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Relationships between response surfaces for tablet characteristics of placebo and API-containing tablets manufactured by direct compression method

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ABSTRACT

In this study, we evaluated the correlation between the response surfaces for the tablet characteristics of placebo and active pharmaceutical ingredient (API)-containing tablets. The quantities of lactose, cornstarch, and microcrystalline cellulose were chosen as the formulation factors. Ten tablet formulations were prepared. The tensile strength (TS) and disintegration time (DT) of tablets were measured as tablet characteristics. The response surfaces for TS and DT were estimated using a nonlinear response surface method incorporating multivariate spline interpolation, and were then compared with those of placebo tablets. A correlation was clearly observed for TS and DT of all APIs, although the value of the response surfaces for TS and DT was highly dependent on the type of API used. Based on this knowledge, the response surfaces for TS and DT of API-containing tablets were predicted from only two and four formulations using regression expression and placebo tablet data, respectively. The results from the evaluation of prediction accuracy showed that this method accurately predicted TS and DT, suggesting that it could construct a reliable response surface for TS and DT with a small number of samples. This technique assists in the effective estimation of the relationships between design variables and pharmaceutical responses during pharmaceutical development.

1. Introduction

The “Quality by Design” (QbD) principle has drawn attention as a new concept in pharmaceutical design and development (ICH, 2009; Tomba et al., 2013). In QbD, product quality is assured by understanding and controlling the variables involved in formulation and manufacturing (Pramod et al., 2016). To achieve this, a scientific understanding of the formulation and the manufacturing method is required. To gain insight into pharmaceutical formulations and to identify the crucial factors, a quantitative visualization technique is required to demonstrate the relationships between the causal factors and pharmaceutical responses. However, it can be hard to achieve an overall view of the multivariate data obtained.

The response surface method (RSM) allows modeling of explanatory and objective variables. RSM is widely used in pharmaceutical development to define and visualize the causal relationships between design variables and pharmaceutical responses quantitatively (Bansal et al., 2015; Duangjit et al., 2014; Giannakou et al., 2002; Ohno et al., 2007; Otsuka et al., 2011; Voinovich et al., 2001). RSM allows the determination of the optimal formulation and process parameters by combining desirability functions or Euclidean distance (Derringer and Suich, 1980; Takayama and Nagai, 1991). Moreover, RSM can be used to construct a design space, which is defined as the multidimensional combination and interaction of input variables and process parameters that have been demonstrated to provide quality assurance (Chatzizaharia and Hatziavramidis, 2015; Giry et al., 2010; Hayashi et al., 2013; Takayama et al., 2003). In general, a linear regression model, such as a quadratic polynomial and a multiple regression formula, is applied to determine the quantitative relationships between factors. Nonlinear regression analysis, e.g., an RSM that incorporates multivariate spline interpolation (RSM-S), is an effective technique when it is not possible to obtain sufficient prediction accuracy using a linear regression method (Arai et al., 2007; Surini et al., 2003), and often shows better prediction accuracy than linear regression models (Hayashi et al., 2013).

To apply the RSM, it is necessary to collect experimental data based on the design of experiments (DoE), e.g., central composite,

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Box–Behnken, and mixture designs (Pramod et al., 2016). Central composite and Box–Behnken designs are mainly employed when the factors are process variables, while mixture design is used for formulation factors. For instance, when there are three process variables, it is necessary to construct approximately 15 sample types, including duplicates of the centroid. In contrast, when there are three formulation factors, a minimum of eight sample types, including duplicates of the centroid, are required. However, it is difficult to collect a dataset based on DoE in the early stages of pharmaceutical development when the candidate compound is particularly expensive. Reducing the cost and human resources used in pharmaceutical development is essential because early proof-of-concept studies are crucial to reducing the total costs related to the development of medicines (Paul et al., 2010).

For efficient construction of a response surface, we focused on the application of placebo data. Therefore, the aim of this study was to clarify the relationships between the response surfaces of placebo and active pharmaceutical ingredient (API)-containing tablets. We also attempted to construct a reliable response surface with a small number of samples by utilizing the association between placebo and API-containing tablets. This approach leads to a substantial decrease in the number of datasets required for the construction of the RSM. In addition, it enables the efficient simultaneous calculation of the optimal formulation and design space, and shortens the pharmaceutical development period.

2. Materials and methods

2.1. Materials

Lactose (LAC, Pharamatose 100 M; DFE Pharma, Goch, Germany), cornstarch (CS, Graflow M; Nippon Starch Chemical Co., Ltd., Osaka, Japan) and microcrystalline cellulose (MCC, Ceolus PH-101; Asahi Kasei Chemicals Co., Ltd., Tokyo, Japan), acetaminophen (ACE; Yamamoto Corporation Co., Ltd., Osaka, Japan), mannitol (MAN, Granutol S; Freund Corporation, Tokyo, Japan) and croscarmellose sodium (CCS, KICCOLATE ND-200; Asahi Kasei Chemicals Co., Ltd., Tokyo, Japan) were purchased from the indicated suppliers. Magnesium stearate (Mg-St), *o*-ethoxybenzamide (ETZ), nicotinic acid (NA) and pyridoxine hydrochloride (PYH) were purchased from Wako Pure Chemical Industries, Ltd. (Osaka, Japan).

2.2. API characterization

Particle size analysis was performed on a laser diffraction particle size analyzer equipped with a Tornado dry powder system (LS 13 320; Beckman Coulter, Inc., CA, USA). The particle shape was analyzed using a scanning electron microscope (SEM) on a Hitachi Miniscope TM1000 (Hitachi High-Technologies Co., Tokyo Japan). The samples were prepared on carbon tape without evaporation coating. The microscope parameter was set to 500× (ACE, NA, PYH) or 1000× (ETZ) magnification.

2.3. Tablet preparation

To minimize the number of unit operations, the direct compression approach, which requires only mixing and tableting steps (Leane et al., 2015), was used in this study. APIs were stored at room temperature and 25% relative humidity for at least 72 h in a desiccator (digitally controlled desiccator DSD-PSPS; AS ONE Co., Ltd, Osaka, Japan). All APIs were sieved through a 355 μm mesh. The other ingredients were dried at 75 °C for 8 h. The ingredients were weighed accurately according to the experimental formulations and all the ingredients were blended in a polyethylene bag for 2 min. The final blend was directly compressed into round-faced tablets (200 mg, 8 mm diameter) using a tableting machine (AUTOTAB-100 W; Ichihachi-Seiki Co., Ltd, Kyoto, Japan). The compression pressure was set at 240 MPa.

Table 1
Formulation of model tablets.

	(mg)
API (ACE, ETZ, NA or PYH)	20
Lactose (LAC)	X_1
Cornstarch (CS)	X_2
Microcrystalline cellulose (MCC)	X_3
Magnesium stearate	1.2
Total	200

2.4. Tablet formulation

Tablets containing 10% API, 0.6% Mg-St and 89.4% powder blend composed of LAC, CS, and MCC (Table 1) were prepared. Various amounts of LAC (X_1), CS (X_2), and MCC (X_3) were selected as the formulation factors. Based on the preliminary experiments, the lower and upper limits of the levels of each factor were set as follows:

$$0 \le X_1 \le 107.3 \text{ (mg)} \quad (1)$$

$$0 \le X_2 \le 107.3 \text{ (mg)} \quad (2)$$

$$71.5 \le X_3 \le 160.9 \text{ (mg)} \quad (3)$$

$$X_1 + X_2 + X_3 = 178.8 \text{ (mg)} \quad (4)$$

Therefore, the achievable experimental region in the simplex-lattice design was a trapezoidal shape. The formulation factors were assigned according to an extreme vertices design, as shown in Fig. 1, and ten formulations, including duplicates of the centroid, were prepared.

2.5. Evaluation of tensile strength and disintegration time

Tensile strength (TS) and disintegration time (DT) were selected as the tablet characteristics for the model. These are important properties in the early development phase of direct compression formulations because they are related to the tablets' friability, tabletability, and dissolution properties.

The tablet hardness was determined using a tablet hardness tester (Portable checker PC-30; Okada Seiko, Tokyo, Japan). TS was calculated as:

$$\text{TS} = \frac{2F}{\pi dt} \quad (5)$$

where F is the maximal diametrical crushing force, and d and t are the diameter and thickness of the tablet, respectively. The TS of each formulation was measured in triplicate.

The disintegration test was performed according to the Japanese Pharmacopoeia, 17th edition (JP17) disintegration test for tablets using a disintegration tester (NT-20H; Toyama Sangyo Co., Ltd, Osaka,

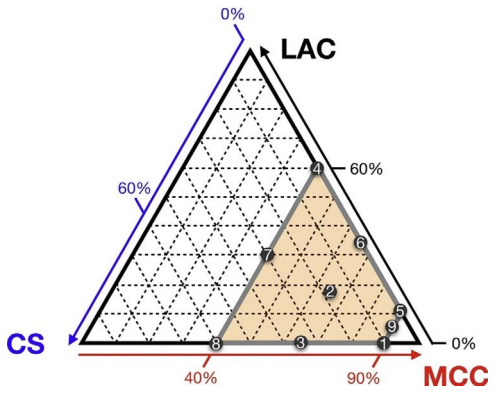

Fig. 1. Excipient composition of model tablets. Each point represents the excipient composition and formulation number of one model tablet.