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Research paper

A Quality by Design approach to investigate tablet dissolution shift upon accelerated stability by multivariate methods

Jun Huang [a,*], Chimanlall Goolcharran [b], Krishnendu Ghosh [c]

[a] Pfizer Inc., Peapack, USA
[b] Pfizer Inc., Groton, USA
[c] Pfizer Inc., Pearl River, USA

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ABSTRACT

This paper presents the use of experimental design, optimization and multivariate techniques to investigate root-cause of tablet dissolution shift (slow-down) upon stability and develop control strategies for a drug product during formulation and process development. The effectiveness and usefulness of these methodologies were demonstrated through two application examples. In both applications, dissolution slow-down was observed during a 4-week accelerated stability test under 51 °C/75%RH storage condition. In Application I, an experimental design was carried out to evaluate the interactions and effects of the design factors on critical quality attribute (CQA) of dissolution upon stability. The design space was studied by design of experiment (DOE) and multivariate analysis to ensure desired dissolution profile and minimal dissolution shift upon stability. Multivariate techniques, such as multi-way principal component analysis (MPCA) of the entire dissolution profiles upon stability, were performed to reveal batch relationships and to evaluate the impact of design factors on dissolution. In Application II, an experiment was conducted to study the impact of varying tablet breaking force on dissolution upon stability utilizing MPCA. It was demonstrated that the use of multivariate methods, defined as Quality by Design (QbD) principles and tools in ICH-Q8 guidance, provides an effective means to achieve a greater understanding of tablet dissolution upon stability.

1. Introduction

As indicated in United States Pharmacopeia (USP) and European Pharmacopeia (EP), *in vitro* dissolution testing is often imperative in assessing pharmacokinetic performance and may be used as surrogate to assess the in vivo drug release and eventual absorption or bio-equivalence if proven to be a bio-relevant method (correlated with drug bioavailability). Being an end-product testing QC tool, the dissolution testing has often been used for evaluating challenges encountered during development of formulation and process and tablet stability to establish drug shelf life [1–3]. For instance, if dissolution profiles are not similar to those previously established, or out of specification, a root-cause investigation will need to be carried out. The FDA SUPAC guidelines for solid dosage forms require that the dissolution profiles of the pre-change and post-change products be consistent [4,5]. In order to quantitatively compare dissolution profiles with specifications, several methods have been previously developed and reported in the literature, such as ANOVA-based, model-dependent, model-independent and PCA-based approaches [1,6–9].

The purpose of this paper is, however, not to develop such methods for comparing dissolution profiles and deriving difference/similarity factors, but rather to link the dissolution variations among DOE batches, to upstream manufacturing process and material attributes and to identify what causes the dissolution shift upon stability.

It is of crucial importance to take into account the entire dissolution profile instead of a single point when examining batch-to-batch variability. For instance, although tablets from two batches may dissolve at a certain percentage at a specific time, the dissolution profiles between these two batches may differ significantly. Multivariate tools, such as principal component analysis (PCA), offer opportunities to more effectively and efficiently describe dissolution characteristics by analyzing entire dissolution profiles upon stability, simultaneously. PCA of dissolution data has been reported previously [1,6,7], but the combined use of PCA with DOE effect and response surface analysis appears few in studying dissolution. Also, multi-way PCA (MPCA) of 3D dissolution profiles upon stability has not yet been seen in publication. As Huang et al. previously

Abbreviations: MPCA, multi-way principal component analysis; DOE, design of experiments; QbD, Quality by Design; CPP, critical process parameter; CQA, critical quality attribute; ANOVA, analysis of variance.

* Corresponding author. Pfizer Inc., 100 Route 206 N, Peapack, NJ 07977, USA. Tel.: +1 908 901 6463; fax: +1 973 355 3647.
E-mail address: jun.huang1@pfizer.com (J. Huang).

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pointed out, multivariate data analysis such as PCA are complementary tools to DOE and response surface analysis, which can be combined to form an integrated multivariate approach to elucidate complex relationships and enhance pharmaceutical product and process understanding [10].

The usefulness of multivariate methods in investigating dissolution shift upon stability is demonstrated through two application examples during formulation and process development of the same product. Dissolution has been identified as a critical quality attribute (CQA) of this drug product due to the low solubility of the API in neutral pH, and the tablet is administered orally with food. With food, the pH of the stomach is close to 5 where the drug has a very low solubility. Previous stability studies have shown a significant shift or slow-down in dissolution profile on storage under accelerated condition. Quality risk assessment, e.g. risk filtering and cause-and-effect diagram, was made to identify the potential critical process parameters that impact on dissolution shift. Experiments were designed at the pilot scale to further identify critical process parameters and elucidate their impact on the stability of the product with respect to dissolution. The methodology and its applications presented in this article serve as a case study of utilizing QbD principles and tools that have been systematically used throughout the development of this drug product per ICH guidelines [11–13].

The following sections are organized as such:

In Section 2, experimental and methods for the two application examples are described.

In Section 3.1, Application I is discussed. DOE, response surface analysis and optimization are utilized to investigate and address dissolution shift (slow-down) observed during accelerated stability testing for the immediate release tablets, as well as to provide guidance on proposing optimal process conditions that ensure desired dissolution and minimize dissolution shift; the use of PCA for studying batch relationships with respect to dissolution upon stability is presented.

In Section 3.2, Application II is discussed. The use of PCA for studying the impact of varying tablet breaking force on dissolution shift upon stability is demonstrated.

2. Experimental and methods

2.1. Manufacturing of tablets

Each batch consists of 40% (w/w) BCS Class 4 compound granulated with 10% (w/w) aqueous solution of povidone (Kollidon K25; BASF Corporation, Ludwigshafen, Germany). A top-spray fluid bed granulator, GPCG-2 LabSystem (Glatt GmbH, Germany), was utilized for the granulation and drying of the granules. The API was pre-blended with the intra-granular excipient in accordance with the DOE plan (Table 1). The pre-blend was screened into the GPCG-2 LabSystem granulator. Immediately after charging the fluid bed, the material was dried for 2 min prior to granulation. The granulating solution was sprayed at 12 g/min with an inlet air temperature of 70 °C. The granules were subsequently dried to a moisture content of 1.5–2.5% with an inlet air temperature of 70 °C. The granules were then blended with extragranular excipient, filler and disintegrant to produce the final blend.

In Application I, the final blend was divided into four portions at this stage, lubricant added to each portion and then blender in accordance with the DOE plan (Table 1). The tabletting blends were subsequently compressed using a Korsch XL 100 Pro Tablet Press (Korsch AG, Germany).

In Application II, to study the impact of various tablet breaking force on stability, core tablets were compressed using different tablet breaking forces of 110 N, 160 N, 200 N and 260 N. The tablet porosity was determined under controlled pressure using AutoPore IV 9500 Mercury Porosimeter (Micromeritics®, GA).

Table 1
A custom design, randomized complete block design, with two granulations followed by a 2^2 factorials for lubrication.

Run #	Excipient addition order (Block)	Blender speed (rpm)	Lubrication time (min)
1	1	10	2
2	1	40	20
3	1	10	20
4	1	40	2
5	2	40	20
6	2	10	2
7	2	40	2
8	2	10	20

2.2. Dissolution testing

The tablets were packaged separately in sealed HDPE bottles and stored under accelerated conditions (51 °C/75% RH) in climate controlled chamber (KBF 720 Constant Climate Chamber, Binder Inc., NY). The samples were pulled out at 0, 1, 2 and 4 weeks from the climate controlled chamber and subjected to dissolution testing. The dissolution testing was performed on six tablets as directed in the USP, using Apparatus 2 (paddle) in 900 mL of dissolution media (0.1 N HCl) at 37 °C ± 0.5 °C with UV detection. The paddle speed was established at 50 rpm with the amount of drug dissolved recorded at intervals of 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55 and 60 min.

Dissolution shifts were calculated between the stability time intervals and across multiple drug release time points. The dissolution profiles and dissolution shifts were analyzed as response variables for the DOE analysis.

2.3. Design of experiments (DOE) in Application I

The outcome of quality risk assessment exercises has identified lubrication time in a bin blender and the blender speed during lubrication as potential critical process parameters that may significantly affect the tablet dissolution upon stability. However, it was debated whether the order of addition of excipient prior to fluid bed granulation (granulation blends) would cause variation within the experimental units to significantly affect the CQA. The two proposed orders of addition of excipient are illustrated in Fig. 1.

Therefore, it was decided to include the order of addition of excipient in the experimental design to account for its extraneous causes and elucidate its effect on dissolution. However, due to limited resources, only two granulation batches could be executed for this study, which translated into changing the order once in the design. This constraint resulted in two groups or blocks of experimental units (granulation blends). In order to isolate the variability due to different order of addition of excipient, this factor was introduced to the custom experimental design as blocking factor. As shown in Table 1, each granulation batch was split into four blending batches (experimental units), followed by a 2^2 full factorial design within each block for lubrication. In this randomized complete block design [14], lubrication time and blender speed during lubrication were two-level continuous factors and randomized within the blocks rather than across the entire study. There were four runs per block, in which each treatment was applied in each block once.

The purpose of the custom design is to evaluate the effects of order of addition of excipient, blender speed during lubrication and lubrication time design factors on the response – dissolution upon accelerated stability, and provide guidance on optimal

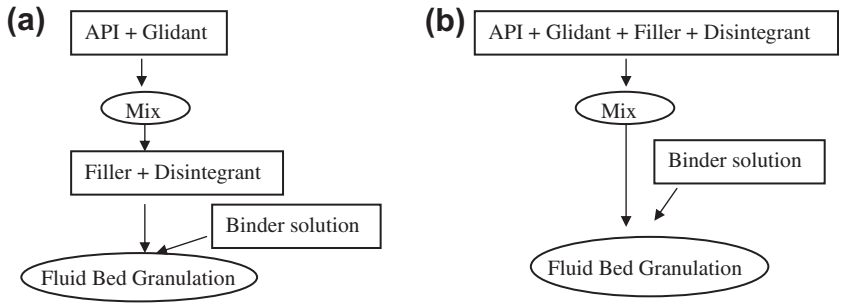


Fig. 1. Excipient addition orders for fluid bed granulation. (a) Order I. (b) Order II.

process conditions to achieve desired dissolution profiles and minimize dissolution shift. The experimental design and analysis, including effect estimates, response surface analysis and optimization, were conducted in JMP 8 (SAS Institute Inc., NC).

2.4. Experimental in Application II

An experiment was conducted to study the impact of tablet breaking force on dissolution and dissolution shift upon stability. The tablets from common granules were compressed on a Korsch XL 100 using four levels of tablet breaking force, 110 N, 160 N, 200 N and 260 N. The tablet weight was maintained for all breaking force levels. These tablets were packaged, stored and subjected to dissolution testing as described in Section 2.2 above.

2.5. Multi-way principal component analysis (MPCA)

As shown in Fig. 2, dissolution profiles from multiple batches during stability test can be arranged as a 3D data array $\underline{\mathbf{X}}$ $(I \times J \times K)$, where the three dimensions represent I batches, J time points of release and K time points of stability, respectively. Along stability at K time points, the same dissolution test is repeated. J spans from 0 to 60 min during release, whereas along K direction it consists of 1-week, 2-week, 3-week and 4-week time points during stability.

Analysis of such higher-dimension data matrix requires special data arrangement and multi-way methods. Multi-way modeling, such as MPCA, PARAFAC and Tucker3 models, can be used for decomposing the 3D data array directly [15–17]. In this study, we only demonstrate a more straightforward approach, multi-way PCA (MPCA), that unfolds the 3D array into a 2D matrix, preprocesses it if necessary and then performs PCA on the unfolded 2D matrix subsequently [18–21]. Therefore, MPCA is essentially equivalent to performing PCA on a 2D array re-arranged by unfolding the 3D array. However, different ways of unfolding a 3D array lead to different results and interpretations. Which unfolding method to use depends on the purpose of the study.

For example, in Application I, the 3D array is unfolded in such a way that the vertical slices $(I \times J)$ of $\mathbf{X}$ are placed side by side to form a resulting 2D matrix of size $(I \times (J \times K))$. Dissolution shifts between initial and 4 week can also be appended to this matrix as variables, as indicated in Fig. 2. This particular unfolding allows one to analyze variability among batches by extracting information with respect to both tablet release time and stability time intervals.

In Application II, however, the 3D data array from batches manufactured at different levels of tablet breaking force is unfolded such that the horizontal slices $(I \times K)$ of $\mathbf{X}$ are stacked on top of one another, resulting in a 2D matrix $((I \times K) \times J)$, as shown in Fig. 3. Note that the way of unfolding in Application II is different from that in Application I. Through this type of unfolding, variability along stability and among different levels of breaking force can be analyzed by summarizing information with respect to tablet release time points.

MPCA is algorithmically consistent with PCA, which finds orthogonal latent variables, or principal components, capturing systematic variations (major trends) in a data set, in the order of decreasing variance [22]. PCA decomposes the data matrix $\mathbf{X}$ into a structure approximated by the sum of outer product of a series of score vectors and loading vectors, $\mathbf{TP}'$, plus a matrix of residuals ($\mathbf{E}$).

$$\mathbf{X} = \sum_{i}^{A} \mathbf{t}_i \otimes \mathbf{p}_i' + \mathbf{E} = \mathbf{TP}' + \mathbf{E} \tag{1}$$

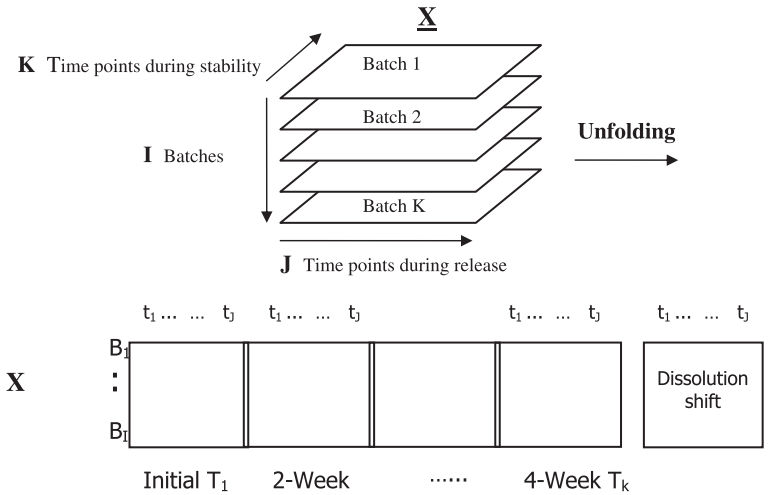


Fig. 2. Unfolding of a three-way matrix $\underline{\mathbf{X}}$ $(I \times J \times K)$ into a two-way matrix $\mathbf{X}$ $(I \times (J \times K))$ in Application I. I batches use different sets of process conditions according to DOE.

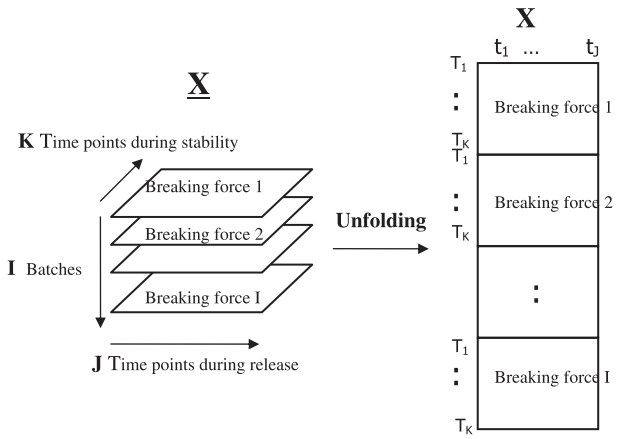


Fig. 3. Unfolding of a three-way matrix $\underline{\mathbf{X}}$ ($I \times J \times K$) into a two-way matrix $\mathbf{X}$ ($(I \times K) \times J$) in Application II. I batches use different levels of tablet breaking force.

where $\mathbf{X}$ is the matrix of dissolution profiles; $\mathbf{T}$ is the matrix of score vectors, $\mathbf{t}_i$; $\mathbf{P}$ is the matrix of loading vectors, $\mathbf{p}_i$; $\otimes$ is the outer product operator; A is the number of principal components retained in the model; $\mathbf{E}$ is the residual matrix.

It is worth mentioning an important diagnostic tool used in these applications, score contribution plot, which can be used to understand why an observation(s) differs from the others in an $\mathbf{X}$ score space and to identify which variables contribute to the difference. Score contribution is computed as

$$\text{Contribution (scores)} = \Delta\mathbf{X} * \text{weight}$$

where $\Delta\mathbf{X}$ is the difference between the observations for comparison and the default weight is the component loading, $\mathbf{p}$ [23].

In both applications, the MPCA proceeds as follows: First, the 3D array $\mathbf{X}$ is unfolded in the ways illustrated above. Each column of the resulting matrix is then mean centered and scaled to unit variance (autoscaled). PCA as described in above Eq. (1) is then applied to the unfolded $\mathbf{X}$. All MPCA analysis was performed in SIMCA-P + 12 by Umetrics Inc., NJ.

3. Results and discussion

3.1. Application I. Investigation into dissolution shift by DOE, response surface analysis and PCA

3.1.1. Dissolution upon stability

As described earlier, the custom design was used to study how the design factors, order of addition of excipient, lubrication time and blender speed during lubrication affect the responses, dissolution and dissolution shift upon stability. Fig. 4 shows the initial, 1-week, 2-week and 4-week dissolution profiles of all eight DOE runs. Dissolution at each time point shown in Fig. 4 is an average of testing results from six tablets. For each time point, the dissolution RSD of the six tablets was less than 5%, and therefore, the error bars is not shown in the figure for clarity. It can be visually observed that dissolution varies from run to run as well as across stability test intervals. However, it is difficult to study within- and between-batch variability by visualization. To provide an efficient and effective summary of the dissolution data, multivariate methods can be advantageous.

3.1.2. Effects of design factors on dissolution

Effect tests of three design factors were performed on the response variables – dissolution profiles upon stability. Table 2 displays the sorted effect estimates of model terms on select dissolution, initial dissolution and 4-week dissolution at 30 min, respectively. In the case of initial dissolution at 30 min, lubrication time and blender speed during lubrication impact dissolution the most, followed by their interaction, while the blocking factor, order of addition of excipients, shows no significant effect, as indicated by the p-value > 0.05. All of the parameters appear to have negative effects on the initial dissolution at 30 min, as evidenced by the negative estimates and bar graph. As for the 4-week dissolution at 30 min, lubrication time and blender speed still show significant effects, but the effect of their interaction has decreased to non-significant. The blocking factor, order of addition of excipient, with p-value of 0.8199, continues to be insignificant. By inspection of effect tests on dissolution, the order of addition of excipient was found to be insignificant at all release time points and stability test

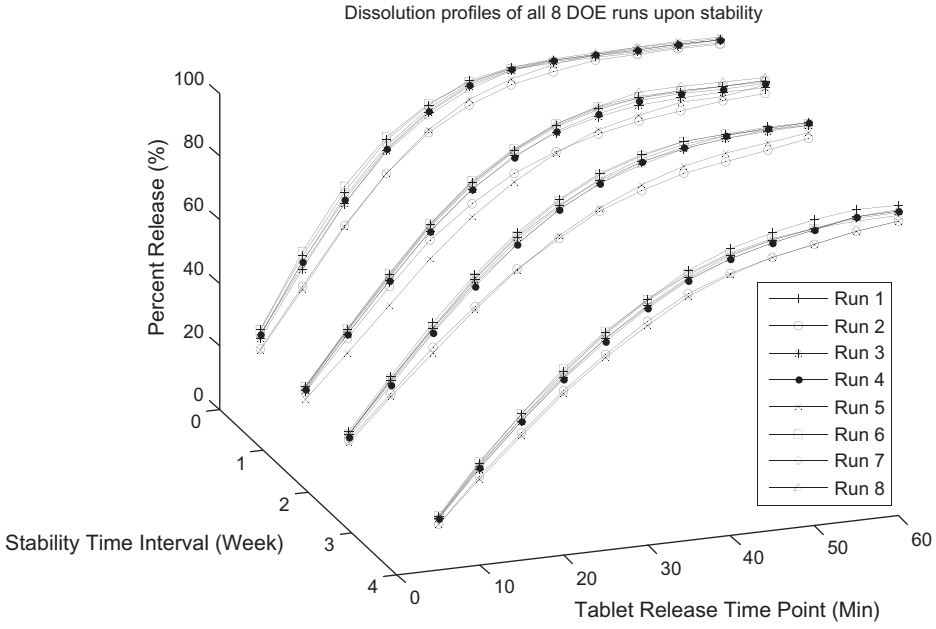
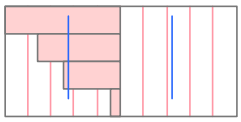
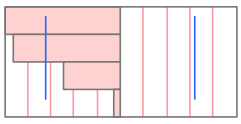


Fig. 4. Dissolution profiles of initial, 1-week, 2-week and 4-week stability samples for all eight DOE runs.

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

Sorted parameter estimates		Response: Initial dissolution at 30 min			
Term	Estimate	Std Error	*t*-Ratio		Prob > |*t*|
Lubrication time (2, 20)	−1.925	0.27157	−7.09		0.0058*
Blender speed (10, 40)	−1.375	0.27157	−5.06		0.0149*
Blender speed * lubrication time	−0.95	0.27157	−3.50		0.0395*
Excipient addition order [1]	−0.15	0.27157	−0.55		0.6192
		Response: 4-week dissolution at 30 min			
Lubrication time (2, 20)	−2	0.402596	−4.97		0.0157*
Blender speed (10, 40)	−1.85	0.402596	−4.60		0.0194*
Blender speed * lubrication time	−0.975	0.402596	−2.42		0.0940
Excipient addition order [1]	−0.1	0.402596	−0.25		0.8199

* *p*-Value < 0.05 indicates significance level.

intervals (not shown here for brevity). The blocking factor (order of addition of excipient) was not removed from the model because the assignment of treatments was based on blocks. The blocks represent a restriction on the randomization and therefore remain in the model [14]. However, the blocking effect by the order of addition of excipient was not found to be helpful in this experiment and thus will not be included in future study.

The interaction profile, as shown in Fig. 5, reveals how the two factors, lubrication time and blender speed, interact each other in terms of the response variable, initial dissolution at 30 min. It can be observed that lubrication time has little impact at low blender speed; however, at high blender speed, lube time significantly impacts dissolution at 30 min. Similarly, blender speed shows much greater impact at higher lubrication time. The interaction profile also suggests that a lower lubrication time and a lower blender speed can be used to increase initial dissolution at 30 min.

3.1.3. Effect of design factors on dissolution shift

Dissolution shift was calculated as difference between dissolution at specific release time points between initial and 4-week stability (under accelerated condition) intervals. Dissolution shift, or slow-down, upon stability in this case was observed for all DOE runs at all release time points (5–60 min), as seen in Table 3. Analysis of variance (ANOVA) was performed for all responses – dissolution shift between initial and 4-week dissolution and summarized in Table 3. The response surface models with high *F*-ratio > 10 and associated *p*-value < 0.05 are significant, indicating the design factors affect the response significantly. The models that are significant may be potentially used for optimization.

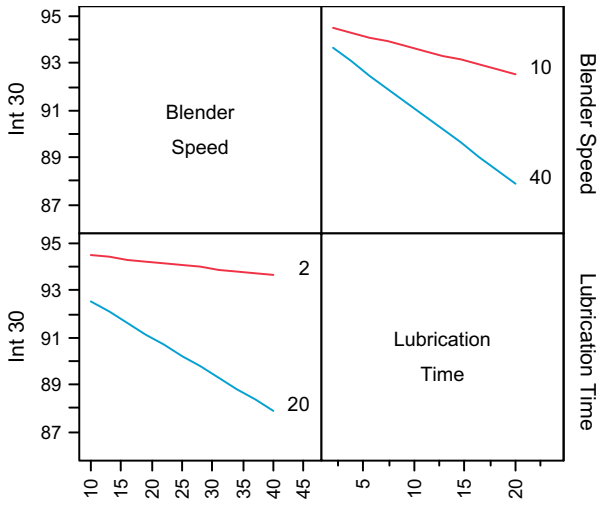


Fig. 5. Interaction profile of design factors, lubrication time and blender speed on the initial dissolution at 30 min.

Table 4 summarizes, in more detail, sorted parameter estimates for select dissolution shift between initial and 4 week at 15, 30 and 45 min. The evaluative statistics suggest that lubrication time and blender speed have significant ($p < 0.05$) impact on dissolution shift at 15 and 45 min. It was, however, interesting to see that none of the factors have shown significant effects on dissolution shift at 30 min. At earlier release time points (15 min), both lubrication time and blender speed show negative effects on dissolution shift, while this phenomenon is reversed after about 30 min during release profile, as the effects switch from negative to positive at 45 min, Table 4.

It has been postulated that the reversed effect observed at 15 min and 45 min of dissolution, negative and positive effects respectively, may be due to a change in the mechanism of tablet dissolution. At 15 min, the tablet dissolute predominantly by disintegrating and increased lubrication efficiency, i.e., increase lubrication time and blender speed, will hinder the ability of the tablet to disintegrate. On the other hand, at 45 min, the tablet dissolute mainly by erosion and increased lubrication efficiency will assist in tablet erosion and dissolution.

At the 30 min time point, both mechanisms of dissolution may be operating and the effects of lubrication efficiency may be counteracting each other, leading to a nullification of the effects of lubrication time and blender speed.

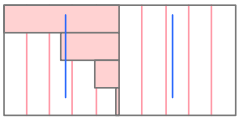
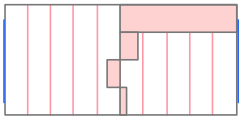
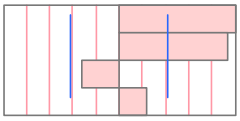
As mentioned in Section 3.1.2, the lubrication time and blender speed have a significant negative effect on the initial ($t = 0$) dissolution at 30 min for the tablets. For these initial tablets, the predominant pathway of dissolution at 30 min is disintegration but as the tablets age during accelerated stability, the effectiveness of the disintegrant is diminished (unpublished results) and erosion plays a greater role in the dissolution of the tablets at 30 min.

The above DOE analysis (effect estimates and ANOVA) indicates that lubrication step has a significant influence on both dissolution and dissolution shift upon stability. Therefore, the lubrication step is identified as a critical unit operation. Longer lubrication time and higher blender speed appear to lead to greater dissolution shift during stability. Dissolution slow-down could be attributed to the conventional wisdom, hydrophobic nature of the lubricant which could potentially coat the API and retard dissolution [24–27]. To elucidate the optimal combination of blender speed and lubrication time that yield desired dissolution with minimal dissolution shift, response surface methodology in conjunction with optimization was employed.

Table 3
Response variables: Dissolution shift (slow-down) between initial and 4 week upon accelerated stability (% release), and ANOVA – Influence of design factors on dissolution shift and significance of response surface models.

Dissolution shift between initial and 4 week at	Run #1	Run #2	Run #3	Run #4	Run #5	Run #6	Run #7	Run #8	*F*-ratio	Prob > F
5 min	6.6	3.1	4.6	5.8	2.8	6.5	5.6	5.4	27.6	0.011
10 min	13.2	8.3	11.2	12.7	7.9	14.4	12.4	10.9	30.7	0.009
15 min	18.3	13.4	16.7	17.9	13.6	19.7	17.9	15.5	15.3	0.025
20 min	20.9	16.9	20	20.8	17.9	21.6	19.9	18.9	7.0	0.071
25 min	20	18	19.4	20.8	19.8	19.8	19.5	18.5	0.7	0.657
30 min	16.7	16.3	16.9	18.4	19.1	16.5	16.6	16.5	0.3	0.893
35 min	12.2	13.9	13.3	14.8	16.7	12.2	13.4	13.9	1.7	0.346
40 min	7.4	11.6	9.6	10.5	14.3	8.1	9.9	10.7	7.8	0.061
45 min	3.8	10.1	6.3	7.2	11.9	5.3	7	7.5	28.9	0.010
50 min	1.2	8	3.9	4.6	9.9	3.3	4.9	4.9	36.4	0.007
55 min	0.2	5.6	2	2.1	7.9	2.7	3.2	2.3	18.1	0.019
60 min	0	3.8	1.6	1.9	6.1	2.5	3	1.5	7.3	0.067

Table 4
Sorted parameter estimates for dissolution shift between initial and 4-week dissolution at 15, 30 and 45minutes.

Sorted parameter estimates		Response: Shift between initial and 4-week dissolution at 15 min			
Term	Estimate	Std error	*t*-Ratio		Prob > |*t*|
Lubrication time (2, 20)	−1.825	0.266145	−6.86		0.0063*
Blender speed (10, 40)	−0.925	0.266145	−3.48		0.0402*
Blender speed * lubrication time	−0.375	0.266145	−1.41		0.2536
Excipient addition order [1]	−0.05	0.266145	−0.19		0.8630
		Response: Shift between initial and 4-week dissolution at 30 min			
Blender speed (10, 40)	0.475	0.483908	0.98		0.3987
Lubrication time (2, 20)	0.075	0.483908	0.15		0.8867
Excipient addition order [1]	−0.05	0.483908	−0.10		0.9242
Blender speed * lubrication time	0.025	0.483908	0.05		0.9620
		Response: Shift between initial and 4-week dissolution at 45 min			
Blender speed (10, 40)	1.6625	0.221148	7.52		0.0049*
Lubrication time (2, 20)	1.5625	0.221148	7.07		0.0058*
Excipient addition order [1]	−0.5375	0.221148	−2.43		0.0933
Blender speed * lubrication time	0.3875	0.221148	1.75		0.1780

* *p*-Value <0.05 indicates significance.

3.1.4. Response surface analysis and optimization

It should be noted that the DOE used in this study is not an optimization design due to limited resources. However, if a response surface model shows good model evaluative statistics and is significant, it could be used to find optimal combination of input variables that would ensure desired outputs through optimization, though the optimal solutions may not necessarily be as accurate as the model based on more levels of design factors. An example will be given here to illustrate the optimization procedure. The prediction profiler in Fig. 6 displays profile traces for select responses (initial dissolution at 30 min and dissolution shift between initial and 4 week at 45 min), as a function of input variables (blender speed during lubrication and lubrication time). An interactive study of input variables and responses in the profiler is a useful means to visualize how varying input variables impact these responses and to identify the optimal ranges of input variables in terms of desired responses. The objective of optimization here is to maximize initial dissolution at 30 min and at the same time minimize dissolutions shift between initial and 4 week at 45 min. The JMP software thus maximizes desirability for both input factors and responses and finds a factor level combination that maximizes initial dissolution at 30 min and minimizes dissolution shift at 45 min. The optimal solution is to set lubrication time of 2 min and blender speed during lubrication at 10 rpm. That is, initial dissolution at 30 min can be increased and the dissolution shift at 45 min can be decreased by using lower lubrication time and blender speed during lubrication. The predicted initial dissolution at 30 min is 94.3% and dissolution shift at 45 min is 4.5%. Similarly, the optimization can be performed for other responses, depending on the objectives.

3.1.5. Study batch relationships by multi-way PCA of dissolution profiles upon stability

All eight DOE runs are included in the MPCA modeling as samples, while dissolution profiles (tablet release time points 5–60 min) across stability test intervals (initial, 1 week, 2 week and 4 week) are arranged as variables as shown in Fig. 2. As described in Section 2.5, the particular unfolding allows us to analyze variability among batches by extracting information with respect to both tablet release time and stability time intervals. Dissolution shifts between initial and 4 week are also appended to the unfolded matrix as variables. Scores scatter 2D plot (t_1–t_2) derived from MPCA, Fig. 7, reveals the possible presence of outliers, groups or patterns among batches. The score t_1 (first component) explains the largest variation of the X space 80% ($R2X[1]$), followed by t_2 explaining 12%($R2X[2]$). Runs #1–4 from Block 1, as defined in the blocking DOE, are overlapped with Runs #5–8 from Block 2, indicating there is no clear difference between Block # and Block

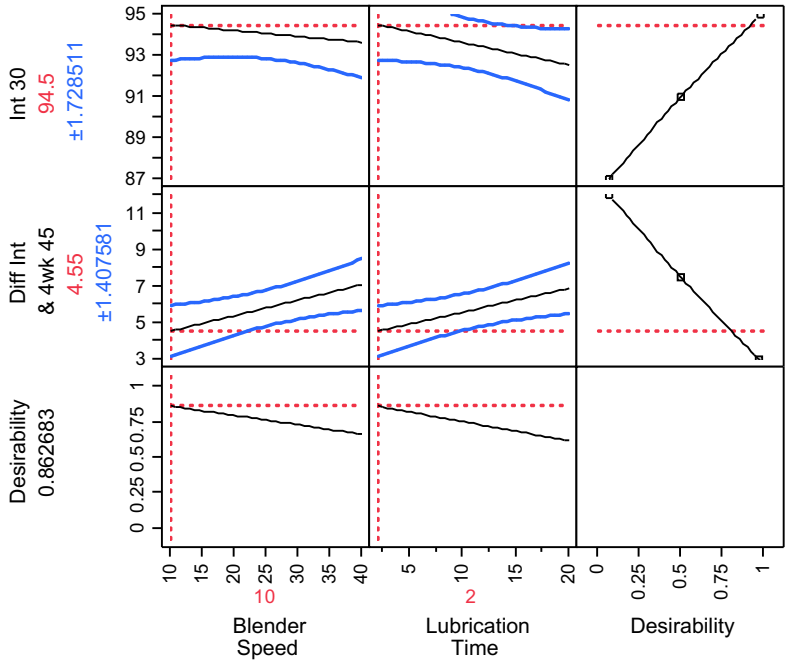


Fig. 6. Prediction profiler with desirability functions (for select responses).

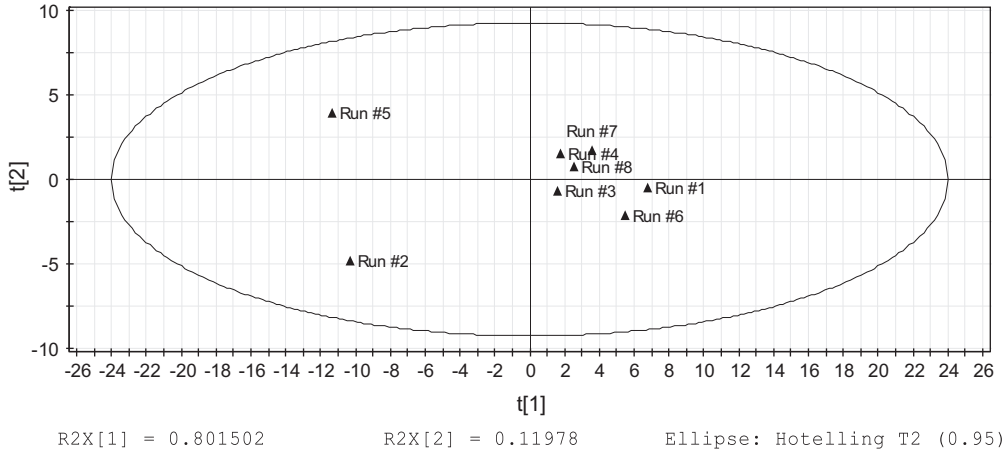


Fig. 7. Scores plot (t_1–t_2) displaying batch relationships.

#2. The PCA analysis is therefore consistent with the DOE effect tests in which the blocking factor, excipient addition order, shows no significant effect. No outliers lie outside the ellipse (95% confidence interval). It can be observed that Run #2 and Run #5 are clearly separated from the rest of runs as they are located further away especially along the t_1 direction (spans 80% variation), indicating these two batches are more different from the rest.

A score contribution plot, Fig. 8, explains why these two batches (Runs #2 and 5) are so much different from the rest and identify which variables are most contributing to the difference. The variables represent weighted difference between the groups, and larger positive and lesser negative values are more important in differentiating the groups. It is clear that these two batches exhibit significantly slower dissolution across all release time points upon all stability test intervals. Interestingly, dissolution shift of these two batches was lesser before 30 min, whereas it became greater after 30 min than that of the rest of batches.

A similar score contribution analysis can be performed to identify why Runs #2 and 5 are different (not shown here). It would be difficult to sort out within- and between-batch variations by direct visualization of dissolution profiles at different stages of stability. As can be seen from the MPCA analysis, MPCA allows for more efficient and effective extraction of information from entire dissolution profiles upon stability.

3.2. Application II. Study impact of tablet breaking force on dissolution shift upon stability by multi-way PCA

In the second application, an experiment was conducted to study the impact of tablet breaking force on dissolution and dissolution shift upon stability. Core tablets were compressed at different tablet breaking force of 110 N, 160 N, 200 N and 260 N, respectively. Dissolution profiles of the tablets at different tablet breaking force levels during an accelerated stability study are shown in Fig. 9. It can be visualized that softer tablets exhibit larger shift in dissolution than harder tablets.

As described in Section 2.5, the 3D array is unfolded such that the variability along stability test intervals and at different levels

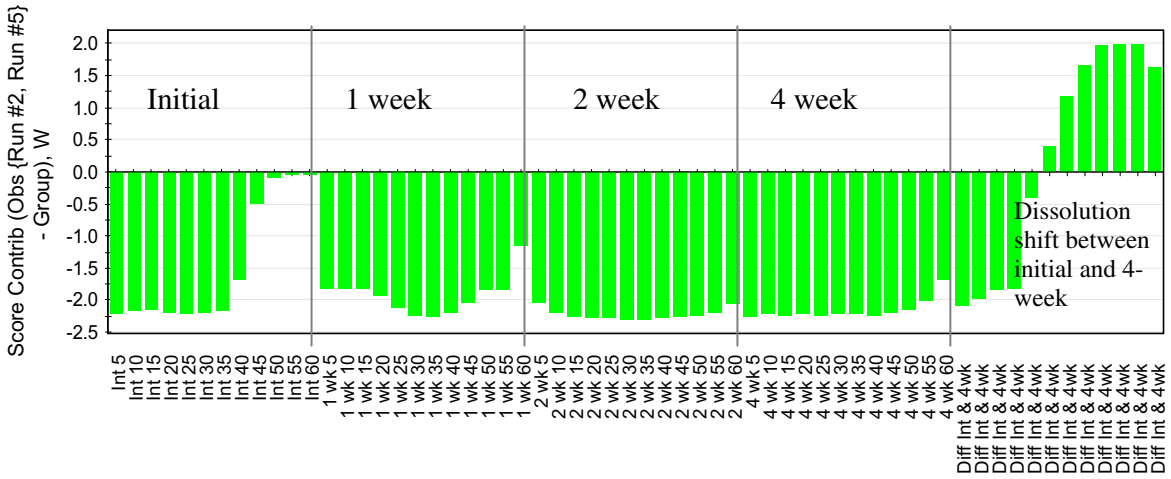


Fig. 8. Score contribution plot showing variables contributing to the difference between batches 2 and 5 vs. the rest of batches.

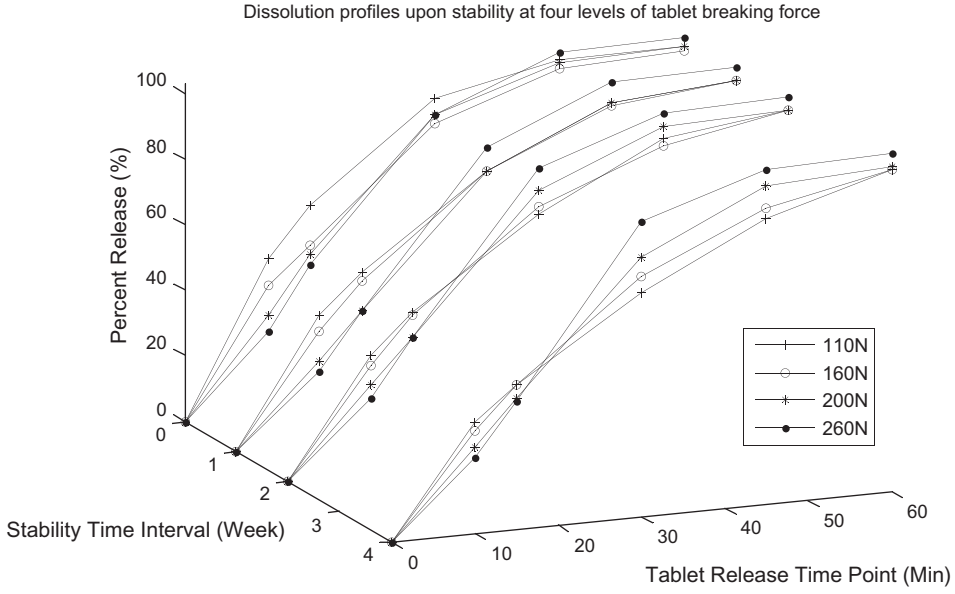


Fig. 9. Dissolution profiles of tablets with different tablet breaking force upon stability.

of breaking force can be studied. The PCA Scores plot (t_1–t_2), Fig. 10, indicates that tablet breaking force clearly has an impact on dissolution profiles. Each point represents a dissolution profile from stability test at different tablet breaking force. Four groups of different tablet breaking force levels are well separated along t_1 (the first principal component) which accounts for 61% variation, while t_2, explaining 33% variation, appears to separate dissolution along stability test intervals. At 110 N tablet breaking force level, there is a considerable amount of systematic variation along t_2, with dissolution slowing down over stability. As tablet breaking force increases, dissolution shift over stability at the tablet breaking force level decreases. It can be observed that dissolution shift becomes less significant when tablet breaking force reaches above 200 N. It can be seen that multi-way PCA of dissolution profiles upon stability not only reveals between-batch variations (at different tablet breaking force), but also reveals within-batch variations (the same batch at the same tablet breaking force) upon stability.

A score contribution plot, Fig. 11, can be used to identify which variables contribute to the difference between 260 N and 110 N. Interestingly, it can be seen that softer tablets dissolve faster before 30 min, whereas harder tablets dissolve faster after 30 min.

It can be concluded that upon stability softer tablets experienced greater dissolution shift and more variations in dissolution profiles than harder tablets, whereas harder tablets exhibited negligible changes. Furthermore, good correlation was found between tablet porosity and tablet breaking force based on the pore size distribution and the volume pore size distributions of the tablets obtained from mercury porosity measurements (data not shown), in consistent with published literature [28]. Li et al. have previously reported that the physical changes of tablets mediated by moisture were the main causes for decline in dissolution rate upon stability under stressed conditions [28]. They implicated that the disintegrant in the tablet may hydrate and swell prematurely due to moisture uptake prior to the contact with dissolution media, resulting in changes in the pore structure of the tablets. This moisture uptake, prior to the contact with dissolution media, may be more pronounced in the softer tablets, with the larger pore sizes and volumes. Consequently, this leads to a more prominent dissolution slow-down in the softer tablets during accelerated storage condition.

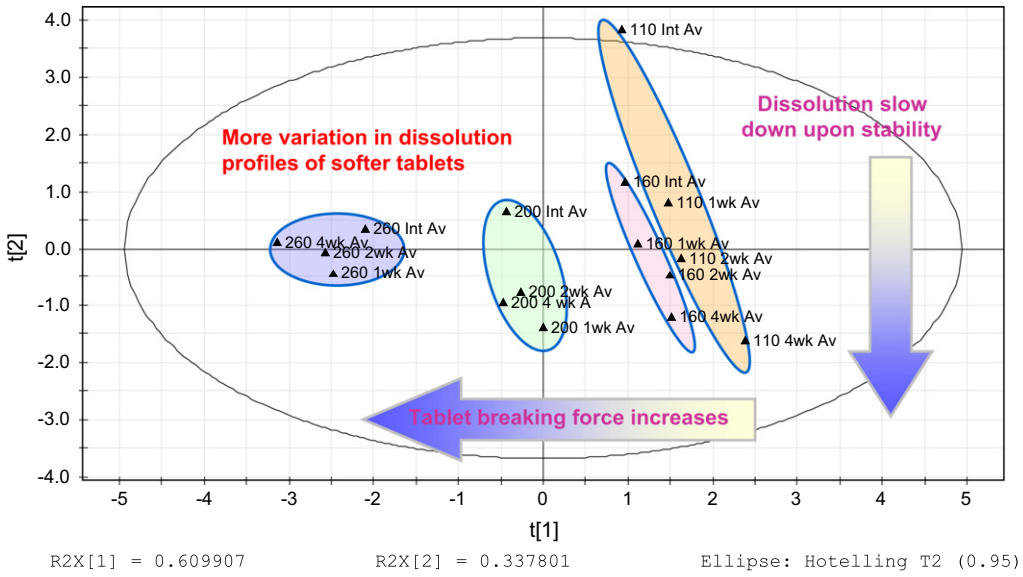


Fig. 10. Scores plot (t_1–t_2) displaying impact of tablet breaking force on dissolution upon stability.

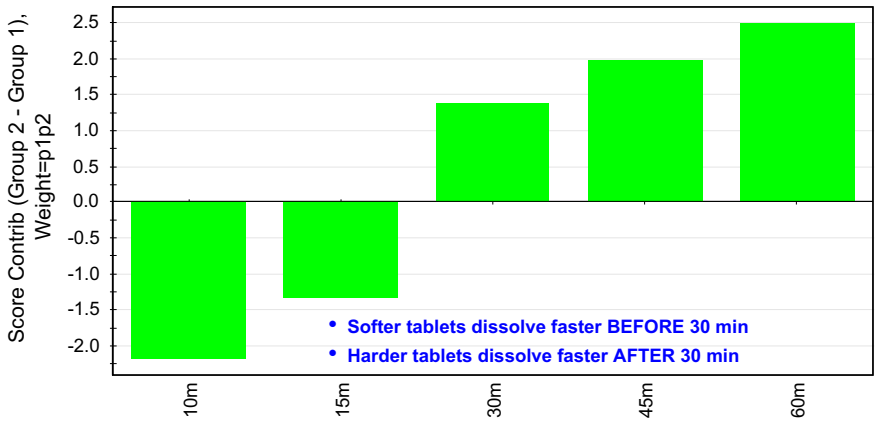


Fig. 11. Score contribution plot: 260 N vs. 110 N Dissolution profiles. Similar trend observed for 200 N vs. 160 N (not shown here).

4. Conclusions

It was demonstrated that multivariate methods, such as experimental design, response surface modeling, optimization and multi-way PCA (MPCA), can be applied to systematically identify the root-cause or source of variability of dissolution shift upon stability and propose optimal process conditions that ensure desired final product quality attributes – dissolution upon stability.

In Application I, lubrication time and blender speed during lubrication were found to impact significantly on dissolution upon stability and dissolution shift (slow-down) between initial and 4-week stability samples across release time points (5–20 min and 40–60 min). It was demonstrated that lubrication time and blender speed during lubrication can be optimized to achieve faster dissolution and minimal dissolution shift upon stability. Excipient addition order was found to have no significant effect on dissolution as well as dissolution shift upon stability.

Both Applications I and II show that MPCA provides an effective and efficient way to utilize entire dissolution profiles and reveal between- and within-batch variations upon stability, especially in the situation where many batches are involved. MPCA can also provide additional information, for example, on batch relationships and diagnosing why certain groups are different.

It can be concluded that multivariate methods, as Quality by Design (QbD) principles and tools, play an important role in facilitating a higher-level of process understanding and create opportunities for root-of-cause investigation and developing control strategies in formulation and process development.

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