CASE 10

Use of a Dynamic Operating Window for Herbal Medicine Granulation

Abstract: This study applies the dynamic operating window analysis method in granulation technology. The original SN ratio, calculated from $M \times \beta$, was named the speed difference method, whereas the new one, calculated from the ratio of larger-the-better and smaller-the-better characteristics, was called the speed ratio method. In this study, parameter design was used for the granulation of herbal medicines.

1. Introduction

In 1994, Taguchi introduced the dynamic operating windows method for chemical reactions. Since then several applications have been reported. Later, a new analysis method was introduced to combine the larger-the-better and smaller-the-better characteristics, the former representing the main chemical reaction and the latter, side reactions. This new method was based on a practice that no noise factors are assigned for chemical reactions, although side reactions behave as noise to the main reaction.

2. Granulation

Granulation is a universal technology, used widely in various industries, such as fertilizer, food, catalysts, agricultural chemicals, and ceramics. In this study, parameter design was used for the granulation of herbal medicines. There are two types of granulation: dry and wet. Most of the granulation processes for medicines use the wet method. Since this study belongs to upstream technology development and no restrictions were to be followed, laboratory-scale equipment was used, without considering the scale of manufacturing. Instead, efficiency of development was considered the top priority.

Two types of granulation are used to obtain a uniform-particle-size product: either increasing or reducing the particle size. Most cases are of the former type. In fact, the latter is a crushing process and therefore is not described here. This study introduces a granulating process using the speed ratio method based on the concept that fine particles grow by contact in exponential fashion.

In the herbal medicine industry, efforts are being made to develop high-value-added products. Today, the traditional excellence of herbal medicines is reviewed, and further technological advancement through the use of quality engineering is expected. The development of medicines includes research departments to search for new substances; pharmacology departments to study the mechanism of medical effects, side effects, or the safety of medicines, and product planning departments. Once a product is designed and reaches the stage of production engineering, its engineering approaches are almost identical to those in other manufacturing industries.

In this case, evaluation of the granulating function is described from the quality engineering viewpoint. Granulation is an important process in the pharmaceutical industry to pretreat raw material or produce an objective product shape, such as granules. There are Japanese Pharmacopoeia regulations regarding particle-size distribution for

medicines, and it is desirable to produce a medicine with uniform particle-size distribution and high yield.

3. Basic Reaction Theory

To correspond to chemical reactions from the viewpoint of quality engineering, an example of dissolution of a substance is used for explanation. When a reaction progresses,

$$aA + bB + \cdots \longrightarrow pP + qQ + \cdots \qquad (1)$$
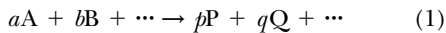
its reaction speed is given by

$$V = k[A]^a[B]^b \qquad (2)$$

The total of exponents of concentration of reacting substances A, B, ... , denoted by $a + b + \cdots = n$, is called *order*. V, the speed of A being dissolved and B increased, is expressed as

$$V = -\frac{dA}{dt} = \frac{dB}{dt} = k[A][B] \qquad (3)$$

It changes by the concentration of A and B.

There are different types of reactions: zeroth-, first-, and second-order reactions. Different order reactions are used depending on the subject being discussed. In quality engineering, only one type (e.g., first order) is considered. For example, let the concentration of substance A be denoted by [A]. In the case of a first-order reaction, the speed of A reacting to become P is given by

$$-\frac{d[A]}{dt} = k[A] \qquad (4)$$

Letting the initial concentration of A be $[A_0]$,

$$\ln[A] = -kt + \ln[A_0] \qquad (5)$$
$$[A] = [A_0]e^{-kt} \qquad (6)$$
$$-\ln \frac{[A]}{[A_0]} = kt \qquad (7)$$

Therefore, [A] decreases exponentially.

For second-order reactions, a reaction speed of A = B $\cdots$ P is

$$-\frac{d[A]}{dt} = -\frac{d[B]}{dt} = k[A][B] \qquad (8)$$

Letting the initial concentration of A and B be $[A_0]$ and $[B_0]$, respectively,

$$\frac{1}{[A_0] - [B_0]} \ln \frac{[B_0][A]}{[A_0][B]} = kt \qquad (9)$$

One can therefore derive a zero-point proportional equation of concentration and time for any first- or second-order equations, as shown in equations (7) and (9). The following discussion is based on a first-order reaction.

There are many parameters in a chemical reaction, such as pH, diffusion speed, or surface area. In scientific research, these parameters are put into equations. But in quality engineering, these are considered as noise factors because it would be ideal if the reaction were not affected by the effects of outer noise, such as temperature or pH. Since a reaction can be discussed at the molecular level, equations that describe phenomena exactly are not necessary.

Let's expand the concept of molecular collision. One mole of a substance includes 6.0231023 molecules. A generic function can be established to express a reaction between single molecules. Letting β be a constant, Y_0 the initial concentration (100%), Y the concentration after dissolving, and Y/Y_0 the fraction of reduction, the reaction is expressed by

$$\frac{d(Y/Y_0)}{dt} = \beta \left(1 - \frac{Y}{Y_0}\right) \qquad (10)$$

Equation (10) is described simply as the relationship between the fraction of reduction of concentration and time. Since the equation essentially expresses the function only, one may judge the equation to be insufficient. But that is the difference between science and engineering.

Let the left side of equation (15.11) be p_0 and solve the equation:

$$1 - \frac{Y}{Y_0} = e^{-\beta t} \qquad (11)$$

$$p = 1 - \frac{Y}{Y_0} \qquad (12)$$

$$-\ln p_0 = \beta t \qquad (13)$$

Rewriting $-\ln p_0$ as y_1, the following generic function is derived.

$$y_1 = \beta t \qquad (14)$$

4. Generic Function

Figure 1 shows the fluidized-bed granulating equipment used in this experiment. Powder is fed into the chamber and heated air is blown from the bottom to fluidize powder. While the particles continue to keep contact with each other, a liquid containing binder is sprayed to make the particles grow. The granulated particles sink by weight; the light particles flow up in the air and continue granulation. The process ends when the blowing air stops. Like the case of spray drying, it is difficult to balance heat energy and blowing energy by adjusting the temperature, liquid feeding speed, or air-blowing speed. Parameter design is an effective approach in these cases.

The growing mechanism in fluidized-bed granulation can be considered in the same way as a chemical reaction that follows exponential function. Letting the fraction of reduction of powder be y_2 and time be t,

$$y_2 = 1 - e^{-\beta t} \qquad (15)$$

Thus, it is ideal that the fine particles in the chamber decrease following equation (15).

Among many available granulating methods, a laboratory-scale fluidized-bed granulating device was selected using about 100 g of powder to conduct one run of the experiment. It was low in cost and easy to operate. The device was small and could be put on a table, as shown in Figure 1. Air was blown from the bottom of the chamber to cause the pow-

der to mobilize and make contact. Binder was sprayed in a mist to keep the powder particles in contact, in which state they grow gradually. An important condition for granulation is to balance the energy of air blowing force and energy of heat to evaporate moisture. The conditions have been determined by experience and accumulated experimental results. In this study we tried to determine the conditions using parameter design.

5. Experimental Design

An L_{18} orthogonal array was used for the experiment. The factors and levels are given in Table 1. Particle size distribution was measured by the screening method shown in Figure 2.

6. Speed Ratio Method

Smaller-the-Better, Larger-the-Better, and Dynamic Operating Window

Since a chemical reaction occurs by collision, it is assumed that the collision in granulation follows equation (15). In the speed difference method of dynamic operating windows, the SN ratio, η^*, and sensitivity, S^*, are calculated from the $S_{M\beta}$ value of the principal and side reactions. The speed ratio method involves increasing the granulating speed, β_1, and reducing the growing speed of coarse particles, β_2. The former corresponds to p, the unreacted part, and the latter correspond to q, the
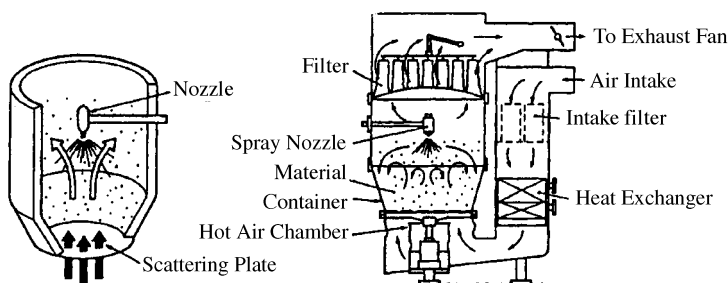
Figure 1
Fluidized-bed granulation equipment

Table 1
Factors and levels

	Control Factor	Level		
		1	2	3
A:	position of spray nozzle	Close	Far	
B:	concentration of binder	Standard	Slightly high	High
C:	amount of herbal extract supplied	Small	Standard	Large
D:	air flow	Small	Standard	Large
E:	nozzle spray pressure	Low	Standard	High
F:	air temperature	Low	Standard	High
G:	amount of fluidity assisting agent	Small	Standard	Large
H:	flow of binding liquid	Small	Standard	Large

overreacted part in Figure 3. In other words, we tried to maximize the operating window, $1 - p - q$.

Since the generic function is expressed by $y_2 = 1 - e^{-\beta t}$:

Unreacted part: $q = e^{-\beta t}$

$$\beta_1: \quad \text{larger-the-better} \qquad (16)$$

Overreacted part: $1 - p - e^{-\beta t}$

$$\beta_2: \quad \text{smaller-the-better} \qquad (17)$$

Over No. 12 sieve (diameter 1400 mm):

overreacted (*p*), coarse

Between No. 12 and No. 42 sieve (diameter 1400 to 355 mm):

target $(1 - p - q)$

Under No. 42 sieve (diameter 355 mm):
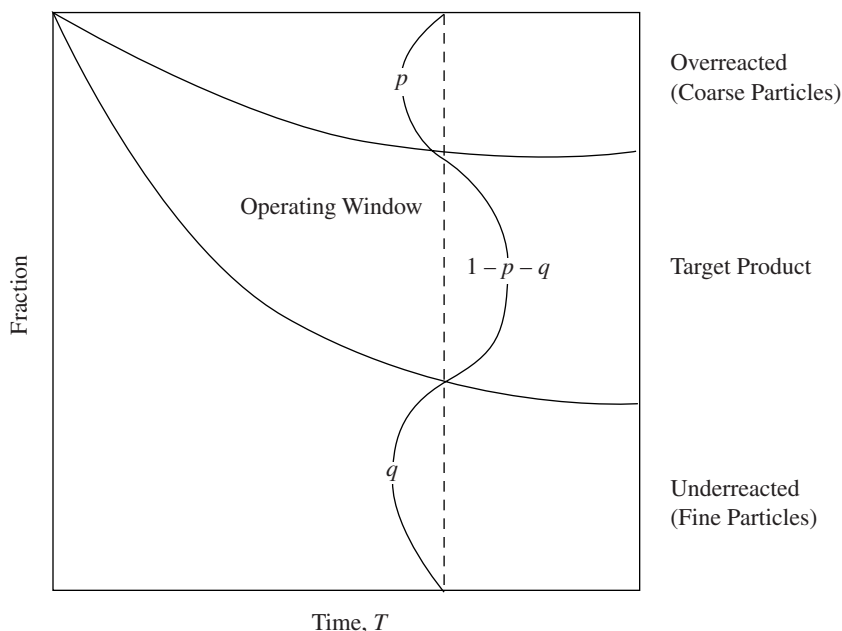
underreacted (*q*), fine

According to product specification, the portion over a No. 12 sieve must be less than 5%, and the portion under a No. 42 sieve must be less than 15%.

Signal and Noise Factors

Three points of time, *T*, were set as signal factor levels to take samples. Among the three points, the two where reaction took place faster were selected

Figure 2
Specification of particle size

Figure 3
Dynamic operating window threshold (specification of particle size)

for calculation. This is because the fraction of the reacted part can be measured more precisely in the neighborhood of 50%. Noise factors were not assigned, considering the efficiency of the study. This was based on the thought that side reactions behave as noise.

7. SN Ratio and Sensitivity

Measuring the fractions of unreacted part (q) and overreacted part (p) at time T, reaction speeds β_1 and β_2 were calculated.

$$\beta_1 = \frac{1}{T} \ln \frac{1}{q} \tag{18}$$

$$\beta_2 = \frac{1}{T} \ln \frac{1}{1 - p} \tag{19}$$

$$\eta_1 = -10 \log \frac{1}{\beta_1^2} \tag{20}$$

$$\eta_2 = -10 \log \beta_2^2 \tag{21}$$

The speed ratio method is to maximize $\eta_1 = \eta_1 + \eta_2$ as the SN ratio.

$$\textit{SN ratio:} \quad \eta = \eta_1 + \eta_2 \tag{22}$$

$$\textit{Sensitivity:} \quad S = 10 \log \beta_1^2 \tag{23}$$

Sensitivity, S, reflects reaction speed. Examples of calculation are shown in Tables 2 and 3 for cases demonstrating progress and no progress, respectively. As mentioned previously, two points were measured. The results in the tables are calculated from the average β^2 from the two points.

From Figures 4 and 5, the optimum configuration was determined as $A_2B_2C_1D_3E_3F_3G_3H_2$. As described later, A_1B_1 was used for the confirmatory experiment instead of A_2B_2. The initial condition was $A_2B_2C_2D_2E_2F_2G_2H_2$. Condition H_2 was selected as the optimum after taking sensitivity into consideration.

Table 2
Calculation of experiment 13: granulation progressed[a]

	Time	
Reaction	**T_1 (25 min)**	**T_2 (40 min)**
Overreacted substance p	0.0060	0.0099
Target substance $1 - p - q$	0.0930	0.0960
Underreacted substance q	0.9010	0.8941
	After Conversion	
	T_1	**T_2**
Overreacted substance p (β_2)	0.0002423	0.002488
Underreacted substance q (β_1)	0.0041715	0.0027974

[a] The results are $\eta_1 = -49.67$ dB, $\eta_2 = 72.20$ dB, $\eta = 22.53$ dB, and $S = -49.67$ dB.

8. Confirmatory Experiment and Improvement

Table 4 shows the results of optimum conditions using the data of one point. If the entire reaction is stable, analysis may be made from one point only. For the confirmatory experiment, condition $A_1B_1 C_1D_3E_3F_3G_3H_2$ was used, which is the optimum SN ratio condition selected from the smaller-the-better characteristic.

Under optimum conditions, the fraction of targeted particle size was high with a small fraction unreacted. The SN ratio was slightly lower, due to a larger overreaction portion (side reaction). In the confirmatory experiment, a gain of 20.86 dB was obtained, which is seen by a comparison of the particle-size distribution. As shown in Figure 6, nearly 80% was unreacted (i.e., fine particles) under the initial conditions. But under the optimum conditions, over 80% was targeted product.

In the confirmatory experiment, the SN ratio of the speed ratio increases, so that the reaction speed increases. But observing the particle-size distribution shown in Figure 7, it appears that the distributions of the two cases were not really very different; only the center of the distribution was shifting. In such a case, it is better to compare both after adjusting the center of distribution. But from the viewpoint of granulation, it looks as if the growth of particles is being hindered due to an im-

Table 3
Calculation of experiment 8: granulation did not progress

|		Level		
Control Factor		**1**	**2**	**3**
A:	position of spray nozzle	Close	Far	—
B:	density of binder	Standard	Slightly high	High
C:	amount of herbal essence supplied	Small	Standard	Large
D:	amount of air flow	Small	Standard	Large
E:	spraying pressure	Low	Standard	High
F:	temperature of heated air	Low	Standard	High
G:	amount of fluidity agent	Small	Standard	Large
H:	amount of binder supplied	Small	Standard	Large
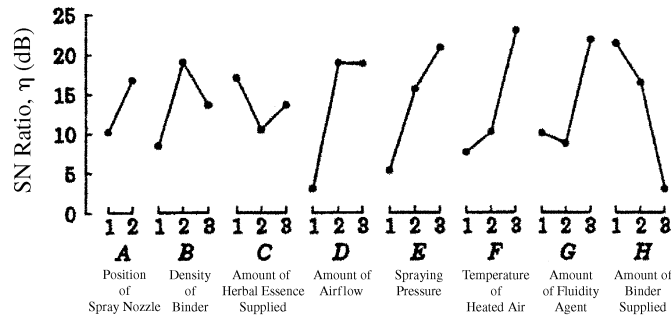
Figure 4
Response graphs of SN ratio
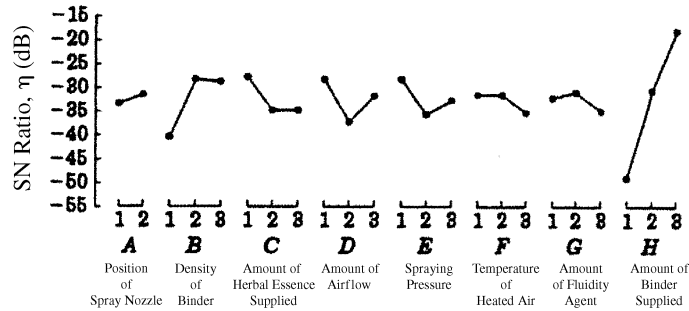
Figure 5
Response graphs of sensitivity

Table 4
Results of optimum configuration

	Time
Reaction	**(37 min)**
Overreacted substance p	0.0539
Target substance $1 - p - q$	0.7494
Underreacted substance q	0.1967
	After Conversion
Overreacted substance (β_1)	0.0014978
Underreacted substance (β_2)	0.0439504

[a] The results are $\eta_1 = -27.14$ dB, $\eta_2 = 56.49$ dB, $\eta = 29.35$ dB, and $s = -27.14$ dB.

balance of evaporation, heat, and airflow, so that it would be difficult to adjust the center to one functioning under optimum conditions, even spending a longer time. This is probably the reason that the SN ratios in Table 5 do not agree. In this regard, calculations were made to estimate the time necessary to move the center of distribution toward that under optimum conditions (the data for the initial conditions are given in Table 6):

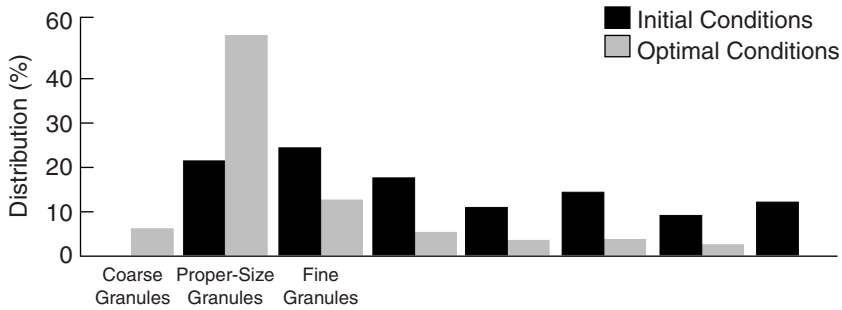$$\beta_{opt} = \frac{\beta_1 + \beta_2}{2} = 0.02272 \qquad (24)$$

$$\beta_{initial} = \frac{\beta_1 + \beta_2}{2} = 0.002545 \qquad (25)$$

$$y = \beta_{opt}\, T = \beta_{opt}\,(37) = 0.8406 \qquad (26)$$

The time corresponds to the center of the initial conditions:
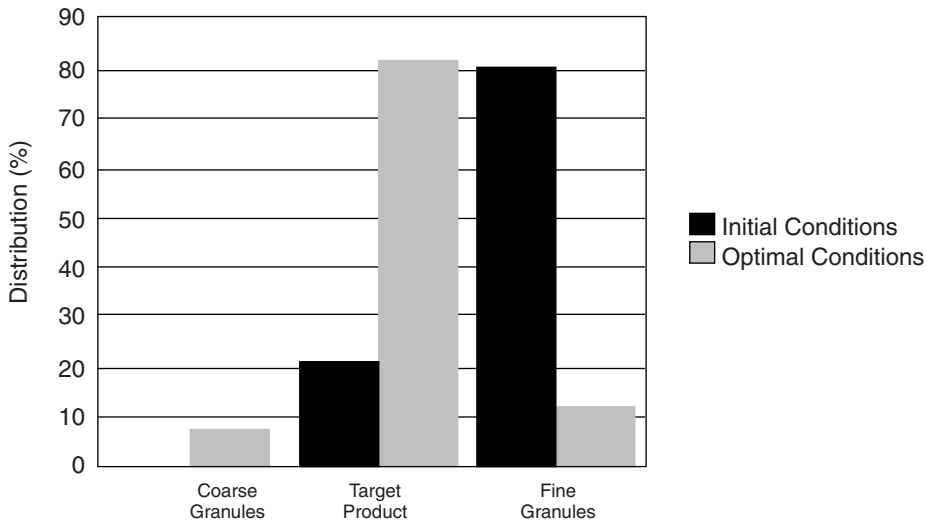
Figure 6
Granule-size distribution before and after optimization

Figure 7
Improved granule-size distribution before and after optimization

$$0.8406 = 0.002545T$$

$$T = 330 \text{ min} \qquad (27)$$

The SN ratio calculated for the initial conditions is

$$\eta_{\text{initial}} = 10 \log \frac{\beta_1^2}{\beta_2^2} = 10 \log \frac{0.003701^2}{0.01388^2}$$

$$= 8.52 \text{ dB} \qquad (28)$$

It is therefore necessary to maintain 330 minutes in order to shift the center of distribution. It seems from past experience, however, that excess reaction

Table 5
Gain of SN ratio from confirmatory experiment (dB)

	Configuration		
	Initial	Optimal	Gain
Estimation	13.78	41.11	27.33
Confirmation	8.49	29.35	20.86

Table 6
Data on initial conditions

Reaction	Time		
	T_1 (10 min)	T_2 (20 min)	T_x (? min)
Overreacted substance p	0.0001	0.0385	0.3675
Target substance $1 - p - q$	0.0258	0.4671	0.3377
Underreacted substance q	0.9741	0.4944	0.2948
	After Conversion		
	T_1	T_2	Average
Overreacted substance p (β_2)	0.00001	0.001963	0.001388
Underreacted substance q (β_1)	0.002624	0.03522	0.003701

Table 7
SN ratio of the smaller-the-better characteristic (dB)

No.	Item[a]			SN Ratio
	Particle Size	Fluidity	Cohesion	
1	△	○	△	−4.7
2	△	△	△	−6.0
3	○	○	○	0.0
4	X	X	X	−9.5
5	△	○	○	−3.0
6	X	X	X	−9.5
7	△	X	X	−8.7
8	△	○	○	−3.0
9	○	X	△	−6.7
10	△	○	○	−3.0
11	○	△	X	−6.7
12	△	X	X	−8.6
13	○	○	○	0.0
14	X	X	X	−9.5
15	△	○	○	−3.0
16	△	△	△	−6.0
17	X	X	X	−9.5
18	△	△	△	−6.0

[a] If ○, score = 1. If △, score = 2. If X, score = 3.

time gives excess contact energy to particles, causing the crashing of particles and thus the production of fine particles. But it is interesting to see that the results calculated agree with those obtained by the speed ratio method.
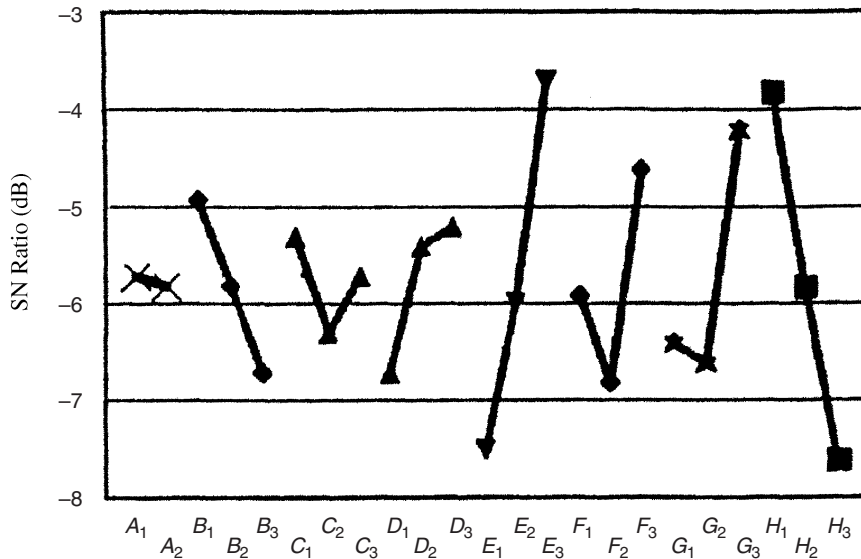
9. Smaller-the-Better SN Ratio Using Scores

Because of time restrictions, an attempt was made to estimate the optimum conditions by eyeball observation of the results instead of using particle-size distribution. Qualitative scores were given by observing items such as particle size, fluidity, and cohesion, with the smaller-the-better SN ratio being used for evaluation:

$$\eta = -10 \log \sigma^2 \qquad (29)$$

This simple method is not quantitative. But to our surprise, the condition determined from this method was close to the optimum conditions using the speed ratio method. The items observed, such as particle size, fluidity, and cohesion, are phenomena in the process of granulation rather than objective characteristics. The dynamic operating window is, of course, a quantitative and more precise method.

For example, the SN ratio of row 1 is calculated as

Figure 8
Response graphs of the smaller-the-better SN ratio

$$\eta = -10 \log \frac{2^2 + 1^2 + 2^2}{3} = -4.7 \text{ dB} \quad (30)$$

Table 7 shows the scores and SN ratios of 18 rows. The confirmatory experiment described in the preceding section was conducted using the optimum conditions of the smaller-the-better SN ratio of scored data instead of using the conditions selected from the speed ratio method: The former used condition A_1B_1 and the latter, A_2B_2. However, this is not a problem.

The optimum condition selected from the response graph of Figure 8 was $A_1B_1C_1D_3E_3F_3G_3H_2$, and the estimated score was about the same, showing good reproducibility. The SN ratios from the speed ratio method and the score were close to each other. It is probably because granulation becomes saturated as time passes, so the particle-size distribution after saturation is proportional to the initial granulating speed, β.

10. Conclusions

Use of the dynamic operating window in conjunction with the speed ratio method applied to gran-

ulation has been described in contrast with the existing dynamic operating window. It is a new concept, combining the smaller-the-better and larger-the-better characteristics instead of using $M\beta$ as the signal. The new approach is not only simpler but makes it possible to reduce the number of samples to be used. The existing method requires at least three data points for analysis, and in the case of incomplete data, sequential analysis has to be used for estimation.

In this granulation study, the reaction progressed rapidly and coagulated in some of the experimental runs, and size distribution could not be measured. But the possibility of analysis from even a single data point opens up critical areas in chemical reactions.

Reference

Kouya Yano, Masataka Shitara, Noriaki Nishiuchi, and Hideyuki Maruyama, 1998. Application of dynamic operating window for Kampo medicine granulation. *Quality Engineering*, Vol. 6, No. 5. pp. 60–68.

This case study is contributed by Kouya Yano.