Regular Article

Application of Response Surface Methodology to Estimate the Design Space of Pharmaceutical Diluents for Dispensing Powdered Formulations

Yasunori Miyazaki,*a Kozo Takayama,b Tomonobu Uchino,a and Yoshiyuki Kagawaa

aDepartment of Clinical Pharmaceutics, School of Pharmaceutical Sciences, University of Shizuoka; 52–1 Yada, Suruga-ku, Shizuoka 422–8526, Japan: and bDepartment of Pharmaceutics, Hoshi University; 2–4–41 Ebara, Shinagawa-ku, Tokyo 142–8501, Japan.

Received July 6, 2016; accepted September 29, 2016

To ensure the quality of drugs and efficacy of drug treatments, scientific methods must shift from the manual empirical method to a mechanical one even in the case of extemporaneous dispensation. It has been reported that powdered drugs dispensed according to the same recipe showed different efficacies depending on the pharmacist who dispensed the drugs.1) This limitation is the result of dispensing procedures, including powder blending. Therefore, we have proposed a powder blending method using a planetary centrifugal mixer (PCM) instead of the manual method involving a mortar and pestle.2) Recently, Saito et al. reported that PCM was the most appropriate method for the preparation of low-dose tacrolimus because of efficiency and consistent quality.3) PCM is a container mixer without any agitators.4) The closed container rotates while it revolves in the mixer, resulting in more powerful mixing. PCM was well established as an ointment mixer, and was introduced to many pharmacies. Furthermore, Miyazaki et al. have applied PCM to dry-powder coatings with fine particles.5) With PCM, the degree of blending is not influenced by operators who have different technical abilities. In addition, cross-contamination is avoided when a disposable counter is used.6) Powdered medicines are frequently used for small children. When the therapeutic dose of drug is low, the amount of the powdered medicine dispensed is small. Then, pharmaceutical inactive agents are added to the powdered medicine as diluents for a precise dispensation. In practice, powdered lactose, crystalline lactose, potato starch, and corn starch have been used as typical diluents. Moreover, adequate mixtures of the above-mentioned diluents have also been used. However, the selection of these has been based on the experience of pharmacists. To obtain the optimal formulation of pharmaceutical diluents, a statistical technique is required, such as the design of experiment (DOE) method. Overall, currently, diluted powdered drugs include: i) powdered formulations, ii) the contents of capsules, and iii) crushed tablets. Capsules are opened and tablets are crushed frequently for various reasons, such as ensuring the correct medication with the desired dose is administered when the formulations with the required strength are not available, and making large tablets swallowable.7,8) Therefore, it is necessary to investigate the optimal formulation of pharmaceutical diluents for each case.

The critical quality attribute when dispensing drugs composed from medicines and diluents is the uniformity of the drug content. In general, the content uniformity is presented as the relative standard deviation (RSD) of the drug content. In the case of dispensation, it is recommended that RSD is smaller than 6.08%.9) In addition, the ease-of-handling is also important when dispensing powdered drugs, and is evaluated in terms of flowability, adhesiveness, fluidity, and so on. Among these properties, flowability is the most important factor in the process of blending powder. Therefore, the angle of repose (AOR) was selected as a secondary marker of quality attributes in this study. Thus, the mixture with a smallest RSD and AOR was defined as the optimal diluent.

The aim of this study was to establish a design space of diluents for the PCM blending method, using the DOE and response surface methodology (RSM). The DOE used here

© 2016 The Pharmaceutical Society of Japan
consisted of a one-mixture process design with three components, e.g. a \([3,2]-\text{Simplex Lattice} \) design and 3-level blending process. At each level, the composition of mixtures was optimized to obtain the formulation with the smallest RSD and AOR. Then, the design spaces of desired diluents for each level were combined to select a common formulation of the diluent for all levels. Finally, we applied the typical formulations selected from the design space to other medicines to confirm their adequacy.

**Experimental**

**Materials** Crystalline lactose, powdered lactose, and corn starch (Mylan Seiyaku Co., Ltd., Tokyo, Japan) were selected as diluents because they are generally used for dispensation. Adona\(^\text{a}\) powder-10\% (carbazochrome sodium sulfonate hydrate, Tanabe-Mitsubishi Pharma Co., Osaka, Japan), Anginal\(^\text{b}\) powder-12.5\% (dipyridamole, Choseido Pharmaceutical Co., Ltd., Tokyo, Japan), and Pontal\(^\text{c}\) powder-50\% (mefenamic acid, Daiichi-Sankyo Co., Ltd., Tokyo, Japan) were obtained to use as model powder formulations. Rifadin\(^\text{b}\) capsules (rifampicin, Daiichi-Sankyo Co., Ltd., Tokyo, Japan), Dantrium\(^\text{b}\) capsules (dantrolene sodium hydrate, Astellas Pharma Inc., Tokyo, Japan), Mexitil\(^\text{b}\) capsules (mexiletine hydrochloride, Nippon Boehringer-Ingelheim Co., Ltd., Tokyo, Japan), Salazopyrin\(^\text{b}\) tablets (Salazosulfapyridine, Pfizer Co., Ltd., Tokyo, Japan), Prednisolone\(^\text{b}\) tablets (Shionogi Co., Ltd., Osaka, Japan), and Longes\(^\text{b}\) tablets (Lisinopril hydrate, Shionogi Co., Ltd., Osaka, Japan) were obtained and used as model medicines. All other reagents were of analytical or HPLC grade.

**Preparation of Diluents** Crystalline lactose, powdered lactose, and corn starch were mixed using a mortar and pestle according to the DOE points as described below.

**Powder Blending** Blending of model medicines and diluents was carried out using a planetary centrifugal mixer (NR-500, Thinky Co., Ltd., Tokyo, Japan) at weight ratios of 1:4, 1:1, and 4:1. Weighted powders (total weight: 5 g) were poured into the vessel (cylindrical container, UG35mL, Umano Chemical Container Co., Ltd., Osaka, Japan), and the vessel was closed with a lid (filling rate: about 25\%). Subsequently, the vessel was set in the mixer with a fitting adaptor. The mixer was operated at the speed of 800 rpm for 60 s. The ratio of revolution and rotation was fixed at 1:1. Before blending, capsule formulations were opened, and capsule formulations were sifted through the sieve (30 \(\mu\)m openings). Tablet formulations were crushed using a mill (Labo-Milser plus, Osaka Chemical Co., Ltd., Osaka, Japan) at the speed of 20000 rpm for 15 s. Then, the resultant powder was sifted through the sieve.

**Experimental Design** A mixture and process design was employed to define the design space of suitable pharmaceutical diluents, for the dispensation accompanied with powder blending. A Simplex Lattice mixture design for 3 components with 2 levels is shown in Fig. 1. The amounts of powdered lactose \((X_1)\), crystalline lactose \((X_2)\), and corn starch \((X_3)\) were selected as independent variables. The lower and upper limits of the levels of components were set as follows:

\[
0 \leq X_1, X_2, X_3 \leq 1
\]  

Then, the blending ratio of the model medicines and diluents was set at 1:4, 1:1, and 4:1, for the one-process design for 3 levels. The resultant mixtures were used for the evaluation of suitability. Content uniformity (RSD, \(Y_1\)) and flowability (AOR, \(Y_2\)) of the mixtures were selected as the dependent variables.

**Determination of Content Uniformity** Five samples from the mixture were analyzed for the content of drug using the color difference signal method or HPLC method. The sample was spread over a powder paper (10×10 cm), and then the images (8.2×6.1 mm) of the sample were taken at five different points. For HPLC method, a 100-mg of the sample was taken from five different points using a spatula. The average \((M)\) and standard deviation (S.D.) of the values were calculated. Then, RSD was obtained from the following equation:

\[
RSD = \frac{\text{S.D.}}{M} \times 100(\%)
\]

The color difference signal method was carried out according to a previous report, and the color difference signal was used as an indicator of the content of colored medicines, such as Adona\(^\text{a}\) powder, Anginal\(^\text{b}\) powder, Rifadin\(^\text{b}\) capsule, Dantrium\(^\text{b}\) capsule, and Salazopyrin\(^\text{b}\) tablet. The images of the mixtures were taken with a microscope (M3, Scalar Co., Ltd., Tokyo, Japan) equipped with a lens (30N, magnification of thirty times), and were analyzed using ImageJ (ver. 6, National Institute of Health, Washington, D.C., U.S.A.).

HPLC methods were performed according to previous reports. The HPLC system was composed of a pump (LC-10AS; Shimadzu Co., Kyoto, Japan), an auto-injector (SIL-10A, Shimadzu Co.), a UV detector (SPD-10A, Shimadzu Co.), an analysis system (Smart Chrom, KYA TECH Co., Tokyo, Japan), and a column. A C8 column (COSMOSIL 5C8-MS, 5 \(\mu\)m, 4.6×150 mm; Nacalai Tesque, Kyoto, Japan) was used for the analyst (C18 column (TSKgel ODS-100V, 3 \(\mu\)m, 4.6×150 mm, Tosoh Co., Tokyo, Japan) was used for the other drugs. The wavelengths were 279, 262, 241, and 225 nm for mefenamic acid, mexiletine hydrochloride, prednisolone, and lisinopril hydrohydrate, respectively.

**Measurement of AOR** According to the Japanese Pharmacopoeia 16th edition, the AOR was determined from the
circular conic formed on a cylinder (20 mm in diameter). The angle was then measured directly.

**Simultaneous Optimization and Estimation of the Design Space for Desired Diluents Formulation Using RSM**

The amounts of powdered lactose ($X_1$), crystalline lactose ($X_2$), and corn starch ($X_3$) were selected as independent variables in this study. RSD ($Y_1$) and AOR ($Y_2$) were taken as responses. In order to predict the response variables, $F(X)$, we used a special cubic model as presented by the following canonical equation:

$$F(X) = \sum_{i=1}^{q} b_i X_i + \sum_{j=1}^{q} b_{ij} X_i X_j + \sum_{i<j<k}^{q} b_{ijk} X_i X_j X_k$$  \hspace{1cm} (4)

where $b_i$, $b_{ij}$, and $b_{ijk}$ represent the regression coefficients of each monomial. That is, $b_i$ is the coefficient for the factor $X_i$. The main effects ($X_1$, $X_2$, and $X_3$) represent the result of changing one factor at a time from its low to high value. The interaction terms ($X_1 X_2$, $X_1 X_3$, $X_2 X_3$, and $X_1 X_2 X_3$) show the changes of the response when two or more factors are simultaneously changed. Thus, the special cubic model is desirable when evaluating the importance of the interaction terms in a Simplex Lattice mixture design. Statistical significance of a special cubic model was analyzed by using SPSS (ver.22.0, SPSS Inc., Chicago, U.S.A.). The model was expressed by the polynomial regression equation using main effects and the interaction terms selected by stepwise backward regression method. The suitability of the model was evaluated, using statistical quantities such as a coefficient of determination ($R^2$), a residual mean squared error (RMSE), and a variance ratio of regression to the error ($F$ value). The response surface plots were generated using Design Expert software (ver.10, State-Ease Inc., Minneapolis, U.S.A.) to graphically demonstrate the influence of each factor on responses. The optimal solution was estimated, using desirability functions. 16) The approach was to convert each response, $Y_i$, into an individual desirability function, $d_i$, which varied over the range:

$$0 \leq d_i \leq 1$$  \hspace{1cm} (5)

where if the response $Y_i$ was at its goal, then $d_i=1$, and if the response was outside an acceptable region, $d_i=0$. Then the design variables were chosen to maximize the overall desirability, $D$:

$$D = (d_1 \times d_2 \times \ldots \times d_n)^{1/n}$$  \hspace{1cm} (6)

where $n$ represents the number of responses. In this study the desirability came into line with minimization of both RSD and AOR so that $d$ was defined as:

$$d = \begin{cases} 1, & Y < T \\ \left( \frac{U-Y}{U-T} \right), & T \leq Y \leq U \\ 0, & Y > U \end{cases}$$  \hspace{1cm} (7)

where, $T$ and $U$ were the target and the upper limit of the response $Y$, respectively.

The desired design space of the diluent formulation was defined as the area where the RSD was smaller than 6.08% and the AOR was smaller than that of model medicine used or 45°. The areas were obtained at each blending ratio of 1:4, 1:1, and 4:1, and then combined to establish a common design space available to all blending ratios.

**Evaluation of Reliability of Typical Diluent**

A typical diluent formulation was selected from the suitable design space in each case. According to the formulations, crystalline lactose, powdered lactose, or corn starch were mixed using a mortar and pestle. Thereafter, the typical diluents were used for the dispensation of other medicines at the blending ratios of 1:4, 1:1, and 4:1. Dry powder blending was conducted using a PCM at 800 rpm for 60s. The RSD and AOR of the dispensed drugs were then evaluated, as described above.

**Results**

**Flowability of Diluents**

All diluent formulations designed by DOE were examined for their AOR before the blending process. The results are summarized in Table 1. Among them, the diluent coded No. 2, made of crystalline lactose alone, shows the smallest AOR, 43°, which is consistent with the manufacturer’s information. 17) When the AOR is smaller than 45°, it is considered to have an acceptable flowability for the dispensing process. 18) The AOR of the other diluents showed low or relatively low flowability. However, in general practice, some of them are actually used for dispensation. Then, the diluents were blended with model medicines using a PCM. The RSD and AOR dispensed mixtures were examined.

**Statistical Analysis**

The obtained experimental data were statistically analyzed by multiple regression analysis based on a special cubic model. The main factors ($X_1$, $X_2$, and $X_3$) were always remained in the regression equation irrespective of statistical significance, and their interaction terms ($X_1 X_2$, $X_1 X_3$, $X_2 X_3$, and $X_1 X_2 X_3$) were remained in the regression equation when the $p$ (risk ratio) value was less than 0.05. The ANOVA was also utilized to evaluate the statistical significance of special cubic models. The statistical quantities calculated by SPSS software are summarized in Tables 2 and 3.

According to Table 2, in many cases only one or two main factors were observed to be significant. The interaction terms rarely influenced RSD. This was because that RSD slightly varied within narrow interval, indicating that sufficient blending was already done in almost all cases. Nevertheless, statistical quantities such as $R^2$, RMSE and $F$ values suggested a highly significant result of relevant models, implying sufficient prediction accuracy of the response. On the other hand, referring to Table 3, not only the main factors but also the interaction terms were significantly remained in many cases. It ap-

| Code No. | X1   | X2   | X3   | AOR (°) |
|---------|------|------|------|---------|
| 1       | 1.00 | 0.00 | 0.00 | 55.9±3.8 |
| 2       | 0.00 | 1.00 | 0.00 | 43.0±0.5 |
| 3       | 0.00 | 0.00 | 1.00 | 55.3±1.5 |
| 4       | 0.50 | 0.50 | 0.00 | 53.3±1.1 |
| 5       | 0.50 | 0.00 | 0.50 | 57.6±1.8 |
| 6       | 0.00 | 0.50 | 0.50 | 54.5±0.9 |
| 7       | 0.33 | 0.33 | 0.33 | 55.3±1.8 |
### Table 2. Multiple Regression Analysis and ANOVA for RSD

| Factor | Adona® powder | Rifadin® capsules | Salazopyrin® tablets |
|--------|---------------|-------------------|----------------------|
|        | 20% | 50% | 80% | 20% | 50% | 80% | 20% | 50% | 80% |
| $X_1$  | 4.448 | 0.081 | 4.468 | 0.048* | 2.247 | 0.062 | 2.326 | 0.051 | 2.406 | 0.017* | 1.453 | 0.116 | 5.307 | <0.001** | 4.193 | 0.050 | 6.302 | 0.034* |
| $X_2$  | 1.994 | 0.358 | 4.136 | 0.067 | 2.179 | 0.068 | 2.234 | 0.057 | 1.41 | 0.083 | 2.121 | 0.043* | 4.101 | 0.001** | 3.708 | 0.053 | 4.990 | 0.067 |
| $X_3$  | 8.627 | 0.011* | 6.672 | 0.016* | 4.899 | 0.005** | 3.710 | 0.012* | 1.522 | 0.068 | 3.049 | 0.014* | 6.053 | <0.001** | 3.677 | 0.068 | 4.082 | 0.110 |
| $X_1X_2$ | 22.43 | 0.043* |                     |                     |                     |                     |                     |                     |                     |                     |                     |                     |                     |                     |                     |                     |
| $X_1X_3$ |                     |                     |                     |                     |                     |                     |                     |                     |                     |                     |                     |                     |                     |                     |                     |
| $X_2X_3$ |                     |                     |                     |                     |                     |                     |                     |                     |                     |                     |                     |                     |                     |                     |                     |
| $X_1X_2X_3$ |                     |                     |                     |                     |                     |                     |                     |                     |                     |                     |                     |                     |                     |                     |                     |
| $R^2$  | 0.904 | 0.922 | 0.942 | 0.929 | 0.912 | 0.920 | 0.998 | 0.970 | 0.888 | 1.921 | 1.652 | 0.876 | 0.845 | 0.612 | 0.725 | 0.304 | 1.445 | 2.429 |
| RMSE   | 12.508 | 15.706 | 21.617 | 17.317 | 13.772 | 15.318 | 306.799 | 24.596 | 10.560 |                     |                     |                     |                     |                     |                     |                     |                     |
| $F$    |                     |                     |                     |                     |                     |                     |                     |                     |                     |                     |                     |                     |                     |                     |                     |                     |

Factors were shown in Fig. 1. $b$: regression coefficient, $p$: risk ratio (* $p < 0.05$, ** $p < 0.01$), $R^2$: coefficient of determination, RMSE: residual mean squared error, $F$: variance ratio.

### Table 3. Multiple Regression Analysis and ANOVA for AOR

| Factor | Adona® powder | Rifadin® capsules | Salazopyrin® tablets |
|--------|---------------|-------------------|----------------------|
|        | 20% | 50% | 80% | 20% | 50% | 80% | 20% | 50% | 80% |
| $X_1$  | 48.676 | <0.001** | 49.111 | <0.001** | 42.215 | <0.001** | 52.407 | <0.001** | 48.558 | <0.001** | 50.395 | <0.001** | 56.437 | <0.001** | 55.393 | <0.001** | 51.953 | <0.001** |
| $X_2$  | 38.545 | <0.001** | 37.546 | <0.001** | 30.286 | <0.001** | 43.981 | <0.001** | 44.962 | <0.001** | 50.230 | <0.001** | 47.710 | <0.001** | 50.454 | <0.001** | 50.453 | <0.001** |
| $X_3$  | 44.830 | <0.001** | 44.043 | <0.001** | 35.461 | <0.001** | 55.842 | <0.001** | 53.694 | <0.001** | 54.312 | <0.001** | 52.408 | <0.001** | 54.032 | <0.001** | 50.597 | <0.001** |
| $X_1X_2$ | 22.470 | <0.001** | 24.470 | <0.001** | 8.493 | 0.016* | 15.525 | 0.001** | 11.471 | 0.014* | 7.285 | 0.045* | 19.449 | <0.001** | 5.677 | 0.028* |                     |                     |
| $X_1X_3$ |                     |                     |                     |                     |                     |                     |                     |                     |                     |                     |                     |                     |                     |                     |                     |                     |
| $X_2X_3$ |                     |                     |                     |                     |                     |                     |                     |                     |                     |                     |                     |                     |                     |                     |                     |                     |
| $X_1X_2X_3$ |                     |                     |                     |                     |                     |                     |                     |                     |                     |                     |                     |                     |                     |                     |                     |                     |
| $R^2$  | 0.988 | 0.999 | 0.998 | 0.999 | 0.998 | 0.998 | 0.999 | 0.998 | 0.998 | 0.999 | 0.999 | 0.998 | 0.997 | 1.000 | 1.000 | 1.201 |                     |
| RMSE   | 1.967 | 1.769 | 1.852 | 1.629 | 2.150 | 2.365 | 1.703 | 2.196 | 1.201 |                     |                     |                     |                     |                     |                     |                     |
| $F$    | 3672.436 | 4261.416 | 3582.898 | 8679.972 | 3869.957 | 5565.963 | 8358.216 | 6876.990 | 13290.512 |                     |                     |                     |                     |                     |                     |                     |

Factors were shown in Fig. 1. $b$: regression coefficient, $p$: risk ratio (* $p < 0.05$, ** $p < 0.01$), $R^2$: coefficient of determination, RMSE: residual mean squared error, $F$: variance ratio.
Fig. 2. Response Surfaces of RSD (Upper Layer), AOR (Middle Layer), and Desirability (Lower Layer) Estimated by RSM as a Function of the Amounts of Powdered Lactose, Crystalline Lactose, and Corn Starch

Keys: The blending ratio of Adona® powder and diluents: left column (a, d, g); 1:4, center column (b, e, h); 1:1, and right column (c, f, i); 4:1.

Fig. 3. Response Surfaces of RSD (Upper Layer), AOR (Middle Layer), and Desirability (Lower Layer) Estimated by RSM as a Function of the Amounts of Powdered Lactose, Crystalline Lactose, and Corn Starch

Keys: The blending ratio of Rifadin® capsule content and diluents: left column (a, d, g); 1:4, center column (b, e, h); 1:1, and right column (c, f, i); 4:1.
peared that AOR was influenced greatly by particle size, density, and shape of the diluents. The $R^2$ value was larger than 0.99 in all cases, indicating an excellent prediction accuracy.

**Response Surface Analysis** To evaluate the contribution of the three components and the quantitative effects of the different proportions of the formulation variables on the response, RSD and AOR, the response surfaces were generated with Design-Expert software. The analyses were carried out separately in the three cases, and were divided based on the type of powdered drugs (powder formulations, capsule contents, or crushed tablet). Then, the optimal formulation with the smallest RSD and AOR was estimated.

**Powdered Formulations** The results of the Adona® powder are shown in Fig. 2. In Fig. 2, RSD increased as the amount of corn starch increased, and AOR increased as the amount of powdered lactose increased regardless of the blending ratio. Thus, the desirability was higher as the amount of crystalline lactose increased. The AOR of Adona® powder is 36.5°, showing the smaller value than those of the diluents. Therefore, the AOR of the mixtures were largely influenced by the property of the diluents. Thus, the optimal formulations were composed of crystalline lactose alone, at any blending ratio.

**Capsule Contents** The results of the contents of Rifadin® capsules are shown in Fig. 3. In Fig. 3, the RSD values of all samples were smaller than 6.08, indicating a sufficient quality.9) The AOR increased as the amount of corn starch increased (Figs. 3d–f). Therefore, the desirability was lower as the amount of corn starch increased (Figs. 3g–i). The AOR of Rifadin® capsule content was 50.8°. This indicates that the powder has relatively low flowability at the same level as the diluents. Thus, powdered lactose did not have an effect on the AOR of the mixtures in contrast to the powdered formulation. Therefore, the optimal formulation at the blending ratio of 4:1 (Fig. 3i) was shifted from crystalline lactose alone (Figs. 3g, h) to the powdered lactose.

**Crushed Tablets** The results of powdered Salazopyrin® tablets are shown in Fig. 4. In all the blending ratios, the RSD decreased when the amount of powdered lactose increased (Figs. 4a–c). The influence of the amount of corn starch depended on the blending ratio. Powdered Salazopyrin® tablets showed an AOR of 52.9°, indicating low flowability. Moreover, the AOR increased as the amount of powdered lactose increased due to the low flowability of the powdered lactose. At the blending ratio of 4:1 (Fig. 4f), however, the 1:1 mixture of powdered lactose and crystalline lactose showed the lowest AOR. Therefore, the optimal formulation contained a relatively high amount of crystalline lactose, indicating that the 4:1 mixture of crystalline lactose and corn starch was the most optimal.

**Prediction of Design Space of Suitable Diluent Formulations** The design space of suitable diluent formulations for the powder formulation was estimated by RSM and defined by the restrictions of an RSD <6.08% and AOR <45°, as shown in Fig. 5. The RSD of dispensing powders is recommended to be lower than 6.08%.9) An AOR lower than 45° indicates good flowability. Therefore, the suitable design space was defined as the area restricted by an RSD<6.08% and AOR<45°. As the amounts of the diluents increased, the suitable area decreased (Fig. 5a). The mixture containing larger amounts of

---

Fig. 4. Response Surfaces of RSD (Upper Layer), AOR (Middle Layer), and Desirability (Lower Layer) Estimated by RSM as a Function of the Amounts of Powdered Lactose, Crystalline Lactose, and Corn Starch

Keys: The blending ratio powdered Salazopyrin® tablets and diluents: left column (a, d, g); 1:4, center column (b, e, h); 1:1, and right column (c, f, i); 4:1.
the diluents lost a larger suitable area. In general, manufactured powder formulations provide good flowability. In contrast, the diluents that showed a low flowability are described in Table 1. This was because that the optimal formulation was composed of crystalline lactose alone in all blending ratio (points not indicated in figures). Therefore, we selected the crystalline lactose as the typical diluent for powdered formulations.

Then, the design space of suitable diluent formulations for the contents of capsule formulations was estimated by the restrictions of an RSD<6.08% and AOR<50.8°, as shown in Fig. 6. All areas in Fig. 6 satisfied the restriction of an RSD<6.08%. The AOR of the capsule content was 50.8°. Therefore, the area of AOR<50.8° indicated that blending with the diluents improved flowability and was suitable for diluents. The common area in all blending ratios indicated the design space for the suitable formulation. In Figs. 6a and b, the formulation composed powdered lactose alone was the most optimal. In Fig. 6c, however, the optimal formulation was the powdered lactose. Therefore, the mixture of powdered lactose and crystalline lactose at a ratio of 1:4 was selected as the typical formulation for the content of capsules. The formulation was consistent with complex lactose defined in the dispensing guideline X.18)

Finally, the design space of suitable diluent formulation for the powdered tablets was estimated by restriction of an RSD<6.08% and AOR<52.9°, as shown in Fig. 7. The AOR of the powdered tablets was 52.9°. The area was therefore restricted by an AOR<52.9°. The overlaid area near the corn starch disappeared (Fig. 7b). In addition, the area near the 1:1
mixture of powdered lactose and crystalline lactose decreased as the blending ratio of the powdered tablets increased (Fig. 7c). Therefore, the suitable area in Fig. 7b rarely overlapped that in Fig. 7c. The formulation of corn starch and crystalline lactose at a ratio of 1:4 was selected as the typical diluent for crushed tablets from the small common area of the design spaces. The formulation coincided with the optimal composition in Fig. 7a.

**Evaluation of Reliability of Typical Diluent Formulations** On the basis of the design spaces, we selected the typical diluent formulations for the three cases: powdered lactose alone for the powder formulation, a 1:4 mixture of powdered and crystalline lactose for the capsule content, and a 1:4 mixture of corn starch and crystalline lactose for the powdered tablet. We intended to confirm the suitability of the typical diluents by application of the diluents to other medicines for dispensation. The results in three cases are summarized in Table 4. The RSD of all tested medicines showed good values. Moreover, the optimal formulation of the diluents was investigated based on simultaneous optimization using RSM.

However, the optimal diluent formulations for PCM blending are unknown, although the PCM method has been introduced to improve scientific approaches for dispensation. It is important to estimate the design space of the suitable diluent for PCM blending to assure the quality of the dispensing drugs. To solve this problem, we employed a statistical technique, that is, the DOE and RSM.

Powder blending is greatly affected by the physical properties of the powdered medicines, including the particle size, density, and flowability. Obviously we could not examine all medicines in the current market as well as all of blending ratios between medicines and diluents. In this study, the representative data for some medicines are shown. Nevertheless, the approach presented here was applicable to the other medicines if necessary. The data accumulated in this way would be applicable to the other medicines if necessary. This study contributes to the standardization of the powder blending method.

**Acknowledgment** The authors are grateful to Prof. Noriyuki Namiki of the University of Shizuoka for providing the necessary research facilities.

**Conflict of Interest** The authors declare no conflict of interest.

**References**
1) Kojima J., Yashiro T., Kuriyama T., Satoh T., Yonago M., Yakkyoku, 61, 136–140 (2010).
2) Miyazaki Y., Miyawaki K., Uchino T., Kagawa Y., Chem. Pharm. Bull., 62, 54–57 (2014).
3) Saito J., Ishihara S., Imaizumi H., Terakado H., Ishikawa Y., J. Pharm. Sci. Techn. Jpn., 76, 63–74 (2016).
4) Miyama H., Sekine Y., Soeda H., Matsuzawa K., Unezaki S., Akashi T., J. Jpn. Soc. Hosp. Pharm., 40, 395–399 (2004).
5) Miyazaki Y., Miyawaki K., Uchino T., Kagawa Y., J. Pharm. Sci. Tech. Jpn., 20, 21.
6) Saito J., Ishihara S., Imaizumi H., Terakado H., Ishikawa Y., J. Pharm. Sci. Techn. Jpn., 20, 21.
14) Shah S. N., Mirza A. Z., Shamshad H., Shaﬁ N., Naz M. A., Med. Chem. Res., 21, 3591–3597 (2012).
15) “The Japanese Pharmacopoeia,” 16th edition, Ministry of Health, Labour and Welfare of Japan, 2011.
16) Derringer G., Suich R., J. Quality Technol., 12, 214–219 (1980).
17) Interview form of Lactose, Mylan Pharmaceutical Co., 2008.
18) Japan Pharmaceutical Association, “The Japanese Guidelines for Dispensation,” 10th ed., Yakujinippou-sha, Tokyo, Japan, 1996.
19) Nakamura H., Fujinuma Y., Matsumoto M., Ohtani M., Kotaki H., Uchino K., Iga T., Jpn. J. Pharm. Health Care Sci., 27, 491–494 (2001).
20) Okada J., Matsuda Y., Morita S., Wada Y., Onishi H., Yakugaku Zasshi, 88, 827–831 (1968).
21) Okada J., Matsuda Y., Matsuda Y., Yakugaku Zasshi, 89, 1562–1565 (1969).