# A novel multivariate statistical approach of manufacturing process development for oral formulations

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A novel approach to establishing the design space for the oral formulation manufacturing process

# List of Publication

1. Optimization of the manufacturing process for oral formulations using multivariate statistical methods.: Norioka T., Kikuchi S., Onuki Y., Takayama K., Imai K., J. Pharm. Innov., 6, 157-169 (2011), <presented in Chapter 1 of this dissertation>.
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# Abbreviations

| | |
|---|---|
| ANOVA | Analysis of variance |
| AV | Acceptance value |
| BS | Boot strap |
| CI | Confidence interval |
| CPP | Critical process parameter |
| CQA | Critical quality attribute |
| DoE | Design of experiment |
| HPLC | High performance liquid chromatography |
| ICH | International conference on harmonization of technical requirements for registration of pharmaceuticals for human use |
| JP | Japanese pharmacopoeia |
| LOOCV | Leave-one-out cross validation |
| MLR | Multivariate linear regression |
| QbD | Quality by design |
| RSD | Relative standard deviation |
| RSM | Response surface method |
| RSM-S | Response surface method incorporating multivariate spline interpolation |
| *S/N* | Signal noise ratio |
| *S* | Signal |
| UV | Ultraviolet |

# GENERAL INTRODUCTION

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 execution of the QbD concept for the pharmaceutical industry is important not only to achieve a higher level of scientific understanding in pharmaceutical development, but also to obtain regulatory flexibility.

In the later phase of pharmaceutical development studies, once the formulation has been determined, the main issue is the optimization of the manufacturing process to develop a robust and stable commercial manufacturing process. Historically, the optimization of the manufacturing process has mostly involved univariate approaches where the effects of a single causal factor are examined for a small number of conditions. However, responding to the ICH Q8 guideline, the pharmaceutical industry is recently transitioning from univariate approaches to multivariate statistical approaches, in order to improve its "process understanding" that is considered a keystone of the QbD initiatives allows the development of a robust and stable manufacturing process including the establishment of design space with a science-based rationale.

To date, although several examples applying multivariate statistical approaches have been reported [2–4], to our best knowledge, few apply multivariate statistical approaches to the overall manufacturing process, a sequence of multiple unit operations, which should be conducted as a screening study at the first step to extract the critical processes and critical

process parameters (CPPs). Several studies have also been reported using a design-of-experiments (DoE) as multivariate statistical approaches in an optimization study to determine the multidimensional relationships among causal factors and response variables [5-6]. However, few consider the difficulty called multiobjective optimization problem in manufacturing process development that the optimal level for one process parameter is not always desirable for the other process parameters, which is also observed in the formulation development.

A response surface method (RSM) is useful for visual understanding of the derived multidimensional relationships to establish the design space [7–10]. However, the multidimensional relationships that are observed in pharmaceutical development studies are often nonlinear, and therefore predictions based on the linear response surface model obtained by a RSM using polynomial equations often exhibit poor estimation [11]. Furthermore, particularly for the oral formulation manufacturing process, several examples have been reported to establish the design space using a RSM with CPPs, because the RSM is effective at a certain defined scale with particular equipment [12-13]. However, there are always difficulties of scale-gap and equipment-gap, which are inevitably problematic for manufacturing process development [14]. Because CPPs change 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.

These findings indicate that the manufacturing process development for oral formulation needs more practical approach that can overcome these difficulties. This study attempts to show the effectiveness of a novel multivariate statistical approach of manufacturing process development for oral formulation executed according to the "QbD" concept that can overcome all of these difficulties.

In Chapter 1, a DoE is applied to overall manufacturing process to conduct a screening study, which is inevitable for the first step of manufacturing process development for oral

formulation. Then, the three different multivariate statistical analyses are conducted to determine influential causal factors, to find the optimal values for those causal factors and to develop a robust and stable manufacturing process that could achieve the desired performance of the final products with overcoming both the multiobjective optimization problem and the nonlinear problem.

In Chapter 2, the DoE and the several multivariate statistical analyses are conducted not only for a screening study but also for an optimization study to determine the multidimensional relationships among causal factors and response variables considering the multiobjective optimization problem and the nonlinear problem. Furthermore, a novel approach for establishing the design space of manufacturing process for oral formulation is proposed that uses critical quality attributes (CQAs) of intermediate material to overcome scale-gap and equipment-gap.

# CHAPER 1

## Optimization of the manufacturing process for oral formulations using multivariate statistical methods

## 1. Introduction

To date, although several examples applying multivariate statistical approaches have been reported [2-4], to our best knowledge, few apply multivariate statistical approaches to the overall manufacturing process, a sequence of multiple unit operations, which should be conducted as a screening study at the first step to extract the critical processes and CPPs.

In this chapter, a DoE was applied to overall manufacturing process to conduct a screening study, which is inevitable for the first step of manufacturing process development for oral formulation. Then, the three different multivariate statistical analyses were conducted to determine influential causal factors, to find the optimal values for those causal factors and to develop a robust and stable manufacturing process that could achieve the desired performance of the final products with overcoming both the multiobjective optimization problem and the nonlinear problem.

## 2. Materials and methods

### 2.1. Materials

An active ingredient for the treatment of diabetes, which was obtained from Astellas Pharma Inc. (Tokyo, Japan), was selected as the model drug. D-mannitol was obtained from Mitsubishi Shoji Foodtech Co., Ltd (Tokyo, Japan). Ac-Di-Sol was obtained from FMC Biopolymer (Philadelphia, PA, USA). Koridon 30 was obtained from BASF Corporation (Florham Park, NJ, USA). Avicel PH101 was obtained from Asahi Kasei Co. Ltd (Tokyo, Japan). Magnesium stearate was obtained from Merck Japan Ltd (Tokyo, Japan).

### 2.2. Manufacturing process

The model drug, D-mannitol, Ac-Di-Sol, Koridon 30 and Avicel PH101 were mixed for 5 min in a high-speed mixer granulator (FM-VG-25, Powrex Corporation, Hyogo, Japan) and then the mixed powder was granulated with water as a binder in the same instrument and dried in a fluid-bed dryer (Flow Coater Multi, Freund Corporation, Tokyo, Japan). The dried granules were milled using a screen mill (P-3, Fuji Paudal Co. Ltd., Osaka, Japan) and lubricated with magnesium stearate in a drum blender. The final blend was compressed into tablets using a rotary tablet press (HT-X18SS-IIW, Hata Iron Factory, Kyoto, Japan).

### 2.3. Measurement of physical characteristics

Weight and thickness, which it was essential to keep constant between runs, were measured as basic physical properties of the model drug core tablets. Three physical and chemical properties, hardness, dissolution and content uniformity, which were expressed as response variables, were measured as critical quality attributes (CQAs) of the model drug core tablets. The methods of measurement are given below

### 2.3.1. Hardness

The hardness of the model drug core tablets was measured using a hardness tester (TBH-200; Erweka GmbH, Heusenstamm, Germany).

### 2.3.2. Dissolution

Dissolution testing was performed by the paddle method at 50 rpm in 900 ml of Japanese Pharmacopoeia (JP) XV second fluid solution at 37 °C. The dissolved active ingredient was assayed by ultraviolet (UV) spectrophotometry at 277 nm with a 10 mm long quartz cell (dissolution apparatus, Toyama Sangyo Co. Ltd., Osaka, Japan).

### 2.3.3. Content uniformity

Content uniformity was assessed by a high performance liquid chromatography (HPLC) system (Alliance HPLC system, Waters Corporation, Milford, MA, USA) using a YMC-Pack ODS-AM with a column 15 cm long and of 4.6 mm inner diameter (YMC Co. Ltd., Kyoto, Japan). Relative standard deviation (RSD) and acceptance value (AV) were calculated using 10 individual assay values according to the method in the JP XV.

## 2.4. Experimental designs

Three response variables were selected as a representative of CQAs of the model drug core tablets. The desired performance for those CQAs, which was determined based on prior experience and knowledge, is shown in Table 1. Risk communication was conducted, eight process parameters from five manufacturing processes were selected and the levels for these process parameters were determined. The $L_{18}$ orthogonal experimental design was selected, as it was considered appropriate to align eight process parameters with reasonable efficiency and accuracy in the statistical analysis, although there was a limitation with respect to identifying interactions among the

process parameters because of the nature of the $L_{18}$ orthogonal array. The detailed design is summarized in Table 2.

**Table 1 Desired performance of CQAs**

| CQAs | Response variables | Desired performance |
|---|---|---|
| Appearance | Hardness | Individual more than 60N<br>Average more than 65N |
| Uniformity | Content uniformity | RSD[a] less than 6.0%<br>AV[b] less than 15.0% |
| Dissolution | Dissolution at 10min, 20min and 30min | 10 min more than 66.8%<br>20 min more than 80.6%<br>30 min more than 87.1% |

[a]RSD: relative standard deviation.

[b]AV: acceptance value.

**Table 2 Details of $L_{18}$ orthogonal experimental design[a]**

| Process | Granulation | | | Drying | Milling | Blending | Compression | |
|---|---|---|---|---|---|---|---|---|
| Parameters | Binder adding speed (kg/sec) | Binder amount (%) | Granulation time (min) | Drying temperature (°C) | Sieve aperture (μm) | Blending time (min) | Compression force (tonne) | Compression speed (rpm) |
| 1 | 0.46 | 0.55 | 5 | 60 | 710 | 3 | 1.5 | 20 |
| 2 | 0.46 | 0.65 | 10 | 60 | 850 | 5 | 1.8 | 30 |
| 3 | 0.46 | 0.75 | 15 | 60 | 1000 | 10 | 2.0 | 40 |
| 4 | 0.10 | 0.55 | 5 | 60 | 850 | 5 | 2.0 | 40 |
| 5 | 0.10 | 0.65 | 10 | 60 | 1000 | 10 | 1.5 | 20 |
| 6 | 0.10 | 0.75 | 15 | 60 | 710 | 3 | 1.8 | 30 |
| 7 | 0.02 | 0.55 | 10 | 60 | 710 | 10 | 1.8 | 40 |
| 8 | 0.02 | 0.65 | 15 | 60 | 850 | 3 | 2.0 | 20 |
| 9 | 0.02 | 0.75 | 5 | 60 | 1000 | 5 | 1.5 | 30 |
| 10 | 0.46 | 0.55 | 15 | 80 | 1000 | 5 | 1.8 | 20 |
| 11 | 0.46 | 0.65 | 5 | 80 | 710 | 10 | 2.0 | 30 |
| 12 | 0.46 | 0.75 | 10 | 80 | 850 | 3 | 1.5 | 40 |
| 13 | 0.10 | 0.55 | 10 | 80 | 1000 | 3 | 2.0 | 30 |
| 14 | 0.10 | 0.65 | 15 | 80 | 710 | 5 | 1.5 | 40 |
| 15 | 0.10 | 0.75 | 5 | 80 | 850 | 10 | 1.8 | 20 |
| 16 | 0.02 | 0.55 | 15 | 80 | 850 | 10 | 1.5 | 30 |
| 17 | 0.02 | 0.65 | 5 | 80 | 1000 | 3 | 1.8 | 40 |
| 18 | 0.02 | 0.75 | 10 | 80 | 710 | 5 | 2.0 | 20 |

[a] Levels for each process parameter in the experimental design. Binder adding speed (kg/sec): 0.02, 0.10, 0.46; binder amount (%): 0.55, 0.65, 0.75; granulation time (min): 5, 10, 15; drying temperature (°C) 60, 80; sieve aperture value (μm), blending time (min): 3, 5, 10; compression force (tonne): 1.5, 1.8, 2.0; compression speed (rpm): 20, 30, 40

### 2.4.1. Multivariate statistical analysis

Once the response variables were measured, three different multivariate statistical methods, analysis of variance (ANOVA) of response variables, ANOVA of the signal-to-noise ratio (*S/N*) and signal (*S*) and the nonlinear response surface method incorporating multivariate spline interpolation (RSM-S), were applied.

### 2.4.2 ANOVA of response variables

ANOVA is a mathematical procedure for partitioning the variability of a data set into components associated with different effects. The information provided by ANOVA is used to construct statistical tests to determine the significance of each effect. An *F*-statistic is computed for each effect, which is used to test hypotheses about the existence of the effects of variables. Microsoft Excel® (Microsoft Corporation) was used for the calculations. In the ANOVA of response variables, ANOVA was performed for the averages of response variables and the effects of process parameters on the averages of response variables were assessed. The process including the significant process parameter was concluded to be a significant manufacturing process, and a significant process parameter was defined when the *p*-value of the ANOVA was less than 0.05 or 0.01, where process parameters whose $F_0$-values were sufficiently small were pooled into the error. The purpose of the ANOVA of response variables was to identify the most influential process parameters affecting the average of each response variable.

## 2.4. ANOVA of *S/N* and *S*

In the ANOVA of *S/N* and *S*, *S/N* or *S* was determined by the following equations [15]:

$$S/N = -10\log\{(1/n)((1/y_1)^2 + \cdots + (1/y_n)^2)\} \qquad (1)$$

$$S/N = -10\log\{(1/n)((y_1)^2 + \cdots + (y_n)^2)\} \quad (2)$$

$$S/N = 10\log\{(1/(nr))(S_b - V_e)/(V_N)\} \quad (3)$$

$$S = -10\log\{(1/(nr))((S_b - V_e))\} \quad (4)$$

where $n$ is the number of repetitions of the measurement, $y_n$ is the value for the $n$th measurement, $r$ is the sum of the square of each time point of dissolution, $S_b$ is the variance of the dissolution, $V_e$ is the variance of the error and $V_N$ is the total variance of the error.

The *S/N* or *S* is a simple quality indicator that was used to evaluate the effects of particular process parameters on one response variable, considering not only the average but also the variances of the response variable. In particular, when *S/N* and *S* are calculated according to the off-line quality control concept, they can evaluate the effects of particular process parameters by considering the robustness of the product performance. In this study, *S/N* for the larger the better quality characteristic, which is expressed by equation (1), was selected for hardness, and *S/N* for the smaller the better quality characteristic, which is expressed by equation (2), was selected for the RSD and AV of content uniformity. However, *S/N* and *S* for dissolution were calculated according to the off-line quality control concept that enabled us to evaluate the robustness of performance of dissolution. The apparent dissolution rate was evaluated as the performance of dissolution by *S/N* and *S* for dissolution that were calculated according to the off-line quality control concept, which is expressed by equations (3) and (4). By using ANOVA of *S/N*, a significant process parameter was determined when the *p*-value of ANOVA was less than 0.05 or 0.01 where the process parameters whose $F_0$-values were sufficiently small were pooled into the error. As *S/N* is an indicator of additivity, the optimal levels for the process parameters can be determined by

selecting the levels of significant process parameters with the highest *S/N*. Additionally, by ANOVA of *S*, the process parameters that are able to affect the average of the response variables while keeping the variances of response variables the same can be determined.

## 2.4. RSM-S

RSM-S is a nonlinear RSM, which was developed in order to estimate with high accuracy nonlinear relationships between parameters and variables [16–19]. In this study, RSM-S was applied to provide mathematical models and to determine the optimal levels of both process parameters and response variables. The optimal levels of the process parameters and response variables were estimated using mathematical models under the condition that the desired performance for all CQAs could be achieved. The accuracy of the mathematical models was evaluated by leave-one-out cross validation (LOOCV), and then the reliability of the optimal levels of process parameters and response variables were evaluated by the bootstrap (BS) resampling method, a novel method devised recently with an RSM-S, where the number of resamplings with replacement was fixed at 1000 [20-25]. Moreover, the 95% confidence intervals (CI) of the optimal levels of the process parameters and response variables were also calculated by both parametric and nonparametric methods to confirm the reliability of the optimal levels. dataNESIA® Version 3.2 (Yamatake Corp., Tokyo, Japan) was used for RSM-S and BS resampling.

## 3. Results and discussion

### 3.1. Measurement Results

The measurement results are shown in Table 3. As intended, the basic physical properties were constant between the runs, because the weight variance of each run was less than 1% of the target weight and the thickness variance of each run was less than 0.05 mm. However, the response variables were sufficiently variable between the runs. These results suggested that the effects on response variables of the differences in levels of process parameters could be evaluated correctly.

**Table 3 Results of the measurement of the model drug core tablets**

| Run | Weight (n = 30) | | Thickness (n = 10) | | Hardness (n = 10) | Dissolution (n = 3) | | | Content uniformity (n = 1) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Average ± SD[a] (mg) | CV[b] (%) | Average ± SD[a] (mm) | CV[b] (%) | Average (N) | Average (%) 10 min | 20 min | 30 min | RSD[c] (%) | AV[d] (%) |
| 1 | 269.474 ± 0.901 | 0.334 | 3.861 ± 0.009 | 0.233 | 108.4 | 79.23 | 94.00 | 97.00 | 0.31 | 0.7 |
| 2 | 270.781 ± 1.220 | 0.451 | 3.813 ± 0.009 | 0.236 | 118.0 | 75.93 | 88.90 | 93.93 | 0.62 | 1.5 |
| 3 | 271.072 ± 0.789 | 0.291 | 3.801 ± 0.007 | 0.184 | 138.9 | 71.87 | 87.10 | 93.03 | 0.54 | 1.3 |
| 4 | 270.324 ± 0.761 | 0.282 | 3.823 ± 0.013 | 0.340 | 123.0 | 86.57 | 95.87 | 99.37 | 0.53 | 1.3 |
| 5 | 270.662 ± 0.704 | 0.260 | 3.878 ± 0.012 | 0.309 | 115.7 | 73.50 | 86.53 | 92.17 | 0.47 | 1.1 |
| 6 | 270.881 ± 0.946 | 0.349 | 3.825 ± 0.014 | 0.366 | 137.7 | 67.23 | 82.73 | 88.03 | 1.19 | 2.9 |
| 7 | 270.607 ± 1.433 | 0.530 | 3.849 ± 0.012 | 0.312 | 102.4 | 81.07 | 94.63 | 97.30 | 0.53 | 1.3 |
| 8 | 270.969 ± 0.854 | 0.315 | 3.788 ± 0.014 | 0.370 | 130.7 | 72.13 | 86.53 | 92.33 | 0.41 | 1.0 |
| 9 | 270.179 ± 1.073 | 0.397 | 3.878 ± 0.018 | 0.464 | 120.4 | 80.10 | 91.30 | 96.00 | 0.61 | 1.5 |
| 10 | 270.782 ± 1.182 | 0.437 | 3.839 ± 0.016 | 0.417 | 107.0 | 80.23 | 94.33 | 98.37 | 0.93 | 2.2 |
| 11 | 270.802 ± 1.371 | 0.506 | 3.801 ± 0.010 | 0.263 | 123.0 | 73.43 | 86.43 | 92.33 | 0.56 | 1.3 |
| 12 | 270.145 ± 0.929 | 0.344 | 3.892 ± 0.008 | 0.206 | 111.2 | 66.23 | 79.63 | 84.93 | 0.52 | 1.2 |
| 13 | 270.642 ± 1.008 | 0.372 | 3.793 ± 0.015 | 0.395 | 122.0 | 77.53 | 92.77 | 96.27 | 0.76 | 1.8 |
| 14 | 270.767 ± 0.811 | 0.300 | 3.918 ± 0.012 | 0.306 | 96.6 | 71.97 | 85.27 | 91.33 | 0.13 | 0.3 |
| 15 | 270.380 ± 1.036 | 0.383 | 3.798 ± 0.011 | 0.290 | 122.2 | 73.40 | 88.30 | 92.60 | 0.49 | 1.2 |
| 16 | 270.082 ± 0.889 | 0.329 | 3.899 ± 0.006 | 0.154 | 84.9 | 74.37 | 89.23 | 94.10 | 0.61 | 1.5 |
| 17 | 270.686 ± 1.146 | 0.423 | 3.787 ± 0.011 | 0.290 | 138.3 | 74.83 | 88.03 | 93.73 | 1.01 | 2.4 |
| 18 | 270.296 ± 1.232 | 0.456 | 3.771 ± 0.010 | 0.265 | 143.5 | 67.37 | 83.13 | 89.43 | 0.77 | 1.8 |

a SD: standard deviation.
b CV: coefficient of variation.
c RSD: relative standard deviation.
d AV: acceptance value.

## 3.2. ANOVA of response variables

ANOVA of response variables was conducted as the standard analysis for the orthogonal experimental design. The factorial effects of hardness, dissolution at 10 min, 20 min and 30 min and the RSD and AV of content uniformity are described in Fig. 1, and complete ANOVA results are shown in Table 4. From the factorial effects, the effect of process parameters to the averages of response variables could be visually grasped, that is, the process parameters that had higher slope indicated larger effects to the response variables. From the ANOVA, the significant process parameters to the average of response variables could be determined statistically. The results show that the amount of binder and the compression force had significant effects on hardness. The amount of binder, granulation time, drying temperature and blending time had significant effects on dissolution at 10 min and 30 min, whereas the amount of binder, granulation time and drying temperature had significant effects on dissolution at 20 min. However, none of the process parameters had a significant effect on the RSD and AV of content uniformity. The significant manufacturing processes were determined to be granulation, drying, blending and compression, and significant process parameters were determined to be amount of binder, granulation time, drying temperature, blending time and compression force. The results were considered to be reasonable and consistent with prior experience and knowledge. Compression force obviously affects hardness, and the difference in binder amount affects the characteristics of the granule and thereby causes a change in compression behavior, which results in a different hardness. The influence on dissolution of the amount of binder, granulation time, drying temperature and blending time was also considered to be reasonable as the characteristics of the granule, especially particle size, which generally affects the surface area of the granule, affect dissolution, and also the

lubrication of magnesium stearate affects the initial wettability. As a result, the ANOVA of the response variables revealed that prior experience and knowledge derived from the univariate method was correct and meaningful with a science-based rationale.

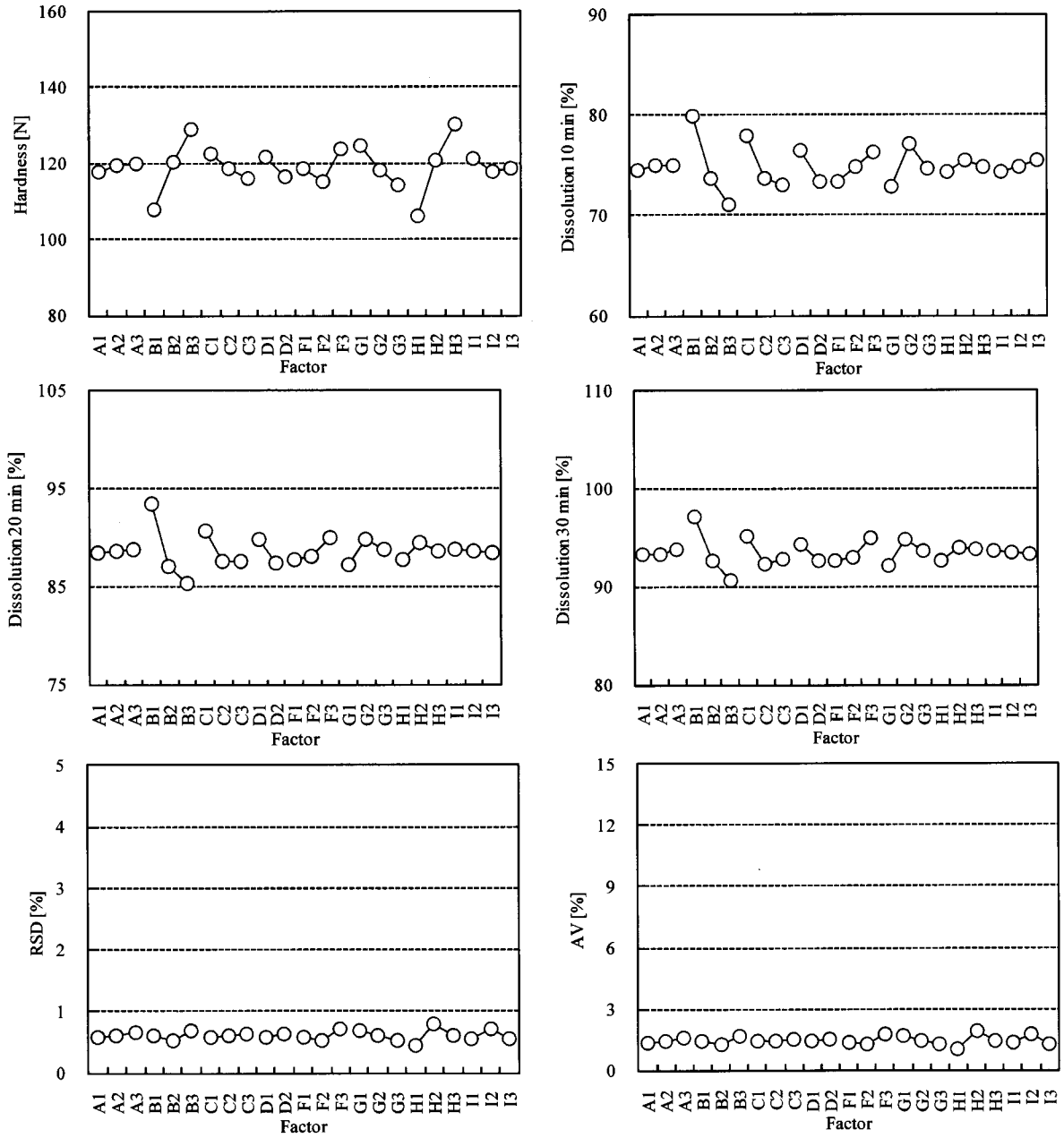



**Fig. 1 Factorial effects in ANOVA of response variables**

A1–I3 indicate process parameters and their levels for each process parameter. A: binder adding speed (kg/sec): 0.02, 0.10, 0.46; B: binder amount (%): 0.55, 0.65, 0.75; C: granulation time (min): 5, 10, 15; D: drying temperature (°C) 60, 80; F: sieve aperture value (μm); G: blending time (min): 3, 5, 10; H: compression force (tonne): 1.5, 1.8, 2.0; I: compression speed (rpm): 20, 30, 40

**Table 4 ANOVA of response variables**

| Factor | Hardness | | | | Dissolution | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 10 min | | | | 20 min | | | |
| | SS[a] | V[b] | $F_0$-value | $p$-value | SS[a] | V[b] | $F_0$-value | $p$-value | SS[a] | V[b] | $F_0$-value | $p$-value |
| Binder adding speed | 159.6 | 79.80 | 0.16 | –[e] | 3.21 | 1.61 | 0.18 | –[e] | 1.52 | 0.76 | 0.07 | –[e] |
| Binder amount | 13374.6 | 6687.3 | 13.02 | 0.00 ** | 735.84 | 367.92 | 41.99 | 0.00** | 663.70 | 331.85 | 31.89 | 0.00** |
| Granulation time | 1317.0 | 658.5 | 1.28 | –[e] | 262.04 | 131.02 | 14.95 | 0.00** | 114.99 | 57.50 | 5.53 | 0.03* |
| Drying temperature | 1216.8 | 1216.8 | 2.37 | 0.16 | 133.10 | 133.10 | 15.19 | 0.00** | 69.57 | 69.57 | 6.69 | 0.03* |
| Sieve aperture | 2293.2 | 1146.6 | 2.23 | 0.17 | 78.95 | 39.48 | 4.50 | 0.05 | 55.23 | 27.62 | 2.65 | 0.13 |
| Blending time | 3211.2 | 1605.6 | 3.13 | 0.10 | 157.14 | 78.57 | 8.97 | 0.01* | 57.50 | 28.75 | 2.76 | 0.12 |
| Compression force | 17571.6 | 8785.8 | 17.11 | 0.00** | 13.40 | 6.70 | 0.76 | –[e] | 30.19 | 15.10 | 1.45 | –[e] |
| Compression speed | 437.4 | 218.7 | 0.43 | –[e] | 11.20 | 5.60 | 0.64 | –[e] | 1.41 | 0.71 | 0.07 | –[e] |

| Factor | Dissolution | | | | Content uniformity | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 30 min | | | | RSD[c] | | | | AV[d] | | | |
| | SS[a] | V[b] | $F_0$-value | $p$-value | SS[a] | V[b] | $F_0$-value | $p$-value | SS[a] | V[b] | $F_0$-value | $p$-value |
| Binder adding speed | 3.50 | 1.75 | 0.27 | –[e] | 0.02 | 0.01 | 0.22 | –[e] | 0.15 | 0.07 | 0.28 | –[e] |
| Binder amount | 386.79 | 193.40 | 29.74 | 0.00** | 0.07 | 0.04 | 0.77 | –[e] | 0.44 | 0.22 | 0.83 | –[e] |
| Granulation time | 81.48 | 40.74 | 6.26 | 0.02* | 0.01 | 0.00 | 0.09 | –[e] | 0.05 | 0.03 | 0.10 | –[e] |
| Drying temperature | 42.77 | 42.77 | 6.58 | 0.03* | 0.02 | 0.02 | 0.39 | –[e] | 0.07 | 0.07 | 0.25 | –[e] |
| Sieve aperture | 59.21 | 29.61 | 4.55 | 0.05 | 0.12 | 0.06 | 1.25 | –[e] | 0.62 | 0.31 | 1.17 | –[e] |
| Blending time | 65.58 | 32.79 | 5.04 | 0.04* | 0.09 | 0.04 | 0.92 | –[e] | 0.45 | 0.22 | 0.85 | –[e] |
| Compression force | 20.64 | 10.32 | 1.59 | –[e] | 0.38 | 0.19 | 4.06 | 0.07 | 2.27 | 1.14 | 4.29 | 0.06 |
| Compression speed | 1.24 | 0.62 | 0.10 | –[e] | 0.12 | 0.06 | 1.30 | –[e] | 0.76 | 0.38 | 1.43 | –[e] |

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

[a] SS: sum of squares.

[b] V: variance.

[c] RSD: relative standard deviation.

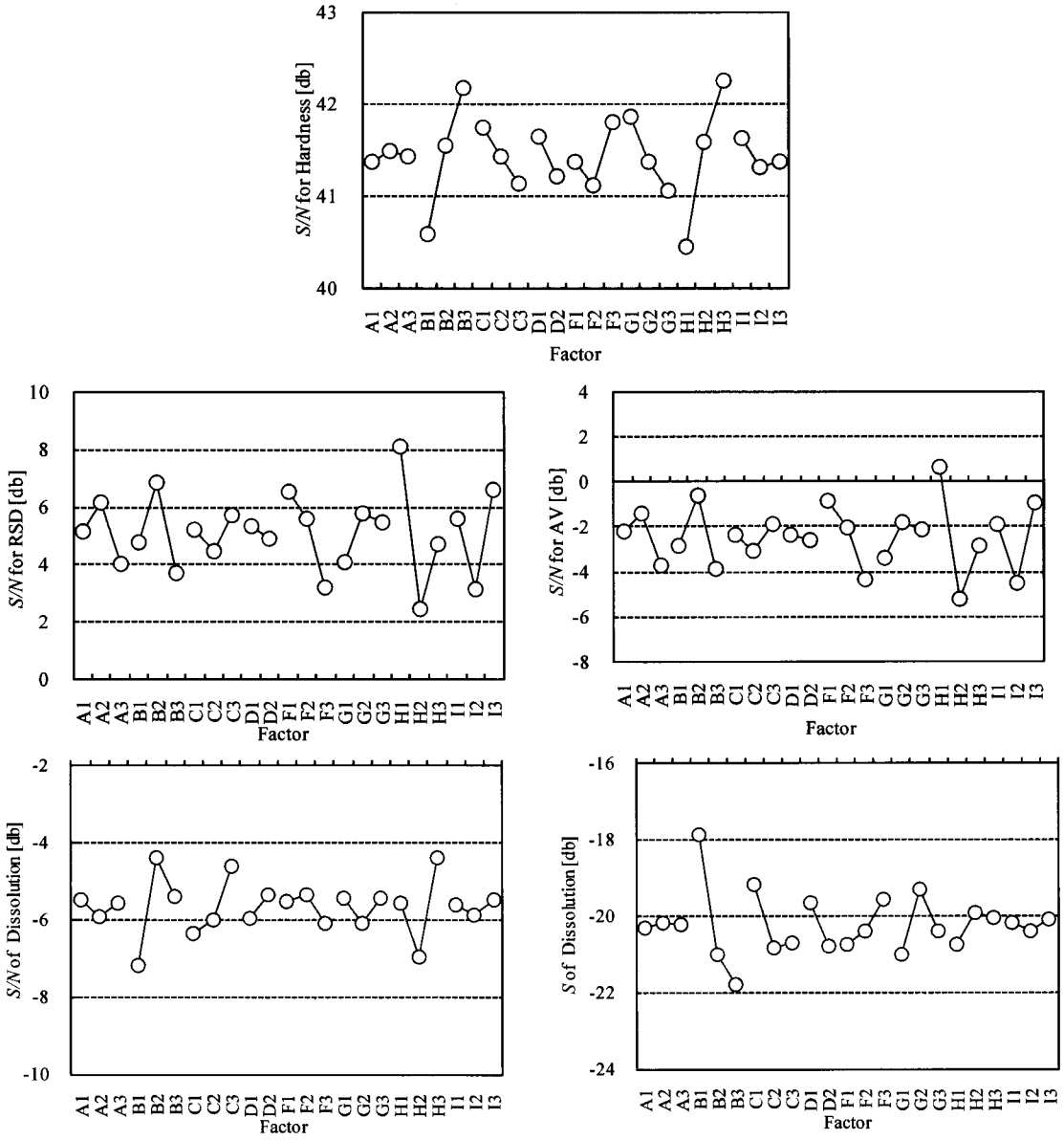
[d] AV: acceptance value.

[e] Process parameters that were pooled into the error.

### 3.3. ANOVA of *S/N* and *S*

ANOVA of *S/N* and *S* was conducted as a specific analysis for the orthogonal experimental design according to the quality-engineering concept, which could determine the optimal levels of plural process parameters for each response variables considering not only the average but also the variance of the response variable. The calculated *S/N* and *S* for the response variables are shown in Table 5. The factorial effects of *S/N* and *S* are described in Fig. 2 and the complete ANOVA results are shown in Table 6. From the factorial effects, the effect of process parameters to the *S/N* and *S* of response variables could be visually grasped, that is, the process parameters that had higher *S/N* indicated the higher robustness of the response variables and the process parameters that had higher *S* indicated the higher sensitivity of the response variables by the process parameters. From the ANOVA, the significant process parameters to the *S/N* and *S* of response variables could be determined statistically. The results showed that the identical process parameters had significant effects on the *S/N* of hardness. Only the amount of binder had a significant effect on the *S/N* of dissolution, although the amount of binder, granulation time, drying temperature, sieve aperture and blending time had significant effects on the *S* of dissolution. This meant that the variance of the apparent dissolution rate was able to be controlled at a low level when the level of binder amount was optimized, and the apparent dissolution rate itself was able to be adjusted by changing any of the process parameters that showed significant effects on the *S* of dissolution except the amount of binder, which also showed a significant effect on the *S/N* of dissolution. None of the factors had a significant effect on the *S/N* of the RSD and AV of content uniformity, which was consistent with the result of the ANOVA of response variables. From these results, by considering not only the average but also the variance of response variables, the number of significant

process parameters could be narrowed down. The desired performance, which includes greater hardness, lower RSD and AV of content uniformity and higher apparent dissolution rate, with smaller variance for each response variable, can be achieved when levels of process parameters are selected at the highest *S/N*. However, it seemed that there was an inverse relationship between hardness and dissolution and it is impossible to determine the optimal levels of process parameters to achieve the desired performance for all response variables at the same time.




## Fig. 2 Factorial effects in ANOVA of *S/N* and *S*

A1–I3 indicate process parameters and their levels for each process parameter. A: binder adding speed (kg/sec): 0.02, 0.10, 0.46; B: binder amount (%): 0.55, 0.65, 0.75; C: granulation time (min): 5, 10, 15; D: drying temperature (°C) 60, 80; F: sieve aperture value (μm); G: blending time (min): 3, 5, 10; H: compression force (tonne): 1.5, 1.8, 2.0; I: compression speed (rpm): 20, 30, 40

**Table 5 Calculated *S/N* and *S* of response variables**

| Run | Hardness | Dissolution | | Content uniformity | |
|---|---|---|---|---|---|
| | | | | RSD[a] | AV[b] |
| | *S/N* | *S/N* | *S* | *S/N* | *S/N* |
| 1 | 40.69 | −6.29 | −18.16 | 10.17 | 3.10 |
| 2 | 41.42 | −5.35 | −20.30 | 4.15 | −3.52 |
| 3 | 42.85 | −2.09 | −20.96 | 5.35 | −2.28 |
| 4 | 41.79 | −7.13 | −15.46 | 5.51 | −2.28 |
| 5 | 41.26 | −5.39 | −21.24 | 6.56 | −0.83 |
| 6 | 42.77 | −6.07 | −23.06 | −1.51 | −9.25 |
| 7 | 40.19 | −9.82 | −17.76 | 5.51 | −2.28 |
| 8 | 42.32 | −3.00 | −21.24 | 7.74 | 0.00 |
| 9 | 41.60 | −8.61 | −18.97 | 4.29 | −3.52 |
| 10 | 40.57 | −9.06 | −16.91 | 0.63 | −6.85 |
| 11 | 41.78 | −4.43 | −21.20 | 5.04 | −2.28 |
| 12 | 40.90 | −5.71 | −24.25 | 5.68 | −1.58 |
| 13 | 41.71 | −6.68 | −18.75 | 2.38 | −5.11 |
| 14 | 39.69 | −3.46 | −21.70 | 17.72 | 10.46 |
| 15 | 41.74 | −6.80 | −20.89 | 6.20 | −1.58 |
| 16 | 38.56 | −4.05 | −20.25 | 4.29 | −3.52 |
| 17 | 42.81 | −4.82 | −20.51 | −0.09 | −7.60 |
| 18 | 43.13 | −3.06 | −22.64 | 2.27 | −5.11 |

[a] RSD: relative standard deviation.
[b] AV: acceptance value.

**Table 6 ANOVA of response variables**

| Factor | Hardness *S/N* | | | | Dissolution | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | *S/N* | | | | *S* | | | |
| | SS[a] | V[b] | $F_0$-value | *p*-value | SS[a] | V[b] | $F_0$-value | *p*-value | SS[a] | V[b] | $F_0$-value | *p*-value |
| Binder adding speed | 0.04 | 0.02 | 0.09 | –[e] | 0.64 | 0.32 | 0.14 | –[e] | 0.04 | 0.02 | 0.07 | –[e] |
| Binder amount | 7.61 | 3.81 | 17.10 | 0.01* | 23.57 | 11.79 | 5.11 | 0.04* | 51.60 | 25.80 | 94.69 | 0.00** |
| Granulation time | 1.12 | 0.56 | 2.52 | 0.20 | 9.97 | 4.99 | 2.16 | 0.18 | 9.75 | 4.87 | 17.88 | 0.00** |
| Drying temperature | 0.87 | 0.87 | 3.91 | 0.12 | 1.80 | 1.80 | 0.78 | –[e] | 5.52 | 5.52 | 20.27 | 0.00** |
| Sieve aperture | 1.41 | 0.71 | 3.17 | 0.15 | 1.93 | 0.97 | 0.42 | –[e] | 4.53 | 2.27 | 8.32 | 0.02* |
| Blending time | 2.00 | 1.00 | 4.49 | 0.09 | 1.87 | 0.93 | 0.41 | –[e] | 8.49 | 4.24 | 15.58 | 0.00** |
| Compression force | 10.03 | 5.02 | 22.54 | 0.01* | 20.16 | 10.08 | 4.37 | 0.05 | 2.55 | 1.27 | 4.67 | 0.06 |
| Compression speed | 0.32 | 0.16 | 0.72 | –[e] | 0.41 | 0.21 | 0.09 | –[e] | 0.33 | 0.17 | 0.61 | –[e] |

| Factor | Content uniformity | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | RSD[c] *S/N* | | | | AV[d] *S/N* | | | |
| | SS[a] | V[b] | $F_0$-value | *p*-value | SS[a] | V[b] | $F_0$-value | *p*-value |
| Binder adding speed | 13.78 | 6.89 | 0.50 | –[e] | 15.44 | 7.72 | 0.54 | –[e] |
| Binder amount | 30.70 | 15.35 | 1.11 | –[e] | 33.14 | 16.57 | 1.17 | –[e] |
| Granulation time | 4.90 | 2.45 | 0.18 | –[e] | 4.10 | 2.05 | 0.14 | –[e] |
| Drying temperature | 0.76 | 0.76 | 0.05 | –[e] | 0.28 | 0.28 | 0.02 | –[e] |
| Sieve aperture | 35.66 | 17.83 | 1.29 | –[e] | 37.54 | 18.77 | 1.32 | –[e] |
| Blending time | 10.02 | 5.01 | 0.36 | –[e] | 8.68 | 4.34 | 0.31 | –[e] |
| Compression force | 96.77 | 48.39 | 3.50 | 0.09 | 104.79 | 52.40 | 3.70 | 0.08 |
| Compression speed | 38.94 | 19.47 | 1.41 | –[e] | 41.77 | 20.89 | 1.47 | –[e] |

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

[a] SS: sum of squares.

[b] V: variance.

[c] RSD: relative standard deviation.

[d] AV: acceptance value.

[e] Process parameters that were pooled into the error.

## 3.4. RSM-S

One of the difficulties in the optimization of a manufacturing process is the trade-off that the optimal level for one process parameter is not always desirable for the other process parameters. This trade-off is called a multiobjective optimization problem and is also observed in the quantitative approach to formulation design. It was impossible to solve the multiobjective optimization problem by ANOVA of response variables or ANOVA of *S/N* and *S* as neither analyses could consider plural response variables simultaneously. In such case, a RSM that could determine the optimal levels of both process parameters and response variables simultaneously by using mathematical models was strongly effective. Although the RSM has been widely used to optimize formulation of pharmaceuticals [7,26-27], its predictions may result in poor estimations. To overcome this shortcoming, RSM-S was developed in order to estimate with high accuracy nonlinear relationships between parameters and variables. The basic concept of multivariate spline interpolation involves a boundary element method [28]. Green functions are used for the minimum curvature interpolation of multidimensional data points and multivariate spline interpolation estimates multidimensional data using a thin-plate spline that represents the sum of interpolations made with a Green function and a linear polynomial equation ("thin-plate estimation") [20,29]. Thus, the method enables the natural incorporation of observational data, including experimental errors. For nonlinear RSMs, such as RSM-S, establishing a method to evaluate the reliability of the optimal solution estimate has remained a challenge. A novel method to address this issue was recently devised. The method makes use of BS resampling with an RSM-S. Once RSM-S is applied and optimal solutions, which are optimal levels of process parameters and response variables, are estimated from the mathematical models, then a large number of BS samples are generated from

the original data set using BS resampling, and a simultaneous optimal solution for each BS sample, the BS optimal solution, is estimated. By comparing the BS optimal solutions to the original optimal solutions, the accuracy of the original optimal solutions can be evaluated. If the accuracy of the BS optimal solution deviates from that of the original optimal solution, the original optimal solution is considered to have a low reliability with regard to accuracy. In addition, the precision of the original optimal solution can also be evaluated using the BS standard deviation. A large BS standard deviation indicates poor precision of the original optimal solution. In this study, although the findings in the ANOVA of response variables suggested that five process parameters should be selected, only four process parameters were selected for RSM-S and BS resampling. This is because more than three levels are required for each process parameter used in RSM-S and one parameter should have two levels in an $L_{18}$ orthogonal design of experiment. Drying temperature was excluded from the RSM-S, even if it had a significant effect, because it had only two levels. The mathematical models of hardness, dissolution at 10 min, 20 min and 30 min and the RSD and AV of content uniformity were generated by RSM-S. The accuracy of each mathematical model was evaluated by using the LOOCV method. The $R^2$ values defined by equation (6) for the response variables were calculated:

$$R^2 = 100 \times (1 - SSE/SST) \qquad (6)$$

where $SSE$ is the sum of the squared error between the predicted and the measured values and $SST$ is the sum of the squared error between each measured value and the average of the measured value .

The LOOCV results are described in Fig. 3. $R^2$ values for hardness and dissolution at 10 min, 20 min and 30 min were sufficiently high. This suggested that the response surfaces for hardness and dissolution at 10 min,

20 min and 30 min were highly reliable. In contrast, the LOOCV results for the RSD and AV of content uniformity were low, as they included no influential process parameters. The simultaneous optimal levels for process parameters and response variables were calculated by RSM-S, under the condition that all response variables achieved the desired performance. To confirm the reliability of the optimal levels of process parameters and response variables, which were denoted as the original optimal levels, the BS resampling method was used. BS datasets were generated by 1000 BS resampling, and BS optimal levels were obtained. As shown in Table 7, the BS optimal levels were similar to the original optimal levels for all process parameters and response variables. The distributions of the BS optimal levels of the process parameters and response variables generated by BS resampling are described in Fig. 4. As BS resampling is a statistical interval analysis that uses a Monte Carlo simulation, the shape of the distribution constructed from the arithmetic means of the BS samples should follow a normal distribution. As all the distributions of BS optimal levels of process parameters and response variables obtained were almost symmetrical, it was considered that the BS resampling was conducted correctly and was very reliable. Moreover, the 95% CIs of the BS optimal levels of process parameters and response variables were calculated by parametric and nonparametric (percentile) methods. No meaningful difference between the parametric and percentile methods was observed and all 95% CIs were reasonably narrow. Thus, the mathematical models and optimal levels of process parameters and response variables derived by RSM-S were accurate and reliable. As a result, it was confirmed that the multiobjective optimization problem could be solved by RSM-S with sufficient reliability and that RSM-S could provide a more profound process understanding in the optimization of manufacturing

processes.

**Table 7 BS optimal levels of process parameters and response variables**

| Process parameters | Binder amount (%) | Granulation time (min) | Blending time (min) | Compression force (tonne) |
|---|---|---|---|---|
| Original optimal level | 3.25 | 10 | 6.0 | 1.77 |
| BS optimal level | 3.25 | 9.97 | 6.00 | 1.77 |
| BS standard deviation | 0.10 | 0.96 | 0.72 | 0.05 |
| Parametric 95% CI[a] | 3.05–3.45 | 8.09–11.85 | 4.59–7.41 | 1.74–1.80 |
| Nonparametric 95% CI[a] | 3.06–3.44 | 8.06–11.94 | 4.67–7.44 | 1.67–1.86 |
| Response variables | Hardness (N) | Dissolution | | |
| | | 10 min (%) | 20 min (%) | 30 min (%) |
| Original optimal level | 115.74 | 76.62 | 89.36 | 94.31 |
| BS optimal level | 117.89 | 75.51 | 88.79 | 93.79 |
| BS standard deviation | 4.18 | 1.46 | 1.15 | 0.90 |
| Parametric 95% CI[a] | 109.69–126.09 | 72.65–78.38 | 86.53–91.05 | 92.04–95.55 |
| Nonparametric 95% CI[a] | 110.66–126.66 | 72.28–77.99 | 86.44–91.02 | 91.91–95.50 |

[a] CI: confidential interval.

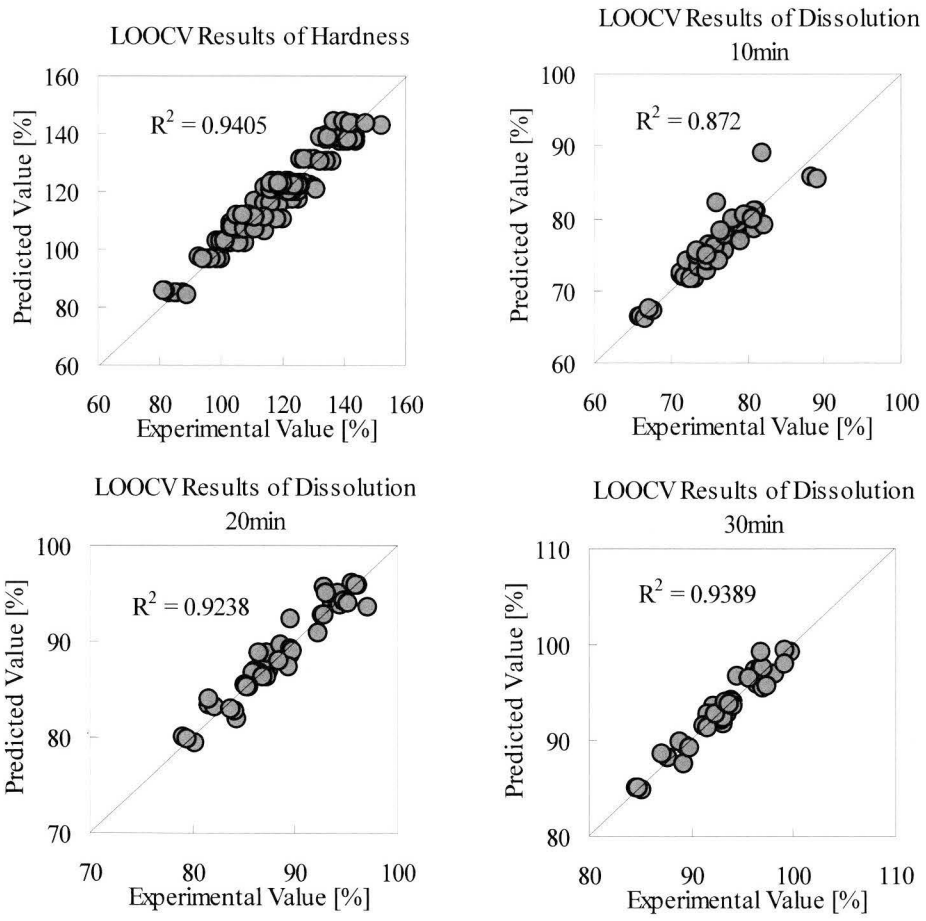



**Fig. 3 Relationship between experimental and predicted values**

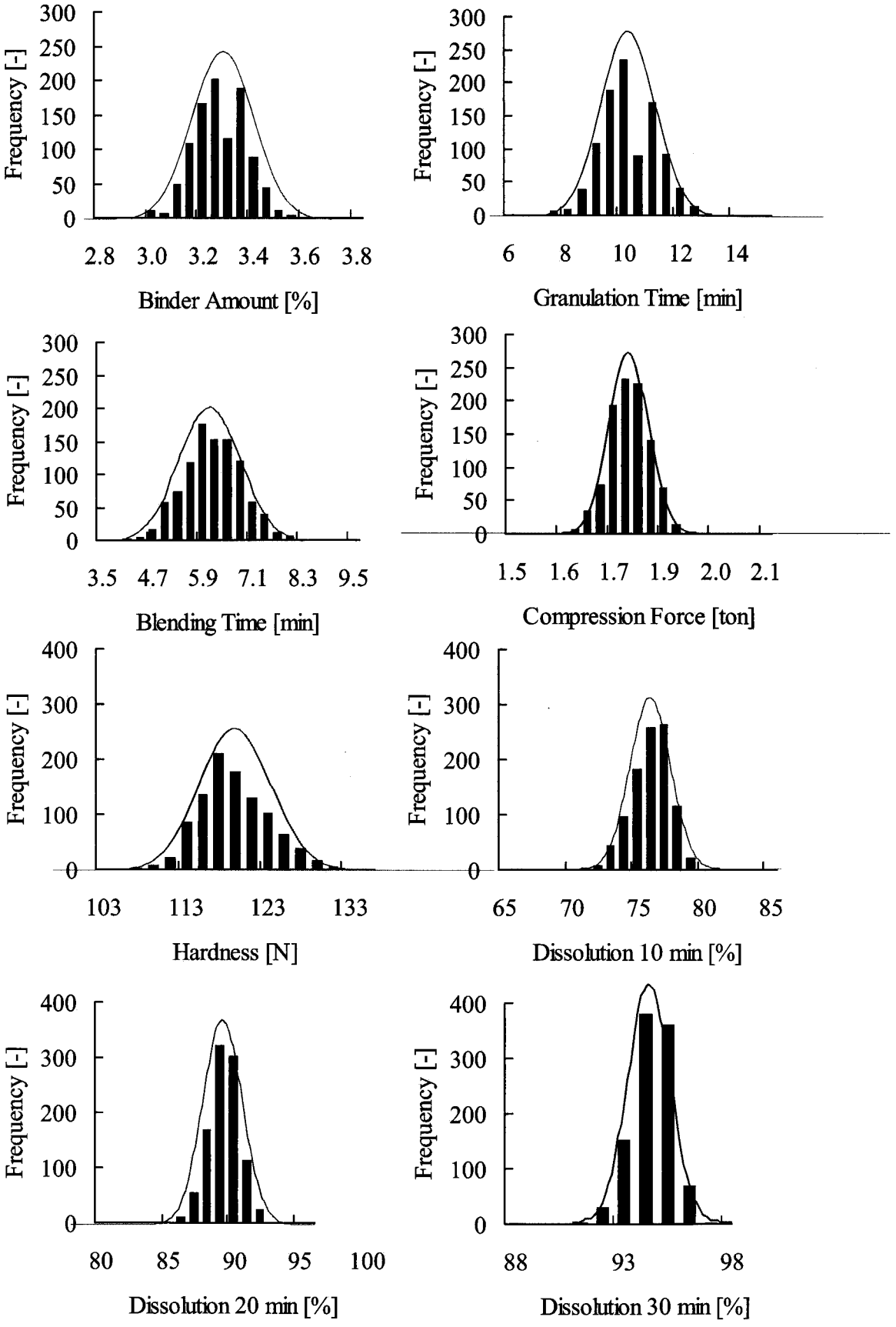



**Fig. 4 Distribution of BS optimal levels**

## 4. Conclusion

The optimization of the manufacturing process for oral formulations was conducted by applying three different multivariate statistical methods. Significant process parameters and significant processes, with respect to both the average of the response variables and their variance, were extracted by the conventional multivariate statistical methods of ANOVA of response variables and ANOVA of *S/N* and *S*. These confirmed that prior experience and knowledge were correct and meaningful with a science-based rationale. In order to overcome the multiobjective problem, an advanced multivariate statistical method, RSM-S, was applied. The optimal levels of process parameters and response variables were determined by mathematical models derived from RSM-S, and their high reliability was confirmed by the BS resampling method and 95% CI. These results revealed the cause-and-effect relationship between process parameters and response variables and a more profound understanding of the processes was obtained. It is considered that these multivariate statistical methods are useful tools for efficiently and accurately developing and optimizing manufacturing processes.

# CHAPER 2

## A novel approach to establishing the design space for the oral formulation manufacturing process

## 1. Introduction

As described in Chapter 1, it was found that the DoE and the several multivariate statistical analyses were useful tools for efficiently and accurately developing and optimizing manufacturing processes. However there is a difficulty that still needs to be overcome, which are scale-gap and equipment-gap of design space, which are inevitably problematic for manufacturing process development [14].

In Chapter 2, the main purpose 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 also 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 in Chapter 1 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 ANOVA.
- Optimization studies at the pilot scale [30] 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 [20-25,31], RSM-S [16-19,32], 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.

## 2. Materials and methods

### 2.1. 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 24,000 tablets per hour and 240,000 tablets per hour, respectively. The inner diameter of the die of the press was 12 mm × 6 mm oval shape.

### 2.2. 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), 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.

## 2.3. 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, 4kg 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, 12kg 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, 120kg scale.

## 2.4. Statistical analysis

ANOVA 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 [31,33-34], for a better understanding, the process for the determination of the conservative border of the design space is shown in Fig. 5 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 [45].

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, USA) 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.

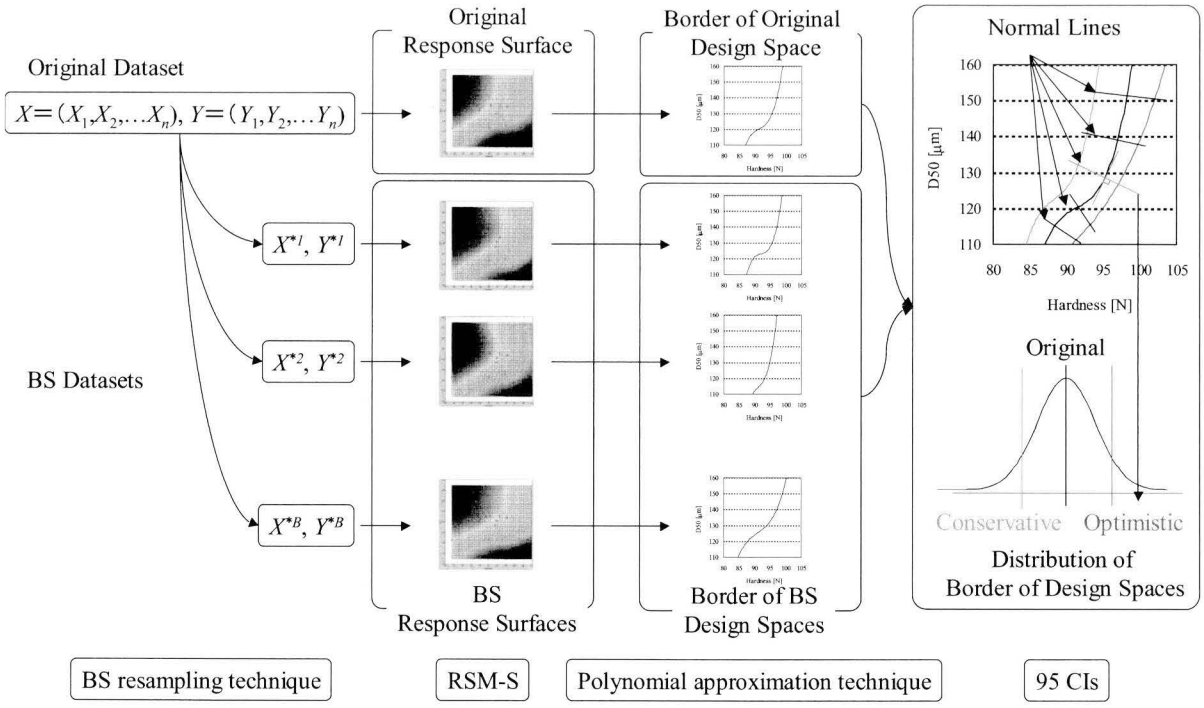



**Fig. 5 Process of determination of the conservative border of design space by BS resampling technique, RMS-S, polynomial approximation technique and 95% CIs**

## 3. Results and discussion

### 3.1. 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 [35], which applied Failure Mode and Effect Analysis [36] 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

### 3.2. 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 [31]. The experimental design and measurement results and factorial effects for the screening study are shown in Table 8 and Fig. 6. 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, 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 9, 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.

**Table 8 $L_{18}$ 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 |

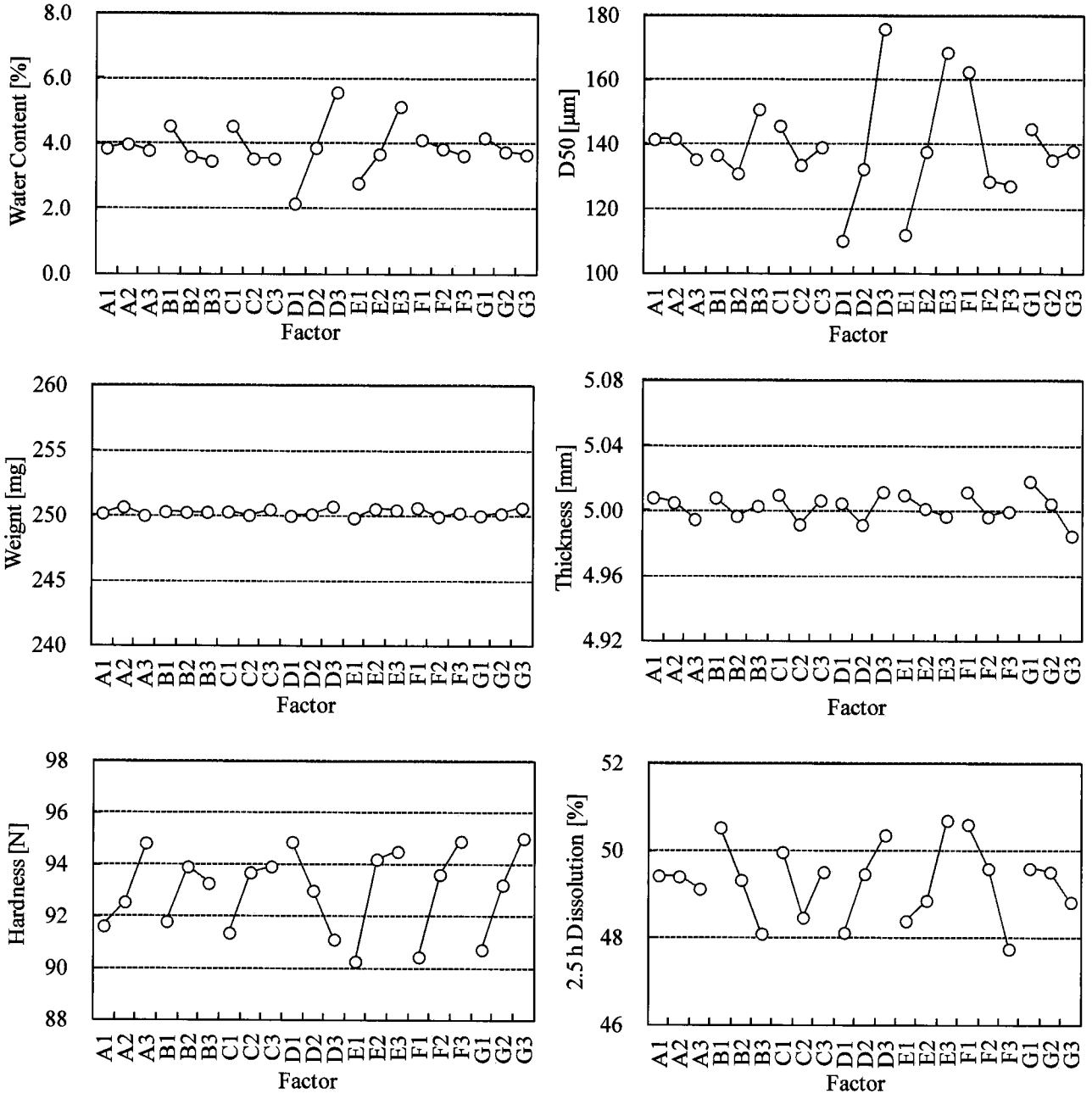



**Fig. 6 Factorial effects of screening study**

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 m3/min, C2: 3.5 m3/min, C3: 4.0 m3/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

**Table 9 Results of ANOVA of screening study**

| Input Variables | Water Content | | | | |
|---|---|---|---|---|---|
| | SS[a] | DF[b] | V[c] | $F_0$-value | $p$-value |
| Mill Speed | _[d] | _[d] | _[d] | _[d] | _[d] |
| 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 | _[d] | _[d] | _[d] | _[d] | _[d] |
| Main Compression Force | _[d] | _[d] | _[d] | _[d] | _[d] |
| Input Variables | $D_{50}$ | | | | |
| | SS[a] | DF[b] | V[c] | $F_0$-value | $p$-value |
| Mill Speed | _[d] | _[d] | _[d] | _[d] | _[d] |
| Inlet Air Flow Temperature | 1264.72 | 2 | 632.360 | 2.870 | 0.11 |
| Inlet Air Flow Rate | _[d] | _[d] | _[d] | _[d] | _[d] |
| 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 | _[d] | _[d] | _[d] | _[d] | _[d] |
| Input Variables | Thickness | | | | |
| | SS[a] | DF[b] | V[c] | $F_0$-value | $p$-value |
| Mill Speed | _[d] | _[d] | _[d] | _[d] | _[d] |
| Inlet Air Flow Temperature | _[d] | _[d] | _[d] | _[d] | _[d] |
| Inlet Air Flow Rate | 0.0011 | 2 | 0.0006 | 0.500 | 0.62 |
| Spray Rate | _[d] | _[d] | _[d] | _[d] | _[d] |
| Spray Amount | _[d] | _[d] | _[d] | _[d] | _[d] |
| Spray Pressure | 0.0008 | 2 | 0.0004 | 0.333 | 0.72 |
| Main Compression Force | _[d] | _[d] | _[d] | _[d] | _[d] |
| Input Variables | Hardness | | | | |
| | SS[a] | DF[b] | V[c] | $F_0$-value | $p$-value |
| Mill Speed | _[d] | _[d] | _[d] | _[d] | _[d] |
| Inlet Air Flow Temperature | _[d] | _[d] | _[d] | _[d] | _[d] |
| Inlet Air Flow Rate | _[d] | _[d] | _[d] | _[d] | _[d] |
| 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 | | | | |
| | SS[a] | DF[b] | V[c] | $F_0$-value | $p$-value |
| Mill Speed | _[d] | _[d] | _[d] | _[d] | _[d] |
| Inlet Air Flow Temperature | 17.759 | 2 | 8.880 | 1.985 | 0.19 |
| Inlet Air Flow Rate | _[d] | _[d] | _[d] | _[d] | _[d] |
| 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 | _[d] | _[d] | _[d] | _[d] | _[d] |

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

[a] SS: sum of squares.

[b] DF: degrees of freedom.

[c] V: variance.

[d] Process parameters that were pooled into the error.

## 3.3. Optimization studies

The experimental designs and measurement results for optimization studies are shown in Tables 10 and 11. 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 12 and 13, water content, $D_{50}$, thickness, hardness, and 2.5 h dissolution varied across the different manufacturing conditions, 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 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 [38], 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.

**Table 10 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 11 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 12 Results of MLR of optimization study for granulation process**

| | Water Content | | | | |
|---|---|---|---|---|---|
| | SS[a] | DF[b] | V[c] | $F_0$-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 | | |
| | $D_{50}$ | | | | |
| | SS[a] | DF[b] | V[c] | $F_0$-value | $p$-value |
| Model | 7751 | 9 | 861.214 | 5.455 | 0.0179* |
| Error | 1105 | 7 | 157.887 | | |
| Adjusted Total | 8856 | 16 | 553.509 | | |

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

[a] SS: sum of squares.

[b] DF: degrees of freedom.

[c] V: variance.

**Table 13 Results of MLR of optimization study for compression process**

| | Thickness | | | | |
|---|---|---|---|---|---|
| | SS[a] | DF[b] | V[c] | $F_0$-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 | | | | |
| | SS[a] | DF[b] | V[c] | $F_0$-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 | | |

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

[a] SS: sum of squares.

[b] DF: degrees of freedom.

[c] V: variance.

## 3.4. 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 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 14, 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 [38]; 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 Fig. 7 and Fig. 8, 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 LOOCV 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. 9. 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 [34]. 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. 10, which were expressed by the following mathematical formulas, both with $R^2 \geqq 0.99$:

$y = 0.0981x^3 - 26.3690x^2 + 2363.3108x - 70499.1660$ (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.

**Table 14 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 |

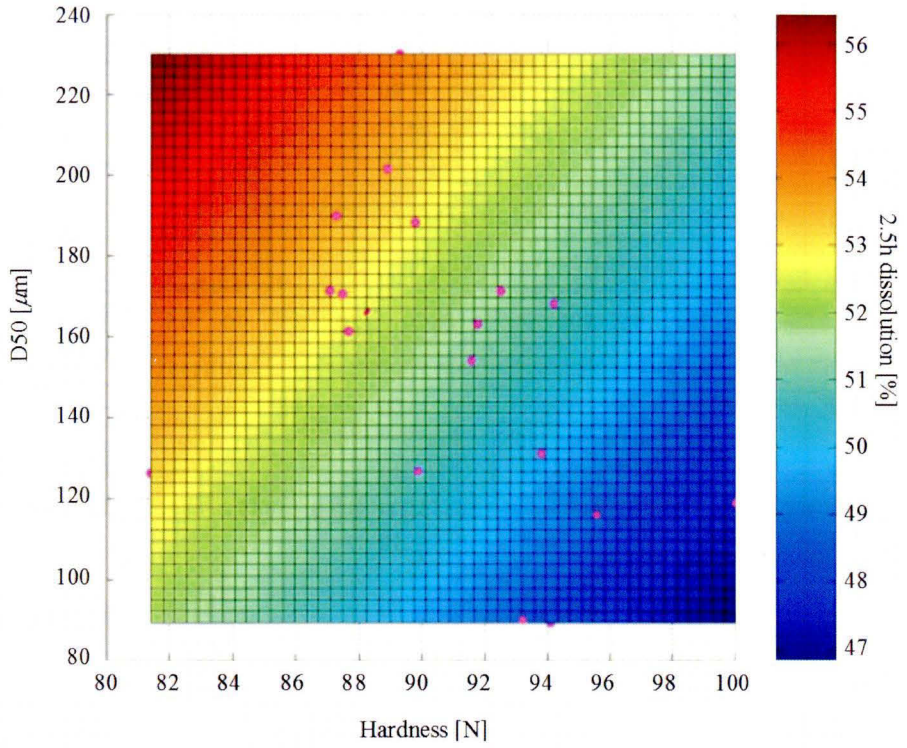



**Fig. 7 Linear response surface of 2.5 h dissolution**

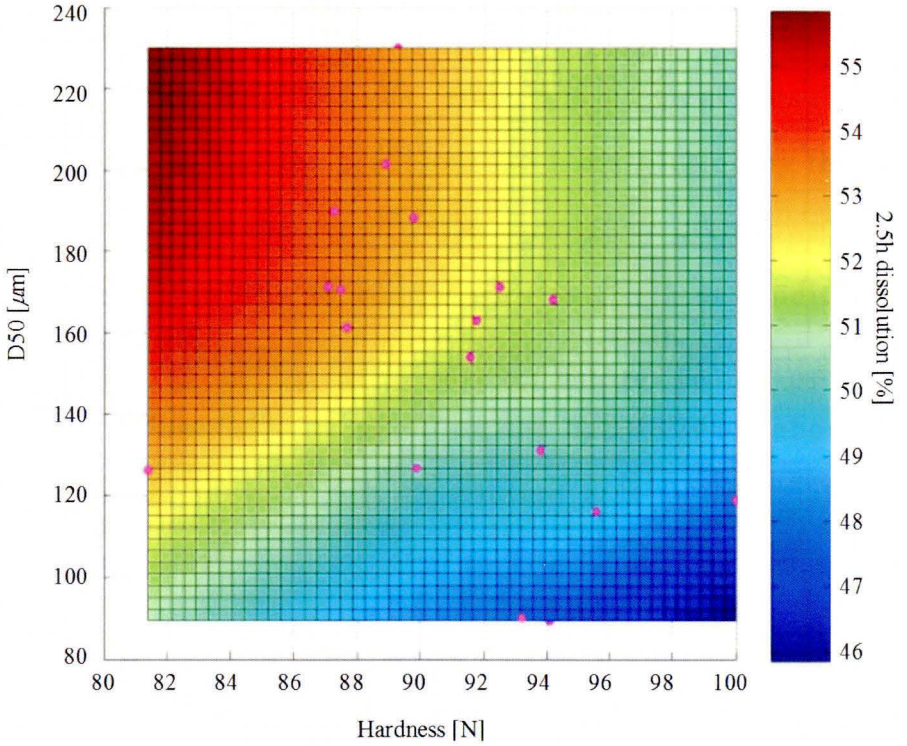



**Fig. 8 Nonlinear response surface of 2.5 h dissolution**

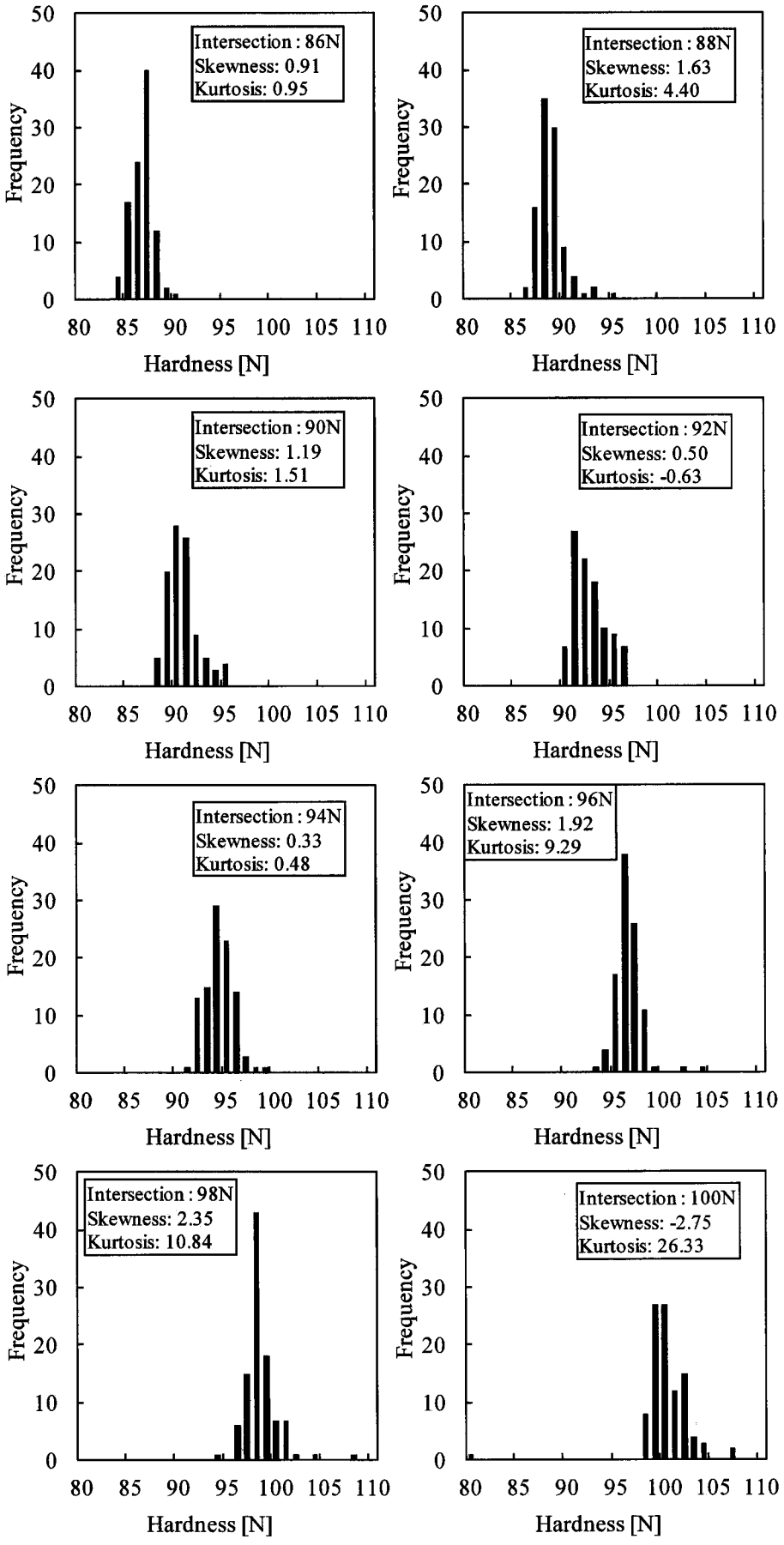



**Fig. 9 Histograms of intersection points**

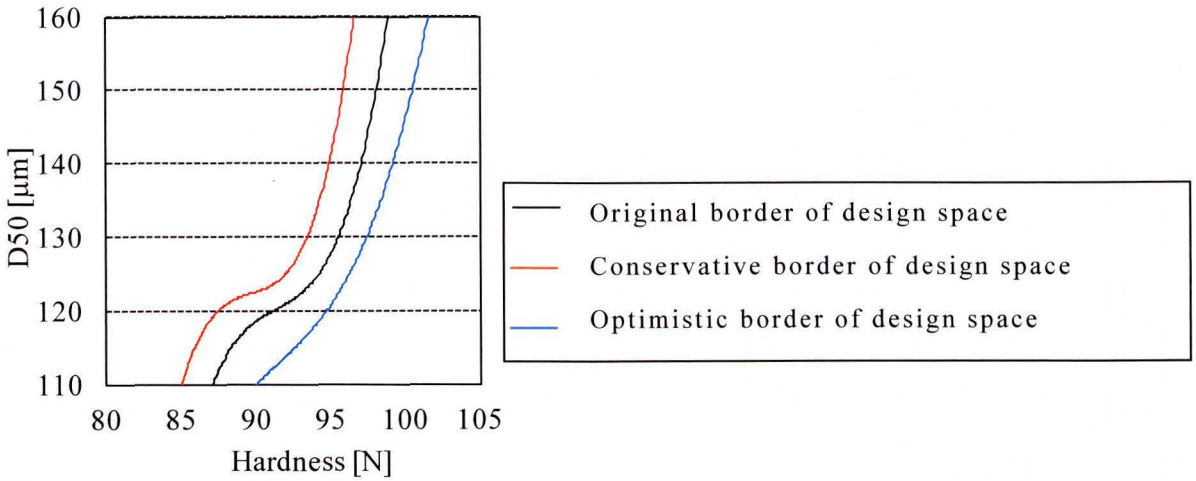



**Fig. 10 Original, conservative and optimistic border of design space**

## 3.5. 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 15. 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.

**Table 15 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.

## 4. 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.

# SUMMARY

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 execution of the QbD concept for the pharmaceutical industry is important not only to achieve a higher level of scientific understanding in pharmaceutical development, but also to obtain regulatory flexibility.

In the later phase of pharmaceutical development studies, once the formulation has been determined, the main issue is the optimization of the manufacturing process to develop a robust and stable commercial manufacturing process. Historically, the optimization of the manufacturing process has mostly involved univariate approaches where the effects of a single causal factor are examined for a small number of conditions. However, responding to the ICH Q8 guideline, the pharmaceutical industry is recently transitioning from univariate approaches to multivariate statistical approaches, in order to improve its "process understanding" that is considered a keystone of the QbD initiatives allows the development of a robust and stable manufacturing process including the establishment of design space with a science-based rationale.

To date, although several examples applying multivariate statistical

approaches have been reported [2-4], to our best knowledge, few apply multivariate statistical approaches to the overall manufacturing process, a sequence of multiple unit operations, which should be conducted as a screening study at the first step to extract the critical processes and CPPs. Several studies have also been reported using a DoE as multivariate statistical approaches in an optimization study to determine the multidimensional relationships among causal factors and response variables [5-6]. However, few consider the difficulty called multiobjective optimization problem in manufacturing process development that the optimal level for one process parameter is not always desirable for the other process parameters, which is also observed in the formulation development.

A RSM is useful for visual understanding of the derived multidimensional relationships to establish the design space [7-10]. However, the multidimensional relationships that are observed in pharmaceutical development studies are often nonlinear, and therefore predictions based on the linear response surface model obtained by a RSM using polynomial equations often exhibit poor estimation [11]. Furthermore, particularly for the oral formulation manufacturing process, several examples have been reported to establish the design space using a RSM with CPPs, because the RSM is effective at a certain defined scale with particular equipment [12-13]. However, there are always difficulties of scale-gap and equipment-gap, which are inevitably problematic for manufacturing process development [14]. Because CPPs change 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.

These findings indicate that the manufacturing process development

for oral formulation needs more practical approach that can overcome these difficulties. This study attempts to show the effectiveness of a novel multivariate statistical approach for manufacturing process development for oral formulation executed according to the "QbD" concept that can overcome all of these difficulties.

In Chapter 1, a DoE is applied to overall manufacturing process to conduct a screening study and the three different multivariate statistical analyses are conducted to determine influential causal factors, to find the optimal values for those causal factors and to develop a robust and stable manufacturing process that could achieve the desired performance of the final products with overcoming both the multiobjective optimization problem and the nonlinear problem. As a result, significant process parameters and significant processes, with respect to both the average of the response variables and their variance, were extracted by the conventional multivariate statistical analyses. Also, the optimal levels of process parameters and response variables were determined by mathematical models derived from RSM-S, and their high reliability was confirmed by the BS resampling method and 95% CI, which have overcome both the multiobjective problem and the nonlinear problem.

In Chapter 2, the DoE and the multivariate statistical analyses were conducted not only for a screening study but also for an optimization study to determine the multidimensional relationships among causal factors and response variables considering the multiobjective optimization problem and the nonlinear problem. Furthermore, a novel approach for establishing the design space of manufacturing process for oral formulation was proposed which was using CQAs of intermediate material to overcome scale-gap and equipment-gap. As a result, the DoE and the multivariate statistical analyses

were successfully performed to achieve the purpose of each study, and the design space was successfully obtained by nonlinear response surface model using CQAs of intermediate material using data sets of laboratory and pilot scales which 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.

In conclusion, it was suggested that the proposed novel multivariate statistical approaches are useful tools for efficiently and accurately developing and optimizing manufacturing process for oral formulation and can overcome all of the difficulties of manufacturing process development for oral formulations.

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# REFERENCES


1) International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, "ICH Harmonized Tripartite Guideline Pharmaceutical Development Q8 (R2)," August (2009).

2) Portillo PM, Ierapetritou MG, Tomassone S, Dade CM, Clancy D, Avontuur PPC, Muzzio FJ., J Pharm Innov., **3**, 258–270 (2008).

3) Varshosaz J, Eskandari S, Tabakhian M., Pharmaceut Dev Technol., **15**, 89–96 (2010).

4) am Ende D, Bronk KS, Mustakis J, O'Conner G, Santa Maria CL., J Pharm Innov., **2**, 71–86 (2007).

5) Montgomery D. C., John Wiley & Sons, USA (1997).

6) Lewis G. A., Mathieu D., Phan-Tan-Luu R., Marcel Dekker, New York (1999).

7) Khuri A. I., Cornel J. A., Marcel Dekker Inc. New York (1987).

8) Takayama K., Nagai T., Int. J. Pharm., **74**, 115–126 (1991).

9) Miyamoto Y., Ogawa S., Miyajima M., Matsui M., Sato H., Takayama K., Nagai T., Int J Pharm., **149**, 25–36 (1997).

10) Huang Y. B., Tasay Y. H., Yang W. C., Chang J. S., Wu P. C., Biol Pharm Bull., **27**, 1626–1629 (2004).

11) Takayama K., Morva A., Fujikawa M., Hattori Y., Obata Y., Nagai T., J Control Release, **68**, 175–186 (2000).

12) Huang J., Kaul G., Cai C., Chatlapalli R., Hernandez-Abad P., Ghosh K., Nagi A., Int J Pharm., **382**, 23–32 (2009).

13) Zacour B. M., Drennen III J. K., Anderson C. A., J. Pharm. Sci., **101**, 2917–2929 (2012).

14) Ogawa S., Kamijima T., Miyamoto Y., Miyajima M., Sato H., Takayama K.,

Nagai T., J. Pharm. Sci., **83**, 439–443 (1993).

15) Yano K., Pharm Tech Japan, **22**, 2119–2127 (2006).

16) Takayama K, Obata Y, Morishita M, Nagai T., Pharmazie, **59**, 392–395 (2004).

17) Onuki Y, Morishita M, Takayama K., J Control Release, **97**, 91–99 (2004).

18) Onuki Y, Hoshi M, Okabe H, Fujiwara M, Morishita M, Takayama K., J Control Release, **108**, 331–340 (2005).

19) Nishikawa M, Onuki Y, Isowa K, Takayama K. AAPS Pharm Sci Tech., **9**, 1038–1045 (2008).

20) Arai H, Suzuki T, Kaseda C, Ohyama K, Takayama K. Chem Pharm Bull., **55**, 586–593 (2007).

21) Onuki Y, Ohyama K, Kaseda C, Arai H, Suzuki T, Takayama K., J Pharm Sci., **97**, 331–339 (2008).

22) Kikuchi S, Takayama K., Int J Pharm., **374**, 5–11 (2009).

23) Arai H, Suzuki T, Kaseda C, Takayama K., Chem Pharm Bull., **57**, 572–574 (2009).

24) Onuki Y, Kikuchi S, Yasuda A, Takayama K., Int J Pharm., **396**, 75–82 (2010).

25) Kikuchi S, Takayama K. Int J Pharm., **386**, 149–155 (2010).

26) Myers Rh, Montgomery DC. Wiley Series in Probability and Statistics, New York, NY (1995).

27) Miyamoto Y, Ryu A, Sugawara S, Miyajima M, Matsui M, Yakayama K, Nagai T., Chem Pharm Bull., **46**, 1432–1437 (1998).

28) Sandwell DT., Geophys Res Lett., **14**, 139–142 (1987).

29) Wahba G., Society for Industrial and Applied Mathematics, Philadelphia, PA (1990).

30) 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," November (1995).

31) Norioka T., Kikuchi S., Onuki Y., Takayama K., Imai K., J Pharm Innov., **6**, 157–169 (2011).

32) Obata Y., Ashitaka Y., Kikuchi S., Isowa K., Takayama K., Int J Pharm., **399**, 87–93 (2010).

33) Arai H., Suzuki T., Yada S., Kaseda C., Onuki Y., Takayama K., Chem Pharm Bull., **59**, 608–617 (2011).

34) Hayashi Y., Kikuchi S., Onuki Y., Takayama K., J Pharm Sci., **101**, 333–341 (2011).

35) International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, "ICH Harmonized Tripartite Guideline Quality Risk Management Q9," November (2005).

36) International Electrotechnical Commission, Analysis Techniques for System Reliability: Procedure for Failure Mode and Effects Analysis (FMEA) – International Standard 60812 (2006).