Design Space Construction of Multiple Dose-Strength Tablets Utilizing Bayesian Estimation Based on One Set of Design-of-Experiments

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Design spaces for multiple dose strengths of tablets were constructed using a Bayesian estimation method with one set of design of experiments (DoE) of only the highest dose-strength tablet. The lubricant blending process for theophylline tablets with dose strengths of 100, 50, and 25 mg is used as a model manufacturing process in order to construct design spaces. The DoE was conducted using various Froude numbers (X_1) and blending times (X_2) for theophylline 100-mg tablet. The response surfaces, design space, and their reliability of the compression rate of the powder mixture (Y_1), tablet hardness (Y_2), and dissolution rate (Y_3) of the 100-mg tablet were calculated using multivariate spline interpolation, a bootstrap resampling technique, and self-organizing map clustering. Three experiments under an optimal condition and two experiments under other conditions were performed using 50- and 25-mg tablets, respectively. The response surfaces of the highest-strength tablet were corrected to those of the lower-strength tablets by Bayesian estimation using the manufacturing data of the lower-strength tablets. Experiments under three additional sets of conditions of lower-strength tablets showed that the corrected design space made it possible to predict the quality of lower-strength tablets more precisely than the design space of the highest-strength tablet. This approach is useful for constructing design spaces of tablets with multiple strengths.

Key words quality by design; design of experiments; multivariate regression; modeling

The International Conference on Harmonization (ICH)[1] has outlined Quality by Design (QbD) as a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management. According to the QbD principle, pharmaceutical quality should not be tested *via* day-to-day release testing, instead, it should be elaborated by design in advance. One of the most significant aspects in the QbD concept is the establishment of a design space based on a multidimensional combination of input formulation parameters, process parameters, or material attributes that have been shown to provide assurance of quality attributes[2].

A design of experiments (DoE) study has been effectively used in order to construct a design space.[3,4] DoE is a useful method for systematically understanding the relationship between input parameters and output quality attributes. A typical design space is established as a superposition of the response surfaces for each quality attribute generated by the response surface method (RSM) using the DoE results.[5–11] RSM includes statistical analyses such as multiple linear regression analysis[12] and artificial neural networks.[13,14] Takayama *et al.* developed RSM-S, a novel RSM that incorporates multivariate spline interpolation.[15] RSM-S is an effective tool for obtaining reliable response surfaces of nonlinear phenomena and calculating optimal solutions. A bootstrap resampling technique and self-organizing map (SOM) clustering have been adopted to qualify the reliability of an optimal solution[16–18] and response surfaces.[19]

In general, the components of commercial tablets containing the same active pharmaceutical ingredient are similar, regardless of the dose strength, because different strengths of tablets were developed on the basis of the same formulation development concept. However, the compositions vary among dose strengths, resulting in varying quality attributes, even when the tablets are manufactured in the same manner. Accordingly, the design space has to be shifted with increasing dose strength. Thus, a separate DoE study is required for each dose strength in order to establish a reliable design space; such a procedure is resource intensive. Therefore, it is necessary to develop a simple and efficient method to construct design spaces for multiple-strength tablets.

Bayesian estimation based on posterior probability distribution can be used to estimate the probability of uncertain phenomena. It finds applications in various fields such as information technology, economics, and population pharmacokinetics in pharmaceutical sciences. The posterior probability distribution can be calculated from the prior probability distribution and a few additional data using Bayes' theorem. Therefore, Bayesian estimation can correct a prior highest-strength design space to a posterior lower-strength design space by using a few lower-strength experimental data.

Previously, we reported that a reliable large-scale design space was constructed using a Bayesian estimation method with a small-scale DoE and five batches of large-scale manufacturing data, without enforcing a large-scale DoE.[20,21] The large-scale design space was more reliable than the small-scale design space, in spite of some discrepancy in the pharmaceutical quality between the manufacturing scales.

In this study, we conducted Bayesian estimation with the highest-strength design space and five batches of manufacturing data for each lower-strength tablet in order to construct a lower-strength design space without conducting a lower-strength DoE study. We selected the lubrication process for theophylline tablets as a model experiment for the design space construction. In addition, we validated the reliability of the estimated design space for predicting lower-strength manufacturing by comparing the estimated design space with the

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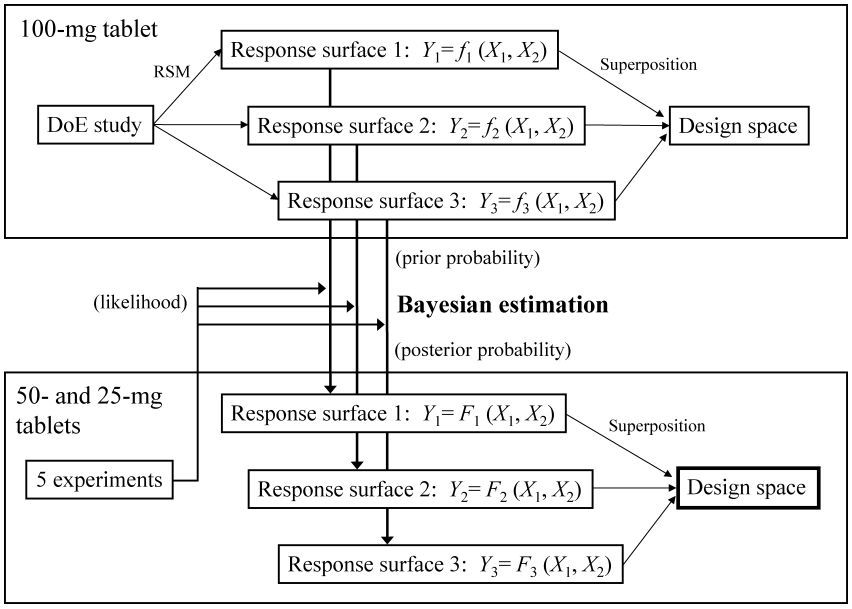

Fig. 1. Construction of Multiple-Dose Design Space Using Bayesian Estimation
X_1, X_2: input parameters, Y_1, Y_2, Y_3: output quality attributes.

highest-strength design space.

Experimental

Figure 1 shows the setup for a lower-strength design space using Bayesian estimation. We constructed a Bayesian design space for the lubrication process of theophylline tablets, applied to lower-strength 50- and 25-mg tablets, by using the design space constructed on the basis of a DoE study of the highest-strength 100-mg tablet, with a limited number of lower-strength experimental data.

Materials Theophylline (Hachidai Pharmaceutical Co., Japan), lactose monohydrate (Dilactose S®, Freund Corporation, Japan), cornstarch (Nihon Shokuhin Kako Co., Japan), microcrystalline cellulose (Ceolus® PH-101, Asahi Kasei Chemicals Co., Japan), and magnesium stearate (Mallinckrodt, Inc., U.S.A.) were used in all the experiments.

Preparation of Theophylline Tablets Tablets containing 100, 50, and 25 mg of theophylline were used in this study. They were produced using the direct compression method with the formulation shown in Table 1. The tablet size for each dose strength is the same.

All ingredients, except magnesium stearate, were blended at 300 g scale in a 1-L V-shaped blender with a Froude number of 0.25 (rotating radius, 0.11 m; rotating speed, 45 rpm) for 15 min. The blended mixture was sieved using a screening mill (Quadro® Comil®, Powrex Corporation, Japan; screen size, 0.991 mm; impeller rotating speed, 300 rpm). After adding magnesium stearate, the mixture was blended to obtain the final blend in the 1-L V-shaped blender at various predetermined rotation speeds and times. The final blend was compressed with 8.5-mm biconvex round punches at 250-mg weight and 7-kN compression force per tablet using a 24-station rotating tableting machine (Correct 24, Kikusui Co., Japan).

DoE in Highest-Strength Tablet The Froude number (X_1) and blending time (X_2) were selected as input variables. The Froude number[22] is defined as

Table 1. Components and Composition of Theophylline Tablets

Components	Quantity (mg/tablet)		
Dose strength	100 mg	50 mg	25 mg
Theophylline	100	50	25
Lactose monohydrate	66.5	101.5	119
Cornstarch	28.5	43.5	51
Microcrystalline cellulose	50	50	50
Magnesium stearate	5	5	5
Total	250	250	250

$$Fr = r(\pi n)^2 / 900g \quad (1)$$

where r (m) is the rotating radius of the blender, n (rpm) is the rotating speed, and g (m/s^2) denotes gravitational acceleration. Nine experiments were conducted to obtain the response surfaces of each response variable according to the two-factor three-level (3^2) experimental design (Table 2).

Evaluation of Powder and Tablet Properties The compression rate of the powder mixture (Y_1), tablet hardness (Y_2), and dissolution rate in 30 min (Y_3) were selected as the response variables.

The compression rate (CR)[23] is an indicator of powder flowability, and it is defined as

$$CR\,(\%) = (\rho_T - \rho_L) / \rho_T \times 100 \quad (2)$$

where ρ_T and ρ_L denote the tapped and loose densities of the powder (kg/m^3), respectively. The tapped and loose densities of the mixture for tableting were measured using tap density equipment (SZ-02, Rinkan Co., Japan).

The hardness of the tablets was measured using a tablet hardness tester (Tablet tester Pharmatest WHT, Pharma Test Apparatebau, Austria). Dissolution testing was performed using a 50-rpm paddle and 900 mL of water at 37°C. The sample solution was assayed using an automated flow-through UV

Table 2. Experimental Design and Properties of Highest-Strength Experiments

Input process parameter			Output quality attribute		
X_1		X_2	Y_1	Y_2	Y_3
Froude number	Rotation speed (rpm)	Blending time (min)	Compression rate	Hardness (N)	Dissolution rate in 30 min (%)
0.10	29	2	0.340	71.7	90.2
0.10	29	30	0.320	51.6	85.0
0.10	29	58	0.289	37.8	81.1
0.25	45	2	0.345	67.3	89.1
0.25	45	30	0.286	39.4	81.1
0.25	45	58	0.242	24.2	75.6
0.40	57	2	0.339	60.3	86.3
0.40	57	30	0.255	31.0	77.4
0.40	57	58	0.240	21.9	67.8

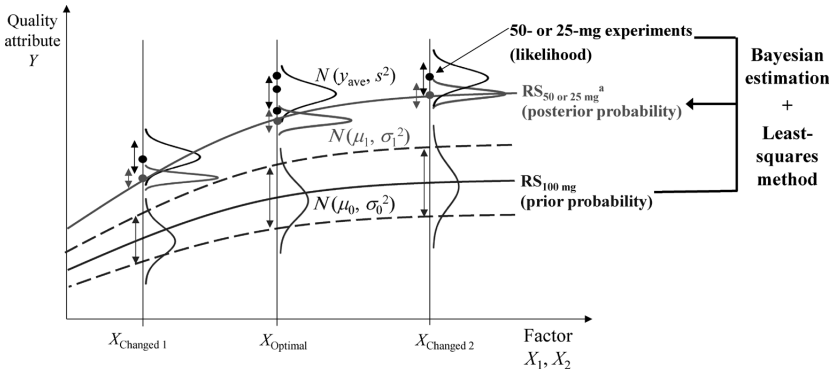

Fig. 2. Bayesian Estimation Process

[a] RS: response surface, $X_{Optimal}$: simultaneous optimal condition, and $X_{Changed\ 1}$ and $X_{Changed\ 2}$: changed lower-strength experimental conditions for Bayesian estimation.

spectrophotometric method at 253 nm with a 10-mm-long cell (Automated dissolution apparatus, Toyama Sangyo Co. and Shimadzu Co., Japan). Three or six tablets were analyzed to calculate the average dissolution rate.

Construction of Response Surfaces and Design Space of 100 mg Tablet and Calculation of Simultaneous Optimal Solution RSM-S was carried out to construct the response surfaces and to calculate the simultaneous optimal solution in the highest-strength tablet using dataNESIA™ Version 3.0 (Yamatake Corp., Tokyo, Japan). dataNESIA™ calculates the simultaneously optimal solution at which the sum of a generalized distance between a predicted value and an individually optimal value in each quality attribute was minimized.[15] The criteria for the quality attributes in this case study were set as follows: Y_1=0.320 (upper limit), Y_2=30 N (lower limit), and Y_3=75% (lower limit). The acceptance areas for each quality attribute were superposed to determine a design space. The standard deviation of the response surfaces, which represented the reliability of the models, was evaluated *via* bootstrap resampling and SOM clustering using dataNESIA™ and Viscovery® (Eudapics Software Gmbh, Austria), respectively, according to a previously reported method.[17,18] Bootstrap resampling was performed 200 times.

Theory of Bayesian Estimation Bayesian estimation is a methodology for constructing a posterior probability distribution for an uncertain phenomenon. The posterior probability distribution is computed on the basis of Bayes' theorem by considering an assumed prior probability and likelihood estimated from newly observed data.

When the prior probability and likelihood are expressed as normal distributions, the posterior probability is also distributed normally.[24] The average and standard deviation of the posterior probability distribution are expressed as

$$\mu_1 = \frac{\frac{1}{\sigma_0^2}\mu_0 + \frac{n}{s^2}y_{ave}}{\frac{1}{\sigma_0^2} + \frac{n}{s^2}} \quad (3)$$

$$\frac{1}{\sigma_1^2} = \frac{1}{\sigma_0^2} + \frac{n}{s^2} \quad (4)$$

where μ_1 and σ_1 are the average and standard deviation of the posterior probability distribution, μ_0 and σ_0 are the average and standard deviation of the prior probability distribution, y_{ave} and s are the average and standard deviation of the likelihood distribution, and n is the number of data obtained in order to calculate the likelihood, respectively. The average of the posterior probability, μ_1, is the value that internally divides the averages of the prior probability and likelihood with the standard deviation of the two. The variance of the posterior probability, σ_1^2, is the harmonic average of the variance of the prior probability and likelihood, which means that the reliability of the posterior probability is higher than those of the prior probability and likelihood.

Construction of Response Surfaces and Design Space of Lower-Strength Tablet by Bayesian Estimation The

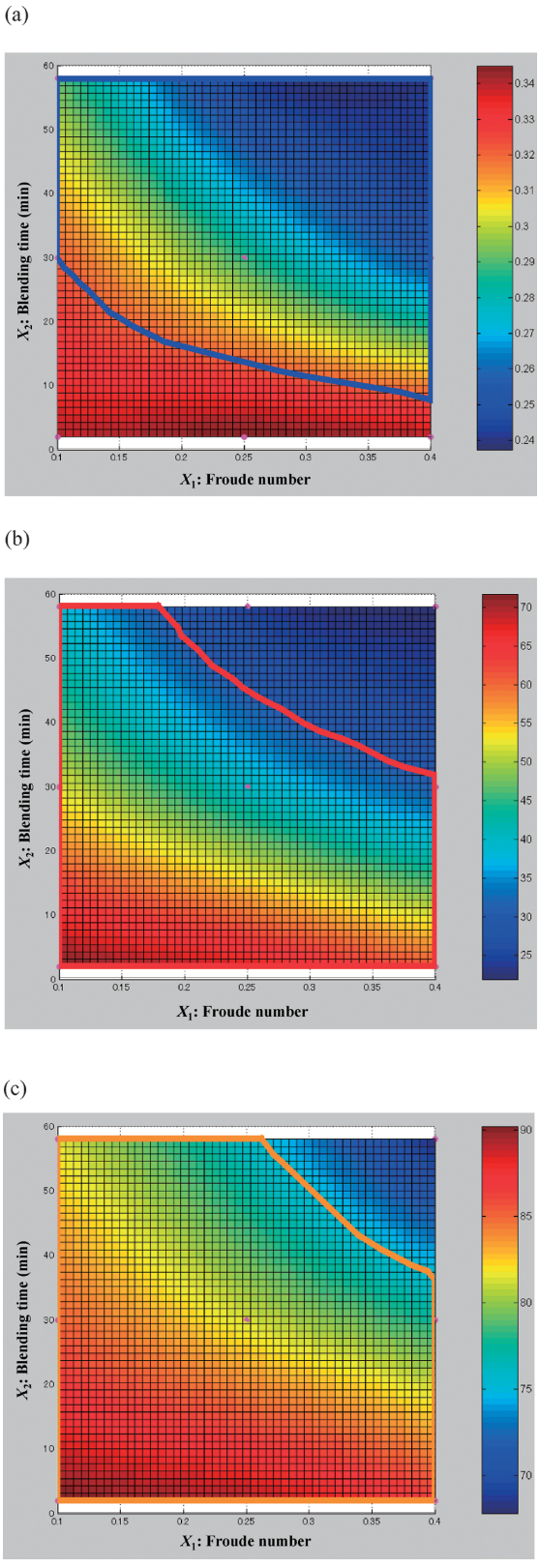

Fig. 3. Response Surfaces for Quality Attributes of Highest-Strength Tablets

(a) Compression rate of powder mixture (Y_1), (b) tablet hardness (Y_2), and (c) dissolution rate in 30 min (Y_3), solid line: edge of the acceptance area for each quality attribute.

Bayesian estimation process is shown in Fig. 2. The value of each quality attribute expressed by the response surfaces

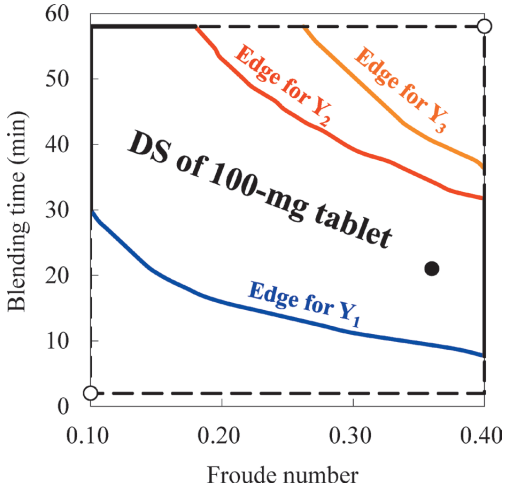

Fig. 4. Design Space of Highest-Strength Tablets

Solid line: edge of the highest-strength design space, (●): simultaneous optimal condition, and (○): changed lower-strength experimental conditions for Bayesian estimation.

of the highest-strength tablet was regarded as the average of the prior probability. The standard deviation of the response surfaces, calculated *via* bootstrap resampling, was considered to be the standard deviation of the prior probability. In order to calculate the likelihood, five batches of lower-strength manufacturing were conducted. Three batches were manufactured under the simultaneous optimal condition to calculate the standard deviation of the likelihood. For the remaining two batches, two different conditions were selected to perform Bayesian estimation. Applying Bayesian estimation outside the region of three lower-strength manufacturing conditions can result in poor prediction accuracy, whereas prediction near the edges of the design space should have high accuracy. Therefore, two different conditions were set in the experimental area outside the design space, far from the optimal condition, in order to interpolate the response surfaces near the edges of the design space. A smaller number of lower-strength experiments may result in a larger predictive error in the estimated response surface. Therefore, the adequacy of five lower-strength experiments was verified by conducting validation experiments, which are described later.

The standard deviation of the likelihood(s) was determined using the equation

$$s = 0.591 \times (\max(Y_{\mathrm{i}}, Y_{\mathrm{ii}}, Y_{\mathrm{iii}}) - \min(Y_{\mathrm{i}}, Y_{\mathrm{ii}}, Y_{\mathrm{iii}})) \quad (5)$$

where Y_{i}–Y_{iii} are the quality attributes obtained from the three lower-strength experimental batches under the optimal condition. This equation can be used to estimate the standard deviation from the range of the obtained data.[25] We assumed that the calculated standard deviation was constant under all manufacturing conditions. If the assumption is wrong, the predictive error of the estimated response surface could increase. Therefore, the validity of the assumption was also verified by the after-mentioned validation experiments. Based on the information for the prior probability and likelihood, the Bayesian estimate for the three input process parameters was calculated using Eqs. 3 and 4.

The response surfaces of the highest-strength tablet were corrected to generate the lower-strength response surfaces using the equation

Table 3. Results of Experiments and Bayesian Estimation of 50-mg Theophylline Tablet

Manufacturing condition		Optimal	Changed 1	Changed 2
X_1 Froude number		0.36	0.10	0.40
X_2 Time (min)		21	2	58
Y_1 Compression rate				
Predicted value from the RS[a] of 100-mg tablet	Average (μ_0)	0.284	0.340	0.240
	SD[b] (σ_0)	0.010	0.017	0.015
Experiment data in 50-mg tablet manufacturing	Individual	0.260, 0.260, 0.256	0.319	0.209
	Average (y_{ave})	0.259	0.319	0.209
	SD (s)	0.002[c]		
	Number of data (n)	3	1	1
Bayesian estimate	Average (μ_1)	0.259	0.319	0.210
	SD (σ_1)	0.001	0.002	0.002
Y_2 Hardness (N)				
Predicted value from the RS of 100-mg tablet	Average (μ_0)	40.9	71.7	21.9
	SD (σ_0)	2.6	2.0	4.5
Experiment data in 50-mg tablet manufacturing	Individual	36.2, 34.8, 34.0	68.4	22.2
	Average (y_{ave})	35.0	68.4	22.2
	SD (s)	1.3[c]		
	Number of data (n)	3	1	1
Bayesian estimate	Average (μ_1)	35.5	69.4	22.2
	SD (σ_1)	0.7	1.6	1.2
Y_3 Dissolution rate in 30 min (%)				
Predicted value from the RS of 100-mg tablet	Average (μ_0)	81.4	90.2	67.8
	SD (σ_0)	0.6	1.5	1.9
Experiment data in 50-mg tablet manufacturing	Individual	97.4, 97.0, 96.1	97.4	97.6
	Average (y_{ave})	96.8	97.4	97.6
	SD (s)	0.8[c]		
	Number of data (n)	3	1	1
Bayesian estimate	Average (μ_1)	91.4	95.9	93.4
	SD (σ_1)	0.4	0.7	0.7

a) RS: response surface. *b*) SD: standard deviation. *c*) The s value computed from the three batch experiments in the optimal condition was used in order to calculate the Bayesian estimates in all conditions.

$$F(X_1, X_2) = a \times f(X_1, X_2) + b \tag{6}$$

where $F(X_1,X_2)$ and $f(X_1,X_2)$ are functions expressing the response surfaces of the lower-strength and highest-strength tablet, respectively, and a and b are correction coefficients. Because the response surfaces of the highest-strength tablet are nonlinear curves, the corrected response surfaces are also nonlinear. The lower-strength response surfaces should pass through three points of the Bayesian estimate. Therefore, the correction coefficients were determined by applying the least-squares method between the Bayesian estimates (objective variable) and the quality attributes estimated from the response surface of the 100-mg tablet (explanatory variable) for the three conditions. The least-squares method was implemented using the statistical software JMP® 8 (SAS Institute Inc., NC, U.S.A.). The lower-strength response surfaces were estimated by correcting the entire response surfaces of the 100-mg tablet using the calculated correction coefficients. The areas in which each quality attribute fulfilled the acceptance criteria for the lower-strength tablet were superposed to construct a design space.

Validation of Response Surfaces Experiments were conducted to validate the estimated response surfaces of the lower-strength tablets under three different conditions, which were different from the three experimental conditions used for Bayesian estimation. The validation experiments were conducted at 300 g scale in a 1-L V-shaped blender as same as the experiments for Bayesian estimation. These experimental conditions were located on the edges of the design spaces of the lower-strength tablets. Root mean square error of prediction (RMSEP) and bias were used as the evaluation indices for the accuracy of the response surfaces. They were calculated using the equations

$$\mathrm{RMSEP} = \sqrt{\frac{\sum_{k=1}^{n} (Y_{\mathrm{actual}} - Y_{\mathrm{predicted}})^2}{n}} \tag{7}$$

$$\mathrm{Bias} = \frac{\sum_{k=1}^{n} (Y_{\mathrm{actual}} - Y_{\mathrm{predicted}})}{n} \tag{8}$$

where n is the number of validation experiments. RMSEP is an estimate of the typical difference between predicted and actual values, whereas bias is the average difference. The prediction accuracy of the models improved as RMSEP decreased and bias approached zero.

Results and Discussion

Construction of Response Surfaces and Design Space of Highest-Strength Tablet and Calculation of Simultaneous Optimal Solution The DoE parameters and the results, namely, the compression rate of the powder mixture (Y_1), tablet hardness (Y_2), and dissolution rate in 30 min (Y_3) of the

Table 4. Results of Experiments and Bayesian Estimation of 25-mg Theophylline Tablet

Manufacturing condition		Optimal	Changed 1	Changed 2
X_1 Froude number		0.36	0.10	0.40
X_2 Time (min)		21	2	58
Y_1 Compression rate				
Predicted value from the RS[a] of 100-mg tablet	Average (μ_0)	0.284	0.340	0.240
	SD[b] (σ_0)	0.010	0.017	0.015
Experiment data in 25-mg tablet manufacturing	Individual	0.245, 0.242, 0.240	0.295	0.200
	Average (y_{ave})	0.242	0.295	0.200
	SD (s)	0.003[c]		
	Number of data (n)	3	1	1
Bayesian estimate	Average (μ_1)	0.244	0.296	0.201
	SD (σ_1)	0.002	0.003	0.003
Y_2 Hardness (N)				
Predicted value from the RS of 100-mg tablet	Average (μ_0)	40.9	71.7	21.9
	SD (σ_0)	2.6	2.0	4.5
Experiment data in 25-mg tablet manufacturing	Individual	34.7, 37.2, 37.4	67.6	18.2
	Average (y_{ave})	36.4	67.6	18.2
	SD (s)	1.6[c]		
	Number of data (n)	3	1	1
Bayesian estimate	Average (μ_1)	36.9	69.2	18.6
	SD (σ_1)	0.9	1.2	1.5
Y_3 Dissolution rate in 30 min (%)				
Predicted value from the RS of 100-mg tablet	Average (μ_0)	81.4	90.2	67.8
	SD (σ_0)	0.6	1.5	1.9
Experiment data in 25-mg tablet manufacturing	Individual	100.6, 100.2, 100.8	100.6	102.1
	Average (y_{ave})	100.5	100.6	102.1
	SD (s)	0.4[c]		
	Number of data (n)	3	1	1
Bayesian estimate	Average (μ_1)	98.5	100.0	100.9
	SD (σ_1)	0.2	0.3	0.3

a) RS: response surface. *b*) SD: standard deviation. *c*) The s value computed from the three batch experiments in the optimal condition was used in order to calculate the Bayesian estimates in all conditions.

highest-strength 100-mg tablet, are listed in Table 2. All the output quality attributes varied in response to the changes in the input blending conditions. The response surfaces of the output quality attributes were generated by RSM-S as functions of two causal factors: the Froude number (X_1) and blending time (X_2) (Fig. 3). The response surface indicated that an increase in the Froude number or blending time improved the flowability of the powder mixture, as indicated by the decrease in the compression rate. Thus, the tabletability could be improved. For an area with a small Froude number and blending time, the upper limit of the compression rate (0.320) was not met. An increase in the blending time resulted in good lubricant dispersibility and reduced the tablet hardness and dissolution rate. The hardness met the criterion (30 N) within the acceptance range. The dissolution rate met the lower limit (75%) in most of the experimental area. The design space of the highest-strength tablets was determined to be a common region of the three acceptance areas (Fig. 4). Furthermore, the simultaneously optimal solution was calculated to be an X_1 of 0.36 and an X_2 of 21 min by using dataNESIA™.

Construction of Response Surfaces and Design Spaces of Lower-Strength Tablets Based on a Bayesian Estimation In addition to the optimal condition ($X_{optimal}$) estimated *via* the highest-strength DoE study, we selected two different conditions for the lower-strength experiments for Bayesian estimation at points $X_{changed\,1}$ (0.10, 2 min) and $X_{changed\,2}$ (0.40, 58 min) in the X_1–X_2 coordinate-system (Fig. 4). The points $X_{changed\,1}$ and $X_{changed\,2}$ were on the edge of the experimental range and far from $X_{optimal}$. The condition $X_{changed\,1}$ was considered to represent poor flowability of the powder mixture, and the condition $X_{changed\,2}$ represented tablets produced with low hardness and dissolution rate. It was assumed that the Bayesian estimations of $X_{optimal}$, $X_{changed\,1}$, and $X_{changed\,2}$ made it possible to correct the entire response surfaces across the edges of the design space.

The quality attributes were predicted on the basis of the highest-strength response surfaces in the three lower-strength experimental conditions ($X_{optimal}$, $X_{changed\,1}$, and $X_{changed\,2}$). The standard deviations of the highest-strength response surfaces under these three conditions were evaluated *via* bootstrap resampling and SOM (Tables 3, 4). Note that if multiple linear regression analysis is applied as a response surface method instead of RSM-S, the standard error of predicted value[26] could be regarded as the standard deviation of the prior probability.

Five batches of lower-strength experiments were carried out under the three lower-strength experimental conditions (three batches under $X_{optimal}$ and one each under $X_{changed\,1}$ and $X_{changed\,2}$). The experimental values for the lower-strength 50- and 25-mg tablets are summarized in Tables 3 and 4, respectively. The lower-strength experiments showed lower compression rates because theophylline powder has low flowability; a low proportion of theophylline in the powder for tableting

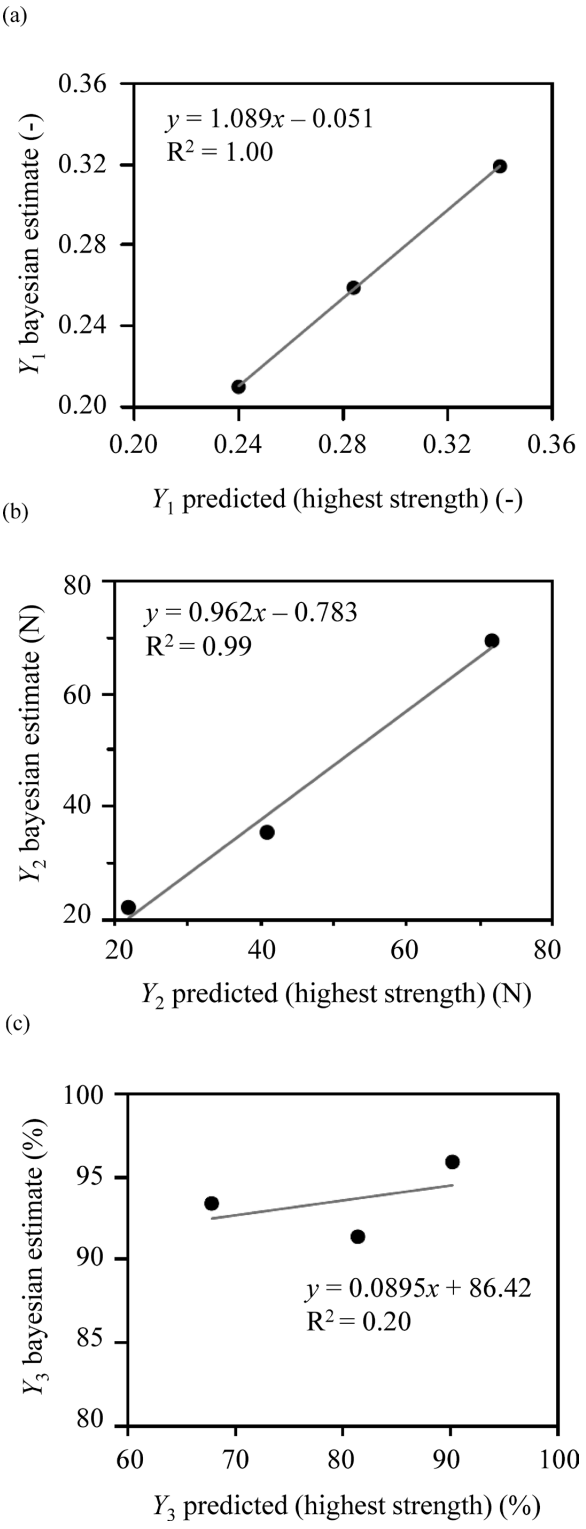

Fig. 5. Results of Least-Square Approximation of 50-mg Theophylline Tablet

(a) Compression rate of powder mixture (Y_1), (b) tablet hardness (Y_2), and (c) dissolution rate in 30 min (Y_3).

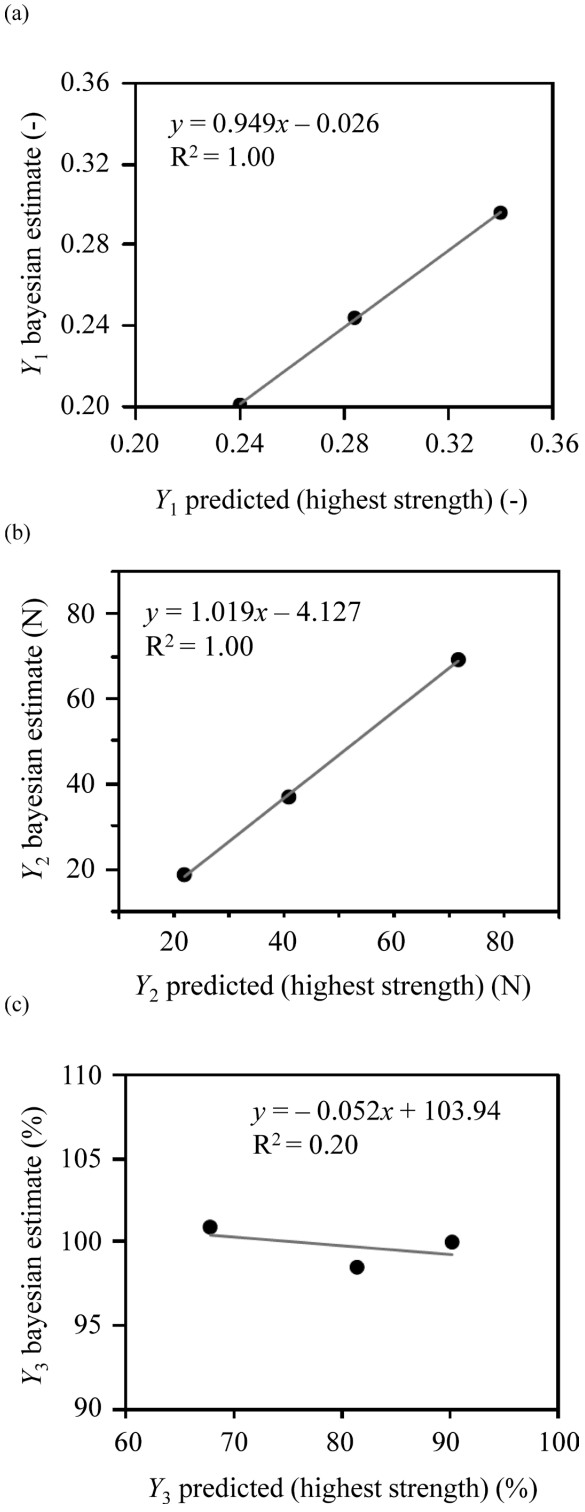

Fig. 6. Results of Least-Square Approximation of 25-mg Theophylline Tablet

(a) Compression rate of powder mixture (Y_1), (b) tablet hardness (Y_2), and (c) dissolution rate in 30 min (Y_3).

indicated higher flowability and a low compression rate. The tablet hardness also decreased with decreasing dose strength. The dissolution rates of the lower-strength experiments were higher than the highest-strength response surfaces and approximately constant under all manufacturing conditions. These results indicated that the quality attributes vary significantly among the dose strengths.

The standard deviations of the likelihood were estimated from the maximum and minimum values of the three batches performed under the optimal conditions according to Eq. 5. Then, considering the highest-strength prediction as the prior probability and the lower-strength data as the likelihood, we

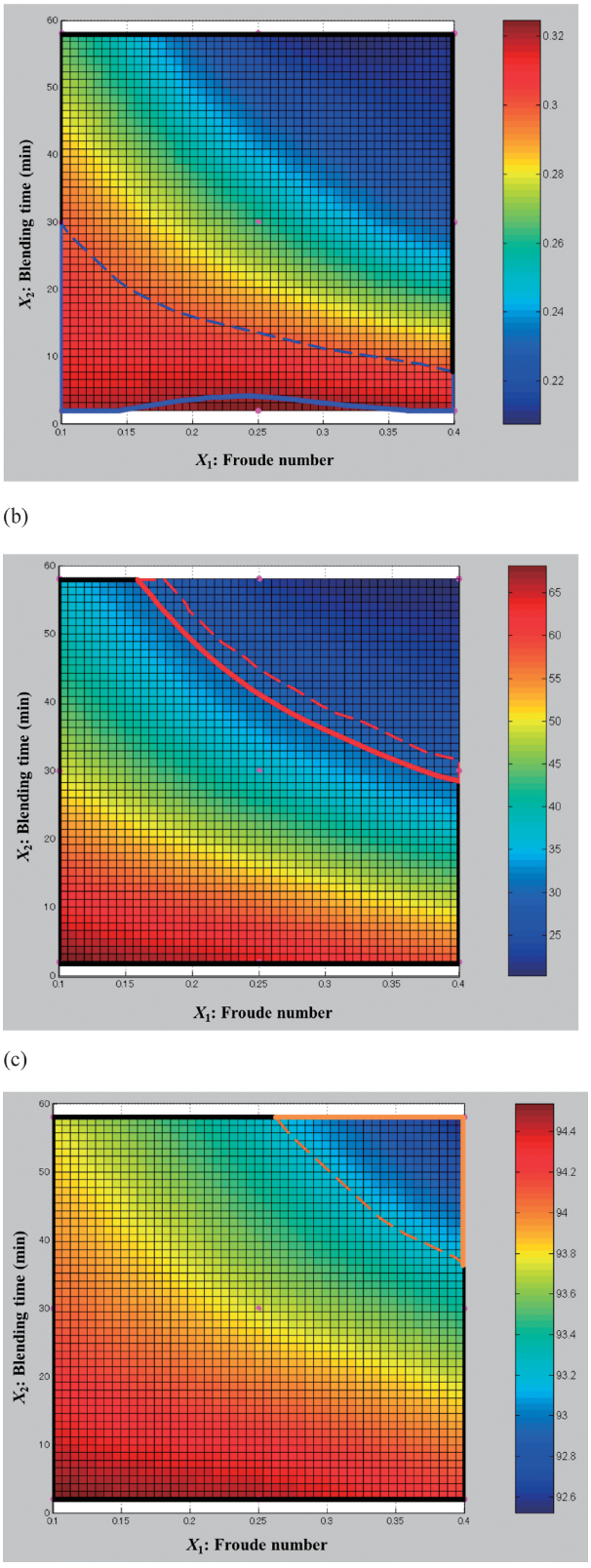

Fig. 7. Response Surfaces for Quality Attributes of 50-mg Theophylline Tablet

(a) Compression rate of powder mixture (Y_1), (b) tablet hardness (Y_2), and (c) dissolution rate in 30 min (Y_3), solid line: edge of the acceptance area of 50-mg theophylline tablet, dashed line: edge of the acceptance area of 100-mg theophylline tablet.

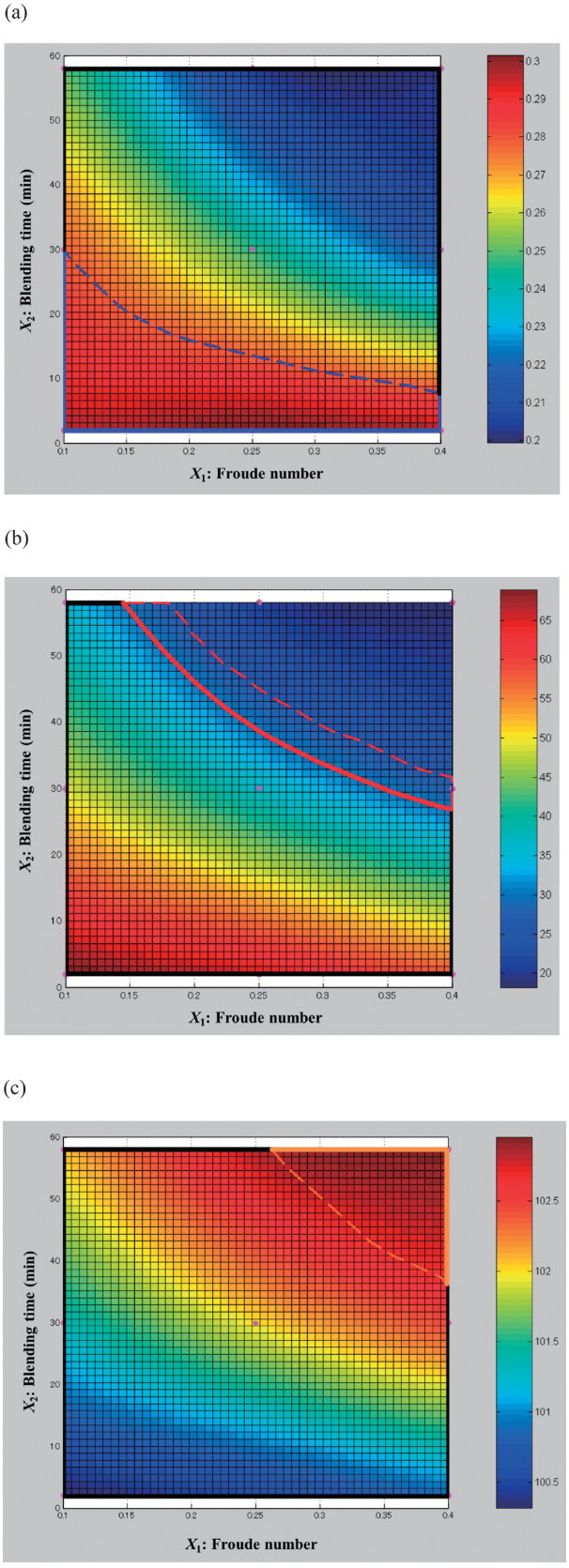

Fig. 8. Response Surfaces for Quality Attributes of 25-mg Theophylline Tablet

(a) Compression rate of powder mixture (Y_1), (b) tablet hardness (Y_2), and (c) dissolution rate in 30 min (Y_3), solid line: edge of the acceptance area of 25-mg theophylline tablet, dashed line: edge of the acceptance area of 100-mg theophylline tablet.

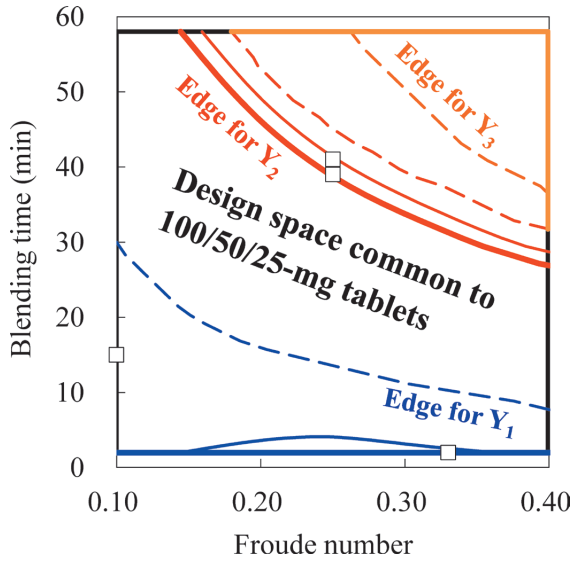

Fig. 9. Comparison of Design Spaces of Theophylline Tablets with Different Dose Strengths

Dashed line: edge of the design space of 100-mg theophylline tablet, solid and bold lines: edges of 50- and 25-mg theophylline tablets, respectively, square: lower-strength experimental conditions for validation of the response surfaces.

conducted Bayesian estimation using Eqs. 3 and 4 (Tables 3, 4).

The least-squares method was applied between the quality attributes estimated from the highest-strength response surface and the Bayesian estimate for the three process parameters to compute the correction coefficients of Eq. 6. The results of a regression analysis are shown in Figs. 5 and 6. Squares of the correlation coefficients (R^2) for the compression rate of the powder mixture and tablet hardness were high ($\geq$0.99), whereas R^2 value for the dissolution rate were much lower owing to the small variance in the Bayesian estimate of the dissolution rate. The need for a high R^2 value for precise Bayesian estimation was confirmed by constructing the following lower-strength response surfaces for the dissolution rate and their validation experiments.

Then, the lower-strength response surfaces were established by correcting all the highest-strength response surfaces on the basis of the calculated regression equations. The corrected response surfaces of the 50- and 25-mg theophylline tablets are shown in Figs. 7 and 8, respectively. The acceptance areas for the compression rate and dissolution rate were broadened with decreasing dose strength. In contrast, the lower-strength acceptance area for hardness was slightly narrowed because of the decrease in compactability. The acceptance areas were superposed to construct a lower-strength design space (Fig. 9). The design space was extended and shifted in the direction of shorter blending time.

The design space of each dose-strength tablet constructed in 1-L V-blender scale can be further corrected to design spaces in commercial scale by performing five batches of commercial-scale experiments and conducting second Bayesian estimation according to previously reported methods.[20,21]

Validation of Response Surfaces Three conditions on the edge of the calculated lower-strength design space were employed for the validation experiments of each lower-strength tablet (Fig. 9). The validation results for the response surfaces of the 50- and 25-mg tablets on the edge of the design space are summarized in Tables 5 and 6, respectively. The estimated design space for both the lower-strength tablets had higher prediction accuracy in terms of all the quality attributes because of Bayesian estimation and the correction of the discrepancy in the quality attributes of dose strengths.

High prediction accuracy of the estimated design space for the dissolution rate indicated that Bayesian estimation of design spaces can be performed even if a R^2 value of the least-square approximation is low. The good validation result indicated the adequacy of the number of lower-strength experiments and the validity of the assumption that the standard

Table 5. Validation Results of Response Surfaces of 50-mg Theophylline Tablet at the Edge of the Design Space

Validation experiment number	1	2	3	RMSEP	Bias
X_1 Froude number	0.25	0.10	0.33		
X_2 Time (min)	41	15	2		
Y_1 Compression rate					
Experiment data	0.245	0.309	0.321		
Predicted value from the RS[a] of 50-mg tablet	0.239	0.308	0.322	0.004	0.002
	(0.006)[b]	(0.001)	(−0.001)		
Predicted value from the RS of 100-mg tablet	0.266	0.330	0.342	0.021	−0.021
	(−0.021)	(−0.021)	(−0.021)		
Y_2 Hardness (N)					
Experiment data	30.3	54.1	67.3		
Predicted value from the RS of 50-mg tablet	30.2	58.6	60.2	4.9	0.9
	(0.1)	(−4.5)	(7.1)		
Predicted value from the RS of 100-mg tablet	32.2	61.7	63.4	5.1	−1.9
	(−1.9)	(−7.6)	(3.9)		
Y_3 Dissolution rate in 30 min (%)					
Experiment data	98.5	98.7	97.1		
Predicted value from the RS of 50-mg tablet	93.5	94.3	94.3	4.2	4.1
	(5.0)	(4.4)	(2.8)		
Predicted value from the RS of 100-mg tablet	78.8	87.5	87.8	14.1	13.4
	(19.7)	(11.2)	(9.3)		

a) RS: response surface. *b*) Error between actual and predicted value.

Table 6. Validation Results of Response Surfaces of 25-mg Theophylline Tablet at the Edge of the Design Space

Validation experiment number	1	2	3	RMSEP	Bias
X_1 Froude number	0.25	0.10	0.33		
X_2 Time (min)	39	15	2		
Y_1 Compression rate					
Experiment data	0.226	0.286	0.314		
Predicted value from the RS[a] of 25-mg tablet	0.230 (−0.004)[b]	0.287 (−0.001)	0.299 (0.015)	0.009	0.003
Predicted value from the RS of 100-mg tablet	0.270 (−0.044)	0.330 (−0.044)	0.342 (−0.028)	0.039	−0.039
Y_2 Hardness (N)					
Experiment data	31.1	53.4	65.4		
Predicted value from the RS of 25-mg tablet	29.8 (1.3)	58.8 (−5.4)	60.5 (4.9)	4.3	0.3
Predicted value from the RS of 100-mg tablet	33.3 (2.2)	61.7 (−8.3)	63.4 (2.0)	5.1	−2.8
Y_3 Dissolution rate in 30 min (%)					
Experiment data	102.2	102.9	99.6		
Predicted value from the RS of 25-mg tablet	102.3 (−0.1)	100.8 (2.1)	100.8 (−1.2)	1.4	0.3
Predicted value from the RS of 100-mg tablet	79.2 (23.0)	87.5 (15.4)	87.8 (11.8)	17.4	16.7

a) RS: response surface. *b*) Error between actual and predicted value.

deviation of the quality attribute was constant under any manufacturing condition.

It was concluded that an accurate lower-strength design space can be constructed by Bayesian estimation without adopting a lower-strength DoE study, irrespective of the coincidence of quality attributes between the dose strengths.

Conclusion

Design spaces for the lubricant-blending process for multiple dose strengths of tablets were successfully constructed using a Bayesian estimation with one set of design of experiments (DoE) of only the highest dose-strength tablet. It was confirmed that the corrected lower-strength design space had higher prediction accuracy, even if there was some discrepancy in the pharmaceutical quality between dose strengths.

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