COMPUTER-AIDED DESIGN AND OPTIMISATION FOR PHARMACEUTICAL FORMULATIONS

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SUMMARY

The response surface method (RSM) has been used to determine acceptable formulations of pharmaceuticals. In a classical way, pharmaceutical responses of relevant formulation are predicted quantitatively by the combination of causal factors on the basis of quadratic polynomial equation. Finally, multi-objective optimisation algorithm has been applied for predicting the best formulation. However, predictions based on the quadratic polynomial are often limited and the results obtained occasionally exhibit poor estimation. We have developed an ingenious RSM, RSM-S, in which multivariate spline interpolation (MSI) is incorporated as a method of generating the response surface. Concurrently, a method to evaluate the reliability of the optimal solution was developed employing a bootstrap (BS) resampling and a Kohonen's self-organizing map (SOM). Predominant feature of a novel RSM approach based on the MSI together with the BS resampling and the SOM clustering techniques was demonstrated by the design and optimisation for the theophylline tablet formulation. The method described in this study should promote the establishment of a science-based rationale for pharmaceutical formulation development.

INTRODUCTION

The ICH Q8 guidelines have necessitated the establishment of a science-based rationale and a design space in pharmaceutical formulation development. The response variables relating to the effectiveness, usefulness, stability, and safely of a drug product are influenced by a number of causal factors in the pharmaceutical formulations and manufacturing conditions. The response surface method (RSM) has been used to determine acceptable formulations of pharmaceuticals (Khuri and Cornel 1987). RSM includes statistical factorial experimental design, modeling between causal factors and response variables, and multi-objective optimisation for selecting the best formulation under a set of pragmatic restrictions. Composite experimental design can be applied for choosing rational model formulations. Response variables of these model formulations are predicted quantitatively by the combination of causal factors. In a classical way, multiple regression analysis has been applied on the basis of a quadratic polynomial equation. Finally, multi-objective optimisation algorithm has been applied for predicting the best formulation. However, predictions based on the quadratic polynomial are often limited and the results obtained occasionally exhibit poor estimation. We have developed an ingenious RSM, RSM-S, in which multivariate spline interpolation (MSI) is incorporated as a method of generating the response surface (Takayama et al. 2004). Concurrently, a method to evaluate the reliability of the optimal solution was newly developed (Arai et al. 2007; Onuki et al. 2008) employing a bootstrap (BS) resampling technique and a Kohonen's self-organizing map (SOM). As a model experiment, formulation optimisation of theophylline tablets was conducted.

MATERIALS AND METHODS

Experimental Design

Theophylline tablets were prepared as model formulations. The amounts of lactose (X_1), cornstarch (X_2), and microcrystalline cellulose (X_3) were selected as mixture variables, and the additional amount of magnesium stearate (Z_1) and the mixing time of the ingredients (Z_2) were selected as the process variables. Mixture variables and process variables were assigned according to a simplex lattice design and a two-factor composite second-order spherical experimental design, respectively. Thus, a hybrid experimental design integrating the two experimental designs was used, and 63 kinds of model formulations were prepared.

Preparation of Theophylline Tablets and Measurement of Response Variables

All the ingredients were mixed for the designated periods using a drum mixer. Samples (250 mg) of the mixtures were directly compressed into flat-faced tablets with a diameter of 10 mm using a hydraulic hand press at a force of 8 kN. Hardness (Y_1) and the 63.2% drug-release time (Y_2) were selected as the response variables of the theophylline tablets. The hardness of the tablets was measured with a tablet hardness tester (Monsanto type). To calculate the 63.2% drug-release time, a dissolution test was performed using a JP XIV dissolution apparatus and the paddle method. Purified water (900 mL) was used as the release medium. Each tablet was immersed in purified water at 37°C with stirring (50 rpm). The concentration of theophylline in the dissolution sample was determined with a spectrophotometer. Based on the dissolution curves, the 63.2% drug release time was calculated using a Weibull distribution function.

Computer Software

For RSM-S and BS resampling, dataNESIA® Version 3.0 (Yamatake Corp., Tokyo, Japan) was used. Viscovery SOMine® Version 4.0 (Eudaptics Software GmbH, Vienna, Austria) was used for SOM clustering. The SOM Ward technique was employed for clustering BS optimal solution as is considered the most efficient in general.

RESULTS AND DISCUSSION

Formulation Optimisation by RSM-S

Figure 1 shows observed and estimated response variables by leave-one-out cross-validation. The correlation coefficients for hardness (Y_1) and 63.2% drug-release time (Y_2) were high enough to suggest that RSM-S successfully estimated the relationships between the factors and response variables. Formulation optimisation of the theophylline tablets was then performed based on the original data set using RSM-S. The maximum value of hardness and the minimum value of 63.2% drug-release time were regarded as being ideal for seeking optimal formulation. Details of the optimisation procedure in RSM-S were described in full, previously (Takayama et al. 2004). The factors and the responses in the optimal solution were estimated as: X_1 = 20.2%; X_2 = 35.6%; X_3 = 44.2%; Z_1 = 2.4 mg; Z_2 = 11.7 min; Y_1 = 11.2 kg/cm; Y_2 = 6.8 min. More often than not, an increase in the hardness of the tablet reduces the release rate of the drug from the tablet. However, the optimal formulation also contains a large amount of lactose (X_1) and cornstarch (X_2), so the tablet is expected to release theophylline rapidly. An optimal solution with acceptable characteristics could be estimated with RSM-S.

Reliability of the Optimal Formulation

The reliability of the original optimal solution was evaluated by using BS resampling and SOM clustering. Histograms of the causal factors as well as the response variables of the BS optimal solutions were deviated from a normal distribution, and some of them, such as X_1 and Z_1, even seemed to be a mixture of several clusters. This is probably because of the risk involved in the BS resampling process. The set of BS optimal solutions can be regarded as a mixture of several clusters composed of a single global and other local otimal solutions. In

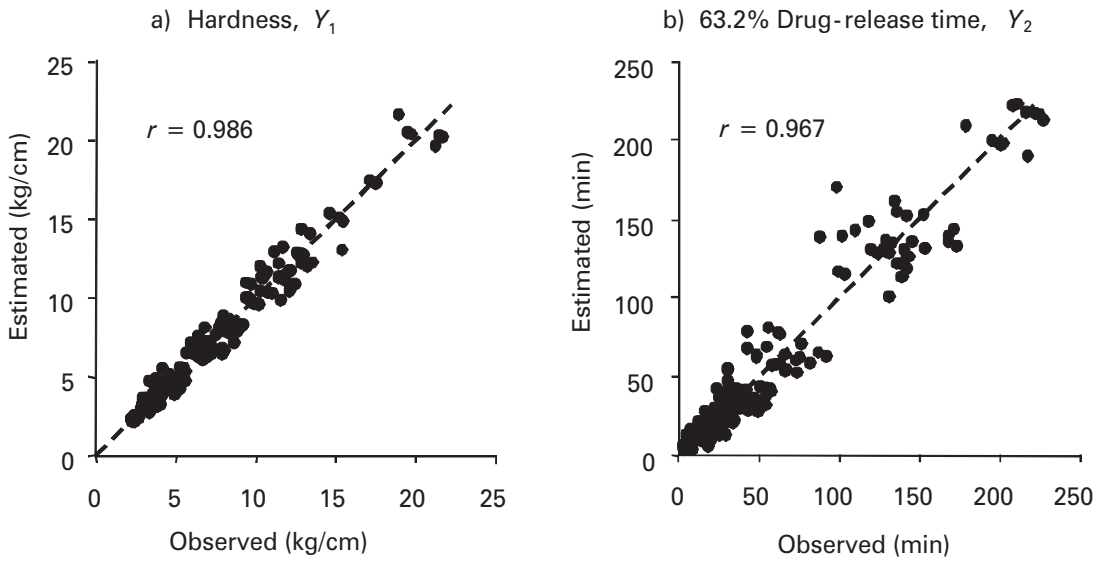

Figure 1. Leave-one-out cross-validated estimated accuracy of the RSM-S model for (a) hardness, and (b) 63.2% drug-release time.

evaluating the reliability of the original optimal solution, producing a cluster of global optima from the BS solutions is inevitable. To resolve this problem, we used SOM clustering. **Figure 2** shows the SOM for the BS optimal solutions. The mixture variables (X_1, X_2 and X_3) and the process variables (Z_1 and Z_2) of the BS optimal solutions were used as the input vectors. The BS optimal solutions were divided into seven clusters by SOM clustering. By using a similarity index as a statistical quantity, a cluster with global optimal solutions was defined (Cluster 1 in **Figure 2**). The 95% confidence intervals (CI) of simultaneous optimal solution were estimated as: CI(X_1) = 17.0~21.9%; CI(X_2) = 34.5~37.1%; CI(X_3) = 43.3~46.2%; CI(Z_1) = 2.2~2.4 mg; CI(Y_1) = 10.9~11.3 kg/cm; CI(Y_2) = 6.6~8.6 min. The CI values of optimal solution were stable irrespective of the number of output nodes in SOM.

Predominant feature of a novel RSM approach based on the MSI together with the BS resampling and the SOM clustering techniques was demonstrated by the design and optimisation for the theophylline tablet formulation. The method described in this study should promote the establishment of a science-based rationale for pharmaceutical formulation development.

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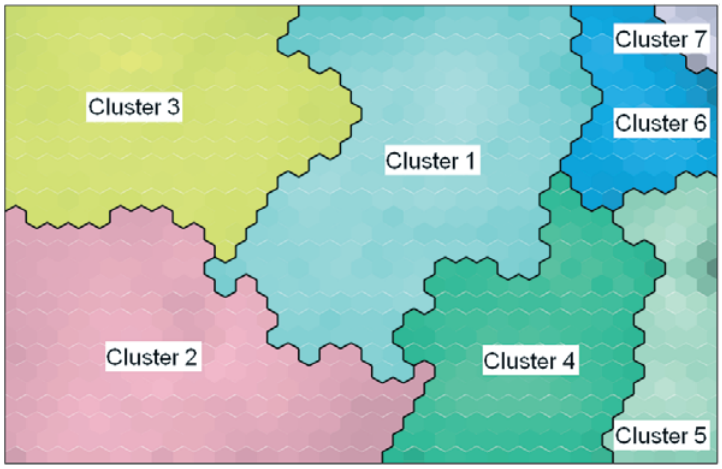

Figure 2. SOM clusters for simultaneous optimal solutions estimated from bootstrap samples in the optimisation of theophylline tablets. Cluster 1 is composed of global solutions and other clusters are composed of diverse local solutions. The reliability of the simultaneous optimal solution was evaluated by the cluster 1 that consists of global solutions.

TIIVISTELMÄ

Monimuuttujasplini-interpolaatiota (MSI) käyttävä vastepintamenetelmä kehitettiin lääketuotteiden optimaalisen koostumuksen kehittämiseen. Optimaalisen formulaation löytämisen luotettavuutta arvioitiin niin kutsutulla saapasremmiuudelleenotannalla (BS) ja Kohosen itseorganisoituvilla kartoilla. Mallikokeena suoritettiin teofylliinitablettien koostumuksen optimointi edellä mainituilla menetelmillä. Tässä tutkimuksessa esitetyt menetelmät edistävät tieteelliseen päättelyyn perustuvaa lääke-koostumuksen kehitystä.

REFERENCES

Arai H, Suzuki T, Kaseda C, Ohyama K, Takayama K: Bootstrap re-sampling technique to evaluate the optimal formulation of theophylline tablets predicted by nonlinear response surface method incorporating multivariate spline interpolation. Chem Pharm Bull 55: 586-593, 2007

Khuri AI, Cornel JA: Response surface: Design and analysis. Marcel Dekker, New York, 1987

Onuki Y, Ohyama K, Kaseda C, Arai H, Suzuki T, Takayama K: Evaluation of the reliability of nonlinear optimal solutions in pharmaceuticals using a bootstrap resampling technique in combination with Kohonen's self-organizing maps. J Pharm Sci 97: 331-339, 2008

Takayama K, Obata Y, Morishita M, Nagai T: Multivariate spline interpolation as a novel method to optimize pharmaceutical formulations. Pharmazie 59: 392-395, 2004