A Novel Approach to Establishing the Design Space for the Oral Formulation Manufacturing Process

Tadashi Norioka,*[a,b] Yoshihiro Hayashi,[a] Yoshinori Onuki,[a] Hirotaka Andou,[b] Daisuke Tsunashima,[b] Kazunari Yamashita,[b] and Kozo Takayama[a]

[a] *Department of Pharmaceutics, Hoshi University; 2–4–41 Ebara, Shinagawa, Tokyo, 142–8501, Japan: and*
[b] *Pharmaceutical Technology and Research Laboratories, Astellas Pharma Inc.; 180 Ozumi, Yaizu, Shizuoka 425–0072, Japan.*
Received August 21, 2012; accepted October 2, 2012

A novel approach to establishing the design space for the oral formulation manufacturing process was investigated. A response surface method incorporating multivariate spline interpolation was applied to overcome the nonlinear problem, which is always problematic in pharmaceutical development studies, and a bootstrap resampling technique, polynomial approximation technique, and 95% confidence intervals based on a nonparametric approach were applied to estimate the reliability of the established design space derived from the nonlinear response surface model. The critical quality attributes (CQAs) of intermediate material rather than the critical process parameters (CPPs) were chosen as the causal factors for the response variables, which were CQAs of the final product to avoid scale-gap and equipment-gap. This enabled the effective use of data sets accumulated during all pharmaceutical development studies. It was confirmed that a conservative border as well as an optimistic border of the design space for practical use was obtained considering the variability of the border of the design spaces on nonlinear response surfaces. Furthermore, the nonlinear response surface model using CQAs of intermediate material derived from data sets of a laboratory scale study and pilot scale studies could predict the CQA of the final product (2.5 h dissolution of commercial-scale study) with high accuracy. Consequently, the proposed novel approach overcame all of the difficulties for the manufacturing process development of oral formulations and this is the first study to demonstrate the effectiveness of the design space using CQA of intermediate material for the oral formulation manufacturing process.

Key words design space; experimental design; response surface method; multivariate statistical analysis; confidence interval; critical quality attribute

In recent years, the "quality by design" (QbD) concept has been introduced by the International Conference on Harmonization (ICH) Q8 guideline. This guideline has recommended establishing a science-based rationale in pharmaceutical development studies for both formulation development and manufacturing process development. The guideline also noted that the multidimensional relationships of causal factors that have been demonstrated to provide specified target values of response variables are defined as the design space, and the establishment of the design space based on scientific understanding gained from pharmaceutical development studies and manufacturing experience provides the regulatory flexibility.[1] Therefore, the establishment of the design space is important not only to achieve a higher level of scientific understanding, but also to gain regulatory flexibility.

To establish the design space, a design-of-experiments (DoE) approach was used effectively to determine the multidimensional relationships among causal factors and response variables.[2,3] A response surface method (RSM) is useful for visual understanding of the derived multidimensional relationships.[4–7] However, the multidimensional relationships that are observed in pharmaceutical development studies are often nonlinear, and therefore predictions based on the linear response surface model using polynomial equations often exhibit poor estimation.[8] To overcome this problem, we have developed a nonlinear RSM incorporating multivariate spline interpolation (RSM-S) that enables us to understand nonlinear multidimensional relationships among causal factors and response variables and to estimate the high-integrity design space. In fact, this method has already been applied to practical cases for both formulation development and manufacturing process development and has already demonstrated its effectiveness.[9–13] In addition, it is important to evaluate the reliability of the design space, and to determine its conservative border to clarify the credibility inside the border of the design space. Although the reliability of the design space derived from a linear response surface model using polynomial equations can be evaluated by statistical analysis, the reliability of the design space derived from a nonlinear response surface model estimated by RSM-S cannot be directly evaluated by statistical analysis. To overcome this drawback, we applied a bootstrap (BS) resampling technique to evaluate the reliability of the design space,[14–20] and a polynomial approximation method with 95% confidence intervals (CIs) based on either a parametric or a nonparametric approach to determine the conservative border of the design space.[21,22] Applying these techniques, we propose an approach to evaluate the reliability of the design space for practical use.

Particularly for the oral formulation manufacturing process, many examples have been reported to establish the design space using a linear response surface model with critical process parameters (CPPs), because the linear response surface model is effective at a certain defined scale with particular equipment.[23,24] However, there are always difficulties of scale-gap and equipment-gap, which are inevitably problematic for pharmaceutical development studies.[25] Because CPPs change

The authors declare no conflict of interest.

* To whom correspondence should be addressed. e-mail: tadashi.norioka@astellas.com
© 2013 The Pharmaceutical Society of Japan

over different scales or with different equipment even at the same scale, a DoE to establish the design space using CPPs should be conducted at the same scale with the same equipment as future commercial production, which is impractical. In contrast, there are a few limited examples that establish the design space using critical quality attributes (CQAs) of intermediate material, which were considered to have no scale or equipment dependency.[26] Therefore, the main purpose of this research was to propose a novel approach for establishing the design space for the oral formulation manufacturing process using CQAs of intermediate material by applying data sets from all pharmaceutical development studies. In this way, the established design space overcame the difficulties of scale-gap or equipment-gap, and the data sets from different scales or equipment for all pharmaceutical development studies were used effectively to establish the design space. In addition, the aforementioned methods and techniques were applied to estimate the high-integrity design space and to evaluate the reliability of the design space, and furthermore, verification of the established design space on a commercial scale was conducted to demonstrate the effectiveness of the proposed novel approach.

To achieve these purposes, the following approach was adopted:

A screening study at the laboratory scale applying the DoE to the overall manufacturing process was conducted to extract CPPs and critical processes using analysis of variance (ANOVA).

Optimization studies at the pilot scale[27] applying the DoE for critical processes were conducted to evaluate the detailed relationships between CPPs and CQAs of intermediate material using multivariate linear regression (MLR).

The design space using CQAs of intermediate material was established using the data set of both a screening study and optimization studies, and the conservative border of the design space was determined applying the BS-resampling technique, RSM-S, polynomial approximation technique, and 95% CIs.

A confirmation study at the commercial scale applying the DoE was conducted to verify the reliability of the design space.

Consequently, a novel approach to establishing the design space for the oral formulation manufacturing process was successfully proposed and demonstrated as a practical application of the "QbD" concept.

Experimental

Preparation of the Core Tablets of the Model Drug Substance An active ingredient provided by Astellas Pharma Inc. (Tokyo, Japan) was used as the model drug substance. To prepare the granules, the de-lumped model drug substance and excipients were granulated and dried using a fluid-bed granulator and sieved using a screen. The fluid-bed granulator used for the laboratory scale and pilot scale tests was GPCG 5/15 (Powrex Corporation, Hyogo, Japan), and the fluid-bed granulator used for the commercial scale test was GPCG 120 (Glatt, Binzen, Germany) whose sizes are geometrically similar and the fluidization mechanism is common. Then, the granules were blended with another excipient using a container mixer to prepare the final blend, and the final blend was subsequently compressed using a rotary tablet press to prepare the core tablets. The rotary tablet press used for the laboratory scale and pilot scale tests was a HT-X20 (Hata Iron Works Co., Ltd., Kyoto, Japan) and the rotary tablet press used for the commercial scale test was a Courtoy R290 Tablet Press (GEA Pharma Systems, Belgium), the compression speeds being 24000 tablets per hour and 240000 tablets per hour, respectively. The inner diameter of the die of the press was 12 mm×6 mm oval shape.

Measurement of Response Variables The water content of the granules at the end of spraying phase was measured on one sample using an HR83 Halogen Moisture Analyzer (Mettler Toledo International Inc., Tokyo, Japan) and the particle size of the granules was measured on one sample using an L-200P particle size distribution analyzer (Seishin Enterprise Co., Ltd., Tokyo, Japan) with 500, 355, 250, 180, 150, 106, 75, and 63 μm sieves. The median diameter (D_{50}) of the granules was calculated from the particle size distribution obtained from the ratio of the residual weight of the granules on each sieve. Weight, thickness, and hardness of the core tablets were measured on 10 tablets using an electronic balance, thickness gauge and Schleuniger 8M Tablet Hardness Tester (Dr. Schleuniger Pharmatron, Manchester, NH, U.S.A.), respectively. Dissolution of the core tablets was performed on six tablets according to the test method of the model drug substance core tablets and the dissolved active ingredient was assayed by HPLC.

Experimental Designs Three DoEs at different scales were performed. First, as a screening study, the L_{18} orthogonal design was selected to extract CPPs and critical processes, and this was conducted at a laboratory scale, 4 kg scale. Second, as optimization studies, a central composite design, and a full factorial design were selected to evaluate the detailed relationships between the extracted CPPs and CQAs of intermediate material within the extracted critical processes, and these were conducted at a pilot scale, 12 kg scale. Third, as a confirmation study, a conventional design, namely, a one-component-at-a-time experiment, was selected to verify the reliability of the design space, and this was conducted at a commercial scale, 120 kg scale.

Statistical Analysis Analysis of variance was conducted for the screening study to extract CPPs and critical processes. MLR was applied for optimization studies to evaluate the detailed relationships between CPPs and CQAs of the intermediate material. RSM-S was applied to estimate the nonlinear multidimensional relationships between CQAs of the intermediate material and of the final product. The BS-resampling technique was applied to estimate the reliability of the design space derived from the nonlinear response surface model estimated by RSM-S. The border of the design space on each nonlinear response surface was calculated using a polynomial approximation technique. A conservative border of the design space was estimated considering the variability of the border of the design spaces, which was estimated using 95% CIs of the distribution of the border of the design spaces derived from either a parametric approach or a nonparametric approach. The distribution of the border of the design spaces was obtained mathematically from the intersection points of normal lines at given points on the border of the original design space and the borders of the BS design spaces. Although a detailed explanation of each statistical analysis was described fully in previous articles,[20–22] for a better understanding, the process for the determination of the conservative

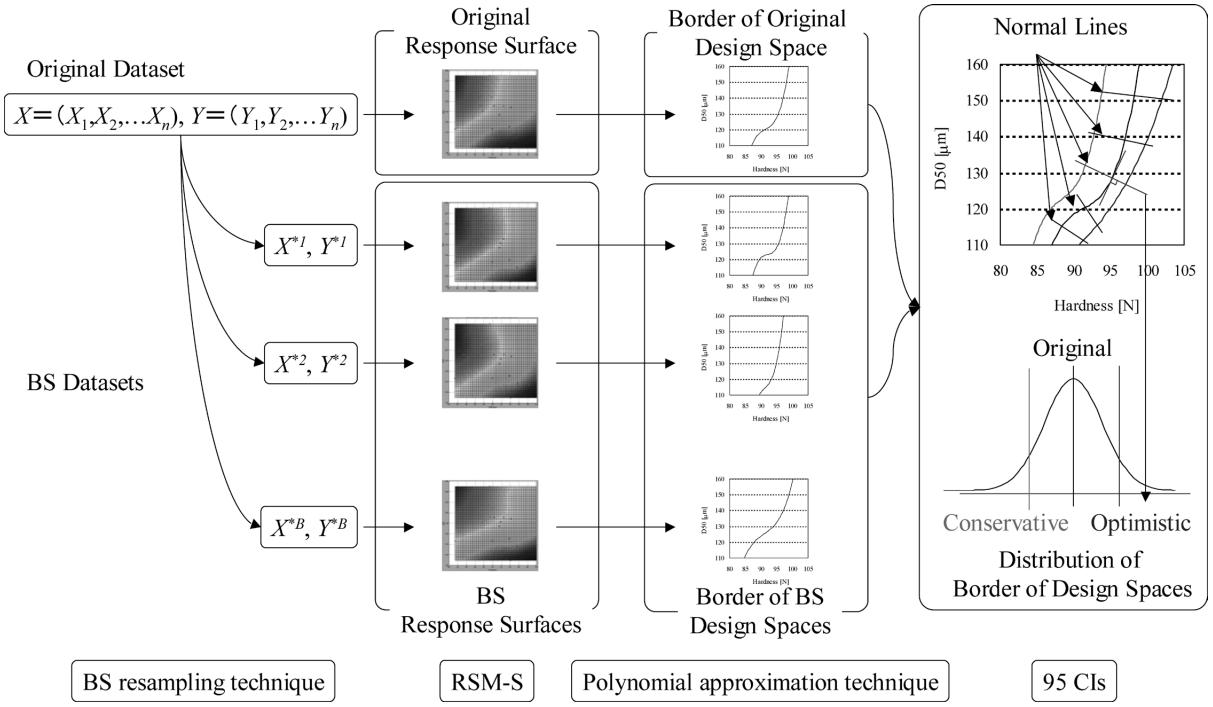

Fig. 1. Process of Determination of the Conservative Border of Design Space by BS Resampling Technique, RMS-S, Polynomial Approximation Technique and 95% CIs

border of the design space is shown in Fig. 1 and is described as follows:

Step 1. The original data set (comprising n data points) was prepared. In this study, n=234 was the number of data points in the original data set, including the individual results from both the screening study and optimization studies.

Step 2. The BS data set corresponding to the original data set was generated by a BS-resampling technique.

Step 3. Step 2 was repeated B times, and B units of BS data sets were generated. In this study, the frequency of BS resampling was set at B=100.[21]

Step 4. The nonlinear response surface was modeled for both the original data set and BS data sets, respectively, applying RSM-S.

Step 5. The border of the design space was calculated for each nonlinear response surface using a polynomial approximation technique.

Step 6. The normal lines at given points (m points) on the border of the original design space were calculated, and the intersection points of the normal lines and the borders of the BS design spaces were calculated mathematically. In this study, the number of given points was set at m=8.

Step 7. The points of the 95% CIs based on either a parametric or a nonparametric approach to the distribution of the border of the design spaces were calculated and a conservative border as well as an optimistic border of the design space were calculated applying a polynomial approximation technique to the points of 95% CIs.

Microsoft Excel® (Microsoft Corporation) was used for the calculation of ANOVA and the polynomial approximation technique. The Unscrambler® (CAMO Software AS, NJ, U.S.A.) was used for the calculation of MLR. dataNESIA® (version 3.2; Azbil Corporation, Tokyo, Japan) was used for implementation of the RSM-S and BS-resampling techniques.

Results and Discussion

Determination of CQA of the Final Product and Possible CPPs and Possible CQAs of Intermediate Material The quality risk-assessment exercises were conducted according to the ICH Q9 guideline,[28] which applied Failure Mode and Effect Analysis[29] for risk management methodology. It was identified that dissolution was the most important CQA of the final product because the safety and the efficacy of the model drug substance was critically affected by dissolution. In addition, although there were multiple time points in dissolution, the percentage dissolved after 2.5 h (2.5 h dissolution) was selected as a response variable for CQA of the final product, which had shown the largest variation as a result of different manufacturing conditions in previous development studies. The quality risk-assessment exercise had also identified that mill speed for the de-lumping process, inlet airflow temperature, inlet airflow rate, spray rate, spray amount, and spray pressure for the granulation process, precompression and main compression forces for the compression process were possible CPPs and water content and D_{50} of the granules, thickness and hardness of the core tablets were possible CQAs of intermediate material that were considered to affect 2.5 h dissolution based on prior knowledge and previous development studies.

Screening Study Because the purpose of the screening study was to extract CPPs and critical processes, the L_{18} orthogonal design was selected, which is generally used to extract significant main effects.[20] The experimental design and measurement results and factorial effects for the screening study are shown in Table 1 and Fig. 2. Water content and D_{50} of the granules, thickness, hardness, and 2.5 h dissolution of the core tablets varied across the different manufacturing conditions, whereas the weight of the core tablets remained constant. To extract CPPs and the critical process, ANOVA was conducted for water content, D_{50}, thickness, hardness,

Table 1. L_{18} Orthogonal Design and Measurement Result at Screening Study

No.	De-lumping	Granulation					Compression	Granules		Core tablets			
	Mill speed (rpm)	Inlet air flow temperature (°C)	Inlet air flow rate (m^3/min)	Spray rate (g/min)	Spray amount (g)	Spray pressure (MPa)	Main compression force (kN)	Water content (%)	D_{50} (μm)	Weight (mg)	Thickness (mm)	Hardness (N)	2.5 h Dissolution (%)
1	1000	35	3.0	30	300	0.2	6	3.17	126.1	249.7	5.08	81.4	52.3
2	1000	40	3.5	50	450	0.3	8	3.13	112.6	249.7	5.00	93.6	50.3
3	1000	45	4.0	70	600	0.4	10	5.86	213.9	251.4	5.02	94.7	50.3
4	2000	35	3.0	50	450	0.4	10	4.94	131.2	250.4	5.00	95.2	48.6
5	2000	40	3.5	70	600	0.2	6	7.17	230.1	250.4	5.03	89.3	52.3
6	2000	45	4.0	30	300	0.3	8	0.57	89.40	249.0	5.03	94.1	46.5
7	3000	35	3.5	30	600	0.3	10	3.61	119.1	250.3	4.99	100.0	51.1
8	3000	40	4.0	50	300	0.4	6	2.35	90.09	249.9	5.03	93.2	48.9
9	3000	45	3.0	70	450	0.2	8	5.86	211.6	251.6	5.05	90.1	52.3
10	1000	35	4.0	70	450	0.3	6	5.81	158.5	250.5	5.01	90.8	50.5
11	1000	40	3.0	30	600	0.4	8	3.28	113.4	249.9	4.98	98.2	47.4
12	1000	45	3.5	50	300	0.2	10	1.90	125.0	250.0	4.96	91.1	45.8
13	2000	35	3.5	70	300	0.4	8	4.37	117.2	251.1	5.00	89.3	48.8
14	2000	40	4.0	30	450	0.2	10	1.31	115.3	252.3	4.98	96.7	49.1
15	2000	45	3.0	50	600	0.3	6	5.58	167.8	250.9	4.99	90.8	51.1
16	3000	35	4.0	50	600	0.2	8	5.40	168.3	250.0	4.97	94.2	51.9
17	3000	40	3.0	70	300	0.3	10	4.44	125.0	249.5	4.96	92.6	48.1
18	3000	45	3.5	30	450	0.4	6	1.10	98.27	248.9	4.97	99.0	42.3

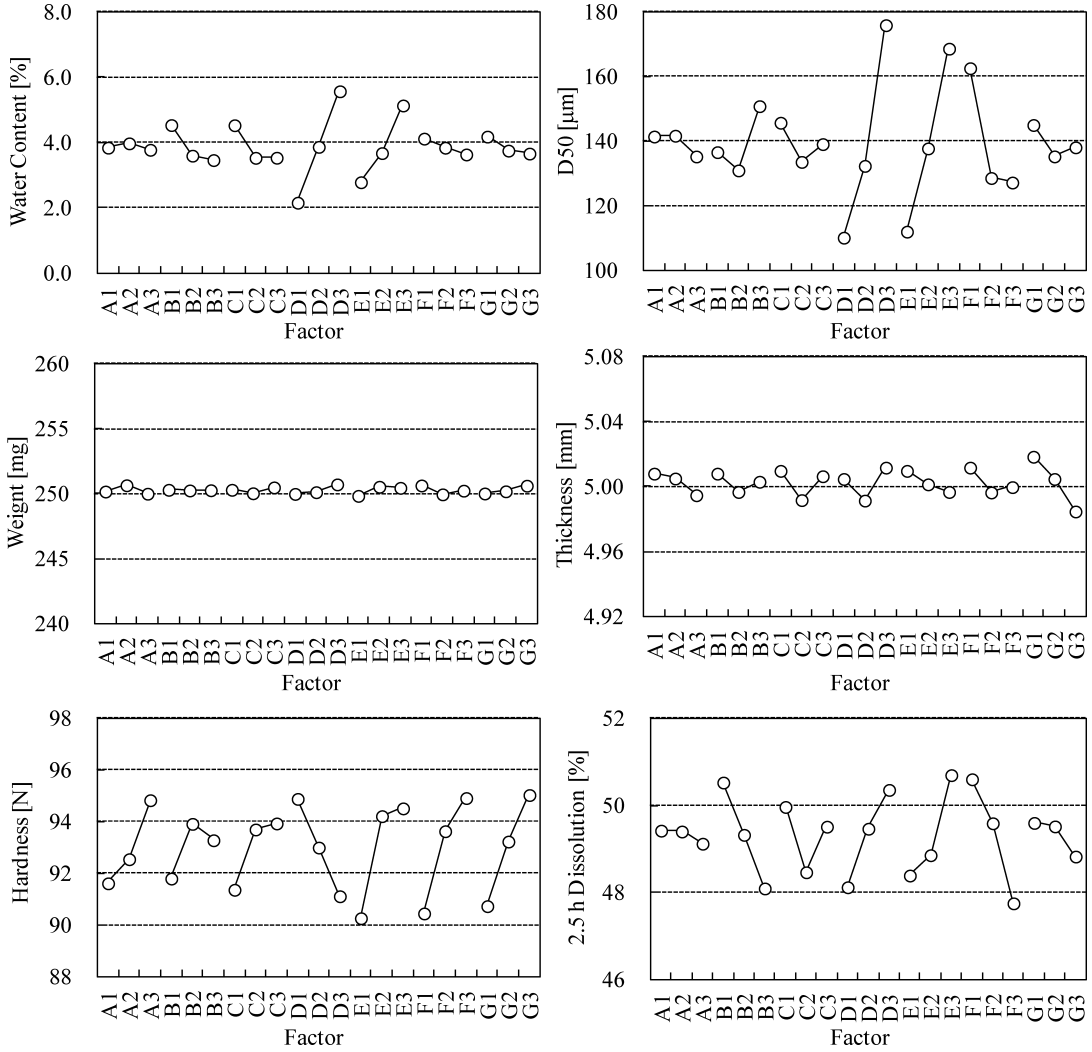

Fig. 2. Factorial Effects of Screening Study

(A) Mill speed, A1: 1000 rpm, A2: 2000 rpm, A3: 3000 rpm, (B) inlet air flow temperature, B1: 35°C, B2: 40°C, B3: 45°C, (C) inlet air flow rate, C1: 3.0 m^3/min, C2: 3.5 m^3/min, C3: 4.0 m^3/min, (D) spray rate, D1: 30 g/min, D2: 50 g/min, D3: 70 g/min, (E) spray amount, E1: 300 g, E2: 450 g, E3: 600 g, (F) spray pressure, F1: 0.2 MPa, F2: 0.3 MPa, F3: 0.4 MPa, (G) main compression force, G1: 6 kN, G2: 8 kN, G3: 10 kN.

and 2.5 h dissolution. Causal factors whose *p*-values from the ANOVA were less than 0.05 or 0.01 were categorized as statistically significant or highly statistically significant, respectively. From the ANOVA results shown in Table 2, no statistically significant causal factor was extracted for thickness, hardness, and 2.5 h dissolution, while some statistically significant causal factors were extracted for water content and D_{50}. Therefore, it was concluded that the CPPs were inlet airflow temperature, inlet airflow rate, spray rate, spray amount, and spray pressure, and the critical process was the granulation process and it was decided to conduct an optimization study for the granulation process. In contrast, no CPP from the compression process was extracted. The reason for this was that the range of the causal factor for the compression process, which was determined for practical use, was relatively narrow considering the nature of the L_{18} orthogonal design where detectability of main effects was restricted because of the low-resolution DoE. However, in this study, based on prior knowledge and previous development studies, which is also important information to extract CPPs and critical processes, it was also decided to conduct an additional optimization study for the compression process. As a result, CPPs and critical processes were extracted from the screening study and the material for optimization studies was successfully decided.

Optimization Studies The experimental designs and measurement results for optimization studies are shown in Tables 3 and 4. Considering the variability of the process parameters in practice, some CPPs extracted by the screening study were eliminated, which generally had less fluctuation and could be well controlled in the actual manufacturing process. As a result, inlet airflow temperature and spray rate and pressure were selected and varied according to a central composite design that had three replications at the standard condition in the optimization study for the granulation process, and then the core tablets were manufactured with constant precompression and main compression pressures, which were 1.0 kN and 8 kN, respectively. On the other hand, precompression and main compression pressures were selected and varied according to a full factorial design in the optimization study for the compression process using the granules obtained at run 15 of the optimization study for the granulation process, which was a standard condition run. As shown in Tables 3 and 4, water content, D_{50}, thickness, hardness, and 2.5 h dissolution varied across the different manufacturing conditions,

Table 2. Results of ANOVA of Screening Study

Input variables	Water content				
	Sum of squares	Degrees of freedom	Variance	F_0-Value	p-Value
Mill speed	—[a]	—[a]	—[a]	—[a]	—[a]
Inlet air flow temperature	4.091	2	2.046	7.550	0.01*
Inlet air flow rate	3.972	2	1.986	7.328	0.01*
Spray rate	34.925	2	17.463	64.439	0.00**
Spray amount	16.888	2	8.444	31.159	0.00**
Spray pressure	—[a]	—[a]	—[a]	—[a]	—[a]
Main compression force	—[a]	—[a]	—[a]	—[a]	—[a]

Input variables	D_{50}				
	Sum of squares	Degrees of freedom	Variance	F_0-Value	p-Value
Mill speed	—[a]	—[a]	—[a]	—[a]	—[a]
Inlet air flow temperature	1264.72	2	632.360	2.870	0.11
Inlet air flow rate	—[a]	—[a]	—[a]	—[a]	—[a]
Spray rate	13439.09	2	6719.545	30.501	0.00**
Spray amount	9650.08	2	4825.040	21.902	0.00**
Spray pressure	4820.77	2	2410.385	10.941	0.00**
Main compression force	—[a]	—[a]	—[a]	—[a]	—[a]

Input variables	Thickness				
	Sum of squares	Degrees of freedom	Variance	F_0-Value	p-Value
Mill speed	—[a]	—[a]	—[a]	—[a]	—[a]
Inlet air flow temperature	—[a]	—[a]	—[a]	—[a]	—[a]
Inlet air flow rate	0.0011	2	0.0006	0.500	0.62
Spray rate	—[a]	—[a]	—[a]	—[a]	—[a]
Spray amount	—[a]	—[a]	—[a]	—[a]	—[a]
Spray pressure	0.0008	2	0.0004	0.333	0.72
Main compression force	—[a]	—[a]	—[a]	—[a]	—[a]

Input variables	Hardness				
	Sum of squares	Degrees of freedom	Variance	F_0-Value	p-Value
Mill speed	—[a]	—[a]	—[a]	—[a]	—[a]
Inlet air flow temperature	—[a]	—[a]	—[a]	—[a]	—[a]
Inlet air flow rate	—[a]	—[a]	—[a]	—[a]	—[a]
Spray rate	42.571	2	21.286	2.109	0.18
Spray amount	67.510	2	33.755	3.345	0.08
Spray pressure	63.445	2	31.723	3.144	0.09
Main compression force	55.960	2	27.980	2.773	0.12

Input variables	2.5 h Dissolution				
	Sum of squares	Degrees of freedom	Variance	F_0-Value	p-Value
Mill speed	—[a]	—[a]	—[a]	—[a]	—[a]
Inlet air flow temperature	17.759	2	8.880	1.985	0.19
Inlet air flow rate	—[a]	—[a]	—[a]	—[a]	—[a]
Spray rate	15.203	2	7.602	1.700	0.24
Spray amount	17.835	2	8.918	1.994	0.19
Spray pressure	25.053	2	12.527	2.801	0.11
Main compression force	—[a]	—[a]	—[a]	—[a]	—[a]

a) Process parameters that were pooled into the error. *$p<0.05$, **$p<0.01$.

Table 3. Central Composite Design and Measurement Result at Optimization Study for Granulation Process

No.	Granulation			Granules		Core tablets			
	Inlet air flow temperature (°C)	Spray rate (g/min)	Spray pressure (MPa)	Water content (%)	D_{50} (μm)	Weight (mg)	Thickness (mm)	Hardness (N)	2.5 h Dissolution (%)
1	34.95	120.00	0.25	4.52	160.7	251.2	5.01	85.6	54.0
2	45.05	120.00	0.25	2.99	154.2	251.1	4.98	91.6	53.9
3	40.00	86.36	0.25	3.36	145.1	251.7	4.99	92.5	49.8
4	40.00	153.64	0.25	4.78	188.2	250.7	4.99	89.8	54.6
5	40.00	120.00	0.17	4.28	166.5	251.2	4.99	88.2	53.9
6	40.00	120.00	0.33	3.78	131.1	251.1	4.98	93.8	53.4
7	37.00	100.00	0.20	3.87	189.8	249.8	4.99	87.3	52.9
8	43.00	100.00	0.20	2.52	188.5	249.0	4.98	86.9	53.5
9	37.00	140.00	0.20	4.83	178.9	249.7	4.96	87.4	51.6
10	43.00	140.00	0.20	4.25	201.4	249.8	4.96	88.9	53.0
11	37.00	100.00	0.30	3.18	116.1	250.5	4.96	95.6	54.4
12	43.00	100.00	0.30	2.39	126.9	250.3	4.97	89.9	51.1
13	37.00	140.00	0.30	4.25	161.4	250.2	4.96	87.7	54.7
14	43.00	140.00	0.30	4.06	171.4	251.5	4.96	89.8	51.5
15	40.00	120.00	0.25	4.10	171.4	250.4	4.97	89.4	52.5
16	40.00	120.00	0.25	3.92	163.1	250.3	4.96	91.8	51.3
17	40.00	120.00	0.25	3.62	170.6	249.0	4.97	87.5	54.3

Table 4. Full Factorial Design and Measurement Result at Optimization Study for Compression Process

No.	Compression		Core tablets			
	Precompression force (kN)	Main compression force (kN)	Weight (mg)	Thickness (mm)	Hardness (N)	2.5 h Dissolution (%)
1	0.3	6	251.5	5.00	83.4	55.5
2	0.5	6	250.8	4.98	83.4	—
3	1.0	6	251.2	4.97	86.1	—
4	1.5	6	251.1	4.96	88.4	—
5	2.5	6	251.2	4.95	90.3	52.3
6	0.3	8	249.8	4.99	83.5	—
7	0.5	8	251.1	4.99	85.3	—
8	1.0	8	251.8	4.98	89.0	—
9	1.5	8	251.0	4.96	90.5	—
10	2.5	8	251.7	4.95	92.8	—
11	0.3	10	251.1	5.00	87.1	54.5
12	0.5	10	251.6	5.00	88.6	—
13	1.0	10	251.5	4.96	90.5	—
14	1.5	10	250.4	4.94	90.8	—
15	2.5	10	250.7	4.93	92.5	52.4

Table 5. Results of MLR of Optimization Study for Granulation Process

	Water content				
	Sum of squares	Degrees of freedom	Variance	F_0-Value	p-Value
Model	7.607	9	0.846	9.269	0.0039**
Error	0.638	7	0.09118		
Adjusted total	8.245	16	0.515		
	D_{50}				
	Sum of squares	Degrees of freedom	Variance	F_0-Value	p-Value
Model	7751	9	861.214	5.455	0.0179*
Error	1105	7	157.887		
Adjusted total	8856	16	553.509		

*$p<0.05$, **$p<0.01$.

Table 6. Results of MLR of Optimization Study for Compression Process

	Thickness				
	Sum of squares	Degrees of freedom	Variance	F_0-Value	p-Value
Model	0.006774	5	0.001355	23.460	0.0001**
Error	0.0005197	9	0.00005775		
Adjusted total	0.007293	14	0.0005210		
	Hardness				
	Sum of squares	Degrees of freedom	Variance	F_0-Value	p-Value
Model	138.297	5	27.659	40.809	0.0000**
Error	6.100	9	0.678		
Adjusted total	144.397	14	10.314		

*$p<0.05$, **$p<0.01$.

Table 7. Correlation Coefficient of Correlation Analysis

	Correlation coefficient			
	Water content	D_{50}	Thickness	Hardness
D_{50}	0.7			
Thickness	0.1	0.0		
Hardness	−0.3	−0.5	−0.2	
2.5 h Dissolution	0.4	0.6	0.0	−0.6

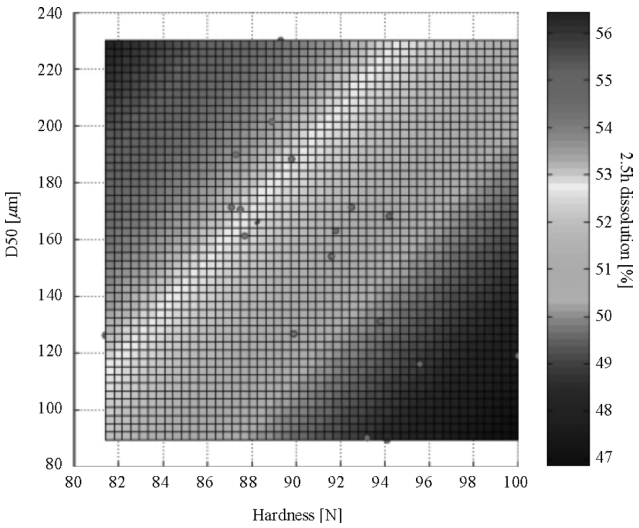

Fig. 3. Linear Response Surface of 2.5 h Dissolution

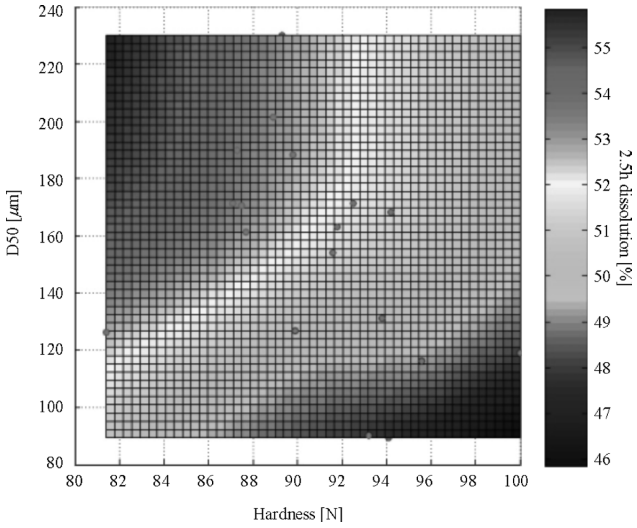

Fig. 4. Nonlinear Response Surface of 2.5 h Dissolution

whereas weight remained constant. As the purpose of the optimization studies was to determine the detailed relationships between CPPs and CQAs of the intermediate material at the same scale with the same equipment, a linear response surface model (MLR) was applied. From the MLR results shown in Tables 5 and 6, the obtained linear response surface models for CQAs of intermediate material were all statistically significant because the model p-values were all less than 0.05, which meant that CQAs of intermediate material could be predicted by CPPs with the obtained linear response surface model and the detailed relationships between CPPs and CQAs of intermediate material were determined successfully. The inconsistencies in the statistical significance between the screening study and the optimization study for thickness and hardness were considered to be due to sensitivity of the DoE. Applying a higher resolution DoE in the optimization study for the compression process showed that both precompression and main compression forces affect the thickness and hardness, which was consistent with prior knowledge and previous development studies. Thus, once the detailed relationships between CPPs and CQAs of intermediate material were shown at a given scale with given equipment, the optimization study at a different scale with different equipment, which has the same operating principle and design characteristic, could also be conducted applying a general consideration of scale-up factors,[25] as it was considered that those detailed relationships were scalable. Consequently, the detailed relationships between CPPs and CQAs of the intermediate material were successfully found by optimization studies.

Novel Approach for Establishing the Design Space The main purpose of this research was to establish the design space using CQAs of intermediate material to predict 2.5 h dissolution. A correlation analysis between CQAs of the intermediate material and 2.5 h dissolution using results of both

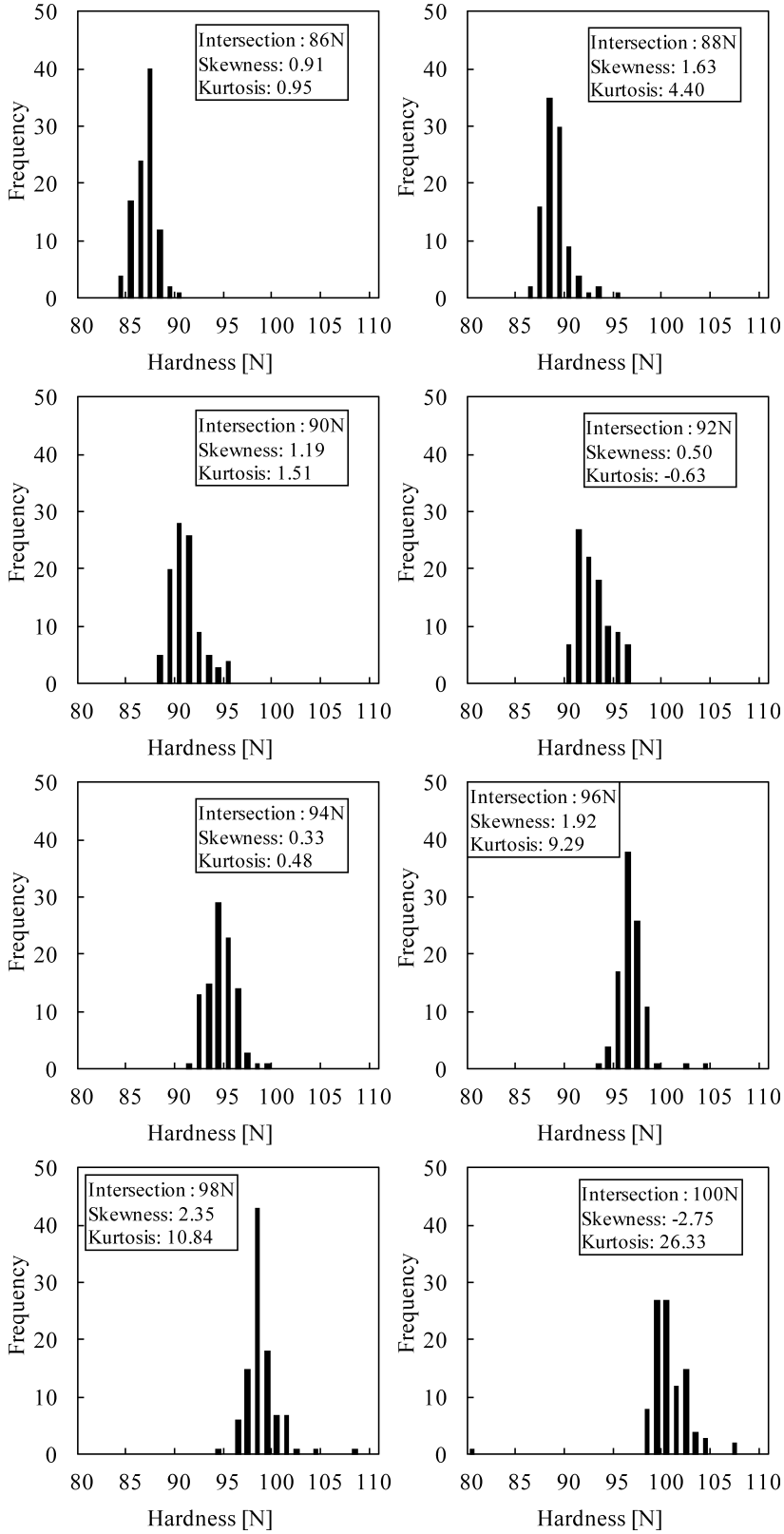

Fig. 5. Histograms of Intersection Points

a screening study and optimization studies was conducted to select the major causal factors from CQAs of the intermediate material for 2.5 h dissolution. As shown in Table 7, high correlation coefficients, (greater than 0.6) were observed between water content and D_{50}, D_{50} and 2.5 h dissolution, as well as hardness and 2.5 h dissolution. A high correlation coefficient between water content and D_{50} was considered normal for a fluidized-bed granulation process[25]; therefore, it was decided to select D_{50} and hardness as causal factors for 2.5 h dissolution. Then, both MLR and RSM-S were applied to compare the linear and nonlinear response surface models. As shown in Figs. 3 and 4, both response surfaces showed that the 2.5 h

dissolution increased when D_{50} increased and hardness decreased, which are new findings for the model drug substance core tablets. The accuracy of both response surface models was evaluated by leave-one-out cross-validation and higher accuracy was observed for RSM-S than MLR, producing correlation coefficients of 0.67 for RSM-S and 0.59 for MLR. Then the reliability of the design space and the conservative border of the design space were considered. A BS-resampling technique was applied for B=100 and the border of the design space of each response surface was calculated using a polynomial approximation technique. As the specification of 2.5 h dissolution was set at more than 50.0%, the border of the original design space that was the boundary of the regions that met or did not meet the specification, was expressed by the following mathematical formula with R^2=0.99:

$$y = 0.0727x^3 - 19.1935x^2 + 1819.3662x - 55320.2579$$
(border of original design space)

where y is D_{50} and x is hardness.

Then, the normal lines at eight points on the border of the original design space were calculated, and intersection points of the normal lines and borders of the BS design spaces were calculated mathematically. Histograms of the intersection points are shown in Fig. 5. Although most histograms seemed to be normally distributed, some histograms seemed to be nonnormally distributed because their skewness and kurtosis, which are the indices of the normality of histograms, were not close to zero.[22] Therefore, 95% CIs based on a nonparametric approach were calculated and the polynomial approximation technique was again applied for each 95% CI point. Thus, conservative as well as optimistic borders of design space were obtained, as shown in Fig. 6, which were expressed by the following mathematical formulas, both with $R^2 \geq 0.99$:

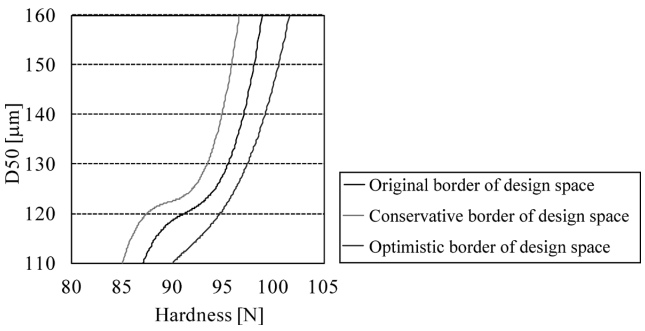

Fig. 6. Original, Conservative and Optimistic Border of Design Space

$$y = 0.0981x^3 - 26.3690x^2 + 2363.3108x - 70499.1660$$
(conservative border of design space)

$$y = 0.0254x^3 - 6.9472x^2 + 635.7071x - 19334.7554$$
(optimistic border of design space)

where y is D_{50} and x is hardness.

Consequently, the conservative border of the design space for practical use was obtained successfully.

Confirmation Study Finally, to verify the reliability of the established design space derived from the nonlinear response surface model by RSM-S using CQAs of intermediate material applying data sets from all pharmaceutical development studies, predictions using the data set from the confirmation study were obtained. The experimental designs and measurement results for the confirmation study as well as the predicted 2.5 h dissolution by the nonlinear response surface model and the actual 2.5 h dissolution are shown in Table 8. Because a good prediction was obtained for three different conditions, it was concluded that the nonlinear response surface model using CQAs of intermediate material obtained by applying the data sets of laboratory scale and pilot scales could predict 2.5 h dissolution at a commercial scale with high accuracy. Therefore, it was verified that the nonlinear response surface model using CQAs of intermediate material could overcome the difficulties of scale-gap and equipment-gap, which refer to the differences of size or individual instruments among the same operating principle and design characteristic in the manufacturing process and could provide highly accurate predictions.

Conclusion

The manufacturing process development for oral formulations applying the "QbD" concept was conducted and a novel approach for establishing the design space was proposed. The DoEs for a screening study and optimization studies were successfully performed to achieve the purpose of each study, and the nonlinear response surface model using CQAs of intermediate material using data sets of laboratory and pilot scales could predict 2.5 h dissolution at the commercial scale with high accuracy. In addition, a conservative border of the design space was obtained successfully considering the reliability of the design space. Subsequently, it was verified that the proposed novel approach overcame all of the difficulties for manufacturing process development for practical use. This is the first study to show that the design space can be established using CQA of intermediate material for the manufacturing process.

Table 8. Conventional Design and Measurement Result at Confirmation Study and Prediction of 2.5 h Dissolution

No.	Granulation			Compression		Granules		Core tablets				
	Inlet air flow temperature (°C)	Spray rate (g/min)	Spray pressure (psig)	Precompression force (kN)	Main compression force (kN)	Water content (%)	D_{50} (μm)	Weight (mg)	Thickness (mm)	Hardness (N)	2.5 h Dissolution (%)	Predicted 2.5 h dissolution (%)
1	40	700	29	0.5	8	4.80	150.3	250.4	5.04	87.3	50.9 (1.1)	52.5
2	40	600	44	0.5	8	4.12	124.9	249.6	5.02	90.5	49.8 (1.1)	50.1
3	40	750	25	0.5	8	5.34	166.0	249.0	5.02	85.1	52.4 (1.3)	53.8

( ): Standard deviation.

Acknowledgment This study was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

References

1) International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. "ICH Harmonized Tripartite Guideline Pharmaceutical Development Q8 (R2).": <http://www.pmda.go.jp/ich/q/q8r2_10_6_28e.pdf>, August, 2009.
2) Montgomery D. C., "Design and Analysis of Experiments," John Wiley & Sons, U.S.A., 1997.
3) Lewis G. A., Mathieu D., Phan-Tan-Luu R., "Pharmaceutical Experimental Design," Marcel Dekker, New York, 1999.
4) Khuri A. I., Cornel J. A., "Response Surface: Design and Analysis," Marcel Dekker, New York, 1987.
5) Takayama K., Nagai T., *Int. J. Pharm.*, **74**, 115–126 (1991).
6) Miyamoto Y., Ogawa S., Miyajima M., Matsui M., Sato H., Takayama K., Nagai T., *Int. J. Pharm.*, **149**, 25–36 (1997).
7) Huang Y. B., Tsai Y. H., Yang W. C., Chang J. S., Wu P. C., *Biol. Pharm. Bull.*, **27**, 1626–1629 (2004).
8) Takayama K., Morva A., Fujikawa M., Hattori Y., Obata Y., Nagai T., *J. Controlled Release*, **68**, 175–186 (2000).
9) Takayama K., Obata Y., Morishita M., Nagai T., *Pharmazie*, **59**, 392–395 (2004).
10) Onuki Y., Morishita M., Takayama K., *J. Control. Release*, **97**, 91–99 (2004).
11) Onuki Y., Hoshi M., Okabe H., Fujikawa M., Morishita M., Takayama K., *J. Controlled Release*, **108**, 331–340 (2005).
12) Nishikawa M., Onuki Y., Isowa K., Takayama K., *AAPS PharmSciTech*, **9**, 1038–1045 (2008).
13) Obata Y., Ashitaka Y., Kikuchi S., Isowa K., Takayama K., *Int. J. Pharm.*, **399**, 87–93 (2010).
14) Arai H., Suzuki T., Kaseda C., Ohyama K., Takayama K., *Chem. Pharm. Bull.*, **55**, 586–593 (2007).
15) Arai H., Suzuki T., Kaseda C., Takayama K., *Chem. Pharm. Bull.*, **57**, 572–579 (2009).
16) Onuki Y., Ohyama K., Kaseda C., Arai H., Suzuki T., Takayama K., *J. Pharm. Sci.*, **97**, 331–339 (2008).
17) Onuki Y., Kikuchi S., Yasuda A., Takayama K., *Int. J. Pharm.*, **396**, 75–82 (2010).
18) Kikuchi S., Takayama K., *Int. J. Pharm.*, **374**, 5–11 (2009).
19) Kikuchi S., Takayama K., *Int. J. Pharm.*, **386**, 149–155 (2010).
20) Norioka T., Kikuchi S., Onuki Y., Takayama K., Imai K., *J. Pharm. Innov.*, **6**, 157–169 (2011).
21) Arai H., Suzuki T., Yada S., Kaseda C., Onuki Y., Takayama K., *Chem. Pharm. Bull.*, **59**, 608–617 (2011).
22) Hayashi Y., Kikuchi S., Onuki Y., Takayama K., *J. Pharm. Sci.*, **101**, 333–341 (2012).
23) Huang J., Kaul G., Cai C., Chatlapalli R., Hernandez-Abad P., Ghosh K., Nagi A., *Int. J. Pharm.*, **382**, 23–32 (2009).
24) Zacour B. M., Drennen J. K. III, Anderson C. A., *J. Pharm. Sci.*, **101**, 2917–2929 (2012).
25) Ogawa S., Kamijima T., Miyamoto Y., Miyajima M., Sato H., Takayama K., Nagai T., *J. Pharm. Sci.*, **83**, 439–443 (1993).
26) Lourenço V., Lochmann D., Reich G., Menezes J. C., Herdling T., Schewitz J., *Eur. J. Pharm. Biopharm.*, **81**, 438–447 (2012).
27) Center for Drug Evaluation and Research. "Guidance for Industry Immediate Release Solid Oral Dosage Forms Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, *In Vitro* Dissolution Testing, and *In Vivo* Bioequivalence Documentation.": <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070636.pdf>, November, 1995.
28) International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. "ICH Harmonized Tripartite Guideline Quality Risk Management Q9." : <http://www.pmda.go.jp/ich/q/q9_06_9_1e.pdf>, November, 2005.
29) International Electrotechnical Commission, Analysis Techniques for System Reliability: Procedure for Failure Mode and Effects Analysis (FMEA)—International Standard 60812, 2006.