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Multivariate statistical approach to optimizing sustained-release tablet formulations containing diltiazem hydrochloride as a model highly water-soluble drug

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ABSTRACT

A multivariate statistical technique was applied to designing a tablet for the sustained release over 24 h of diltiazem hydrochloride, a model highly water-soluble drug. Tablets of a hydrophilic matrix composed of dextran derivatives and hypromellose were prepared. The formulations were optimized using a nonlinear-response surface method incorporating thin-plate spline interpolation (RSM-S). A bootstrap (BS) resampling method was used to estimate the confidence intervals of the optimal formulations. The response surfaces estimated by RSM-S visualized the effects of the formulation factors, and the optimal release profile for diltiazem was predicted quantitatively as a function of the quantities of the formulation factors, using RSM-S. The simultaneous optimal solutions and their confidence intervals were estimated using RSM-S and BS resampling. The results clearly indicate nonlinear relationships between the formulation factors and the response variables. The observed responses of the optimal preparation coincided well with the predicted responses. The optimal hydrophilic matrix tablet allowed almost zero-order release of diltiazem hydrochloride for 24 h. In conclusion, an oral sustained-release tablet formulation, active over a long period, was successfully optimized using RSM-S, and the reliability of the optimal solution was evaluated using BS resampling.

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1. Introduction

The establishment of an oral long-term controlled-release system has an important role in drug therapy management. Directly compressed hydrophilic matrix tablets have been widely used as oral controlled-release devices because they are easy to manufacture and inexpensive, and their release characteristics are versatile (Melia, 1991). Hypromellose (HPMC) is the compound most commonly used to control drug release, and the drug-release properties of HPMC have been widely investigated (Salomen et al., 1979; Alderman, 1984; Ford et al., 1985a,b, 1991; Ranga Rao et al., 1990). In general, various hydrophilic matrix tablets are highly water soluble, show good gelation performance, and are stable and safe. However, orally administered hydrophilic matrix tablets are partly broken down by destructive gastrointestinal (GI) forces (Sako et al., 1996a). In contrast, when incompletely swollen hydrophilic matrix tablets arrive in the colon, any release of the drug from them is suppressed, and a negligible amount of the drug is absorbed because little water is available in the lower GI tract, including the colon (Sako et al., 1996b).

It has recently been reported that oppositely charged dextran derivatives can form a polyion complex, producing a rigid gel layer, and that they are therefore useful excipients for sustained-release matrix tablets (Miyazaki et al., 2003, 2006). A hydrophilic matrix tablet capable of polyion complexation must have both high hydrophilicity and durability. Therefore, it will be resistant to any destructive force in the GI tract and will disintegrate only slightly in the upper GI tract (Miyazaki et al., 2006). Moreover, disintegration could occur through cycles of water penetration and erosion of the gel layer, even in the colon, because the dextran derivatives are highly soluble. Meanwhile, it is difficult to sustain the release of highly water-soluble drugs because they diffuse rapidly through the polyion complex matrix as soon as water penetrates the tablet. Therefore, a further mechanism is required to suppress drug diffusion in the polyion complex matrix. In this study, we investigated the combined use of HPMC and a polyion complex composed of oppositely charged dextran derivatives. Dextran sulfate (DS) as the polyanion and [2-(diethylamino) ethyl] dextran (EA) as the polycation were used to construct this polyion complex matrix.

In recent years, ICH Q8 guideline has proposed the establishment of a science-based rationale. The concept of "quality by design (QbD)" is described in the ICH Q8 recommendations, which propose that the design and development of pharmaceutical formulations and manufacturing processes should ensure a

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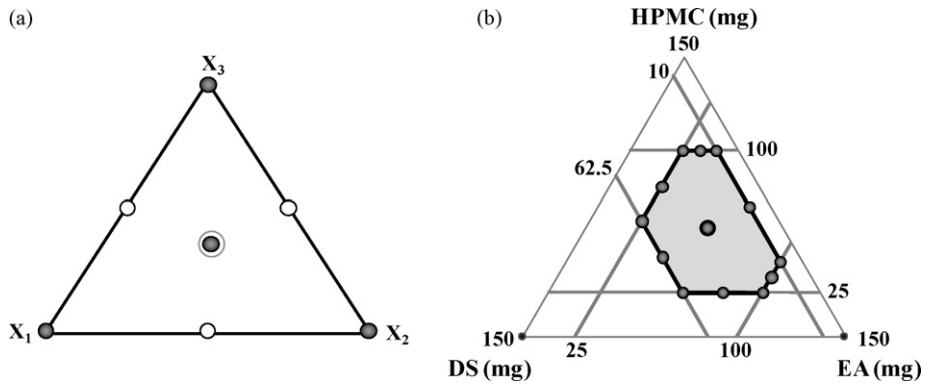

Fig. 1. Geometric representation of the experimental designs: (a) simplex lattice design for three factors, and (b) extreme vertices design for three components. Fourteen formulations were assigned to the extreme vertices design in this study.

predefined quality by understanding of how these factors previously influenced the quality of a drug product (Yu, 2008). Because it is difficult to achieve a mechanism-based design and optimization of pharmaceutical formulations, we applied a multivariate statistical technique to design and optimize long-term sustained-release tablet formulations containing diltiazem hydrochloride (DTZ), a model highly water-soluble drug. We developed an ingenious response surface method incorporating thin-plate spline interpolation (RSM-S), which has been used to determine acceptable formulations (Wahba, 1990; Takayama et al., 2004; Kikuchi and Takayama, 2009). A bootstrap (BS) resampling method was used to evaluate the reliability of the optimal solution estimated by RSM-S (Arai et al., 2007; Onuki et al., 2008). The BS method is a simulation technique based on the empirical distribution of the experimental samples. Skewness and kurtosis were used as the statistical indices to evaluate the normality of the distribution of the BS-optimal solutions determined with BS resampling.

2. Materials and methods

2.1. Materials

Diltiazem hydrochloride (DTZ) was used as the model highly water-soluble drug and was obtained from Wako Pure Chemical Industries Ltd. (Osaka, Japan). Dextran sulfate (DS; Mw 500,000), [2-(diethylamino) ethyl] dextran (EA; Mw 500,000), and hypromellose (HPMC; 4000 cps) were obtained from Sigma–Aldrich Co. (St. Louis, MO, USA). Magnesium stearate was obtained from Wako Pure Chemical Industries Ltd. All chemicals were sifted through a 100 mesh sieve (less than 150 μm).

2.2. Preparation of hydrophilic matrix tablets

All ingredients were mixed by hand with a mortar and pestle. Round-faced tablets, 8 mm in diameter, were prepared by direct compression under 8 kN using a HANDTAB 100 hydraulic press (Ichihashi-Seiki Co. Ltd., Kyoto, Japan). All the formulations were composed of 100.0 mg of DTZ, 150.0 mg of a mixture of DS, EA, and HPMC as the matrix polymers, and 2.5 mg of magnesium stearate.

2.3. Experimental design

Various amounts of DS (X_1), EA (X_2), and HPMC (X_3) were selected as the formulation factors. Based on the drug-release behaviors observed in preliminary experiments, the lower and upper limits of the levels of each factor were set as follows:

$$10.0 \le X_1 \le 62.5\,(\text{mg}) \quad (1)$$

$$25.0 \le X_2 \le 100.0\,(\text{mg}) \quad (2)$$

$$25.0 \le X_3 \le 100.0\,(\text{mg}) \quad (3)$$

$$X_1 + X_2 + X_3 = 150.0\,(\text{mg}) \quad (4)$$

Therefore, the feasible experimental region in the simplex lattice design was a hexagonal shape. The formulation factors were assigned according to an extreme vertices design, as shown in Fig. 1, and 14 kinds of formulations, including duplicate of the centroid, were prepared (Hirata et al., 1992).

2.4. Determination and measurement of the release profiles of DTZ

The release profiles of DTZ from the tablets were tested by dissolution test no. 2 (paddle method) at 37 ± 0.5 °C at a paddle rotation speed of 50 rpm using 900 mL of Japanese Pharmacopoeia XV first fluid (pH 1.2, 0.07 M HCl and 0.0342 M NaCl) or second fluid (pH 6.8, 0.05 M H_2KPO_4 and 0.0236 M NaOH). The samples were withdrawn and filtered at the t-th sampling points, i.e., t = 1, 2, 3, . . ., 11, denoting 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 20, and 24 h, respectively. The concentration of DTZ was determined spectrophotometrically at 240 nm with a JASCO Ubest-30 spectrophotometer (Japan Spectroscopic Co. Ltd., Tokyo, Japan). The drug-release rates at 3, 6, 12, and 24 h in the first fluid (F_4, F_6, F_8, and F_{11}, respectively) and the same points in the second fluid (S_4, S_6, S_8, and S_{11}, respectively) were selected as the response variables. Moreover, the tablets composed of DTZ/DS/EA (100/45/105 mg) and DTZ/HPMC (100/150 mg) were prepared, and the release rates were determined as a reference.

2.5. Evaluation of the similarity of two DTZ release profiles

In evaluating the similarity of the release profiles in the first fluid and second fluid, the difference factor (f_1) and similarity factor (f_2) were used as the response variables. The factors f_1 and f_2 were introduced by Moore and Flanner (1996) as mathematical indices with which to compare dissolution profiles, and constitute the most widely known example of the model-independent approach, which does not require a preconceived or fitted model. This procedure is recommended by the FDA Guidance for Industry (Food and Drug Administration, 1997). Index f_1 represents the percentage (%) difference between the two curves at each time point and is a measure of the relative error between the two curves:

$$f_1 = 100 \left(\frac{\sum_{t=1}^{n} |F_t - S_t|}{\sum_{t=1}^{n} F_t} \right) \quad (5)$$

where the dissolution behavior of a number of samples (n) in the first fluid (F_t) and second fluid (S_t) are compared at the t-th sampling points.

Index f_2 is a logarithmic reciprocal square root transformation of the sum of the squared error at all the points and is a measure of the degree of similarity in the percentage (%) dissolution between the two curves:

$$f_2 = 50 \log \left\{ \left[\left(1 + \left(\frac{1}{n} \right) \sum_{t=1}^{n} (F_t - S_t)^2 \right) \right]^{-1/2} \times 100 \right\} \quad (6)$$

where f_1 is a function of the average absolute difference between the two dissolution curves. In contrast, f_2 is a measure of the similarity in the percentage dissolution between the two curves.

2.6. Simultaneous optimization and reliability assessment of the optimal solution using RSM-S and BS resampling

The optimal solution was estimated based on RSM-S, using a dataset obtained with an extreme vertices design. The BS resampling method was then applied to evaluate the reliability of the optimal solution. The number of resamplings with replacement was fixed at 1000. BS-optimal means and their 95% confidence intervals (CI) were calculated from the BS-optimal solutions. The standard deviations of the BS-optimal solutions were estimated as a parametric quantity, and then the 95% CI was evaluated. Conversely, a percentile method was used to estimate the 95% CI as a nonparametric quantity. Details of the estimation of the original optimal solution and the BS-optimal solutions have been fully described in previous papers (Arai et al., 2007; Onuki et al., 2008). Skewness (α_3) and kurtosis (α_4), which are the indices of normality for the histograms of the BS-optimal solutions, were calculated as:

$$\alpha_3 = \frac{(1/n) \cdot \sum_{i=1}^{n} (x_i - \bar{x})^3}{\left((1/n) \cdot \sum_{i=1}^{n} (x_i - \bar{x})^2 \right)^{3/2}} \quad (7)$$

$$\alpha_4 = \frac{(1/n) \cdot \sum_{i=1}^{n} (x_i - \bar{x})^4}{\left((1/n) \cdot \sum_{i=1}^{n} (x_i - \bar{x})^2 \right)^{2}} \quad (8)$$

where n is the number of BS-optimal solutions (x), and $\bar{x}$ is the mean of x. Original data were transformed to a logit form prior to the histogram analysis, because the BS-optimal solutions have lower and upper limits. When the indices α_3 and α_4 are close to 0 and 3, respectively, the histograms of the BS-optimal solutions are close to a normal distribution.

3. Results

3.1. Prediction of response variables using RSM-S

The response surfaces for each response variable were estimated by RSM-S based on the original dataset. The accuracy of the response surfaces was evaluated by leave-one-out cross-validation. As a result, most of the correlation coefficients for the responses were sufficiently high (more than 0.9). Some of the response surfaces are shown in Figs. 2 and 3. The response surfaces for the release rates of DTZ after 6 h in the first fluid (F_6) and second fluid (S_6) displayed similar patterns, whereas those after 24 h (F_{11} and S_{11}) differed. In particular, the release rates of DTZ in the first fluid from formulations that included large amounts of HPMC increased relative to those in the second fluid. Fig. 2 also shows that the release rate of DTZ decreased as the amount of DS increased, whereas it increased as the amount of EA increased. The similarity between the release profiles of DTZ in the first fluid and second fluid was evaluated using the factors f_1 and f_2. The results are shown in Fig. 3. The response surfaces of f_1 and f_2 were inversely correlated. The formulations containing large amounts of HPMC were estimated to have low similarity (high values of f_1 and low values of f_2). Conversely, excellent similarity was observed in the formulations that included somewhat low amounts of HPMC to intermediate region.

3.2. Formulation optimization using RSM-S

The formulation of the DTZ hydrophilic matrix tablets was optimized based on the original data set using RSM-S. The search

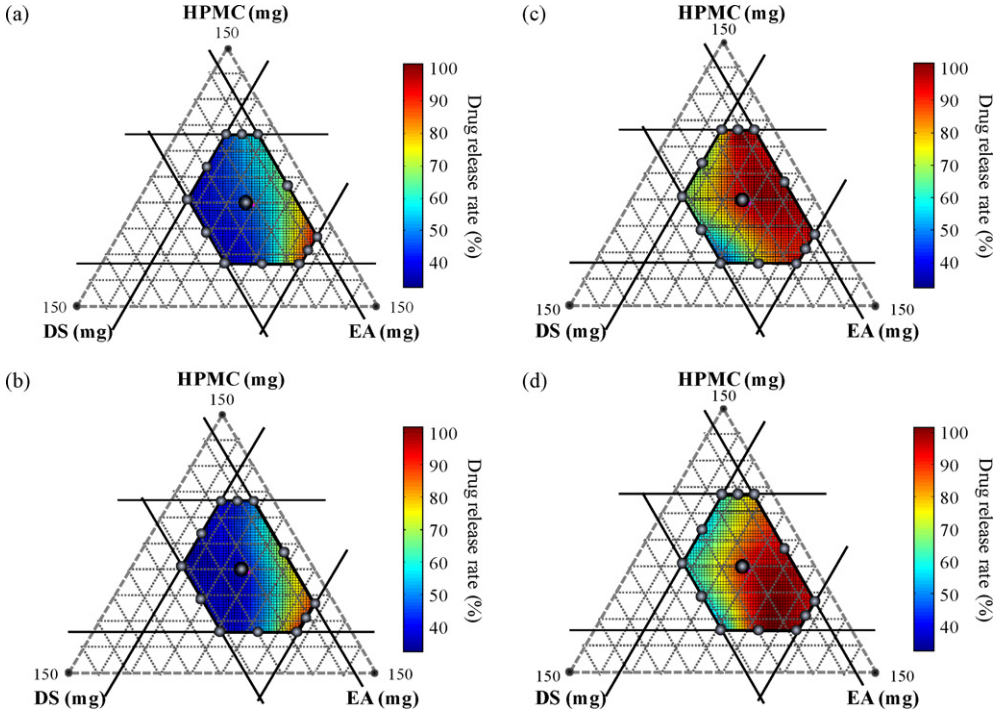

Fig. 2. Response surfaces of the DTZ release rates from hydrophilic matrix tablets estimated by RSM-S, as a function of the amounts of DS, EA, and HPMC included. (a) Release rate at 6 h in the first fluid (F_6), (b) at 6 h in the second fluid (S_6), (c) at 24 h in the first fluid (F_{11}), and (d) at 24 h in the second fluid (S_{11}).

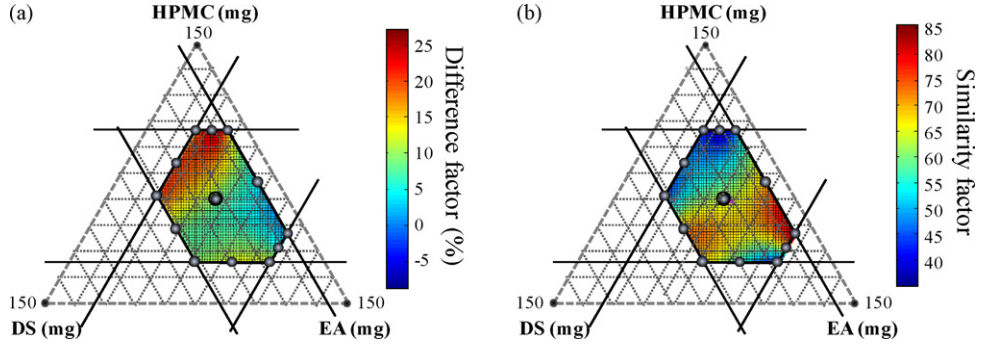

Fig. 3. Response surfaces of (a) the difference factor (f_1), and (b) the similarity factor (f_2) for the hydrophilic matrix tablets, estimated by RSM-S as a function of the amounts of DS, EA, and HPMC included.

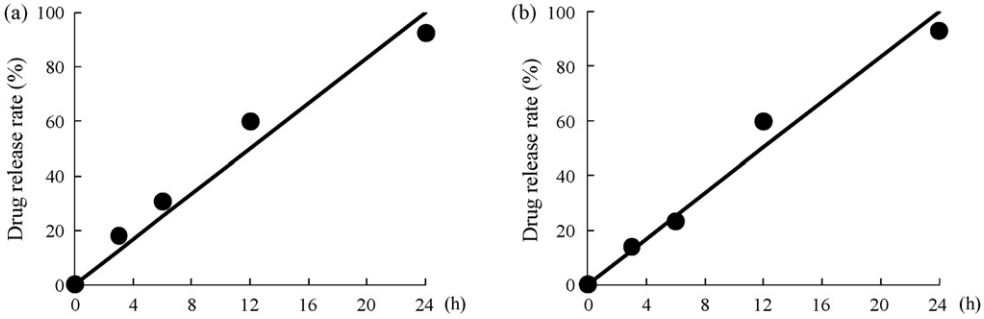

Fig. 4. Simultaneous optimal solutions for the DTZ release profiles from the hydrophilic matrix tablets at each dissolution time in (a) the first fluid, and (b) the second fluid: (—) ideal release curves; (●) optimal release rates estimated by RSM-S.

directions for the response variables were set to produce the characteristics of zero-order release for 24 h and the stable to the pH of the test solutions. The optimization problem was formulated to minimize f_1 and to maximize f_2 with an even weight, and to ensure F_4 and S_4 approached 12.5 (%), F_6 and S_6 approached 25 (%), F_8 and S_8 approached 50 (%), and F_{11} and S_{11} approached 100 (%) as equality constraints in the hexagonal experimental region defined in Eqs. (1)–(4).

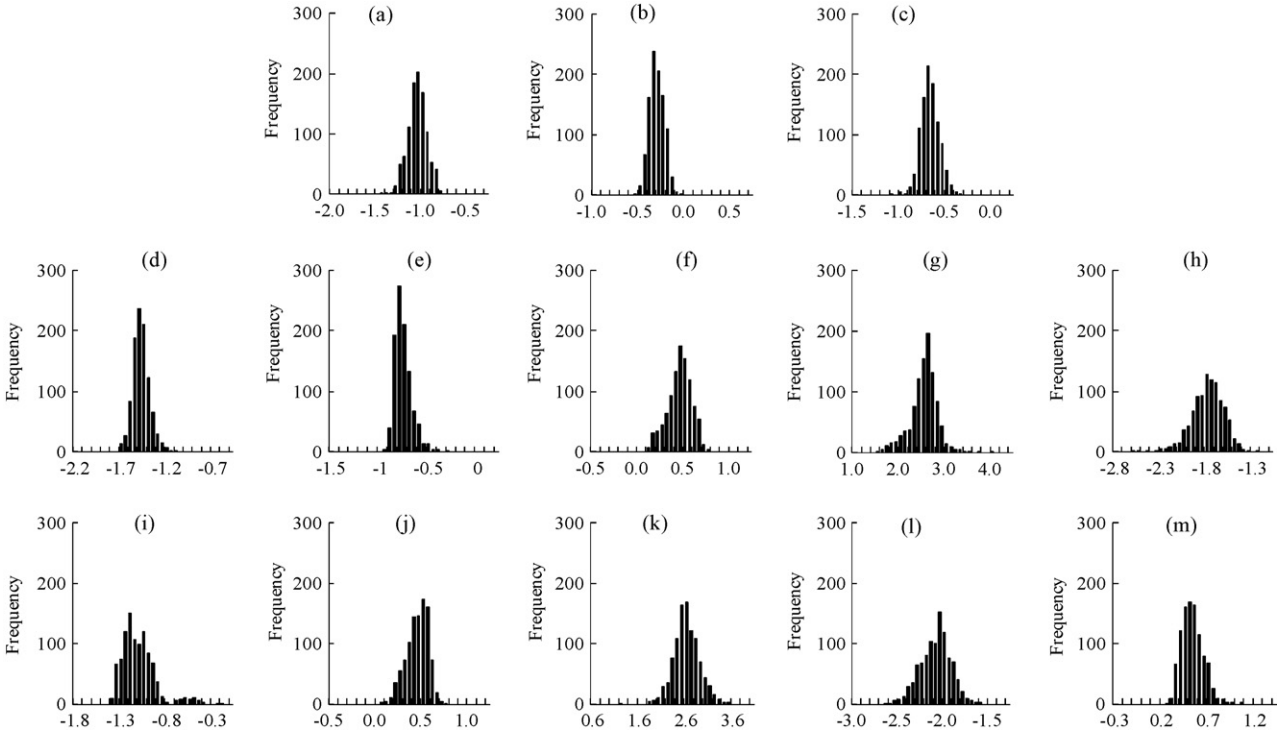

Fig. 5. Histograms of optimal factors and optimal responses estimated by BS resampling. BS resampling was repeated 1000 times. These histograms are composed of 1000 optimal solutions estimated from the BS samples. Original data were transformed to a logit form prior to the histogram analysis: (a) X_1, (b) X_2, (c) X_3, (d) F_4, (e) F_6, (f) F_8, (g) F_{11}, (h) S_4, (i) S_6, (j) S_8, (k) S_{11}, (l) f_1, and (m) f_2.

Table 1
95% confidence intervals (CI) for the optimal solutions estimated from histograms based on the BS resampling method.

	Formulation factors		
	X_1	X_2	X_3
Parametric 95% CI	32.52–43.91	56.65–68.11	43.34–56.31
Nonparametric 95% CI	32.51–43.78	56.88–68.02	43.60–56.54

	Response variables			
	F_4 (%)	F_6 (%)	F_8 (%)	F_{11} (%)
Parametric 95% CI	15.74–20.93	27.77–35.10	54.12–66.11	86.75–95.48
Nonparametric 95% CI	15.92–21.33	28.70–35.85	53.27–65.48	85.44–95.25

	Response variables					
	S_4 (%)	S_6 (%)	S_8 (%)	S_{11} (%)	f_1 (%)	f_2
Parametric 95% CI	10.17–18.97	18.31–31.66	54.54–65.50	88.28–95.64	7.99–14.24	56.81–67.52
Nonparametric 95% CI	10.04–18.12	20.07–35.88	54.13–64.53	88.38–95.74	7.94–13.94	57.80–67.73

X_1 = 38.1 (mg), X_2 = 62.1 (mg), and X_3 = 49.8 (mg) were estimated as the optimal formulation. The following were estimated to be the optimal response variables: F_4 = 18.0 (%), F_6 = 30.6 (%), F_8 = 59.8 (%), F_{11} = 92.2 (%), S_4 = 14.0 (%), S_6 = 23.2 (%), S_8 = 59.7 (%), S_{11} = 93.1 (%), f_1 = 10.7 (%), and f_2 = 62.0. Fig. 4 shows the ideal release curves for DTZ and the estimated release rates of the optimal formulation, which is located near the centroid point in the extreme vertices design. The optimal release profiles can also be assumed to be close to the zero-order release of DTZ over 24 h, and the optimal factors f_1 and f_2 indicate sufficient similarity of the release profiles in the first and second fluids.

3.3. Histograms of the optimal solutions

The reliability of the optimal solution estimated by RSM-S was evaluated using the BS resampling method. Histograms of 1000 BS-optimal solutions for the different formulation factors and responses are shown in Fig. 5. In some cases, such as (e) and (i), the shape of the histograms deviated from a normal distribution. The 95% CI values for the original optimal solution were estimated with both parametric and nonparametric methods, and the results are shown in Table 1. No meaningful difference between the parametric and nonparametric estimates was observed, although considerable deviation was seen in the CI values for S_6. Skewness (α_3) and kurtosis (α_4) are summarized in Table 2. For the values for F_6, F_{11}, S_6, and f_2, α_3 and α_4 deviated greatly from 0 and 3, respectively.

Table 2
Skewness (α_3) and kurtosis (α_4) of the histograms for the optimal formulations and responses.

Factors and responses	α_3	α_4	*JB*
X_1	−0.11	2.94	2.14*
X_2	0.11	2.65	7.27
X_3	0.08	3.41	8.16
F_4	0.46	3.69	54.42
F_6	1.14	5.07	395.76
F_8	−0.36	2.75	24.51
F_{11}	−0.21	4.97	168.84
S_4	−0.51	4.03	87.82
S_6	1.47	6.11	763.54
S_8	−0.48	2.82	39.80
S_{11}	0.01	3.76	24.39
f_1	−0.19	2.97	5.80*
f_2	0.77	4.38	179.44

JB: Jarque–Bera statistics.
* Judged as a normal distribution ($p < 0.05$).

4. Discussion

In this study, hydrophilic matrix tablets composed of DS, EA, and HPMC containing a hydrophilic drug, DTZ, were prepared. DS and EA were chosen as the polyion-complex-forming materials, and HPMC was chosen as the gelation polymer. An optimal formulation was predicted quantitatively using RSM-S. The response variables, such as the release rates ($F_{4,6,8,11}$ and $S_{4,6,8,11}$), together with the difference and similarity factors (f_1 and f_2), were accurately predicted, as is clear from the results of the leave-one-out cross-validation. The release rates for DTZ from the formulations containing large amounts of HPMC in the first fluid were significantly different from those in the second fluid (Fig. 2). HPMC is the most commonly used polymer in forming hydrophilic matrices, and it is stable in the range of pH 3.0–11.0 (Dow Commercial Information, 2002). The release rates of DTZ are considered to have been enhanced in the first fluid relative to the release rates in the second fluid. The drug-release rates were fairly sensitive to the ratio of DS to EA, because the nature of the matrix, such as its hardness and hydrophilicity, is highly dependent on the complexed DS and EA (Miyazaki et al., 2001). The effects of the interactions between DTZ and the polymers should also be taken into consideration, because positively charged DTZ molecules can bind to the negatively charged DS polymer chain.

The similarity in the release profiles for DTZ in the first fluid and second fluid was evaluated using the factors f_1 and f_2. When the two curves are similar, the f_1 value is close to 0 and the f_2 value is close to 100. Compared with the f_1 value, the f_2 value is more sensitive to detect a small difference between release profiles, and then, the f_2 value is widely recognized as an index to evaluate the similarity of release profiles. On the other hand, the f_1 value is intuitive and straightforward factor to understand the difference of release profiles. In this study, we have employed both f_1 and f_2 values as responses to be optimized with an even weight. When the f_2 value is 50, the average difference between the two release curves is 10%. In this study, sufficiently high similarity was seen in the release curves in the first and second fluids, except when relatively high amounts of HPMC were included in the formulation.

To evaluate the accuracy of the optimal solution estimated by RSM-S, a tablet composed of the optimal formulation was prepared and tested. The release rates measured for the optimal formulation coincided well with the predictions, as shown in Fig. 6. This indicates that the DTZ release profiles from the optimal formulation in the first and second fluids followed zero-order kinetics for a sufficient time of around 20 h (Fig. 6). Moreover, the values of f_1 = 8.71 and f_2 = 65.33 clearly show the strong similarity of the two release curves in the first and second fluids. When the tablet

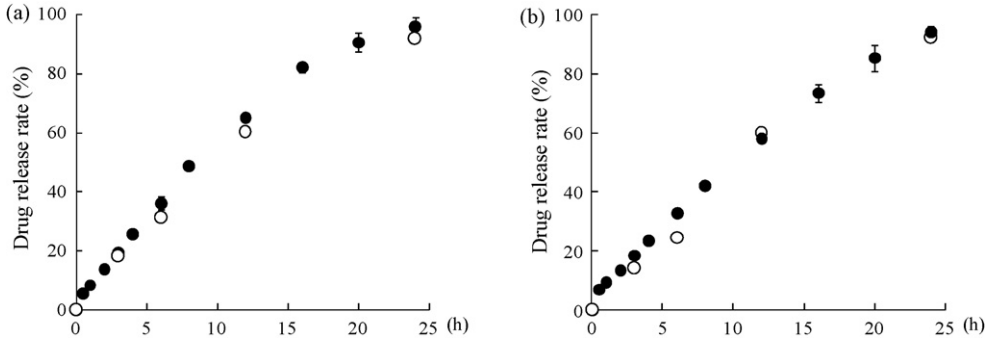

Fig. 6. Release profiles of DTZ from the optimal formulation in (a) the first fluid, and (b) the second fluid: (●) experimental values; (○) optimal values. Each experimental result is a mean ± S.D. ($n = 3$).

was made from a mixture of DS and EA without HPMC, the release of DTZ was completed within 8 h (Tanaka et al., 2007). The f_1 and f_2 values of DTZ/DS/EA tablet were 12.96 and 51.67, respectively. In contrast, about 20% of the DTZ remained in the tablet, even at 24 h, when HPMC was used alone as the tablet excipient. The f_1 and f_2 values of DTZ/HPMC tablet were 19.02 and 46.32, respectively. Results show that the tablets made from only a mixture of DS and EA or HPMC alone as the tablet excipient were unstable to the pH of the test solutions. With the optimal formulation, a fairly stable hydrophilic matrix was formed by the HPMC gelation and the polyion complexation between DS and EA, allowing the ideal release of DTZ.

To evaluate the robustness of the optimal formulation, histograms of the optimal factors and responses were calculated based on the BS resampling method. BS resampling is a statistical interval analysis that uses a Monte Carlo simulation. For the special benefit of the central limit theorem, the shape of the histogram constructed from the arithmetic means of the BS samples follows a normal distribution. It is not possible to hypothesize the central limit theorem from the BS-optimal solutions derived from RSM-S, so the distribution of the BS-optimal solutions must be evaluated. Most of the histograms in Fig. 5 seem to be symmetrical in appearance. However, skewed distributions, such as that for S_6 (Fig. 5(i)), were observed. Skewness (α_3) and kurtosis (α_4) were used as indices of normality to evaluate the shape of the distributions of the BS-optimal solutions (Table 2). The indices α_3 and α_4 for the formulation factors X_1–X_3 were close to 0 and 3, respectively, suggesting that the BS-optimal factors followed a normal distribution, whereas for some of the BS-optimal responses such as F_6, S_6 and f_2, the α_3 and α_4 values were far from 0 and 3, respectively (Table 2), even though the responses are functions of the formulation factors. This indicates that the BS-optimal solutions of these responses are not always normally distributed. The highest skewness value was seen in response S_6. This is closely related to the largest difference, which was also seen between the parametric 95% CI and the nonparametric 95% CI in response S_6 (Table 1). The normality of the histograms of the BS-optimal solutions was tested by the Jarque–Bera hypothesis test (Table 2). The Jarque–Bera test is widely known as a goodness-of-fit measure of departure from normality based on the skewness (α_3) and kurtosis (α_4). As a result, only the histograms of X_1 and f_1 were judged as to be normal distributions (Fig. 5(a) and (l)). The difference of the parametric 95% CI and the nonparametric 95% CI greatly increased with an increase of Jarque–Bera statistics. Consequently, when the shape of the histogram is significantly skewed, the nonparametric confidence intervals of the optimal solutions estimate the reliability of the optimal solutions better than the parametric approach does.

We suggest that the optimal solutions and their confidence intervals reveal the relationships between the formulation factors and the response variables, and that they are satisfactorily estimated using RSM-S and the BS resampling method.

5. Conclusions

Hydrophilic matrix tablets composed of DS and EA as polyion-complex-forming materials and HPMC as the gelation polymer were successfully prepared to achieve the long-term controlled-release of DTZ, a highly water-soluble drug. However, the role of each polymer in the matrix is rather difficult to discern mechanically because of the complex interactions among the polymers. In such a complex system, a multivariate statistical approach is absolutely imperative to optimize the formulations. To estimate the optimal formulations and their confidence intervals, we used RSM-S and the BS resampling technique. The optimal formulation showed the zero-order release of DTZ over 20 h in the first and second fluids, and the two release curves had strong similarity. The confidence interval for the BS-optimal solutions estimated by the parametric approach is not always appropriate when the histograms of the BS-optimal solutions are significantly skewed. In such cases, a nonparametric approach, such as the percentile method, is recommended to evaluate the reliability of the optimal solutions. The multivariate statistical approach described in this study would be a useful tool for the setup a design space under the QbD concept in pharmaceutical formulation development.

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