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Quality by design case study: An integrated multivariate approach to drug product and process development

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ABSTRACT

To facilitate an in-depth process understanding, and offer opportunities for developing control strategies to ensure product quality, a combination of experimental design, optimization and multivariate techniques was integrated into the process development of a drug product. A process DOE was used to evaluate effects of the design factors on manufacturability and final product CQAs, and establish design space to ensure desired CQAs. Two types of analyses were performed to extract maximal information, DOE effect & response surface analysis and multivariate analysis (PCA and PLS). The DOE effect analysis was used to evaluate the interactions and effects of three design factors (water amount, wet massing time and lubrication time), on response variables (blend flow, compressibility and tablet dissolution). The design space was established by the combined use of DOE, optimization and multivariate analysis to ensure desired CQAs. Multivariate analysis of all variables from the DOE batches was conducted to study relationships between the variables and to evaluate the impact of material attributes/process parameters on manufacturability and final product CQAs. The integrated multivariate approach exemplifies application of QbD principles and tools to drug product and process development.

1. Introduction

Pharmaceutical products and processes are complex and multivariate by nature. Scientific understanding of the relevant multi-factorial relationships (e.g. between formulation, process and quality attributes) usually requires the use of multivariate approaches, such as statistical design of experiments, response surface methodology, optimization and multivariate data analysis or chemometrics in conjunction with knowledge management systems. Much of the published material in the past highlights the usefulness of experimental design, but the combined use of DOE, optimization and multivariate data analysis are relatively few when applied to pharmaceutical product and process development (Bolhuis et al., 1995; Lindberg and Lundstedt, 1995; Hwang et al., 1998; Voinovich et al., 1999; Westerhuis and Coenegracht, 1999; Gabrielsson et al., 2002; Xie et al., 2007; Naelapaa et al., 2008). In this context, multivariate data analysis is referred to the application of multivariate techniques such as principal component analysis (PCA) and partial least squares (PLS) specifically, though experimental design and response surface analysis is essentially also a multivariate approach. It is important to recognize that multivariate techniques such as PCA and PLS can handle a large (virtually unlimited) number of variables simultaneously, while DOE effect/response surface analysis deals with a limited number of variables due to limited experimental runs that can be afforded in practice. Multivariate data analysis can be considered a complementary tool to DOE effect and response surface analysis, providing additional information as well as confirmatory information about the product and processes. When combined, the integrated multivariate approach provides a more powerful means to elucidate complex multivariate relationships in pharmaceutical product and process development.

As part of the effort in developing robust drug product and process within the framework of quality by design (QbD) and process analytical technology (PAT), the integrated multivariate approach has been employed during the entire late-stage of this drug product. The flow diagram, Fig. 1, illustrates the major steps of the holistic and risk-based QbD approach used to develop this drug product in accordance with ICH Q8, Q9, Q10 and FDA PAT guidance (FDA, 2004; ICH, 2005; ICH, 2008a,b). The holistic QbD approach began with a predefined target product profile (TPP), and applies various principles and tools at different stages to better understand the product and processes (ICH, 2008a,b; CMC-IM, 2008; Cook et al., 2009). Quality risk assessment (QRA) tools, such as risk filtering, fishbone diagram, and FMEA, were applied to identify an initial list of potential CQAs and CPPs, performed in accordance with ICH

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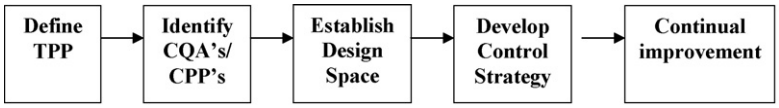

Fig. 1. A quality by design approach to product and process development.

Q9 guidance (ICH, 2005; ICH, 2008a,b). It should be noted that CQAs in this context refer to quality attributes of raw material, intermediate or final product. The terms, intermediate CQAs and manufacturability CQAs, are interchangeable. After QRA, several screening DOEs were performed to further narrow down the list of quality attributes and potential CPPs that impact intermediate and final product quality attributes.

This paper covers the continual study following QRA and screening DOEs, which includes an optimization DOE campaign, in conjunction with multivariate data analysis, to achieve enhanced process understanding and establish design space. A process optimization DOE was used to evaluate effects of the design factors on manufacturability and final product CQAs such as tablet blend flow and tablet dissolution, and establish design space to ensure the desired CQAs. The multivariate analysis of all available variables from the DOE campaign was conducted to study multivariate relationships of all variables from raw materials, intermediates, various unit operations to final product. It should be noted that many variables which were not originally systematically placed in the DOE can be analyzed using multivariate techniques such as PCA/PLS to provide increased understanding of the entire tablet manufacturing process holistically.

2. Materials and methods

2.1. Design of experiments

Prior to this optimization DOE campaign, quality risk assessment, historical data analysis of previous development batches and several screening DOE analysis have identified that high shear wet granulation is the most critical unit operation that impacts downstream intermediate and final product quality attributes. Three critical process parameters were selected as design factors: granulation water amount and wet massing time identified from granulation process, and lubrication time from magnesium stearate lubrication operation. The ultimate goal of the DOE was to optimize three critical process parameters to achieve desired flowability, compressibility and dissolution profiles. A hybrid response surface design with 13 experimental runs was ultimately chosen to conserve active pharmaceutical ingredient (API). See Table 1.

The hybrid design is a combination of a central composite design for the first k-1 factors (2 in this case) and a rotatable or nearly rotatable second-order design for the kth factor (3rd in this case). Note that hybrid designs are generally better than a small central composite design in terms of prediction error at the perimeter of the design but like small central composite designs, are still highly sensitive to outliers and/or missing data (Anderson and Whitcomb, 2005; Myers et al., 2009). The DOE runs were performed in a random order. The DOE was created in Design Expert 7.13 (State-Ease Inc., MN) and the analyses including effect, response surface analysis and optimization were conducted in JMP 8 (SAS Institute Inc., NC).

Table 1
Hybrid design with three factors, and three center points.

Batch/run	Water amount (g)	Wet massing time (min)	Lubrication time (min)
1a	268.7	1	3
2a	306.3	4	2
3a	268.7	5	3
4a	268.7	3	1
5a	268.7	3	5
6a (center point)	287.5	3	3
7a	306.3	4	4
8a (center point)	287.5	3	3
9a (center point)	287.5	3	3
10a	306.3	2	2
11a	306.3	2	4
12a	325	3	3
13a	250	3	3

2.2. Process and equipment

The manufacturing process of this product involves high shear wet granulation, milling, blending, compression and coating. The DOE batches were conducted in small-scale equipment. The small-scale batches were manufactured at 1 kg scale using a Lodige high shear granulator. The API, croscarmellose sodium (disintegrant) and microcrystalline cellulose were pre-blended to obtain a uniform mix. Post pre-blending, the aqueous binder solution comprising of Povidone/poloxamer was added to the dry mix under high shear mixing with the chopper and the impeller on. The addition rate was varied to maintain the same addition time for the binder solution. At the end of binder addition, any material adhering to the walls was scraped down and wet massing conducted with both the impeller and the chopper on. After wet massing, the wet granules were manually screened through a 4.0 mm screen and dried in a fluidized bed drier. The dried granules were then manually dry screened through a 0.8 mm screen and blended with extragranular microcrystalline cellulose and croscarmellose sodium in a turbula blender. The resultant blend was then lubricated with magnesium stearate for times specified per the DOE in a turbula blender. The final tablet blend was then compressed to tablets on a Riva-II Minipress.

2.3. Roadmap from knowledge space to design space

All DOE batches were successfully produced and all provided satisfactory dissolution profiles. Good compressibility was achieved for all batches. However, poor flow was observed for some DOE batches, evidenced by funnel flow or even ratholing during tablet compression on the Riva-II Minipress. The poor flowability subsequently resulted in tablet weight variation in some cases. It was therefore decided to delve into the root cause of the flow issue, and optimize the critical process parameters (CPPs) to achieve desired flowability.

The roadmap from knowledge space to design space for ensuring maximal tablet blend flow of this product can be depicted in Fig. 2.

3. Results and discussion

3.1. DOE effect and response surface analysis

As described earlier, a hybrid response surface design was used to study how three critical process parameters impact key response variables (CQAs). The design factors (CPPs) studied were: (1) water amount (250–325 g); (2) wet massing time (1–5 min); (3) lubrication time (1–5 min). The response variables (manufacturability and final product CQAs) studied were as follows:

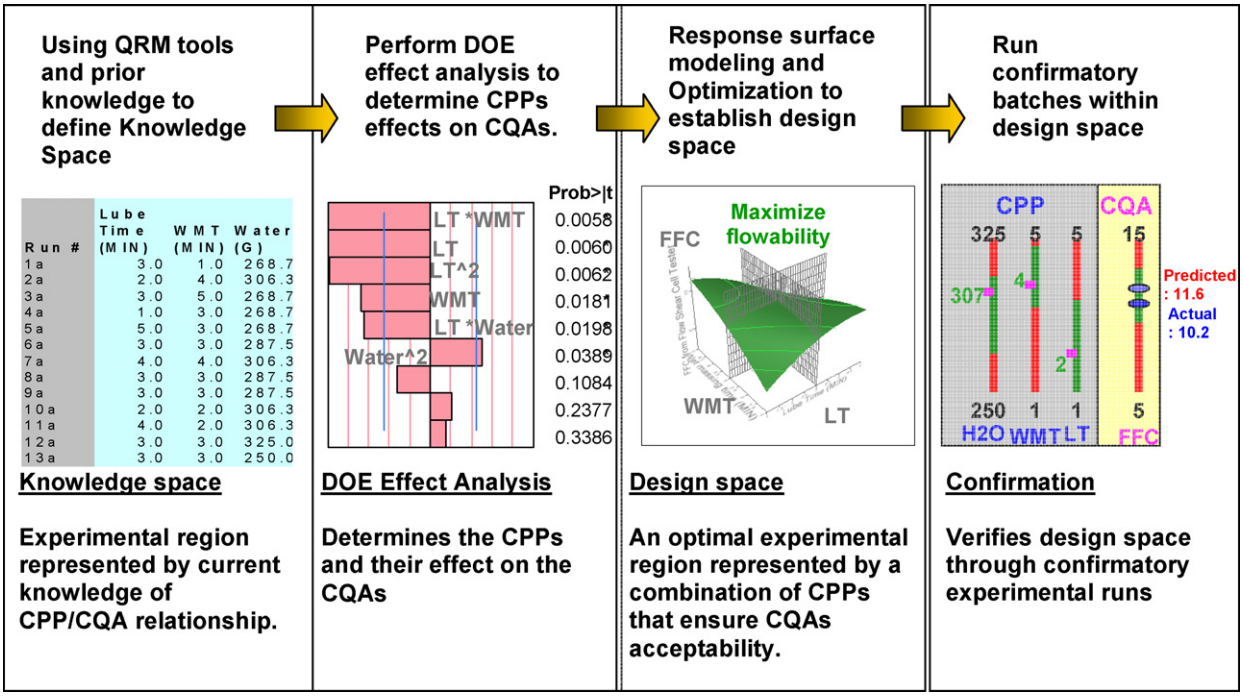

Fig. 2. Roadmap to establish design space from knowledge space by DOE, response surface analysis and optimization.

Table 2
Sorted effect estimates for all terms used in the model.

Term	Estimate	S.E.	*t* ratio	Prob > |*t*|
(Lube time (min) – 3) × (wet massing time (min) – 3)	−1.55	0.219294	−7.07	0.0058*
Lube time (min)	−0.9375	0.13429	−6.98	0.0060*
(Lube time (min) – 3) × (lube time (min) – 3)	−0.671118	0.096829	−6.93	0.0062*
(Wet massing time (min) – 3) × (wet massing time (min) – 3)	−0.456118	0.096829	−4.71	0.0181*
(Lube time (min) – 3) × (water (g) – 287.5)	−0.03258	0.007143	−4.56	0.0198*
(Water (g) – 287.5) × (water (g) – 287.5)	0.0009987	0.000284	3.52	0.0389*
Water (g)	−0.014082	0.006216	−2.27	0.1084
Wet massing time (min)	0.1975	0.13429	1.47	0.2377
(Wet massing time (min) – 3) × (water (g) – 287.5)	0.0081117	0.007143	1.14	0.3386

* $p < 0.05$.

- Tablet blend flow indicated by ratings from visual observations of ratholing/funnel flow, Carr index, and shear cell FFC values;
- Compressibility represented by varied compression force used to achieve target hardness of 14–16 kp;
- Tablet dissolution profiles in 0.1 N HCL and pH 5 acetate buffer with 0.5% (w/w) CTAB dissolution methods.

DOE effect analysis was performed on all response variables. Only effect/response surface analysis on tablet blend flow represented by shear cell FFC values will be discussed in this paper.

3.1.1. *Effects on tablet blend flow*

The flow of final tablet blend was evaluated using FFC values from a shear cell tester (RST-XS by Dietmar Schulze, Germany). Table 2 displays sorted effect estimates of model terms on the FFC value. It can be seen that the interaction of lubrication time and wet massing time impact FFC the most, followed by lubrication time, the 2nd order lubrication time and wet massing time, the interaction of water and lubrication time, and the 2nd order water amount. All these terms have *p*-values <0.05 and thus are significant on influencing flow represented by FFC values.

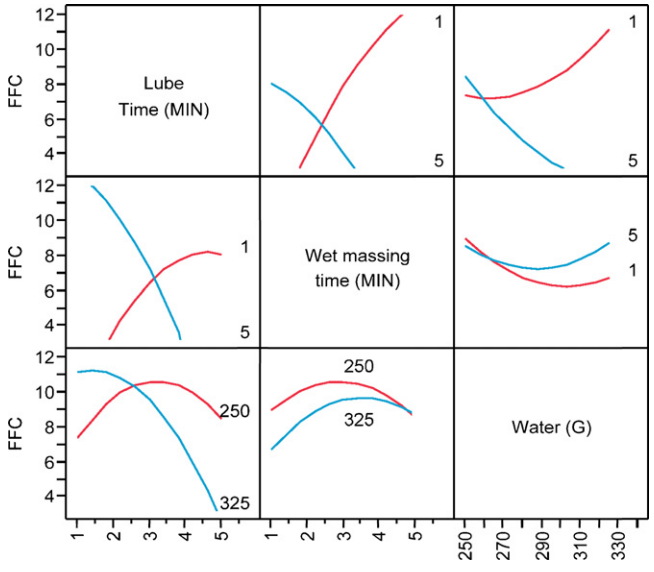

Fig. 3. Interaction profile of design factors on shear cell FFC.

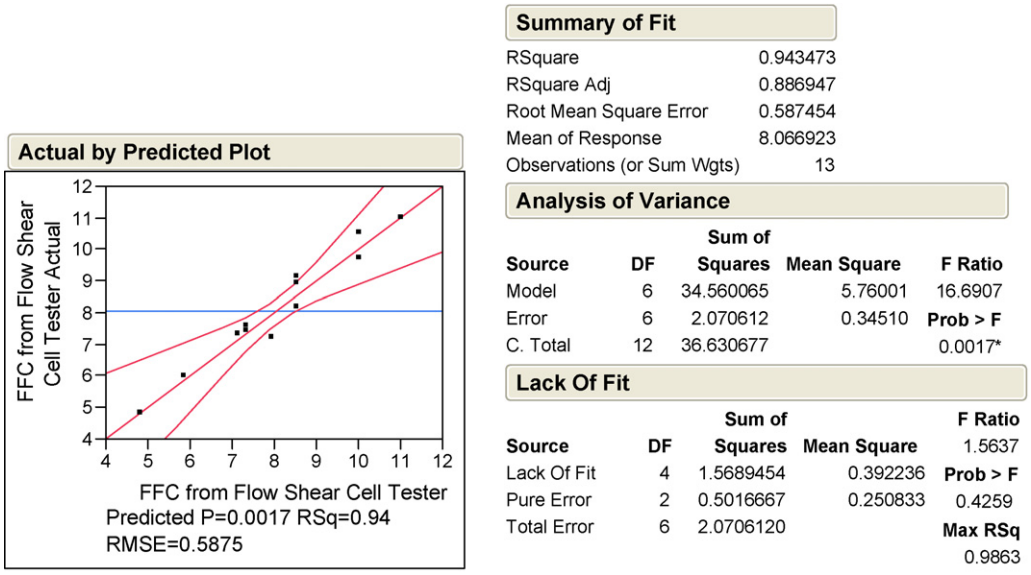

Fig. 4. ANOVA for tablet blend flow represented by shear cell FFC.

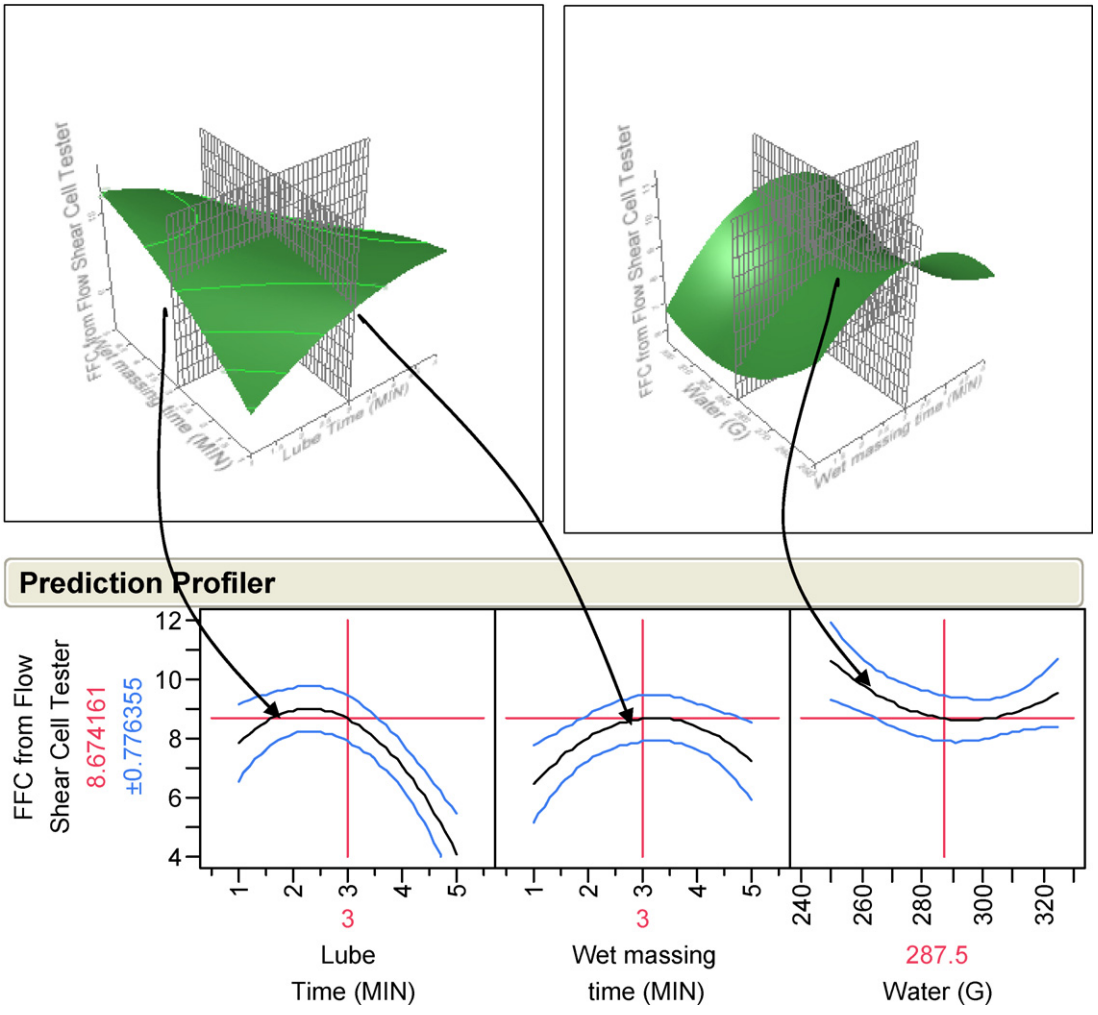

Fig. 5. Prediction profiler for each input variable.

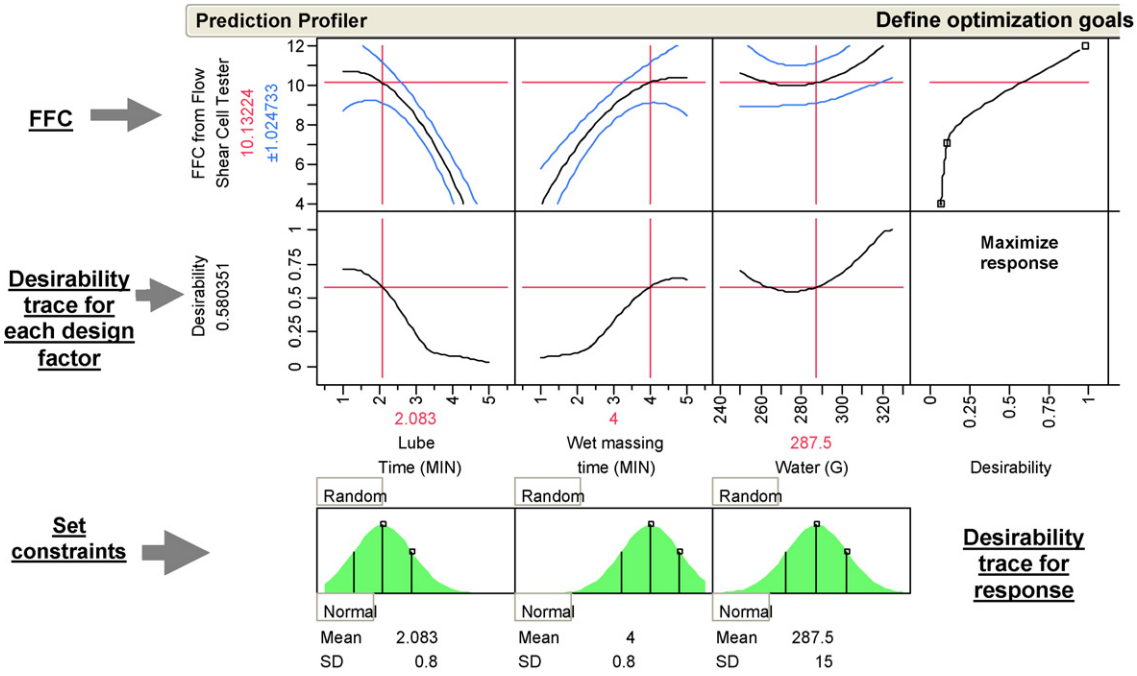

Fig. 6. Optimization of design factors to achieve maximal flow.

As shown in Fig. 3, the interaction profile illustrates that how dependent the effect of one factor is on the level of another factor on the response-tablet blend flow. In other words, the interaction profiles explain how the three factors interact one another in terms of the response variable, FFC. It can be observed that

- At lower wet massing time, higher lubrication time leads to higher FFC (better flow) while lower lubrication time results in lower FFC (worse flow). The effect on flow reverses at higher wet massing time. This could be explained by the fact that at low wet massing times, the granule formation is incomplete and that flow may be poor to begin with, any increases in lube times would then be expected to improve flow by reducing inter-granular friction. At higher wet massing times, the effect is reversed due to the fact that the granules have good flow to begin with and long lubrication times may result in over lubrication that may worsen flow.
- The impact of lubrication time on flow is larger with higher water amount; and the impact of water amount on flow is smaller with higher wet massing time.
- At lower water amount, the level of either wet massing time or lubrication time does not appear to impact FFC significantly. Increasing lubrication time at higher water amount results in a rapid decrease in FFC, while increasing wet massing time at higher water amount leads to higher FFC (better flow). An increase in water during granulation has been found to affect the granulation characteristics including granulation endpoint and granule particle size. Also the size and shape and the granule hardness has been shown to change at higher water amounts (data not shown). All of these factors can then affect the way the granules

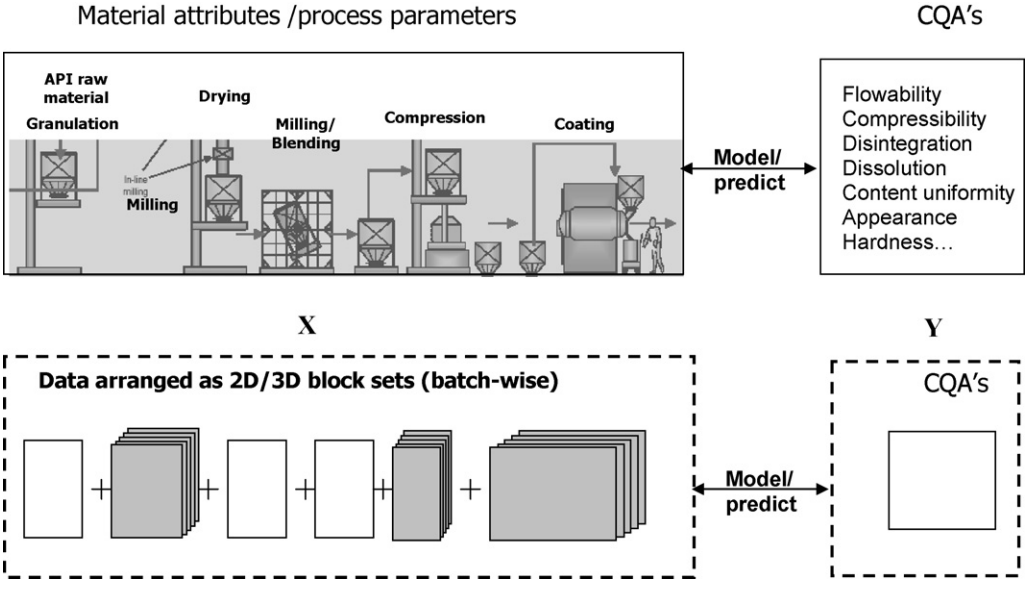

Fig. 7. Multivariate data modeling in the tablet manufacturing process.

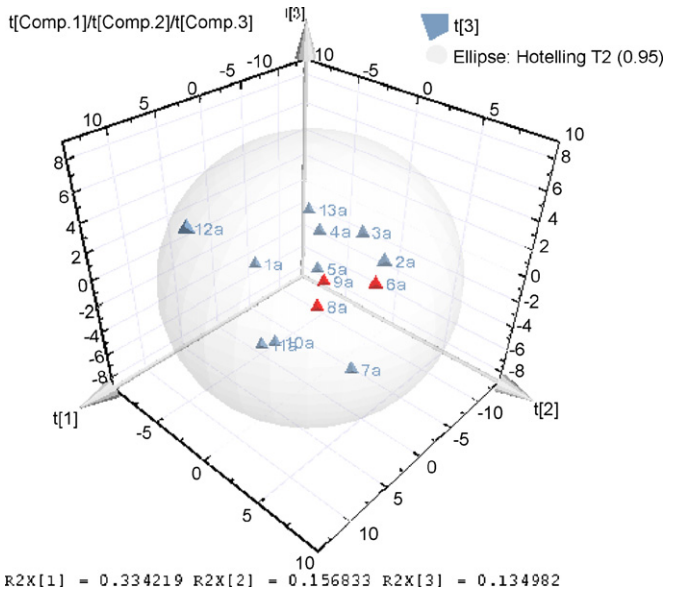

Fig. 8. Score scatter 3D plot (first three principal components t1, t2 and t3) displaying batch relationships.

behave toward the lubricant and lubrication times. Increasing wet massing can promote the free available water between granules into the granules and modify the morphology. Increased wet massing at high water amounts has resulted in spherical granule morphology as observed through a particle video microscope (PVM). These spherical particles are expected to have better flow characteristics and high FFC values.

- An increase in water amount can be compensated for an increase in wet massing time and/or a decrease in lubrication time to produce a better flow.

A final model fit for response-tablet flow was performed after the insignificant model terms were removed to make the model more parsimonious. The ANOVA and model fit statistics are summarized in Fig. 4. Evaluative statistics indicate a very good model fit, with R^2 adjusted of 0.887. Model is significant with p-value of 0.0017, while lack of fit is insignificant with p-value of 0.4259.

3.1.2. Establish design space through response surface analysis and optimization

There are different approaches to establish design space for a product (ICH, 2008a,b). In this work, response surface methodology in conjunction with optimization was used to establish design space to achieve desired tablet blend flow and dissolution. Per ICH Q8 guidance, design space is a multi-dimensional combination and interaction of input variables/process parameters that ensure product quality. The statistical effect analysis verified that the selected process variables and/or their interactions have shown significant effects on the manufacturability CQA – blend flow. The linkage between CPPs and CQAs was established through response surface modeling.

The quadratic response surface of FFC as a function of wet massing time and lubrication time (holding water constant) is shown in Fig. 5 (upper left), and that as a function of water and wet massing time (holding lubrication time constant) in Fig. 5 (upper right).

The prediction profiler in Fig. 5 (bottom) displays profile traces for each input variable, water, wet massing time and lubrication time. The profile traces can be viewed as cross-sectioning of the response surfaces. The profiler is a way of changing one variable at a time and looking at the effect of a design factor on the predicted response-FFC. The profiler re-computes the profiles and predicted responses (in real-time) as the value of the design factor is varied (Anderson and Whitcomb, 2005; Myers et al., 2009).

Optimization is an approach to search along response surface for optimal range of input variables to satisfy a goal such as maximizing/minimizing/targeting a response variable. For more information, see references Bolhuis et al. (1995), Lundstedt et al. (1998), and Myers et al. (2009). The objective of optimization here is to maximize FFC or flowability through the prediction profiler as shown in Fig. 6. A critical step of optimization is to define appropriate desirability functions for both responses and design factors. In JMP 8, desirability value ranges from 0 to 1, with 1 representing most importance. In terms of response, a higher FFC value of the blend indicates better blend flow. Therefore, more desirability was given to higher FFC values in the desirability function for

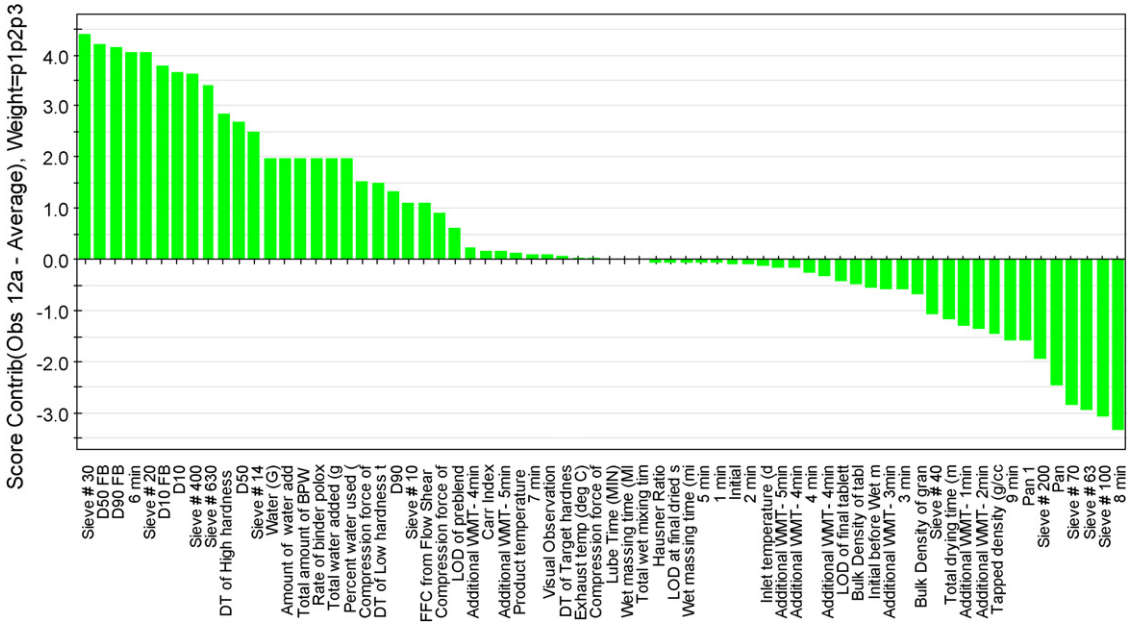

Fig. 9. Score contribution plot showing variables contributing to the difference between batch 12a and the average of all batches.

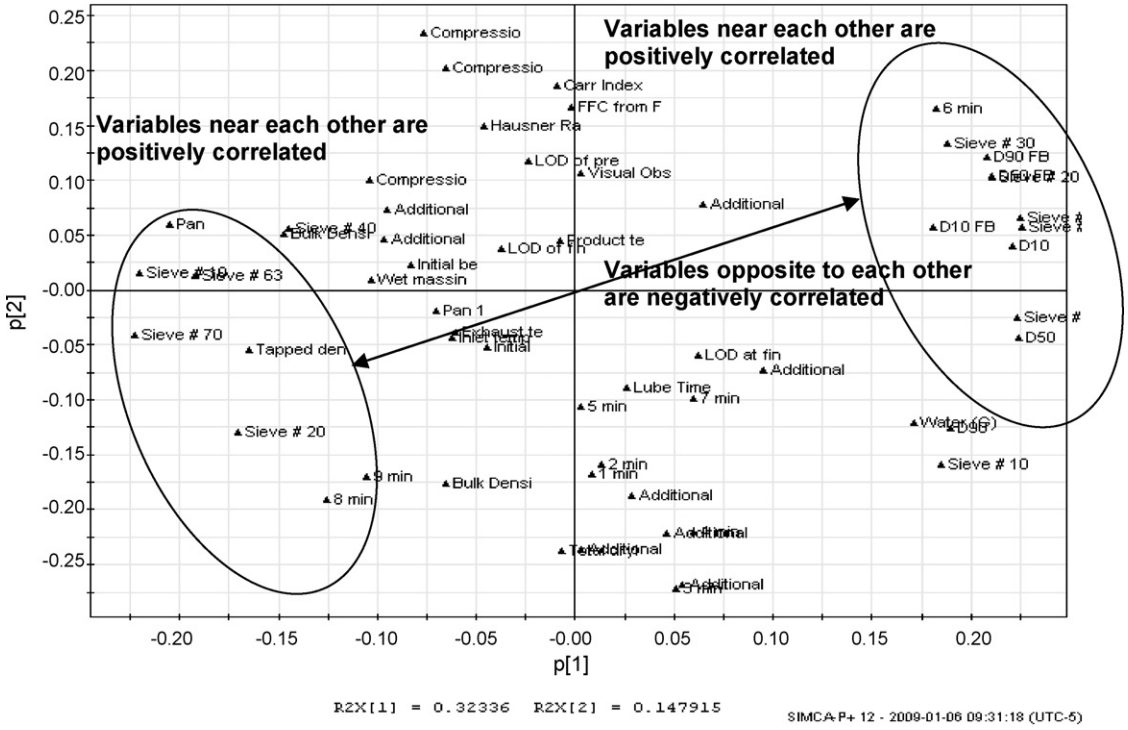

Fig. 10. Loading plot (p1–p2) displaying variable relationships.

response, FFC, in Fig. 6. Once the desirability function for a response has changed, the desirability traces will change accordingly for design factors. An interactive study of desirability traces for both design factors and a response variable provides a useful means to visualize optimization and obtain a rough idea of where the optimal ranges of design factors might be according to a desired response. After the objective function and constraints were specified in Fig. 6, a searching algorithm was then applied to search response surfaces or multi-dimensional space for optimal solutions that would satisfy optimization criteria. It is important to recognize that design space in many cases needs to be searched or defined through the above approach, instead of being a simple collection of ranges of design factors. A number of optimization solutions from maximizing blend flow were generated based on defined desirability for both design factors and response. An optimal solution with water amount = 307 g, wet massing time = 4 min, and lubrication time = 2 min, was used for confirmation. The predicted FFC value was 11.6 from this optimal solution. A confirmatory batch using this optimal setting showed excellent flow, FFC value 10.2.

3.2. Multivariate analysis of all available variables

In addition to the variables studied in the DOE effect analysis, there are many other variables across all unit operations, including both process parameters and quality attributes. The tablet

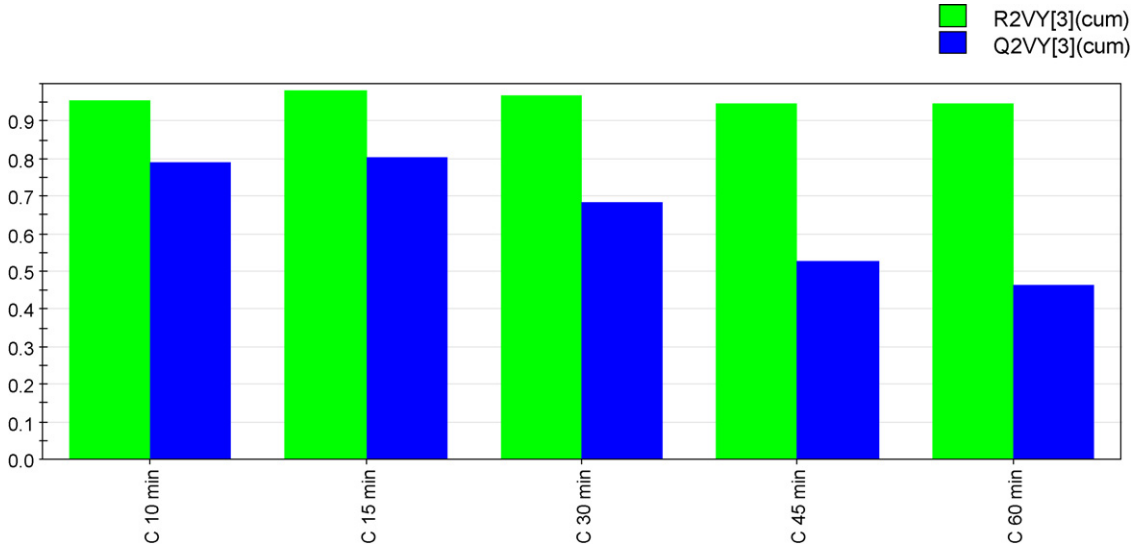

Fig. 11. Cumulative R2 (R2VY(cum)) and Q2 (Q2VY(cum)) for CTAB dissolution at 10, 15, 30, 45 and 60 min, respectively. The *y*-axis represents the percent (full scale is 1, or 100%).

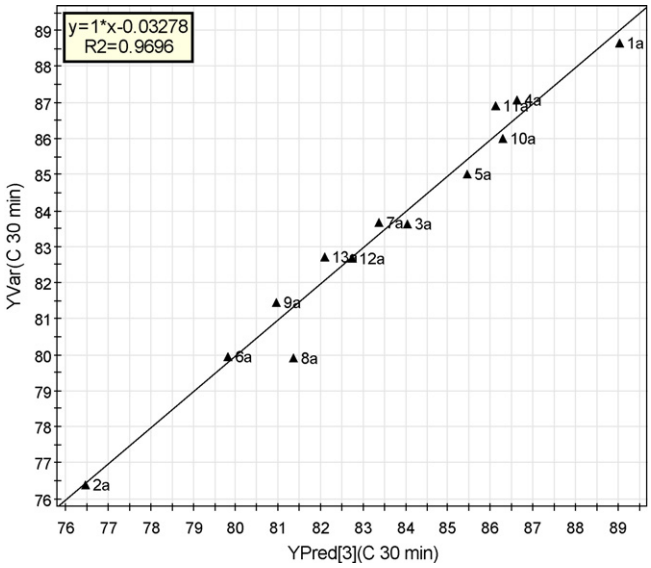

Fig. 12. Predicted vs. measured plot for CTAB dissolution at 30 min.

manufacturing process of this product consists of multiple unit operations, each of which generates a large amount of multivariate data resulting in as many as hundreds of variables. See Fig. 7. Data from multiple unit processes can be arranged as 2D or 3D block sets, where row represents batches, and column represents variables. If available, the third dimension may be time points within a batch for some unit operations where process parameters are acquired during batch evolution, resulting in a 3D matrix. It should be noted that variables from the same or different unit operations may be heavily correlated, and upstream unit operations/variables are likely to impact on downstream unit operations/variables. The elucidation of such complex relationships requires use of multivariate methods such as PCA and PLS. More information can be found in reference Wold et al. (1987), Martens and Naes (1989), Miller (1995), Forinaa et al. (1998), Esbensen (2002), and Kourti (2004). It would be difficult to study relationships of such a large number of variables through the DOE effect analysis as only limited number of variables can be practically handled. Thus, PCA and PLS are multivariate methods complementary to the DOE effect/response surface analysis for improved process understanding. The methods can be performed on individual unit operations separately, as well as combined unit operations jointly, depending on the objective of the study. All multivariate analysis was performed in SIMCA-P+12 by Umetrics Inc., NJ.

3.2.1. *Principal component analysis (PCA)*

The objective of PCA is to examine both batch/sample and variable relationships in this DOE campaign. All 13 DOE batches were included in the PCA modeling. Approximately 70 variables were analyzed, including process parameters from granulation, blending, compression, and quality attributes such as particle size/distribution, bulk/tapped density, LOD, hardness and dissolution. PCA was performed to study multiple combined unit operations as a whole, as well as individual unit operations separately.

3.2.1.1. Batch relationship. Scores scatter 3D plot (t1–t2–t3) in Fig. 8 reveals the possible presence of outliers, groups, or patterns among batches. The scores t1, t2 and t3, are the orthogonal latent variables, or principal components summarizing the X-variables. The score t1 (first component) explains the largest variation of the X space 33.4%, followed by t2 explaining 15.7% and t3 13.5%. Observations near each other are more similar, while those far away from each other are more dissimilar. The scores plot exhibits a good degree of variations among the DOE batches, which is expected as the three DOE design factors are varied to deliberately create systematic variations. No obvious groupings can be observed, and no outliers lie outside the ellipse (95% confidence interval). It can be seen that the center-point batches 6a, 8a and 9a are near each center, indicating good reproducibility. Batch 12a appears more different from the rest of batches as it is located further away from the other batches. A score contribution plot, Fig. 9, can be used to study why batch 12a is more different and identify which variables are contributing factors to the difference most. The score contribution plot displays the contributing variables in a sorted order. The variables with larger positive and lesser negative values are more important in differentiating batch 12a from the rest. It is clear that

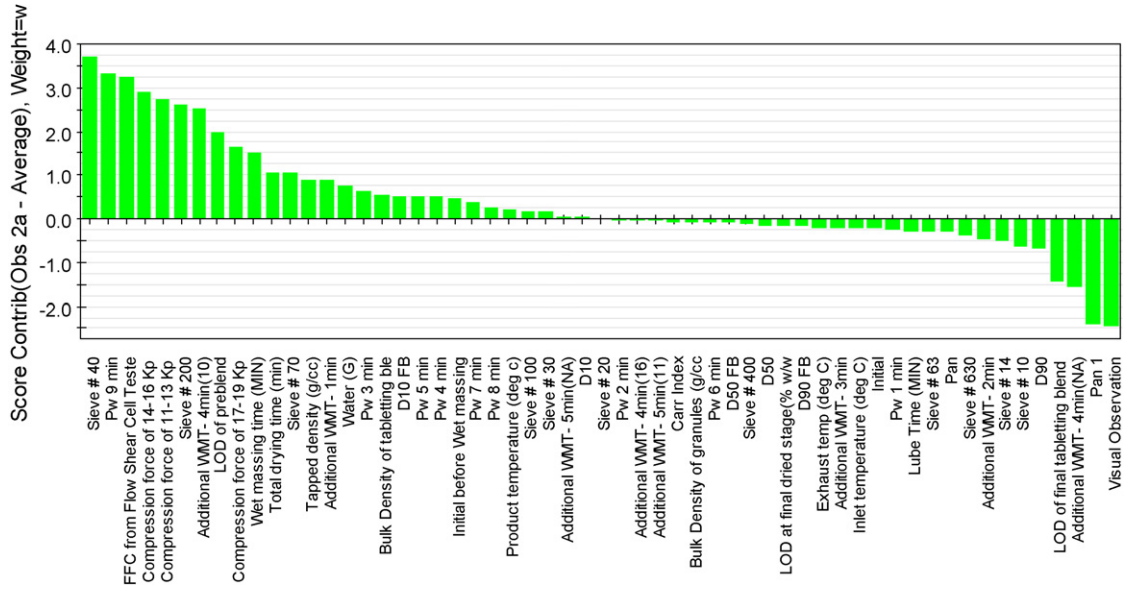

Fig. 13. Score contribution plot for pH 5 acetate buffer with 0.5%CTAB dissolution at 30 min.

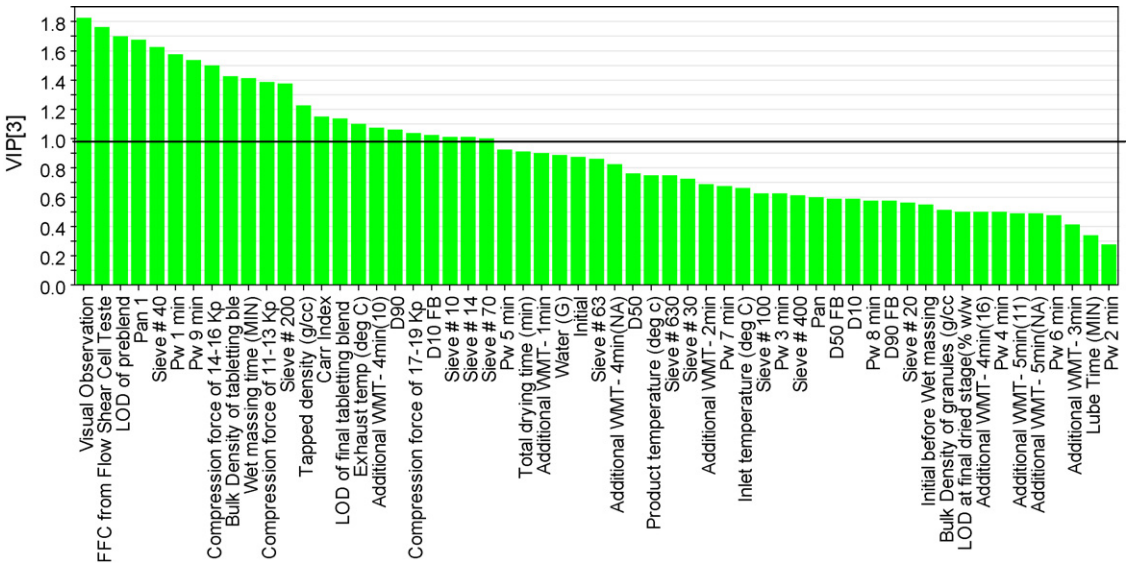

Fig. 14. VIP plot displaying very important variables in terms of dissolution profiles.

batch 12a exhibits significantly coarser particle size in granules at granulation stage, after drying and final blend.

3.2.1.2. Variable relationship. Loading plot in Fig. 10 shows relationships among the X-matrix variables, excluding final drug product CQAs. Variables near each other are positively correlated, while those opposite to each other from origin are negatively correlated. Variables close to origin are less influential to the model, while those away from origin are more influential. However, care must be taken when interpreting variable relationships in a loading plot. The amount of explained variations by the plotted principal components should be used in combination with the distance between variables. If plotted principal components do not account for sufficient variation, then the third or later components should also be plotted to examine the distances among variables. For instance, the first two components in this PCA model explain 32% and 15%, respectively. Although Carr index and FFC appear near each other in loading plot (p1–p2), they are not close to each other by examining loading plot (p1–p3).

Key interpretations from the loading plot (Fig. 10), along with later principal components (not shown here), are as follows:

- Overall quality attributes such as particle size exhibit more variations than process parameters as they are further away from origin.
- Particle size and distribution span major variation of the data set, e.g. D10, D50 and D90 from wet granulation, and particle size distribution from final tablet blend.

3.2.2. Regression analysis using partial least squares (PLS)

The objective of PLS is to study how all available material attributes and process parameters, besides the three design factors, impact intermediate and final product quality attributes. PLS was used here to establish relationship between 65 X-variables (material attributes/process parameters) and 5 Y-variables (CTAB dissolution profiles).

Fig. 11 displays the cumulative R2 and Q2 for the Y matrix, using three components. R2Y is the percent of the variation of Y explained by the model indicating how good the model fit is, while Q2Y is the percent of the variation of Y that can be predicted by the model. A good model should have both R2Y and Q2Y above 0.5. As can be seen in Fig. 11, a good degree of correlation can be established for CTAB dissolutions, especially at 10–30 min, evidenced by R2Y and Q2Y greater than 0.5. However, further model validation/assessment will be needed if the model is to be used for future prediction. It should be noted that the primary purpose of the PLS model here is to study the relationship between X and Y, not necessarily to use the model for future prediction.

Fig. 12 shows predicted vs. measured plot for CTAB dissolution at 30 min from calibration model. Higher R2 and slope indicates good model fit. Batch 2a clearly shows lowest dissolution. With score contribution plot, the variables contributing to the low dissolution can be identified and ranked according to its importance. As can be seen in Fig. 13, batch 2a shows noticeably much larger FFC value, indicating good flowability but slower dissolution. This is consistent with the DOE effect analysis and optimization. A compromise will have to be reached between blend flow and tablet dissolution to achieve optimal results.

The VIP (variable importance) in Fig. 14 reflects the importance of terms (variables in the plot) in the model both with respect to Y (CTAB dissolution), i.e. its correlation to all the responses, and with respect to X (the projection). VIP is normalized, and the average squared VIP value is 1. Terms in the model with a VIP > 1 are deemed important to the model. It appears that FFC, LOD, particle size, 1 and 9 min power consumption values, compression force, wet massing time, water amount, and some others are important variables with respect to CTAB dissolution.

4. Conclusion

The case study exemplified the application of QbD principles and tools to drug product and process development. It was demonstrated that the DOE effect/response surface analysis was a powerful tool in studying the effects of selected factors (water amount, wet massing time and lubrication time) on response variables, and establishing design space to ensure the desired manufacturability—tablet blend flow. Multivariate analysis (PCA and PLS) showed its figures of merit in being capable of handling all available variables, most of which could not be included in the DOE effect/response analysis. With multivariate data analysis, complex multivariate relationships of both batches and variables can be understood holistically, as well as how material attributes/process parameters impact on intermediate and final product quality attributes (e.g. CTAB dissolution). It is clear that DOE effect/response surface analysis and multivariate data analysis

are complementary tools for pharmaceutical product and process development. The level of understanding would not be achieved with either approach alone.

It is evident from this study that the combined use of experimental design, response surface modeling, optimization, and multivariate data analysis (PCA and PLS) facilitates enhanced product/process understanding, and offers opportunities for developing control strategies to ensure final product quality. The integrated multivariate approach will continue to be implemented in all steps of our formulation and process development. With availability of more advanced process automation and data infrastructure system, it is only a matter of time before the main elements of such an integrated multivariate approach are implemented real-time, from process understanding to multivariate statistical process control.

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