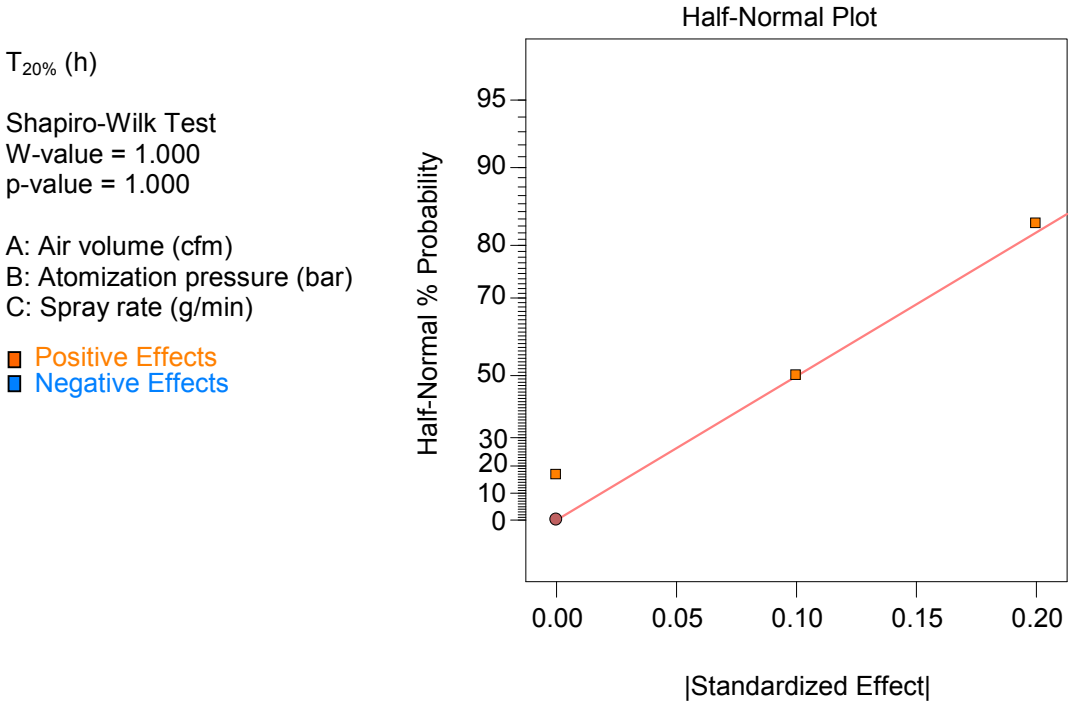

Figure 44. Half-normal plot of the process parameter effects on $T_{20\%}$ of ER coated beads

Note to Reader: At this scale, the edge of failure for process parameters was not defined because all relevant quality attributes were met in the studied ranges.

Table 78. Design space at 40 kg scale for the ER polymer coating unit operation (Glatt GPCG-60 with an 18″ Wurster HS insert)

Process Parameters	Ranges
Product temperature	31 ± 3 °C
Atomization pressure	2.5 ± 0.5 bar
Air volume	660 ± 60 cfm
Spray rate	120 ± 20 g/min

ER Beads Curing Process Confirmation Study

Because of the low MFT (8 °C) for Kollicoat SR 30 D with 5% TEC as plasticizer, the vendor claims that a thermal after-treatment (curing) of coated beads is not required. Drug release profiles of coated and uncoated beads showed no curing effect in the formulation feasibility study conducted in Glatt GPCG-1. This study was conducted to investigate if curing is required for beads coated in large scale equipment due to high attrition. The beads manufactured in the pilot scale confirmation study (Batch No. 55) were cured in a laboratory oven at 60 °C for 12 and 24 hours. Figure 45 compares the obtained drug release profiles with that of the uncured beads. The percent of drug released from the ER coated beads is calculated based on the nominal dose of 7 mg. The study confirmed that curing has little impact on the drug release from ER coated beads.

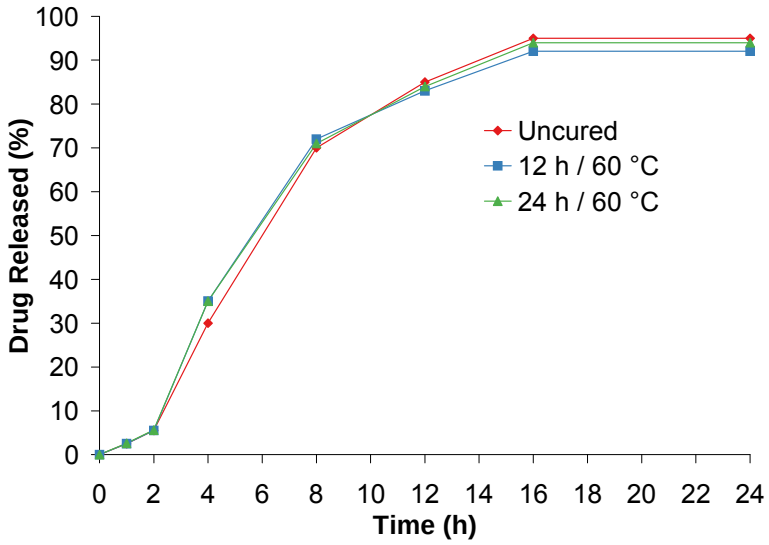

Figure 45. Effect of curing on the drug release profiles of ER coated beads

Updated Risk Assessment of the ER Polymer Coating Process Variables

Table 79 presents the risk reduction for the drug layering process as a result of the development work.

Table 79. Updated risk assessment of the ER polymer coating process variables

Unit Operation: ER polymer coating		
Output Material CQA: Drug release from the ER coated beads		
Spraying Variables	**Risk Assessment**	**Justification for the Reduced Risks**
Product temperature	Low	Product temperature range was identified. In the studied range, ER coated beads with consistent quality were produced at the 40 kg scale. Spray drying and agglomeration were minimized. Product temperature is a scale-independent parameter and will be applied to other scales. The risk of product temperature to impact drug release from the ER coated beads is reduced from high to low.
Air volume	Medium	Air volume range was identified. In the studied range, ER coated beads with consistent quality were produced at the 40 kg scale. An optimal fluidization pattern was achieved. Air volume is a scale-dependent parameter. However, processing equipment change from an 18″ to a 32″ Wurster is a scale-out process instead of a scale-up process. For commercial scale, air volume will be increased 3-fold. Further adjustment may be necessary. The risk of air volume to impact drug release from the ER coated beads is reduced from high to medium.
Spray rate	Medium	Spray rate range was identified. In the studied range, ER coated beads with consistent quality were produced at the 40 kg scale. Spray rate is a scale-dependent parameter. However, a processing equipment change from an 18″ to a 32″ Wurster is a scale-out process and each of the three nozzles used in the 32″ Wurster are identical to the one used in the 18″ Wurster. The spray rate per nozzle will be kept the same. The total spray rate will be increased 3-fold. Further adjustment may be necessary. The risk of spray rate to impact drug release from the ER coated beads is reduced from high to medium.

Unit Operation: ER polymer coating		
Output Material CQA: Drug release from the ER coated beads		
Spraying Variables	**Risk Assessment**	**Justification for the Reduced Risks**
Atomization air pressure	Low	Atomization air pressure was identified. In the studied range, ER coated beads with consistent quality were produced at the 40 kg scale. Neither attrition nor agglomeration was an issue within the identified range. Atomization air pressure is an equipment-dependent parameter. As this is a scale-out process and each of the three nozzles used in the 32″ Wurster are identical to the one used in the 18″ Wurster, the atomization air pressure for each nozzle will be kept the same. The risk of atomization air pressure to impact drug release from the ER coated beads is reduced from high to low.

2.3.4 Blending and Lubrication Process Development

Initial Risk Assessment of the Blending and Lubrication Process Variables

The initial risk assessment of the overall manufacturing process presented in Table 51 identified blending and lubrication as high risk steps that could impact tablet CU and drug release from split tablets. Subsequently, blend uniformity of the final blend was identified as a CQA for the blending and lubrication step. Process variables that could directly impact blend uniformity were assessed to identify which variables may cause poor blend uniformity. The results of the initial risk assessment of the blending and lubrication process variables are summarized in Table 80.

Table 80. Initial risk assessment of blending and lubrication process variables on blend uniformity

Unit Operation: Blending and Lubrication		
Output Material CQA: Blend uniformity of the final blend		
Variables	**Risk Assessment**	**Justification and Initial Strategy**
Input Material Attributes		
IR granules assay	Low	The approved commercial IR granulation process (ANDA aaaaaa) routinely produces granules with an assay of 95 – 105%. The risk of the IR granule assay to impact blend uniformity is low.
IR granules content uniformity	Low	At commercial scale, the IR granules routinely demonstrate good blend uniformity (RSD < 5%) and Example IR Tablets show acceptable CU as per USP <905>. The risk of the IR granule CU to impact blend uniformity is low.
IR granules size distribution	Medium	The granule size distribution is fixed by ANDA aaaaaa: Retained on 45 mesh (> 350 µm): NMT 5% Retained on 60 mesh (> 250 µm, but < 350 µm): NLT 85% Retained on fine collector (< 250 µm): NMT 10% Due to the differences in size distribution, density, shape and aspect ratio between IR granules and ER beads, segregation is possible. The risk is medium.
ER coated beads assay	Low	The drug layering process was optimized to minimize spray drying and agglomeration. Assay of the drug-layered beads within 95 – 105% was achieved and the ER polymer coating step did not cause attrition to the drug layer. The risk of ER coated beads assay to impact blend uniformity is low.

Unit Operation: Blending and Lubrication		
Output Material CQA: Blend uniformity of the final blend		
Variables	**Risk Assessment**	**Justification and Initial Strategy**
ER coated beads size distribution	Medium	Fixed: 350 – 590 µm. Due to the differences in size distribution, density, shape and aspect ratio between IR granules and ER beads, segregation is possible. The risk is medium.
MCC Grade 200 and MCC Grade 101 PSD	Low	The total amount of MCC was optimized and the formulation demonstrated good compressibility. Two grades of MCC were used to prevent segregation. The ratio between MCC 200 (d_{50}: 150 -250 µm) and MCC 101 (d_{50}: 30-80 µm) was optimized and fixed at 65:35. A uniform tablet was achieved with the optimized formulation. The risk of cushioning agent PSD to impact blend uniformity is low.
Sodium starch glycolate, Type A (SSG) PSD	Low	Due to the low level of SSG used in the final formulation, the risk of its PSD to impact blend uniformity is low.
Magnesium stearate specific surface area	Low	The impact of magnesium stearate specific surface area on blend uniformity and tablet quality attributes was studied during formulation development. Within the range studied (6-10 m^2/g), the impact of magnesium stearate specific surface area on all the response variables was not significant.
Blending Variables		
Blender type	Medium	Fixed: V-blender
Order of addition	Medium	The risk of the order of addition to impact blend uniformity is medium. To reduce the potential for damage to the coating on the ER beads during loading into the V-blender, a "sandwich" approach will be used, i.e. the cushioning agent MCC will be added first followed by ER coated beads and SSG. Then, IR granules will be added last. After the blending endpoint is determined by inline NIR, magnesium stearate will be added.
Rotation speed (rpm)	Medium	The risk of rotation speed to impact blend uniformity is medium. The rpm is fixed by equipment constraint: lab scale (16 qt, 25 rpm) pilot scale (7.5 cu ft, 15 rpm) commercial scale (30 cu ft, 10 rpm)
Intensifier bar (on/off)	Medium	The intensifier bar is kept off to prevent damage to the ER coated beads. The risk of not using the intensifier bar to impact BU is medium.
Number of blender revolutions	High	Under- or over-blending may occur if the number of revolutions is not optimized. Investigate to reduce the risk.
Blender fill level	High	Under-blending may occur due to a suboptimal blender fill level. Investigate to reduce the risk.
Holding time	High	Segregation may occur during holding. The risk of impact on BU is high. Investigate to reduce the risk.
Blender discharge	High	Segregation may occur during discharge. The risk of impact on BU is high. Investigate to reduce the risk.
Drum-to-Hopper transfer	High	Segregation may occur during transfer. The risk of impact on BU is high. Investigate to reduce the risk.
Environment temperature	Low	Fixed: 25 ºC ± 5%. The risk is low.
Environment RH	Low	Fixed: 40% – 60%. The risk is low.

Unit Operation: Blending and Lubrication		
Output Material CQA: Blend uniformity of the final blend		
Variables	**Risk Assessment**	**Justification and Initial Strategy**
Lubrication Variables		
Number of blender revolutions	Low	Investigated during formulation development. A proven acceptable range for N_{rev} (60 – 120) was established based on drug release profile and tablet appearance. The risk of the number of blender revolutions during lubrication to impact BU is low. The target setting is 90 revolutions.

Effect of Number of Revolutions on Blend Uniformity

Note to Reader: NIR method validation is beyond the scope of the pharmaceutical development report and the details are not discussed in this example. The validation report should be included in Section 3.2.P.5.3 Validation of Analytical Procedures.

Inline NIR provides a real time response and eliminates the challenges and errors associated with thief sampling blends. An inline validated NIR spectrophotometric method with specificity for drug substance Z was used to determine the blending endpoint for development work. During validation, blend uniformity data collected at various time points by the NIR method was compared to that obtained by traditional thief sampling followed by offline HPLC analysis and was found to be comparable. Based on these findings, NIR is capable of accurately assessing the real-time homogeneity of the blend and can be used to control the endpoint of the blending process.

During blending, one spectrum was acquired non-invasively through the sight glass of the V-blender for each revolution as the V-blender was in the inverted position. To assess the homogeneity of the blend, RSD was calculated for each moving block of ten consecutive spectra and plotted as a function of time. The blend was considered uniform once the RSD was below 5% for ten consecutive measurements.

Figure 46 shows the NIR measurements for a lab scale and pilot scale (Lot # XXX-10-058) batch. Blend uniformity was achieved in 12 minutes at the lab scale (16 qt V-blender, 25 rpm, 300 revolutions) and 20 minutes at the pilot scale (7.5 cu ft V-blender, 15 rpm, 300 revolutions). No demixing was observed at either scale when the V-blender was operated well beyond the blending endpoint. Figure 46 clearly supports that while blending time and blender speed are not scalable, the number of revolutions is scalable. For further drug product batches, 300 revolutions (25 minutes) are proposed to achieve blend uniformity and RSD values that are within the acceptable range.

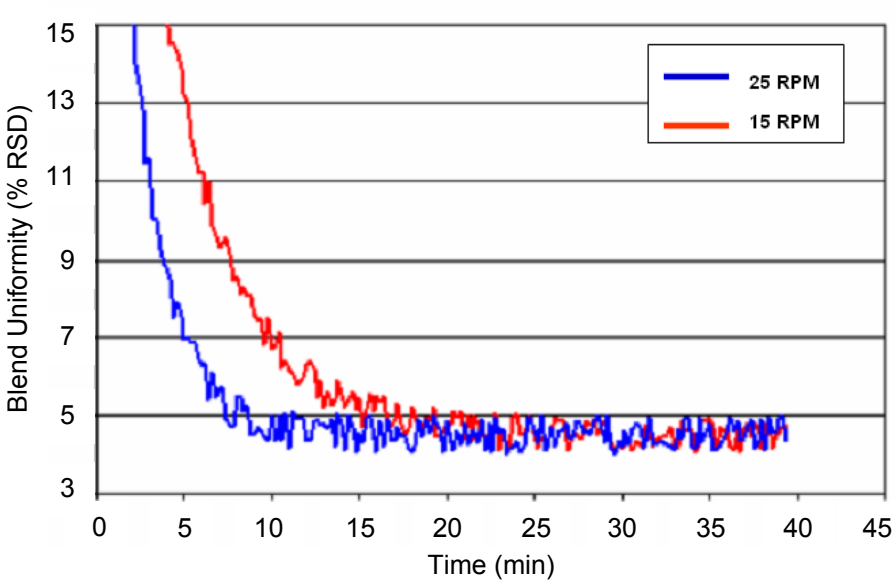

Figure 46. Blend uniformity of prototype F-2 determined by a validated inline NIR method at both lab (25 rpm) and pilot (15 rpm) scale.[12]

The final blend was sampled for blend uniformity in the blender 24 hours post blending and again in the drum after discharge. The data in Table 81 were obtained.

Table 81. Blend uniformity of the final blend for Example MR Tablets, 10 mg

Batch No: XXX- 10-058		
Sample point	**Final blend (in blender, 24 hrs after mixing)**	**Final blend (in drum after discharge)**
	(% w/w of label claim)	**(% w/w of label claim)**
1	105.8	93.1
2	95.7	99.2
3	102.5	92.4
4	108.4	96.8
5	97.5	98.3
6	99.3	91.6
7	96.1	106.5
8	94.8	109.5
9	104.8	104.7
10	91.1	90.4
Mean	99.6	98.3
RSD	5.6	6.8
Minimum	91.1	90.4
Maximum	108.4	109.5

[12] Figure modified from Pharmaceutical Development Case Study: "ACE Tablets", Prepared by CMC-IM Working Group, March 13, 2008, Version 2.0.

The results in Table 81 suggest that blend segregation occurred in the blender during the 24 hour holding period. Furthermore, the data suggest that the extent of segregation was exacerbated during discharge to the drum. The blend was also tested using a segregation tester[13] and the data showed significant variability in average particle size, thus corroborating the earlier findings.

To address the issue of segregation in the final blend and to reduce the risk of poor content uniformity, MCC 101 (bulk density: 0.28 g/cm^3, d_{50}: 50 µm) was combined with MCC 200 (bulk density: 0.32 g/cm^3, d_{50}: 180 µm) to fill the void volume between ER beads and IR granules. The ratio between MCC 200 and MCC 101 was optimized at 65:35 (see Table 42 in Section 2.2.1.4 for optimization data).

Confirmatory Study of the Effect of Number of Revolutions on Blend Uniformity

Upon optimizing the ratio of extragranular fillers in the final blend, a second 40 kg trial batch (XXX-10-110) was manufactured in a 7.5 cu ft V-blender at 15 rpm and monitored using an NIR probe. Blend uniformity was achieved after 20 minutes (300 revolutions) of blending. Samples were taken from the blender 24 hours after mixing and from the drum after discharge. Table 82 shows the blend uniformity results of these samples.

Table 82. Blend uniformity of the optimized final blend for Example MR Tablets, 10 mg

Batch No: XXX-10-110		
Sample point	**Final blend (in blender, 24 hrs after mixing)**	**Final blend (in drum after discharge)**
	(% w/w of label claim)	**(% w/w of label claim)**
1	101.3	100.4
2	100.2	101.9
3	102.5	98.7
4	101.8	99.5
5	99.4	99.2
6	99.3	100.3
7	101.5	101.5
8	101.2	102.7
9	101.5	102.3
10	98.9	99.7
Mean	100.8	100.6
RSD	1.2	1.4
Minimum	98.9	98.7
Maximum	102.5	102.7

Unlike in the first segregation study, the optimized final blend with MCC Grade 200 and MCC Grade 101 in the ratio of 65:35 had acceptable blend uniformity (RSD < 2%) both in the blender (24 hours post blending) and after discharging into the drum.

[13] An automated fluidization segregation tester was used where particle-size measurements were carried out with a laser-diffraction sensor system equipped with a dry-powder feeder system.

Effect of Blender Fill Level on Blend Uniformity

A study was performed to evaluate the impact of blender fill level (40% to 60%) on blend uniformity. Each blend was mixed in a 7.5 cu ft (212.4 L) V-blender at 15 rpm and monitored using an NIR probe. Blend uniformity was achieved after 20 minutes (300 revolutions) of blending for all three fill levels, 40%, 50% and 60%.

Effect of Transfer Method on Blend Uniformity

In addition, a study was conducted to look at the effect of drum-to-hopper transfer method on blend uniformity in the compression machine hopper. The blends were transferred to the hopper by charging from a higher location (with respect to the hopper) or by manual scooping, respectively. As shown in Table 83, blend uniformity data for the blend transferred by using either of these two methods met the acceptance criteria. Since manual scooping is time consuming, the method of charging from a higher location was selected for future processing.

Table 83. Blend uniformity of the final blend after it is transferred to the hopper

Batch No: XXX-10-111		
Sample point	Drum-to-Hopper: dropping from a higher location	Drum-to-Hopper: scooping manually
	(% w/w of label claim)	(% w/w of label claim)
1	96.5	98.5
2	98.5	98.9
3	104.3	96.3
4	102.5	100.5
5	96.6	99.7
6	96.9	98.7
7	97.6	96.5
8	100.5	102.3
9	102.5	104.2
10	98.1	98.9
Mean	99.4	99.5
RSD	2.9	2.4
Minimum	96.5	96.3
Maximum	104.3	104.2

Summary of Proposed V-blender Operating Parameters

Table 84 lists the V-blender operating parameters optimized for laboratory and pilot scale blending. The operating parameters proposed for commercial scale are based on 300 revolutions and will need to be verified. NIR monitoring will be used to determine the end point of blending.

Table 84. Summary of V-blender operating parameters

Scale	Amount	Blender Capacity	Blending Speed	Blending Time	N_{rev}	Volume Fill Ratio
	(kg)		(rpm)	(min)		(%)
Lab	4	16 qt	25	12	300	~50
Pilot	40	7.5 cu ft	15	20	300	~50
Commercial	180	30 cu ft	10	30*	300*	~50

*Proposed initial parameters to be verified at commercial scale as discussed in Section 2.3.7

Updated Risk Assessment of the Final Blending Process Variables

Table 85 presents the update risk assessment after blending process study. The justification for the reduced risks is also provided.

Table 85. Updated risk assessment of the blending and lubrication process variables

Unit Operation: Blending and Lubrication		
Output Material CQA: Blend uniformity of the final blend		
Blending Variables	**Risk Assessment**	**Justification for the Reduced Risks**
Number of blender revolutions	Low	Target: 300 revolutions The blending process was optimized and monitored using inline NIR. The blending endpoint is reached when the moving block RSD is < 5.0% for the last ten revolutions of the blending process. The risk of the number of blender revolutions to impact BU is reduced from high to low.
Blender fill level	Low	Acceptable BU (RSD < 2%) was achieved for blender fill levels of 40-60%. With inline NIR monitoring, the risk of blender fill level to impact BU is reduced from high to low.
Holding time	Low	The optimized formulation showed good BU (RSD < 2%) after holding 24 hours in the blender before discharge to drums. The risk is reduced from high to low.
Blender discharge	Medium	Study results suggested that BU was not impacted by blender discharge at pilot scale. Therefore, the risk is reduced; however, due to the potential change of the effective length of the mixer at commercial scale, the risk of discharge to impact BU is considered medium.
Drum-to-hopper transfer	Medium	Study results suggested that BU is not impacted by drum-to-hopper transfer. Therefore, the risk is reduced, however, due to potential change of transfer distance at commercial scale, the risk of transfer to impact BU is considered medium.

2.3.5 Tablet Compression Process Development

Initial Risk Assessment of the Tablet Compression Process Variables

Based on the initial risk assessment of the overall manufacturing process shown in Table 51, the risk of the compression step to impact tablet physical attributes (size and splitability), assay, content uniformity and drug release from both whole and split tablets was identified as high. Process variables that could directly impact these five CQAs were assessed to identify which variables may cause a CQA failure. The results of the initial risk assessment of the compression process variables are summarized in Table 86.

Table 86. Initial risk assessment of the tablet compression process variables

Unit Operation: Compression			
Drug Product CQAs: Physical attributes (size and splitability), assay, content uniformity, drug release from both whole and split tablets			
Variables	**Drug Product CQAs**	**Risk Assessment**	**Justification and Initial Strategy**
Input Material Attributes			
Blend assay	**Physical Attributes (size and splitability)**	Low	Tablet size is determined by the formulation and tooling design. Splitability is determined by the formulation, tooling design and compression force. Therefore, the risk of the blend assay to impact the physical attributes (size and splitability) of the tablet is low.
	Assay	Low	The blending and lubrication process variables were optimized and the assay of the final blend was consistently within 95-105%. The risk of the blend assay to impact tablet assay, CU, and both whole and split tablet drug release is low.
	Content Uniformity	Low	
	Drug Release – whole tablets	Low	
	Drug Release – split tablets	Low	
Blend uniformity	**Physical Attributes (size and splitability)**	Low	Tablet size is determined by the formulation and tooling design. Splitability is determined by the formulation, tooling design and compression force. Therefore, blend uniformity has little impact on the physical attributes (size and splitability) of the tablet. The risk is low.
	Assay	Low	Inline NIR monitoring was used to achieve adequate BU (RSD < 5%). The risk of blend uniformity to impact tablet assay, CU, and both whole and split tablet drug release is low.
	Content Uniformity	Low	
	Drug Release – whole tablets	Low	
	Drug Release – split tablets	Low	
Blend bulk density	**Physical Attributes (size and splitability)**	Low	The bulk density of the final blend is consistently between 0.45 – 0.52 g/cc. The chosen tooling design yields a tablet similar in size and score configuration to the RLD. The risk of blend bulk density to impact tablet physical attributes (size and splitability) is low.
	Assay	Low	The die cavity can sufficiently accommodate the blend amount needed to obtain the target tablet assay. The risk of blend bulk density to impact tablet assay is low.
	Content Uniformity	Low	Tablet CU is directly related to BU and flowability and is not affected by bulk density. Therefore, the risk of bulk density to impact tablet CU is low.
	Drug Release – whole tablets	Low	The observed bulk density variability during formulation development (0.45 – 0.52 g/cc) did not have any impact on drug release from whole or split tablets. Therefore, the risk is low.
	Drug Release – split tablets	Low	

Unit Operation: Compression			
Drug Product CQAs: Physical attributes (size and splitability), assay, content uniformity, drug release from both whole and split tablets			
Variables	**Drug Product CQAs**	**Risk Assessment**	**Justification and Initial Strategy**
Blend flowability	**Physical Attributes (size and splitability)**	Low	If the flowability of the blend is poor, then the die filling and resultant tablet size and splitability could be variable during the compression run. However, adequate flow was achieved during formulation development based on a minimum orifice diameter of 20 mm as determined by Flowdex. The risk of blend flowability to impact tablet physical attributes (size and splitability) is low.
	Assay	Low	Blend flowability could impact powder flow from the hopper to the feeder frame and ultimately to the die cavity. However, adequate flow was demonstrated during formulation development. Thus, the risk of blend flowability to impact tablet assay, CU and drug release is low.
	Content Uniformity	Low	
	Drug Release – whole tablets	Low	
	Drug Release – split tablets	Low	
Blend compressibility and compactability	**Physical Attributes (size and splitability)**	Low	Compressibility and compactability were optimized during prototype tablet formulation development. The tablet size is similar to the RLD. The patient population found the tablet splitability to be acceptable. Thus, the risk of blend compressibility and compactability to impact tablet physical attributes (size and splitability) is low.
	Assay	Low	Tablet assay is mainly related to blend flowability, uniformity and tablet weight control. Compressibility and compactability are unlikely to impact tablet assay. The risk is low.
	Content Uniformity	Low	Tablet CU is directly related to BU and flowability. The compressibility and compatibility of the blend, while important, have no direct impact on tablet CU. The risk is low.
	Drug Release – whole tablets	Low	If the compressibility and compactability of the final blend are suboptimal, then a greater compression force may be required to form a tablet which may rupture the polymer coating on the ER beads. However, the compressibility and compactability were optimized during prototype development. The risk of impact on drug release from whole tablets is low.
	Drug Release – split tablets	Low	The risk of the blend compressibility and compactability to impact both tablet CU and drug release from whole tablets is low; therefore, the risk of impact on drug release from split tablet is also low.
Drug release from the IR and ER components of the blend	**Physical Attributes (size and splitability)**	N/A	The drug release profile of the IR granules and the ER coated beads is not applicable to tablet physical attributes (size and splitability), assay, or CU.
	Assay	N/A	
	Content Uniformity	N/A	

Unit Operation: Compression			
Drug Product CQAs: Physical attributes (size and splitability), assay, content uniformity, drug release from both whole and split tablets			
Variables	**Drug Product CQAs**	**Risk Assessment**	**Justification and Initial Strategy**
	Drug Release – whole tablets	Medium	Example IR Tablets consistently demonstrate rapid disintegration (< 5 min) and drug release (ANDA aaaaaa in Appendix I). During formulation development, the drug release from IR granules was unaffected when compressed with placebo beads. The risk of the IR component of the blend to impact whole tablet drug release is low. The target drug release profile of ER coated beads was obtained using a 30% theoretical polymer coating. However, drug release is sensitive to polymer coating level based on the BE studies. Therefore, the risk of the ER component of the blend to impact whole tablet drug release is medium.
	Drug Release – split tablets	Medium	Since the risk of the ER component of the blend to impact whole tablet drug release is medium, the risk of impact on drug release from split tablets is also medium.
Compression Variables			
Press model and number of stations used	**Physical Attributes (size and splitability)**	Low	The press model was selected based on equipment availability and all 49 stations will be used. The equipment selection is fixed. The same tablet press model and number of stations will be used for pilot scale and commercial scale manufacture. The risk of impact on the tablet CQAs is low.
	Assay	Low	
	Content Uniformity	Low	
	Drug Release – whole tablets	Low	
	Drug Release – split tablets	Low	
Tooling design	**Physical Attributes (size and splitability)**	Low	Tooling design was selected to compress a tablet with a similar size, shape, and score as the RLD. The tooling is fixed and the risk of its design to impact all tablet CQAs is low.
	Assay	Low	
	Content Uniformity	Low	
	Drug Release – whole tablets	Low	
	Drug Release – split tablets	Low	
Feeder speed	**Physical Attributes (size and splitability)**	Low	Tablet size and score configuration is determined by tooling design. Tablet splitability is mainly related to the formulation compactability and compression force. The risk of feeder speed to impact tablet physical attributes (size and splitability) is low.
	Assay	High	A higher than optimal feeder speed may impact drug release by damaging the ER bead coating integrity or causing over lubrication. A lower than optimal feeder speed may cause inconsistent die filling and variable tablet assay, CU and drug release. The risk is high. Investigate to reduce the risk.
	Content Uniformity	High	
	Drug Release – whole tablets	High	
	Drug Release – split tablets	High	

Unit Operation: Compression			
Drug Product CQAs: Physical attributes (size and splitability), assay, content uniformity, drug release from both whole and split tablets			
Variables	**Drug Product CQAs**	**Risk Assessment**	**Justification and Initial Strategy**
Feeder fill depth	**Physical Attributes (size and splitability)**	Low	Tablet size and score configuration is determined by tooling design. Tablet splitability is mainly related to the formulation compactability and compression force. The risk of feeder fill depth to impact tablet physical attributes (size and splitability) is low.
	Assay	High	A greater than optimal feeder fill depth may result in excessive powder that could jam the feeder. This would cause processing interruptions and variable tablet CU. A less than optimal feeder fill depth will not deliver enough powder for consistent die filling. This may cause variable tablet assay, CU and drug release. The risk is high. Investigate to reduce the risk.
	Content Uniformity	High	
	Drug Release – whole tablets	High	
	Drug Release – split tablets	High	
Pre-compression force	**Physical Attributes (size and splitability)**	High	A greater than optimal pre-compression force will increase tablet hardness and may subsequently impact tablet splitability. A lower than optimal pre-compression force may trap air in the tablets, leading to capping. The risk of pre-compression force to impact tablet physical attributes (size and splitability) is high. Investigate to reduce the risk.
	Assay	Low	Tablet assay and CU are dominated by blend flowability and uniformity. The pre-compression force is unrelated to tablet assay and CU; therefore, the risk of pre-compression force to impact tablet assay and CU is low.
	Content Uniformity	Low	
	Drug Release – whole tablets	High	A greater than optimal pre-compression force may cause lamination and affect drug release from whole tablets. A lower than optimal pre-compression force may trap air in the tablets, leading to capping. The risk of pre-compression force to impact drug release from whole tablet is high. Investigate to reduce the risk.
	Drug Release – split tablets	High	The risk of pre-compression force to impact tablet CU is low. However, the risk of impact on drug release from whole tablets is high. Therefore, the risk of impact on drug release from split tablets is also high. Investigate to reduce the risk.
Compression force	**Physical Attributes (size and splitability)**	High	A greater than optimal compression force will increase tablet hardness and may subsequently impact tablet splitability. A lower than optimal compression force may result in tablets that are friable. The risk of compression force to impact tablet physical attributes (size and splitability) is high. Investigate to reduce the risk.

Unit Operation: Compression			
Drug Product CQAs: Physical attributes (size and splitability), assay, content uniformity, drug release from both whole and split tablets			
Variables	**Drug Product CQAs**	**Risk Assessment**	**Justification and Initial Strategy**
	Assay	Low	Tablet assay and CU are dominated by blend flowability and uniformity. The pre-compression force is unrelated to tablet assay and CU; therefore, the risk of pre-compression force to impact tablet assay and CU is low.
	Content Uniformity	Low	
	Drug Release – whole tablets	High	A greater than optimal compression force may damage the ER bead coating and affect drug release from whole tablets. A lower than optimal compression force may result in tablets that are friable. The risk of compression force to impact drug release from whole tablets is high. Investigate to reduce the risk.
	Drug Release – split tablets	High	The risk of compression force to impact tablet CU is low. However, the risk of impact on drug release from whole tablets is high. Therefore, the risk of compression force to impact drug release from split tablets is also high. Investigate to reduce the risk.
Ejection force	**Physical Attributes (size and splitability)**	Low	The level of lubricant was optimized during formulation development and tablets had acceptable appearance. In addition, ejection force will be monitored during tablet compression. The risk of ejection force to impact all tablets CQAs is low.
	Assay	Low	
	Content Uniformity	Low	
	Drug Release – whole tablets	Low	
	Drug Release – split tablets	Low	
Press speed	**Physical Attributes (size and splitability)**	Medium	Tablet size and score configuration is determined by tooling design. The risk of press speed to impact physical attributes (size) is low. Tablet splitability is mainly related to the formulation compactability and compression force. However, if a change in press speed leads to a change in dwell time, then the tablet hardness and splitability may be affected. The risk of press speed to impact tablet physical attributes (splitability) is medium.
	Assay	High	A faster than optimal press speed may cause inconsistent die filling and affect tablet assay, CU, and hardness. Subsequently, it may impact release from whole and split tablets. To improve manufacturing efficiency, the press speed will be set as fast as practically possible without adversely impacting tablet quality. The risk of press speed to impact tablet assay, CU and drug release is high. Investigate to reduce the risk.
	Content Uniformity	High	
	Drug Release – whole tablets	High	
	Drug Release – split tablets	High	

Unit Operation: Compression			
Drug Product CQAs: Physical attributes (size and splitability), assay, content uniformity, drug release from both whole and split tablets			
Variables	**Drug Product CQAs**	**Risk Assessment**	**Justification and Initial Strategy**
Hopper design and vibration	**Physical Attributes (size and splitability)**	Low	Tablet size and score configuration is determined by tooling design. Tablet splitability is mainly related to the formulation compactability and compression force. The risk of hopper design and vibration to impact tablet physical attributes (size and splitability) is low.
	Assay	Medium	The flow of the blend and the potential for segregation may be impacted by the tablet press vibrations and the hopper angle design. Therefore, hopper design may impact tablet assay, CU, and drug release. The risk is medium.
	Content Uniformity	Medium	
	Drug Release – whole tablets	Medium	
	Drug Release – split tablets	Medium	
Hopper fill level	**Physical Attributes (size and splitability)**	Low	Tablet size and score configuration is determined by the tooling design. Tablet splitability is mainly related to the formulation compactability and compression force. The risk of hopper fill level to impact tablet physical attributes (size and splitability) is low.
	Assay	Medium	If the hopper fill level is suboptimal, the mass effect on flow could be insufficient to supply a consistent amount of blend to the feeder frame, thus impacting tablet assay, CU, and drug release. Ideally, the hopper fill level should be maintained at a constant level during the compression step. The risk of hopper fill level to impact these tablet CQAs is medium. It will be monitored during the compression step.
	Content Uniformity	Medium	
	Drug Release – whole tablets	Medium	
	Drug Release – split tablets	Medium	
Drop height of finished tablets	**Physical Attributes (size and splitability)**	Medium	A higher than optimal finished tablet drop height may affect tablet appearance. If the tablets chip, crack, cleave or break, then all tablet CQAs could be affected. The risk of the drop height on finished tablet CQAs is medium.
	Assay	Medium	
	Content Uniformity	Medium	
	Drug Release – whole tablets	Medium	
	Drug Release – split tablets	Medium	
Environment temperature	**Physical Attributes (size and splitability)**	Low	Routine environment temperature set point in the cGMP manufacturing facility is 25 ºC ± 5%. It will be monitored during tablet compression. The risk of environment temperature to impact tablet CQAs is low.
	Assay	Low	
	Content Uniformity	Low	
	Drug Release – whole tablets	Low	
	Drug Release – split tablets	Low	

Unit Operation: Compression			
Drug Product CQAs: Physical attributes (size and splitability), assay, content uniformity, drug release from both whole and split tablets			
Variables	**Drug Product CQAs**	**Risk Assessment**	**Justification and Initial Strategy**
Environment RH	**Physical Attributes (size and splitability)**	Low	Routine environment RH set point in the cGMP manufacturing facility is 40%-60%. It will be monitored during the compression step. The risk of environment RH to impact tablet CQAs is low.
	Assay	Low	
	Content Uniformity	Low	
	Drug Release – whole tablets	Low	
	Drug Release – split tablets	Low	

A series of experiments were undertaken to investigate the relationship between the input material attributes and process parameters related to compression and the output drug product quality attributes. Three lots of the optimized final blend (RD 64-66, 40 kg each) were manufactured at the pilot scale using a 7.5 cu ft blender for the compression studies. The observed bulk density for these three batches ranged from 0.45 g/cc to 0.52 g/cc.

Effect of Feeder Speed and Feeder Fill Depth

A screening study to investigate the impact of the compression process parameters on the tablet quality attributes was conducted. The study confirmed that feeder speed (8-20 rpm) and feeder fill (low to full) have no impact on quality over the ranges investigated.

Effect of Pre-compression Force, Compression Force and Press Speed

Pre-compression force, compression force and press speed (which is related to dwell time) can affect numerous quality attributes including hardness, friability, uniformity of weight, disintegration, and drug release. Therefore, a 2^3 full factorial DOE with one center point was performed to understand the effects of these parameters on these quality attributes. Table 87 presents the study design and acceptance criteria for the responses.

Table 87. Design of the 2^3 study to optimize tablet compression

Defining Relation **Resolution**	N/A (No aliased term in full factorial DOE)		
Input Material	Blend Batch No. RD-64, Pilot Scale, 40 kg Magnesium Stearate: 0.8% lubricated at 90 revolutions Tablet target weight: 263.44 mg		
Factors: Process Parameters		**Levels**	
		-1	**+1**
A	Pre-compression force (kN)	0.5	2.0
B	Compression force (kN)	7	11
C	Press speed (rpm)	20	60
Responses		**Target Ranges**	
Y_1	Hardness	4	11
Y_2	Friability	NMT 1.0 %	
Y_3	Weight Variability	Individual: Target ± 5% Composite: Target ± 3%	
Y_4	Disintegration Time	NMT 5 min	
Y_5	Drug Release	0.5 h: 25 – 35% 3 h: 35% – 45% 6 h: 55% – 75% 12 h: NLT 80%	
Y_6	Assay	95 – 105%	
Y_7	Content Uniformity	AV < 15	

Note to Reader: For demonstration purposes, hardness is the only response presented for data analysis.

The tablets were sampled after the press was run at the steady state of the specified DOE run conditions for at least five minutes. The half-normal plot presented in Figure 47 shows that only the main compression force had a significant impact on tablet hardness ($\alpha = 0.05$). Pre-compression force and press speed did not affect tablet hardness within the range studied. There was no interaction between these three parameters. The main effects plot in Figure 48 illustrates that an increase in main compression force resulted in an increase in tablet hardness. The compression force was specified at 7.0-11.0 kN, corresponding to the hardness range of 4.7-10.6 kP.

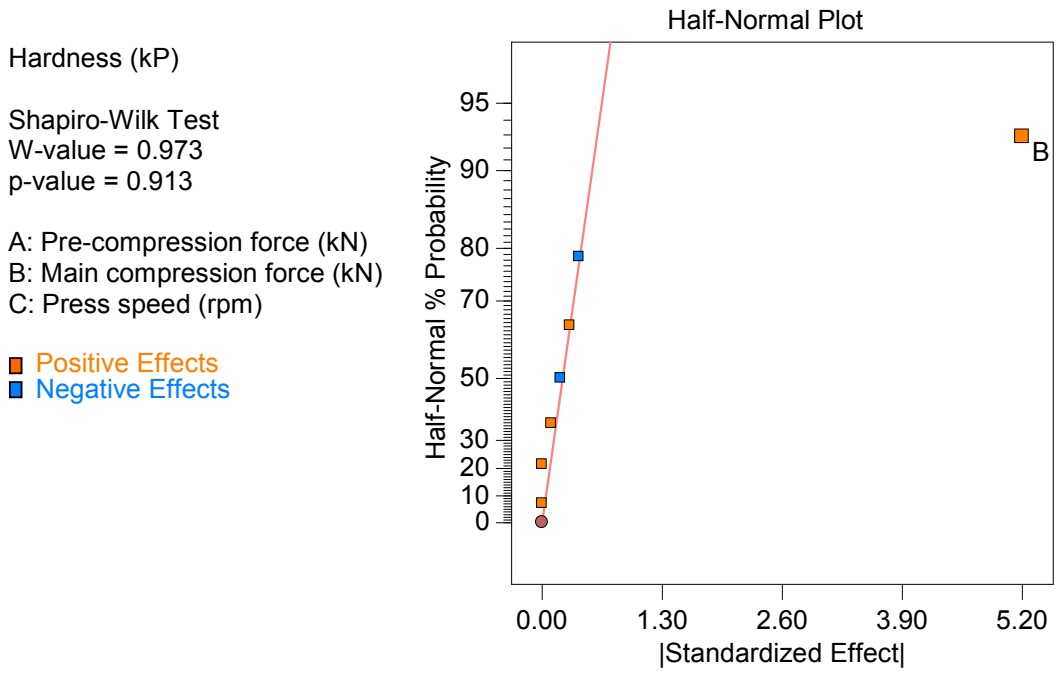

Figure 47. Half-normal plot of the process parameter effects on tablet hardness

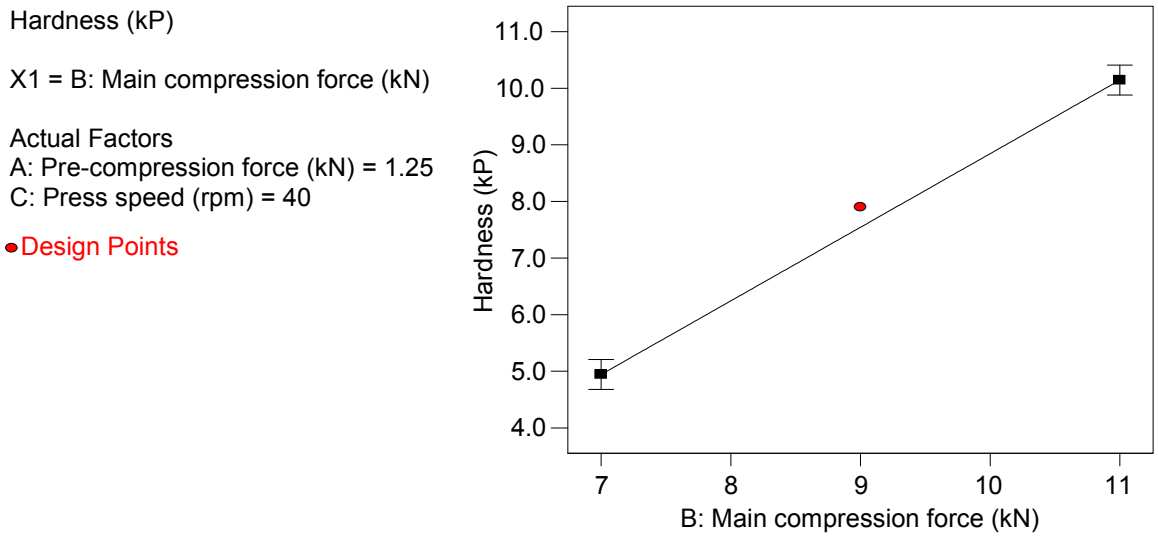

Figure 48. Main effect of the main compression force on tablet hardness

Bead integrity was examined using SEM on tablets compressed at 11 kN. Tablets shown in Figure 49 had a hardness of 10.6 kP. These images corroborate the drug release data as there was not any evidence of bead fracture in the tablets compressed at the highest compression force. Additionally, the drug release profile of the pre-compressed beads matched that of compressed tablets (f2 = 79).

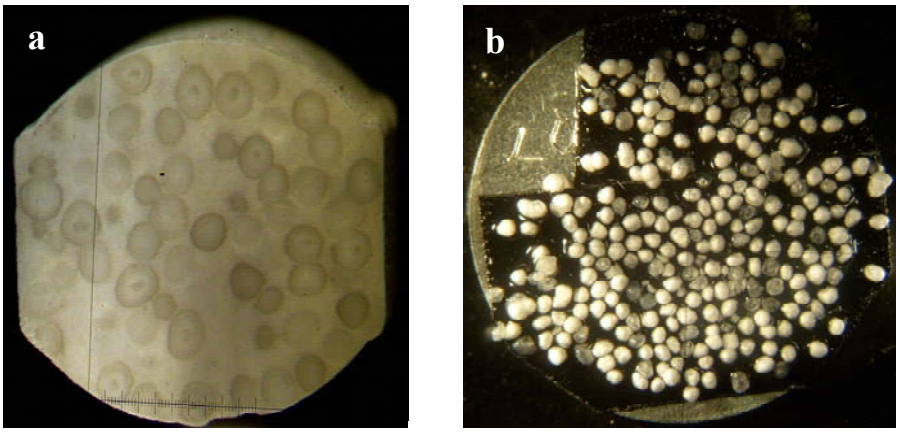

Figure 49. SEM images demonstrating bead integrity: (a) Cross section of a tablet compressed at 11 kP; (b) ER beads recovered from dissolution medium after 5 min

Within the range studied, pre-compression force, main compression force, and press speed did not show a significant impact on responses Y_2-Y_7 ($\alpha = 0.05$, data not shown). The pre-compression force, which is generally overridden by the compression force, was specified at 0.5-2.0 kN. Based upon the target individual tablet weight range of 263.44 mg (± 5 %), the press speed range was specified at 20-60 rpm.

Evaluation of Potential Segregation and Weight Variation during Compression at Pilot Scale

The compression process must provide the desired dose in each tablet by avoiding segregation of the uniform blend. Segregation during compression may occur due to longer run times and vibrations of the hopper and the press. Blend uniformity was demonstrated as described in Section 2.3.4. The potential for segregation of the blend during compression was investigated during compression of a 40 kg pilot scale batch (RD-65) by measuring content uniformity of tablets taken from ten approximately evenly spaced time points throughout the entire batch. The results of these studies are summarized in Figure 50 and demonstrate that content uniformity was well controlled. This data showed no evidence of segregation during compression as no trend for tablet strength was observed throughout the entire compression run.

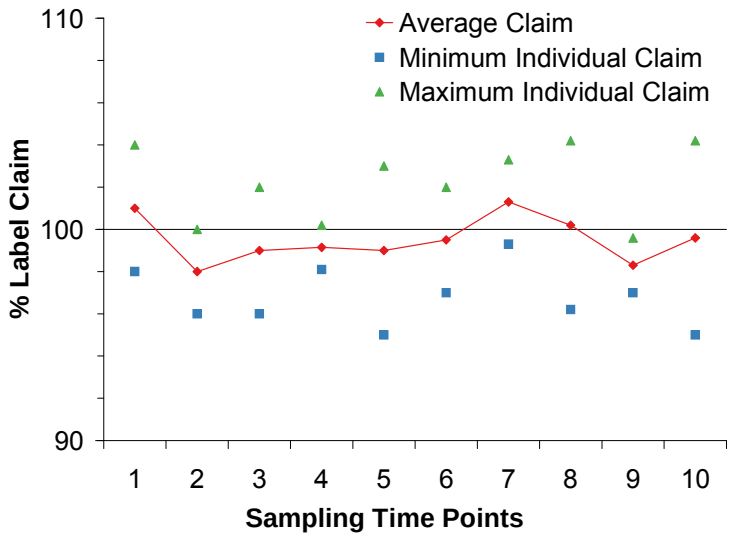

Figure 50. Content uniformity of the tablets at ten evenly space sampling time points during compression

A sample size of 20 tablets was pulled at each of the ten sampling time points. Weight variability was evaluated by weighing a composite sample of tablets (n = 20) as well as individual tablets (n = 10) collected at each time point. The results shown in Figure 51 demonstrate that weight variability was well controlled for the individual tablets within ± 5% of the target weight. The average tablet weight for a sample size of 20 tablets was controlled within ± 3% of the target weight. No trend for tablet weight was observed throughout the entire compression run.

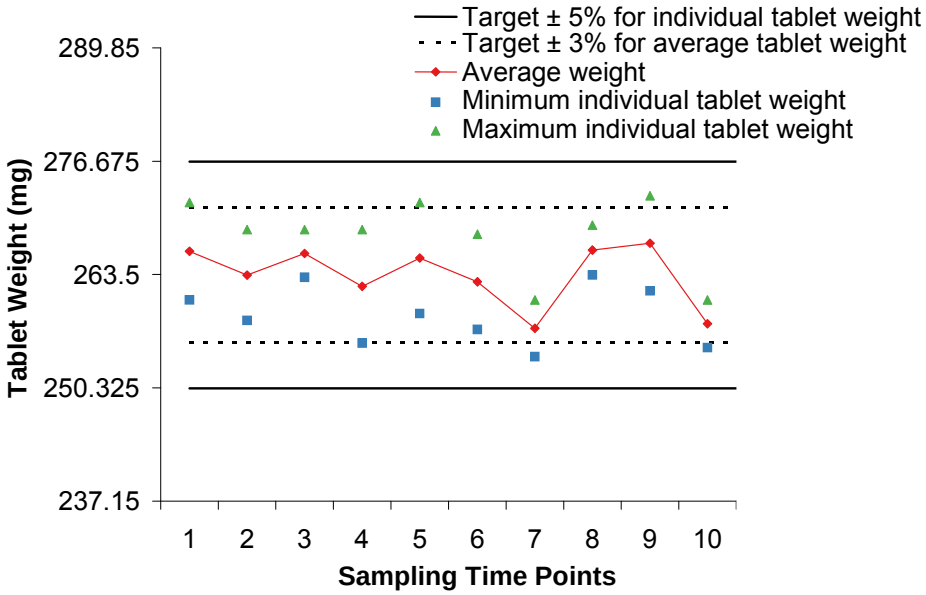

Figure 51. Weight variation of the tablets at ten evenly spaced sampling time points during compression

Performance of Split Tablets

To evaluate the performance of split tablets at both ends of the target hardness range, a 40 kg pilot scale blend batch (RD-66) was compressed with the pre-compression force and press speed set to 1.25 kN and 40 rpm, respectively. The first half of the batch used a main compression force set point of 7 kN and the second half of the batch used a main compression force set point of 11 kN. Table 88 presents the responses measured for both whole and split tablets.

Table 88. Evaluation of tablet quality attributes for both whole and split tablets (1.25 kN pre-compression force and 40 rpm press speed)

	Compression Force	Hardness	Weight Loss		Friability	Assay	CU	Disintegration Time	Drug Release			
			Hand	Tablet Splitter					0.5 h	3 h	6 h	12 h
	(kN)	(kP)			(%)	(%)	(AV)	(min)	(%)	(%)	(%)	(%)
Whole	7	4.7-5.1	N/A	N/A	0.09	97.3	4.2	1.25	31	38	60	84
	11	9.6-10.6	N/A	N/A	0.1	98.5	4.7	1.75	33	41	63	81
Split (n=12)	7	N/A	1.1	1.2	0.1	98.4	6.2	1.0	32	42	59	82
	11	N/A	1.0	0.9	0.2	97.6	5.9	1.25	31	39	64	85

The results of the investigation indicated that split tablets had well below 3% weight loss whether the tablets were split by hand or with a tablet splitter. Friability was not affected by tablet splitting as tablets with lower hardness (4.7 kP) still had acceptable friability results. Split tablets also met predefined targets for assay, content uniformity, disintegration and drug release. Drug release profiles for whole and split tablets were comparable at both the low end (f2 = 84) and high end (f2 = 83) of the target hardness range. The drug release profiles of the pre-compressed beads versus the compressed split tablet portions were also comparable (f2 = 81). In summary, the split tablets demonstrated equivalent performance to the whole tablets, suggesting that Example MR Tablets are designed effectively for half dosing.

Summary of Compression In-Process Controls

Based on the results of the studies undertaken to understand the process variables affecting compression, Table 89 lists the proposed in-process controls for the compression step.

Table 89. Proposed in-process controls for the compression step

Test	Frequency	Limits
Individual tablet weight (n = 10)	20 min	263.44 mg ± 5%
Composite tablet weight (n = 20)	20 min	5.269 g ± 3%
Hardness (n = 10)	20 min	Target: 8.0 kP Range: 4.7-10.6 kP
Thickness (n = 10)	20 min	Target: 5.75 mm Range: 5.60-5.90 mm
Disintegration* (n = 12)	3x during run	NMT 5 min
Friability* (sample weight = 6.5 g)	3x during run	NMT 1.0%

*Tested at the beginning, middle and end of the run.

Updated Risk Assessment of the Tablet Compression Process Variables

Risks identified during initial assessment of the compression process were reduced through development studies. The updated risk assessment is presented in Table 90.

Table 90. Updated risk assessment of the tablet compression process variables

Unit Operation: Compression			
Drug Product CQAs: Physical attributes (size and splitability), assay, content uniformity, drug release from both whole and split tablets			
Compression Variables	**Drug Product CQAs**	**Risk Assessment**	**Justification for the Reduced Risks**
Feeder speed	**Assay**	Low	In the range studied, the feeder speed had no impact on tablet assay, CU, or drug release. The same tablet press model will be used for pilot scale and commercial scale manufacture. Thus, the risk of feeder speed to impact tablet assay, CU and drug release is reduced from high to low.
	Content Uniformity	Low	
	Drug Release – whole tablets	Low	
	Drug Release – split tablets	Low	
Feeder fill depth	**Assay**	Low	In the range studied, the feeder fill depth had no impact on tablet assay, CU, or drug release. Thus, the risk of impact on tablet assay, CU and drug release is reduced from high to low.
	Content Uniformity	Low	
	Drug Release – whole tablets	Low	
	Drug Release – split tablets	Low	
Pre-compression force	**Physical Attributes (size and splitability)**	Low	The pre-compression force settings that were investigated did not result in tablet lamination or capping. No effect on tablet physical attributes (size and splitability), or drug release from whole or split tablets was observed. Thus, the risk of pre-compression force to impact the tablet physical attributes (size and splitability) and drug release is reduced from high to low.
	Drug Release – whole tablets	Low	
	Drug Release – split tablets	Low	
Compression force	**Physical Attributes (size and splitability)**	Low	The compression force is correlated to tablet hardness. However, in the range of force studied, there was no impact on the tablet physical attributes (size and splitability) or drug release from whole or split tablets. Thus, the risk of impact on these CQAs is reduced from high to low.
	Drug Release – whole tablets	Low	
	Drug Release – split tablets	Low	
Press speed	**Assay**	Low	The range of press speeds investigated had no impact on tablet assay, CU, or drug release. Thus, the risk of press speed to impact these tablet CQAs is reduced from high to low.
	Content Uniformity	Low	
	Drug Release – whole tablets	Low	
	Drug Release – split tablets	Low	

2.3.6 Exhibit Batch

Based on the product and process understanding gained throughout development and the established IVIVR, an exhibit batch (Batch No. ZAb041911) at pilot scale (40 kg) was manufactured. The in-process and release performance characteristics of the drug product were evaluated and are summarized in Table 91 and Table 92, respectively. Split tablets met the finished product release

requirements for assay, content uniformity, and drug release. Whole and split tablets met the similarity factor (f2) criteria for drug release.

The exhibit batch was used for a pivotal BE study which demonstrated bioequivalence to the RLD (see Section 1.4.3). In addition, an *in vitro* alcohol-induced dose dumping study was conducted using 0.1 N HCl with 5%, 20% and 40% (v/v) of Alcohol USP. For each condition, 12 units were tested and data was collected every 15 minutes for a total of two hours. Based on an analysis of the means, range and RSD, both whole and split tablets performed comparably to the RLD under each condition (data included in module 5.3).

Table 91. In-process testing results for the exhibit batch (Batch No. ZAb041911)

Test	In-process Control	Range Observed for Entire Batch
Individual tablet weight (n = 10)	Target: 263.44 mg ± 5% Range: 250.27 – 276.61 mg	259.32 – 266.21 mg
Composite tablet weight (n = 20)	Target: 5.269 g ± 3% Range: 5.006 – 5.532 g	5.157 – 5.386 g
Hardness (n = 10)	Target: 8.0 kP Range: 4.7 – 10.6 kP	7.5 – 9.3 kP
Thickness (n = 10)	Target: 5.75 mm ± 0.15 mm Range: 5.60 – 5.90 mm	5.67 – 5.81 mm
Disintegration (n = 12)	NMT 5 min	1.0 – 1.75 min
Friability (sample weight = 6.5 g)	NMT 1.0 %	0.09 – 0.1%

Table 92. Release testing results for the exhibit batch (Batch No. ZAb041911)

Test	Acceptance Criteria	Results	
		Whole Tablets	Split Tablets
Description	White capsule-shaped tablet debossed with "OGD" on one side of the breakline and "123" on the other side	White capsule-shaped tablet debossed with "OGD" on one side of the breakline and "123" on the other side	N/A
Identification	A. HPLC Retention time: corresponds to standard B. UV spectrum: corresponds to standard	Corresponds to standard	N/A
Assay	95.0% – 105.0%	99.6%	99.3%
Content Uniformity	AV < 15	4.2	6.1
Degradation Products	Individual unknown degradation product: NMT 0.2% Total degradation products: NMT 1.0%	Individual unknown degradation product: 0.06% Total degradation products: 0.3%	N/A
Drug Release (N = 12)	30 min: 25 – 35% 3 h: 35% – 45% 6 h: 55% – 75% 12 h: NLT 80%	30 min: 32% 3 h: 41% 6 h: 65% 12 h: 83%	30 min: 34% 3 h: 39% 6 h: 68% 12 h: 86%
		f2 = 83	
Residual Solvents	Complies with USP <467> Option 1	Complies with USP <467> Option I	N/A

2.3.7 Scale-up to Commercial Scale

Note to Reader: Currently, scale-up information is limited at the time of submission. The applicant should discuss product specific scale-up principles including their planned approach to the scale-up process. OGD will evaluate the applicant's plan to determine its adequacy. However, if a substantial amendment needs to be submitted due to the inadequacy of the scale-up plan, it may significantly extend the review process. It is the firm's discretion to submit scale-up data such as actual process verification information at the time of submission for a complex drug product which has a high risk of scale-up failure; however, in some cases it may be requested by OGD.

2.3.7.1 Scale-up of IR Granulation

Scale-up using a high shear granulator Collete Gral was performed previously for the IR granule formulation in ANDA aaaaaa, Section 2.3 (Appendix I). Table 93 summarizes the scaled granulation process utilizing the same equipment design and operating principles.

Table 93. Scale-up and acceptable operating ranges for the IR granulation

	Lab Scale	Pilot Scale	Commercial Scale
Batch load	2.0 kg	40.0 kg	180 kg
Active Powder Mixing			
Equipment model	Collette Gral 10	Collette Gral 300	Collette Gral 1200
Impeller speed	Low (285 rpm)	Low (125 rpm)	Low (75 rpm)
Mixing time	5 min	5 min	5 min
Granulation using Purified Water			
Equipment model	Collette Gral 10	Collette Gral 300	Collette Gral 1200
Impeller speed	Low (285 rpm)	Low (125 rpm)	Low (75 rpm)
Chopper speed	Low	Off	Off
Solution addition rate	60 g/min	1.3 kg/min	10.0 kg/min
Mixing time	12 min	12 min	12 min
Drying			
Equipment	Fluid Bed Dryer	Fluid Bed Dryer	Fluid Bed Dryer
Bed air temperature	52ºC (50 – 55 °C)	52ºC (50 – 55 °C)	52ºC (50 – 55 °C)
Milling			
Equipment	Fitzmill L1A	Fitzmill DA6	Fitzmill DA6
Screening mill	Screen size: 20 mesh	Screen size: 20 mesh	Screen size: 20 mesh
	Speed: 4740 ± 20 rpm	Speed: 2500 ± 20 rpm	Speed: 2500 ± 20 rpm

2.3.7.2 Scale-up of ER Beads Drug Layering and Polymer Coating

Scale-up Principles for Bottom Spray Fluid Bed Coating

Process variables most likely to impact the quality of coated beads were optimized at the pilot batch scale. A batch at commercial scale was used to confirm the critical process parameter ranges and consistent product performance for the drug layering and ER polymer coating unit operations. The commercial batch was processed in a Glatt GPCG -120 with a 32″ Wurster HS insert. The 32″ insert has three partition columns and spray nozzles. Figure 52 illustrates the key operational features of this equipment, specifically the three partition columns and spray nozzles. Each of these three configurations has the same geometry and dimensions as the single-spray unit (18″ Wurster HS insert with a partition column diameter of 219 mm) used for pilot scale processing.

Figure 52. Glatt GPCG-120 with a 32″ Wurster insert used at commercial scale

Linear scale-up of drug layering using a fluid bed process is possible by utilizing properly designed distribution plates and chambers and by maintaining the ratios of air volume to distribution plate area and spray rate to air volume. Assuming that bed fill levels are the same and that the chamber design and the distribution plate in each piece of equipment is geometrically similar, fluid bed scaling from a coater with an 18″ insert to one with a 32″ insert is straightforward. The number of nozzles, air volume, and total spray rate at the 32″ insert scale are all a direct multiple of the parameters optimized in a single nozzle unit at the 18″ insert scale. The spray rate and atomization air pressure per nozzle are maintained the same as those optimized at the pilot scale. The linear air flow rate in the equipment is kept constant as the process is scaled up. The air volume is scaled up by a factor of three based upon the distribution plate area.

During scale-up, product temperature and relative humidity of the inlet air (dew point) are scale-independent variables and kept the same as the values optimized in the pilot scale process development study. Table 94 compares the fluid bed equipment used at pilot and commercial scale.

Table 94. Fluid bed equipment for pilot and commercial scale

	Lab Scale	Pilot Scale	Verification Batch at Commercial Scale
Equipment model	Glatt GPCG - 5	Glatt GPCG - 60	Glatt GPCG - 120
Fluid bed insert	7″ Wurster	18″ Wurster	32″ Wurster
Equipment working capacity*	8.3 L	102 L	405 L
Partition column diameter	89 mm	219 mm	219 mm
Number of partition columns	1	1	3
Nozzle diameter	1.0	1.2 mm	1.2 mm
Number of spray nozzles	1	1	3

*Volume outside of the partition column at rest on the orifice plate

Scale-up of the Drug Layering Process

A verification batch at commercial scale was manufactured using the target settings listed in Table 95 based on linear scale-up of the pilot scale process robustness study. The spray rate and atomization air pressure were maintained at the pilot scale settings per nozzle. Partition height was set at 40 ± 10 mm on the basis of prior experience to maintain optimal fluidization.

Table 95. Equipment and process parameters for pilot and commercial scale drug layering

	Pilot Scale	Verification Batches at Commercial Scale
Equipment model	Glatt GPCG - 60	Glatt GPCG - 120
Starting weight of substrate	40 kg	140 kg
Theoretical ending weight of batch (~ 41% weight gain based on coating substrate weight)	56 kg	198 kg
Estimated use of capacity*	65%	58%
Partition height	45 ± 3 mm	45 ± 3 mm
Product temperature (°C)	45 ± 3 °C	45 ± 3 °C
Dew point (°C)	10 ± 2 °C	10 ± 2 °C
Air volume (cfm)	600 ± 90 cfm	1800 ± 270 cfm
Spray rate per nozzle (g/min)	210 ± 30 g/min	210 ± 30 g/min
Total spray rate (g/min)	210 ± 30 g/min	630 ± 90 g/min
Atomization air pressure per nozzle (bar)	2.5 ± 0.5 bar	2.5 ± 0.5 bar

*Calculated based on bulk density of drug-layered beads = 0.85 g/cc
Note: All coating process parameter settings were target values at steady state.

Table 96 presents the data collected for the quality attributes of the drug-layered beads. The drug-layered beads manufactured at commercial scale were carried forward for further processing.

Table 96. Quality attributes of drug-layered beads manufactured at commercial scale

LOD	PSD			Assay	Process Efficiency
	Fines < 250 µm	Agglomerates > 420 µm	250 µm < usable fraction < 420 µm		
(%)	(%)	(%)	(%)	(%)	(%)
0.8	0.8	0.2	98.8	99.9	99.6

Scale-up of the ER Polymer Coating Process

Similar to drug layering, scale-up of the ER polymer coating process was also a linear scale-up from an 18″ to a 32″ Wurster HS insert. A verification batch at commercial scale was manufactured using the equipment and process parameters optimized during the pilot scale process robustness study. The target settings are detailed in Table 97. Drug-layered beads from the previous unit operation were loaded into the fluid bed coater after testing was completed for performance characteristics such as particle size distribution and LOD.

Table 97. Equipment and process parameters for pilot and commercial scale ER polymer coating

	Pilot Scale	Verification Batches at Commercial Scale
Equipment model	Glatt GPCG - 60	Glatt GPCG - 120
Starting weight of drug-layered beads	40 kg	180 kg
Theoretical ending weight of batch (~ 36% weight gain based on drug-layered bead weight)	54 kg	245 kg
Estimated use of capacity*	62%	71%
Partition height	45 ± 3 mm	50 ± 3 mm
Product temperature (°C)	31 ± 3	31 ± 3
Dew point (°C)	10 ± 2 ºC	10 ± 2 ºC
Air volume (cfm)	660 ± 60	1980 ± 180
Spray rate per nozzle (g/min)	120 ± 20	120 ± 20
Total spray rate (g/min)	120 ± 20	360 ± 60
Atomization air pressure per nozzle (bar)	2.5 ± 0.5	2.5 ± 0.5

*Calculated based on the bulk density of the ER coated beads = 0.85 g/cc

Note: All coating process parameter settings were target values at steady state.

Based on previous experience with Wurster coating, it is possible for process efficiency to differ between pilot and commercial scale. The actual polymer coating level applied to the beads will vary based on the process efficiency. During the verification batch, samples were pulled at different theoretical polymer coating levels of 26%, 27%, 28%, 29%, 30%, 31% and 32% to determine the optimum theoretical polymer coating level that would result in the desired drug release profile. These samples were dried until the LOD was less than 2% and evaluated for drug release by dissolution testing.

Table 98 presents the data collected for the quality attributes of the ER coated beads.

Table 98. Quality attributes of the ER coated beads manufactured at commercial scale (Batch No. COM001)

LOD	PSD			Assay	Process Efficiency
	Fines < 350 µm	Agglomerates > 590 µm	350 µm < usable fraction < 590 µm		
(%)	(%)	(%)	(%)	(%)	(%)
0.9	0.7	0.1	99.2	98.9	99.0

The first commercial verification batch (Batch No. COM001) of ER coated beads with a theoretical polymer coating level between 30-32% exhibited slower release when compared to the pivotal bio-batch (Lot No. ZAb041911) manufactured at pilot scale and failed the predefined drug release

specification (data not shown). The ER coated beads with 26% theoretical polymer coating showed faster drug release when compared to the pivotal bio-batch. However, there was no significant difference between beads with 27-29% theoretical polymer coating and the pivotal bio-batch.

The ER coated beads were further examined using SEM and no obvious difference in film quality was observed. In order to understand whether the drug release failure was due to a film coat thickness change, the usable ER beads (350-590 µm) were further sieved to minimize the effect of bead size on film thickness measurement. The fraction between sieve No. 40 and 35 (420-500 µm) was collected from both the verification batch (Lot No. COM001) and the pivotal bio-batch. Samples were sent to an outside testing laboratory for film thickness testing by Terahertz Pulse Imaging (TPI)[14] and the data presented in Figure 53 was obtained.

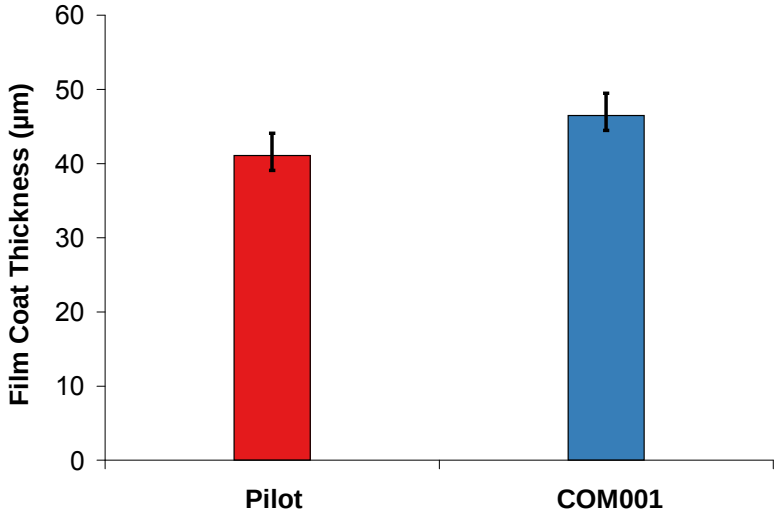

Figure 53. Film coat thickness of beads with 30% theoretical polymer coating from pilot (red) and commercial (blue) batches

Drug-layered beads with 30% theoretical polymer coating showed an increase in total film thickness from 41 ± 2 µm at pilot scale to 46 ± 3 µm at commercial scale. The $T_{50\%}$ increased from 5.6 hours to 6.6 hours and failed to meet the pre-defined CQA acceptance criteria. This could potentially be attributed to the fact that in the commercial scale equipment, 71% of capacity was utilized compared to 62% use of capacity at pilot scale. When the bed fill level was low at pilot scale, the partition height was also set low, which may limit the mass flow of beads into the partition column. Therefore, coating material may be lost to the partition column wall, resulting in overall lower process efficiency at pilot scale.

In order to achieve similar drug release and bioequivalence results as those obtained at the pilot scale, the theoretical polymer coating level was reduced from 30% to 28% based on the drug release

[14] Taday P.F., *et al.* Nondestructive analysis of tablet coating thickness using terahertz pulsed imaging, *J. Pharm. Sci. 2005; 94 (1); 177-183.*

results of samples with different coating levels (26-32%) pulled during the first verification batch. Using the same process parameters, a second verification batch (Batch No. COM002) at commercial scale was manufactured with a 28% theoretical polymer coating. Table 99 summarizes LOD, PSD, assay and process efficiency results.

Table 99. Quality attributes of the ER coated beads manufactured at commercial scale (Batch No. COM002)

LOD	PSD			Assay	Process Efficiency
	Fines < 350 µm	Agglomerates > 590 µm	350 µm < usable fraction < 590 µm		
(%)	(%)	(%)	(%)	(%)	(%)
0.8	0.7	0.2	99.1	98.6	99.0

Similar to the evaluation of the first verification batch (Batch No. COM001), a non-destructive TPI method performed at an outside testing lab was used to measure polymer coating thickness of the second verification batch (Batch No. COM002). Results indicated that a difference in film thickness between the pivotal bio-batch and the second verification batch was not statistically significant ($\alpha = 0.05$). Similarity in drug release characteristics for the ER coated beads was also tested and confirmed using the established discriminatory dissolution method (data not shown).

ER coated beads (Batch No. COM002) were subsequently blended with extragranular excipients and compressed into tablets. The final drug product exhibited a drug release profile equivalent to tablets from the pilot scale bio-batch and the RLD as shown in Figure 54.

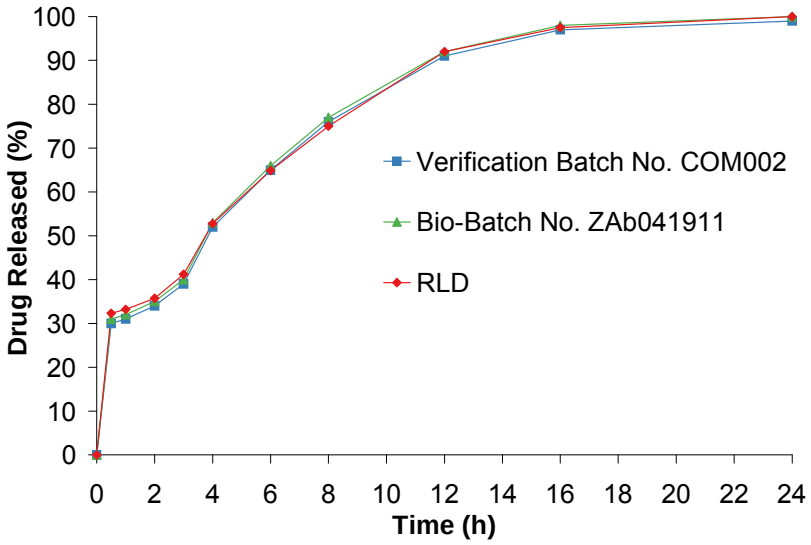

Figure 54. Drug release profiles of the 2nd verification batch (COM002) and the bio-batch (ZAb041911)

Although the formulation for Example MR Tablets was modified to reduce the theoretical polymer coating level by 2%, no additional bioequivalence studies were necessary. The comparable *in vitro* drug release between the second commercial batch and the bio-batch demonstrated in Figure 54 and the established IVIVR ensure the desired performance of the drug product *in vivo*.

2.3.7.3 Scale-up of Blending and Compression

The equipment employed in the critical unit operations to manufacture the trial, pilot and commercial batches have the same principle of operation as outlined in Table 100. However, the equipment capacity varies based on the intended size of the commercial batches. In order to avoid scale-up issues, the same type of equipment was used.

Table 100. Scale-up of MR Tablet blending, lubrication and compression

Unit Operation	Lab Scale	Pilot Scale	Commercial Scale	Operating Principle	Constant Parameter
Blending	V (tumble) blender (16 qt)	V (tumble) blender (7.5 cu ft)	V (tumble) blender (30 cu ft)	Diffusion Mixing	N_{rev} = 300 Use inline NIR for endpoint determination
Lubrication	V (tumble) blender (16 qt)	V (tumble) blender (7.5 cu ft)	V (tumble) blender (30 cu ft)	Diffusion Mixing	N_{rev} = 90
Compression	10-station Rotary Tablet Press with 'B' type tooling	49-station Rotary Tablet Press with 'B' type tooling	49-station Rotary Tablet Press with 'B' type tooling	Compression	Individual Weight: 263.44 mg ± 5% Hardness: 8.0 kP (4.7 – 10.6 kP) Thickness: 5.75 mm ± 0.15 mm

Scale-up of the Blending Process

The inline NIR method developed and validated at pilot scale was verified at commercial scale and will be used for blending endpoint determination of all commercial batches. The target endpoint for blending will remain at 300 revolutions of the blender; however, the actual endpoint is based on inline NIR measurements. To assess the homogeneity of the blend, a moving block RSD was calculated for each moving block of ten consecutive spectra and plotted as a function of time. The blend was considered uniform once the RSD was below 5% for ten consecutive measurements. Table 101 summarizes the blending process parameters and endpoints for the different scales.

Table 101. Scale-up of blending process parameters for diffusion mixing in a V-blender

Scale (V-blender size)	Blender rotation speed	Target N_{rev}	Target mixing time	Blend Uniformity by NIR
	(rpm)		(min)	(% RSD)
Lab Scale (16 qt)	25	300	12	1.19
Pilot Scale (7.5 cu ft)	15	300	20	1.02
Commercial Scale (30 cu ft)	10	300	30	1.20

Scale-up of the Tableting Process

The tablet compression machine is equipped with a modern compression force feedback control that adjusts the fill depth to ensure target tablet weight and, consequently, content uniformity. Based on compression force feedback, the fill cam below the die table adjusts the lower punch to the

appropriate height to control fill depth (and ultimately tablet weight). Detailed parameters that affect the tableting process were already explored and discussed in Section 2.3.5. Commercial batches of drug product produced comparable results as those presented in Section 2.3.5 because the same model of rotary tablet press was used and tablets were compressed at the same speed. Therefore, dwell time remains unchanged during scale-up.

2.3.8 Updated Risk Assessment of the Drug Product Manufacturing Process

During process development, high risks for each unit operation were addressed. Experimental studies were defined and executed in order to establish additional scientific knowledge and understanding, to allow appropriate controls to be developed and implemented, and to reduce the risk to an acceptable level. After detailed experimentation, the initial manufacturing process risk assessment was updated in-line with the current process understanding. Table 102 presents how the application of the control strategy to the manufacturing process has reduced the identified risks. Table 103 provides the justification for the reduced risk following process development.

Table 102. Updated risk assessment of the manufacturing process for Example MR Tablets, 10 mg

	Process Steps						
Drug Product CQAs	**IR granulation**	**ER beads: drug layering**	**Sieving I**	**ER beads: polymer coating**	**Sieving II**	**Blending and Lubrication**	**Compression**
Physical Attributes (size and splitability)	Low*	Low*	Low*	Low*	Low*	Low*	Low
Assay	Low*	Low	Low*	Low*	Low*	Low	Low
Content Uniformity	Low*	Low	Low*	Low*	Low*	Low	Low
Drug Release – Whole tablets	Low*	Low*	Low*	Medium	Low	Low	Low
Drug Release – split tablets	Low*	Low	Low*	Medium	Low	Low	Low
Drug Release – alcohol-induced dose dumping	N/A*	N/A*	N/A*	Low*	Low*	Low*	Low*

*The level of risk was not reduced from the initial risk assessment.

Table 103. Justification for the reduced risks of the manufacturing process for Example MR Tablets, 10 mg

Process Steps	Drug Product CQAs	Justification
ER beads: drug layering	**Assay**	The drug layering process was optimized to minimize spray drying and agglomeration. Fines and agglomerates generated during the verification batch were both below 1%. Drug-layered beads had an assay within the target range of 95.0 – 105.0%. Within the range studied, the risk of drug layering process variables to impact tablet assay is reduced from high to low.
	Content Uniformity	Optimal fluidization and uniform spray was achieved using process parameters within the range studied. The drug-layered beads had acceptable uniformity. Thus, the risk of drug layering process variables to impact tablet CU is reduced from medium to low.

Process Steps	Drug Product CQAs	Justification
	Drug Release – split tablets	Split tablets had adequate CU with an AV < 7 and the drug release profile between whole and split tablets met the similarity factor (f2 > 80) criteria. The risk of the drug layering process variables to impact drug release from split tablet is reduced from medium to low.
ER beads: polymer coating	**Drug Release – whole tablets**	The ER polymer coating process was optimized to minimize spray drying and agglomeration. Fines and agglomerates were both below 1% in the verification batches. Within the range studied, the risk of ER polymer coating process variables to impact drug release from whole tablets is reduced at pilot scale. However, some variability in process efficiency and ER polymer coating layer thickness was observed during scale-up from pilot to commercial scale. The theoretical polymer coating level was decreased from 30% to 28% to achieve the target drug release profile. The impact of ER polymer coating process variability on drug release from whole tablets needs to be further monitored during validation and routine commercial manufacturing to gain additional knowledge and to facilitate continual improvement. Therefore, the risk for drug release from whole tablets is considered acceptable but at a medium level.
	Drug Release – split tablets	Split tablets had adequate CU with an AV < 7 and comparable drug release to whole tablets (f2 > 80). The risk is reduced but because drug release is sensitive to polymer coating level based on the BE studies, further evaluation during process validation and routine commercial manufacturing is needed to gain additional knowledge. Therefore, the risk of ER polymer coating process variables to impact split tablet drug release is medium.
Sieving II	**Drug Release – whole tablets**	The risk of damaging the coated beads is reduced with the instructions "do not use force during sieving" included in the batch record. The risk of sieving II to impact drug release from whole tablets is reduced from medium to low.
	Drug Release – split tablets	Split tablets had adequate CU with an AV < 7. The risk of sieving II to impact drug release from whole tablet is reduced from medium to low. As such, the risk of this step to impact drug release from split tablets is also reduced from medium to low.
Blending and Lubrication	**Assay**	The blending process was optimized and the risk of segregation was reduced during prototype formulation optimization by using two MCC grades. The risk of the blending and lubrication process variables to impact tablet assay is reduced from medium to low.
	Content Uniformity	Inline NIR was utilized to ensure blend uniformity and no segregation was observed after discharge from the blender. In addition, tablet CU met the requirements set forth in USP <905>. The risk of the blending and lubrication process variables to impact tablet CU is reduced from high to low.
	Drug Release – whole tablets	The blending process was optimized and blend uniformity was achieved by utilizing inline NIR for endpoint determination. The lubrication process was also optimized. Whole tablets demonstrated acceptable CU with an AV < 5, exhibited rapid disintegration, and met the target drug release profile. The fact that the tablets showed rapid disintegration and had no appearance defects during the entire compression run provides evidence that the disintegrant and lubricant were adequately distributed in the final blend. Therefore, the risk of the blending and lubrication process variables to impact drug release from whole tablet is reduced from medium to low.
	Drug Release – split tablets	Both whole and split tablets complied with USP <905> and demonstrated acceptable CU. Similar drug release profiles between whole and split tablets were obtained (f2 > 80). The risk is reduced from high to low.
Compression	**Physical Attributes (size and splitability)**	The shape and score configuration of the tablets were defined and compression process parameters were optimized. The tablet has a similar size as the RLD tablet. Tablets were easily split by the target patient population. Thus, the risk of the compression process variables to impact tablet physical attributes (size and splitability) is reduced from high to low.

Process Steps	Drug Product CQAs	Justification
	Assay	Feeder speed, feeder fill depth and press speed were investigated and acceptable tablet assay (95 – 105%) was achieved within the studied ranges. The risk of the compression process variables to impact tablet assay is reduced from high to low.
	Content Uniformity	Tablets were sampled at ten evenly spaced time intervals during compression of a batch and CU testing at each time point was performed. The data revealed no evidence of segregation in the hopper. The risk of impact on tablet CU is reduced from high to low.
	Drug Release – whole tablets	The compression process was optimized. Bead integrity was confirmed after tablet compression at the highest force studied. The drug release from whole tablets was not significantly impacted by the compression force within the studied range. Therefore, the risk of the compression process variables to impact drug release from whole tablets is reduced from high to low.
	Drug Release – split tablets	The split tablet portions demonstrated adequate CU and comparable drug release to the whole tablets. Thus, the risk of the compression process variables to impact drug release from split tablets is reduced from high to low.

2.4 Container Closure System

To be consistent with the RLD, the drug product Example MR Tablets, 10 mg, is intended to be labeled for storage at 25 °C (77 °F) with excursions permitted to 15-30 °C (59 – 86 °F). The innovator has chosen round white opaque HDPE bottles with an induction seal liner and child resistant (CR) closure. Example MR Tablets, 10 mg, will be similarly packed and the bottle pack details are summarized in Table 104.

Table 104. Proposed commercial packaging for Example MR Tablets, 10 mg

Count	HDPE Bottle	Closure
30 Tablets	40 cc	33 mm white CR cap with pulp liner
90 Tablets	60 cc	38 mm white CR cap with pulp liner

Information on conformance to USP <661> and USP <671>, food safety certification, and stability data available to date can be found in the relevant sections of Module 3. The selected commercial packaging provides adequate protection from light, heat, oxygen, and moisture and is suitable for its intended use.

2.5 Microbiological Attributes

An accelerated stability study of prototype F-2 demonstrated that the drug product has low water activity and is not capable of supporting microbial growth. Routine microbiological testing of Example MR Tablets is unnecessary due to the low water activity of the product, controls on incoming raw materials, and controls on in-process water content.

2.6 Compatibility

This section is not applicable because the drug product is a solid oral dosage form and there are no reconstitution diluents.

2.7 Control Strategy

Note to Reader: The control strategy is "a planned set of controls, derived from current product and process understanding, that assures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control."[15]

The control strategy for Example MR Tablets is built upon the outcome of extensive product and process understanding studies. These studies investigated the material attributes and process parameters that were deemed high risk to the CQAs of the drug product during the initial risk assessment. In some cases, variables considered medium risk were also investigated. Through these systematic studies, the CMAs and CPPs were identified and the acceptable operating ranges were established. For the drug layering and the ER polymer coating unit operations, a design space was established at both lab and pilot scale. All variables ranked as high risk in the initial risk assessment are included in the control strategy because the conclusion of the experiments was dependant on the range studied and the complex multivariate relationship between variables. Thus, the control strategy is an integrated overview of how quality is assured based on current process and product knowledge. The control strategy may be further refined based on additional experience gained during the commercial lifecycle of the product. However, any post-approval changes should be reported to the agency in accordance with CFR 314.70 and should follow steps as outlined by guidances used for scale-up and post-approval changes.

2.7.1 Control Strategy for IR Granules

The control strategy for the commercial manufacture of IR granules was first submitted in ANDA aaaaaa (Appendix I). Table 105 summarizes the proven acceptable ranges for each critical material attribute and process parameter involved in the granulation unit operation for the IR portion of the MR tablets.

[15] ICH Harmonised Tripartite Guideline: Q10 Pharmaceutical Quality Systems. June 2008.

Table 105. Control Strategy for IR granules

Factor	Attribute/ Parameter	Range studied	Set point for the verification batch	Validated operating range for commercial scale (min, max)	Purpose of control
IR Granules Input Material Attributes					
Z	Particle size distribution	d_{10}: 1- 10 µm d_{50}: 10-30 µm d_{90}: 25-50 µm	d_{10}: 5 µm d_{50}: 20 µm d_{90}: 35 µm	d_{10}: 1- 10 µm d_{50}: 10-30 µm d_{90}: 25-50 µm	To reduce granulation process variability
Microcrystalline Cellulose (MCC), Grade 200	Particle size distribution	d_{50}: 150-250 µm	d_{50}: 196 µm	d_{50}: 150 -250 µm	
Lactose Monohydrate	Particle size distribution	d_{50}: 50-100 µm	d_{50}: 65 µm	d_{50}: 50-100 µm	
Povidone (PVP), K30	K-value	Used material within in-house spec (K-value: 29-32)	30	29-32	To ensure consistent binding functionality
Sodium Starch Glycolate (SSG), Type A	Particle size distribution	d_{50}: 50-100 µm	d_{50}: 65 µm	d_{50}: 50-100 µm	To ensure batch to batch consistency
	Degree of substitution*	0.25-0.35	0.30	0.25-0.35	
Powder Mixing and Granulation Process Variables (Validated Process)					
	Impeller speed	Low and High	Low	Low	To ensure IR granule CQAs (PSD and bulk density) are met consistently
	Chopper speed	On and Off	Off	Off	
	Powder mixing time	2-10 min	5 min	2-10 min	
	Granulation mixing time	10-20 min	12 min	10-20 min	
	Solution addition rate	5-20 kg/min	10 kg/min	5-20 kg/min	
	Granulation fluid quantity*	32-42% w/w	36.5% w/w	35-38% w/w	
Drying Process Variables and In-Process Controls (Validated Process)					
	Drying	50-55 °C	52 °C	50-55 °C	To ensure low water activity in order to prevent microbial growth
	Water content	NMT 2.0%	NMT 2.0%	NMT 2.0%	
Milling and Blending Process Variables and In-process controls (Validated Process)					
	Milling Speed	4740 rpm	2500 rpm	2500 ± 20 rpm	To ensure IR granule PSD is met consistently
	Mill screen size	20	20	20	
	Blend Uniformity, (% RSD)*		95.0-105.0% NMT 3.0%	95.0-105.0% NMT 3.0%	To ensure tablet CU is met consistently
IR Granules In-Process Controls					
Granule size distribution*		Retained on 45 mesh (coarse granules > 350 µm): NMT 5% Retained on 60 mesh (> 250 µm, but < 350 µm): NLT 85% Retained on fine collector (< 250 µm): NMT 10%			
LOD		< 2.0%			
Dissolution*		NLT 80% in 30 min in 0.1 HCl			
Assay*		95.0 – 105.0% w/w of label claim			

*critical input material attributes (CMA), critical process parameters (CPP) or critical quality attributes (CQA) of in-process material or final drug product

2.7.2 Control Strategy for ER Coated Beads

Since extensive DOE studies were carried out during the formulation and process development of the ER coated beads, a pilot scale (40 kg) design space for critical parameters has been established. Table 106 summarizes the proposed ranges for the commercial manufacture of ER coated beads. Because dissolution apparatus 3 has been used to establish an IVIVR, this method was selected and validated for quality control of the ER coated beads and the release assay of the final drug product.

Note that the process parameters presented in the control strategy are the target values achieved at steady state.

Table 106. Control Strategy for ER beads

Factor	Attribute/ Parameter	Range studied	Set point for the verification batch	Proposed operating range for commercial scale (min, max)[1]	Purpose of control
ER Coated Beads Input Material Attributes					
Z	Particle size distribution	d_{10}: 1- 10 µm d_{50}: 10-30 µm d_{90}: 25-50 µm	d_{10}: 5 µm d_{50}: 20 µm d_{90}: 35 µm	d_{10}: 1- 10 µm d_{50}: 10-30 µm d_{90}: 25-50 µm	To ensure batch to batch consistency (same as Example IR Tablets)
Microcrystalline Cellulose (MCC) beads	Bead size distribution*	Fraction between 250-350 µm was used	Fraction between 250-350 µm was used	Fraction between 250-350 µm was used	To prevent segregation and to reduce coating process variability
Povidone (PVP), K30	K-value	Used material within in-house spec (K: 29-32)	30	29-32	To ensure consistent binding functionality
Kollicoat SR 30 D	Acetic acid content	0.5-1.5%	1.4%	NMT 1.5%	To ensure desired drug release from ER coated beads is achieved consistently
	Poly vinyl acetate content	Used material within in-house spec (25-29 g/100g)	27 g/100g	25-29 g/100g	
	Povidone* content	Used material within in-house spec (2.5-2.9%) + 0-2.7% additional	2.7% (as is) 0% additional	2.5-2.9% (as is) 0% additional	
	Apparent viscosity	50-90 mPa•s	88 mPa•s	50-90 mPa•s	
Talc	Particle size	Used material within in-house spec d_{50}: 2-8 µm NLT 99% passing 325 mesh (44 µm) Used as-is	d_{50}: 4.7 µm 99.9% passing 325 mesh (44 µm)	d_{50}: 2-8 µm NLT 99% passing 325 mesh (44 µm)	To ensure batch to batch consistency and to reduce nozzle and tubing clogging

Factor	Attribute/ Parameter	Range studied	Set point for the verification batch	Proposed operating range for commercial scale (min, max)[1]	Purpose of control
Drug Layering Process Parameters					
Drug solution preparation	Mixing time	Mix until dissolved but NLT 1 hour	Mix until dissolved (1.5 hour)	Mix until dissolved but NLT 1 hour	To ensure target assay of drug-layered beads is achieved consistently
Drug solution	Holding time	0-48 hr	8 hr	Up to 48 hr	
Wurster column coating	Atomization air pressure	1.2 -2.0 bar (lab) 2.0-3.0 bar (pilot) 2.5 bar (bio-batch)	2.5 bar	2.5 ± 0.5 bar	
	Spray rate per nozzle*	25-45 g/min (lab) 180-240 g/min (pilot) 210 g/min (bio-batch)	210 g/min (total spray rate: 630 g/min)	210 ± 30 g/min (total spray rate: 630 ± 90 g/min)	
	Product temperature*	42-50 °C (lab) 42-48 °C (pilot) 45 °C (bio-batch)	45 °C	45 ± 3 °C	
	Air volume*	80-120 cfm (lab) 510-690 cfm (pilot) 600 cfm (bio-batch)	1800 cfm	1800 ± 270 cfm	
	Use of capacity	79% (lab) 65% (pilot)	58%	58%	
Drug-Layered Beads In-Process Controls					
Beads size distribution*		Retained on 40 mesh (Agglomerates > 420 μm): NMT 5% Retained on 60 mesh (250 μm < usable fraction < 420 μm): NLT 90% Retained on fine collector (Fines < 250 μm): NMT 5%			
LOD		< 2.0%			
Assay*		95.0 – 105.0% w/w of label claim			
Content Uniformity*		RSD < 5.0%			

Factor	Attribute/ Parameter	Range studied	Set point for the verification batch	Proposed operating range for commercial scale (min, max)[1]	Purpose of control
ER Polymer Coating Process Parameters					
Coating dispersion preparation	Mixing time	Mix for at least 1 hour before spraying and mix continuously during the entire coating process	Mix for at least 1 hour before spraying and mix continuously during the entire coating process	Mix for at least 1 hour before spraying and mix continuously during the entire coating process	To ensure desired drug release from ER coated beads is achieved consistently
Coating dispersion	Holding time	0-48 hr	8 hr	Up to 48 hr	
Wurster column coating	Air volume*	70-170 cfm (lab) 600-720 cfm (pilot) 660 cfm (bio-batch)	1980 cfm	1980 ± 180 cfm	
	Atomization air pressure	1.2-2.0 bar (lab) 2.0-3.0 bar (pilot) 2.5 bar (bio-batch)	2.5 bar	2.5 ± 0.5 bar	
	Spray rate per nozzle*	10-30 g/mim (lab) 100-140 g/min (pilot) 120 g/min (bio-batch)	120 g/min (total spray rate: 360 g/min)	120 ± 20 g/min (total spray rate: 360 ± 60 g/min)	
	Product temperature*	25-39 °C (lab) 28-36 °C (pilot) 31 °C (bio-batch)	31 °C	31 ± 3 °C	
	Use of capacity	77% (lab) 62% (pilot)	71%	71%	
	Theoretical polymer coating level*	20-40% (formulation study) 25% (1st BE) 30% (passed) and 35% (failed) (2nd BE) 30% (process study) 30% (bio-batch)	30% (1st verification batch failed[2]) 28% (2nd verification batch passed)	28 ± 1%	
ER Coated Beads In-Process Controls					
Beads size distribution*		Retained on 30 mesh (Agglomerates > 590 µm): NMT 5% Retained on 45 mesh (350 µm < usable fraction < 590 µm): NLT 90% Retained on fine collector (Fines < 350 µm): NMT 5%			
LOD		< 2.0%			
Assay*		95.0 – 105.0% w/w of label claim			
Drug release*,[3]		$T_{20\%}$ 2.5 ± 0.2 h $T_{50\%}$ 4.5 ± 1.0 h $T_{80\%}$ 10.0 ± 2.0 h			

*critical input material attributes (CMA), critical process parameters (CPP) or critical quality attributes (CQA) of in-process material or final drug product

[1] The proposed operating range for commercial scale will be qualified and continually verified.

[2] Failed drug release specification for ER beads.

[3] The validated apparatus 3 method is used.

2.7.3 Control Strategy for Example MR Tablets, 10 mg

The control strategy for the commercial manufacture of the final product is presented in Table 107. In addition to input material specifications, critical process parameters and the proposed operating

ranges are given for the blending, lubrication and compression steps. Release specifications for the final product are provided in Table 108.

Table 107. Control Strategy for Example MR Tablets, 10 mg

Factor	Attribute/ Parameter	Range studied	Set point for the verification batch	Proposed operating range for commercial scale (min, max)[1]	Purpose of control
MR Tablet Input Material Attributes					
IR granules	Particle size distribution	Retained on 45 mesh (> 350 µm): NMT 5% Retained on 60 mesh (> 250 µm, but < 350 µm): NLT 85% Retained on fine collector (< 250 µm): NMT 10%	Retained on 45 mesh (> 350 µm): NMT 5% Retained on 60 mesh (> 250 µm, but < 350 µm): NLT 85% Retained on fine collector (< 250 µm): NMT 10%	Retained on 45 mesh (> 350 µm): NMT 5% Retained on 60 mesh (> 250 µm, but < 350 µm): NLT 85% Retained on fine collector (< 250 µm): NMT 10%	To ensure batch to batch consistency. MR formulation and manufacturing process is designed to accommodate the IR granule properties defined in approved ANDA aaaaaa.
ER beads	Particle size*	Fraction between 350 µm and 590 µm was used	Fraction between 350 µm and 590 µm was used	Fraction between 350 µm and 590 µm was used	To prevent segregation of the blend
Microcrystalline Cellulose (MCC), Grade 200	Particle size*	d_{50}: 150-250 µm	d_{50}: 196 µm	d_{50}: 150-250 µm	
Microcrystalline Cellulose (MCC), Grade 101	Particle size*	d_{50}: 30-80 µm	d_{50}: 55 µm	d_{50}: 30-80 µm	
Sodium Starch Glycolate (SSG), Type A	Particle size distribution	d_{50}: 50-100 µm	d_{50}: 65 µm	d_{50}: 50-100 µm	To ensure batch to batch consistency
	Degree of substitution*	0.25-0.35	0.30	0.25-0.35	
Magnesium Stearate	Specific surface area	6-10 m^2/g	8.2 m^2/g	6-10 m^2/g	To ensure sufficient lubrication and to reduce the risk of retarded drug release

Factor	Attribute/ Parameter	Range studied	Set point for the verification batch	Proposed operating range for commercial scale (min, max)[1]	Purpose of control
Blending and Lubrication Process Parameters					
V-blender	Blending uniformity*	25 rpm, 12 min (lab) 15 rpm, 20 min (pilot) 15 rpm, 20 min (bio-batch)	Blend to endpoint < 5.0% RSD	Blend to endpoint < 5.0% RSD	Inline NIR is used for endpoint determination to ensure BU is met consistently
	Lubrication	25 rpm, 3-7 min (lab) 15 rpm, 4-8 min (pilot) 15 rpm, 5 min (bio-batch)	N_{rev} = 90	N_{rev} = 60-120 Target N_{rev} = 90	To ensure lubricant is well distributed and to avoid over-lubrication
	Estimated use of capacity	40-60% (pilot) 50% (bio-batch)	~50%	40-60%	
Compression Process Parameters					
Rotary press	Press speed	20-60 (rpm)	40 (rpm)	40 ± 20 (rpm)	To ensure all tablet CQAs (size, splitability, assay, CU and drug release) are met consistently
	Pre-compression	0.5-2.0 (kN)	1.0 (kN)	0.5-2.0 (kN)	
	Compression*	7.0-11.0 (kN)	7.0-11.0 (kN)	7.0-11.0 (kN)	
Compression In-Process Controls					
Individual weight (n=10; every 20 min)		262.77 mg ± 5%			
Composite weight (n=20; every 20 min)		5.255 g ± 3%			
Hardness (n=10; every 20 min)		8.0 (4.7-10.6) kP			
Thickness (n=10; every 20 min)		5.75 mm ± 0.15 mm			
Disintegration (n=12; 3x during run)		NMT 5 min			
Friability (sample weight = 6.5 g; 3x during run)		NMT 1.0 %			

*critical input material attributes (CMA), critical process parameters (CPP) or critical quality attributes (CQA) of in-process material or final drug product

[1] The proposed operating range for commercial scale will be qualified and continually verified.

Table 108. Example MR Tablets, 10 mg, release specifications

Test	Acceptance Criteria
Description	White capsule-shaped tablet debossed with "OGD" on one side of the breakline and "123" on the other side
Identification	A. HPLC Retention time: corresponds to standard B. UV spectrum: corresponds to standard
Assay	95.0%-105.0%
Content Uniformity	AV < 15
Degradation Products	Individual unknown degradation product: NMT 0.2% Total degradation products: NMT 1.0%
Drug Release (N=12)	30 min: 25 - 35% 3 h: 35% - 45% 6 h: 55% - 75% 12 h: NLT 80%
Residual Solvents	Complies with USP <467> Option I

Through development work, the split tablets were shown to meet finished product release requirements for assay, content uniformity, and drug release. Split tablets are not tested routinely at drug product release but, if tested, would conform to finished drug product release specifications.

2.7.4 Product Lifecycle Management and Continual Improvement

Upon approval, the manufacturing process for Example MR Tablets will be validated using the lifecycle approach that employs risk-based decision making throughout the drug product lifecycle as defined in the FDA process validation guidance.[16]

The QbD approach taken during pharmaceutical development of Example MR Tablets, 10 mg, facilitated product and process understanding relevant to Stage 1 (Process Design) of process validation. During Stage 1, the commercial manufacturing process was defined based on knowledge gained through development and scale up activities and a strategy for process control was developed. The goal of Stage 2 (Process Qualification) is to evaluate if the process is capable of reproducible commercial manufacturing. We will design the manufacturing facility according to cGMP regulations on Building and Facilities.[17] Activities will be taken to demonstrate that utilities and equipment are suitable for their intended use and perform properly. The protocol for process performance qualification will be written, reviewed, approved, and then executed to demonstrate that the commercial manufacturing process performs as expected. The goal of Stage 3 (Continued Process Verification) is continual assurance that the process remains in a state of control (the validated state) during commercial manufacture.

Throughout the product lifecycle, the manufacturing process performance will be monitored to ensure that it is working as anticipated to deliver the desired product quality attributes. Process stability and process capability will be measured and evaluated. If any undesired process variability is

[16] U.S. Food and Drug Administration. Guidance for Industry. Process Validation: General Principles and Practices. January 2011.
[17] 21 CFR Part 211 Current Good Manufacturing Practice for Finished Pharmaceuticals, Subpart C.

detected, appropriate actions will be taken to correct, anticipate, and prevent future problems so that the process remains in control. The additional knowledge gained during routine manufacturing will be utilized for adjustment of process parameters as part of the continual improvement of the drug product. As a commitment, the regulatory agency will be notified in accordance with CFR 314.70 regarding each change in each condition beyond the variability already provided in this application.

A.1 Appendix I

Note to Reader: This is where the referenced sections of ANDA aaaaaa for Example IR Tablets, 3 mg, would reside. A reference to the specific section and page number of ANDA aaaaaa where the information is located would be provided. Additionally, a concise summary of the information in ANDA aaaaaa and its relevance to this ANDA is expected.

List of Abbreviations

ANDA:	Abbreviated New Drug Application
ANOVA:	Analysis of Variance
AUC:	Area Under the Curve
AV:	Acceptance Value
BE:	Bioequivalence
BU:	Blend Uniformity
CCF:	Central Composite Face-centered
CFR:	Code of Federal Regulations
CMA:	Critical Material Attribute
C_{max}:	Concentration Maximum
CPP:	Critical Process Parameter
CQA:	Critical Quality Attribute
CU:	Content Uniformity
df:	degrees of freedom
DOE:	Design of Experiments
DS:	Drug Substance
ER:	Extended Release
f2:	Similarity factor
HPC:	Hydroxypropyl Cellulose
HPMC:	Hydroxypropyl Methylcellulose
ICH:	International Conference on Harmonization
IR:	Immediate Release
IVIVC:	*In Vitro-In Vivo* Correlation
IVIVR:	*In Vitro-In Vivo* Relationship
LOD:	Loss on Drying
MCC:	Microcrystalline Cellulose
MFT:	Minimum Film-forming Temperature
MR:	Modified Release
NIR:	Near-infrared
No.:	Number
N_{rev}:	Number of revolutions
PEG:	Polyethylene Glycol
PG:	Propylene Glycol
PSD:	Particle Size Distribution
PVAc:	Polyvinyl Acetate
PVP:	Polyvinylpyrrolidone, Povidone
QTPP:	Quality Target Product Profile
R^2:	Coefficient of Determination
RLD:	Reference Listed Drug
RSD:	Relative Standard Deviation
RT:	Room Temperature
SLS:	Sodium Lauryl Sulfate
SSG:	Sodium Starch Glycolate
TEC:	Triethyl Citrate
T_{max}:	Time for achieving Maximum Plasma Concentration
TPI:	Terahertz Pulse Imaging
XRPD:	X-Ray Powder Diffraction