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Multivariate spline interpolation as a novel method to optimize pharmaceutical formulations

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One of the difficulties in the quantitative approach for formulation design is the difficulty in understanding the actual relationship between causal factors and individual pharmaceutical responses. In this regard, several techniques were applied to determine the relationship between causal factors and the pharmaceutical responses. The generation of response surfaces using multivariate spline interpolation (MSI) has provided rapid and detailed information. Nevertheless, no application of MSI in the pharmaceutical field has been reported to date, even though it promises potential applications. To overcome the shortcomings of the classical response surface method, we newly developed a multi-objective simultaneous optimization method, in which MSI had been incorporated. The method was applied to the optimization problem of a transdermal hydrogel formulation for ketoprofen containing several chemical enhancers. Results suggested a superior function of the MSI approach.

1. Introduction

A pharmaceutical formulation is composed of several formulation factors and process variables. Several responses relating to the effectiveness, usefulness, stability, as well as safety must be optimized simultaneously. One of the difficulties in the quantitative approach for formulation design is approximating the actual relationship between causal factors and pharmaceutical responses. Another difficulty is that an optimal formulation for one property is not always desirable for the other characteristics. This is called a multi-objective optimization problem.

A response surface method (RSM) has been used for seeking acceptable formulations of pharmaceuticals (Khuri and Cornel 1987). RSM includes statistical factorial experimental design, modeling between causal factors and response variables, and multi-objective optimization for selecting the best formulation under a set of experimental restrictions. Composite experimental design can be applied for choosing rational model formulations. We can greatly reduce the number of experiments preparing the model formulations, compared with a one-factor-at-a-time experiments. 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, since theoretical relationships between causal factors and response variables are not clear. Finally, multi-objective optimization algorithms are applied for predicting the best formulation. However, prediction of pharmaceutical responses based on the quadratic polynomial is often limited and may result in the poor estimation of optimal formulations. To overcome the shortcomings of the poor estimation based on the quadratic polynomial, application of a multivariate spline interpolation (MSI) has been investigated (Wahba 1990). Among MSIs, a biharmonic spline has been effectively used as a tool to interpolate altimeter data in the field of geophysics. As a typical example, the contour plot for the ocean bed has been accurately made by using GEOS-3 and SEASAT altimeter data (Sandwell 1987). Algorithms can be applied to the multi-dimensional interpolating problems.

The basic concept of biharmonic spline interpolation is a boundary element method. Green functions of the biharmonic operator are used for minimum curvature interpolation of multi-dimensional data points (Sandwell 1987). As usual, observational data include experimental error. To avoid the fitting problem, multi-dimensional data surface including experimental error should be estimated as a sum of interpolations with a Green function and a linear polynomial equation (thin-plate estimation). This is a basic concept of thin-plate spline interpolation (Wahba 1990). Smoothing parameter, which is the ratio of Green function interpolation and thin-plate approximation, is automatically estimated by a generalized cross validation technique. The thin-plate spline interpolation has the superior function for interpolating the observational data including experimental error.

Superior function of the multi-objective simultaneous optimization technique including the MSI approach was demonstrated by optimization of a dermatological hydrogel formulation containing ketoprofen as a model drug.

2. Investigations, results and discussion

2.1 Multi-objective simultaneous optimization

When the optimization problem includes several objectives, response variables $[F_k(\mathbf{X}),\ k = 1, 2, 3, \ldots, n]$ should be incorporated into a single function in order to consider

all the responses simultaneously. Although there are some incorporation methods, we can employ a reasonable approach based on the standardized Euclidian distance between the predicted value of each response and the optimum one that was obtained individually (Takayama and Nagai 1991).

$$T(\mathbf{X}, r) = \left(\sum_{k=1}^{n} \left\{ \frac{FD_k(\mathbf{X}) - FO_k(\mathbf{X})}{SD_k} \right\}^2 \right)^{1/2} + r^{-1} \sum_{i=1}^{p} \{\varphi_i, G_i(\mathbf{X})\}^2 + r^{-1} \sum_{j=1}^{q} \{H_i(\mathbf{X})\}^2 \quad (1)$$

where $T(\mathbf{X}, r)$ is the transformed objective function, r is the perturbation parameter ($r > 0$). $FD_k(\mathbf{X})$ is the optimum value of each response variable optimized individually over the experimental region and $FO_k(\mathbf{X})$ is the estimated value of all the responses given in the same set of causal factors, $\mathbf{X}$. SD_k is the standard deviation of the observed values. $G_i(\mathbf{X})$ and $H_j(\mathbf{X})$ are the inequality and equality constraints, respectively. φ_i is a step function by which the distance function is penalized. The simultaneous optimum solution is estimated as the point, $\mathbf{X}(r)$, which gives minimum value of $T(\mathbf{X}, r)$ when the value of r is sufficiently close to zero.

2.2. *Ketoprofen hydrogel containing chemical enhancers*

A large number of chemical enhancers were synthesized by using L-menthol as a lead compound (Obata et al. 2000). Among these chemicals, 1-*O*-ethyl-3-*n*-butylcyclohexanol (OEBC) was found to be a promising compound with potent enhancement activity and relatively low skin irritation (Obata et al. 2001). Diisopropyl adipate (DIA) has also been reported to enhance the permeation of nonsteroidal anti-inflammatory drugs (Okuyama et al. 1999). In addition, several studies have reported that the lipophilic penetration enhancer combination with a short-chain alkanol, such as isopropanol (IPA), could produce a synergistic enhancement and decrease the skin irritation (Goodman et al. 1989). The combined effect of penetration absorption as well as skin irritation was evaluated in the ketoprofen hydrogel formulation incorporating OEBC, DIA and IPA (Wu et al. 2001).

2.2.1. *Preparation of model formulations*

A three-factor spherical second-order composite experimental design was used (Table). Sixteen types of ketoprofen hydrogels composed of hydroxypropylcellulose (HPC) and hydroxyethylcellulose (HEC) as gel bases, OEBC and DIA as penetration enhancers, and IPA and water as solvents were prepared. The quantities of OEBC (X_1), DIA (X_2) and IPA (X_3) were selected as causal factors. The amounts of ketoprofen, HPC, and HEC were fixed at 3, 1, and 1%, respectively. The total amount of each hydrogel was adjusted to 100% by the addition of water. The gel bases, HPC and HEC, were dissolved in water. Ketoprofen was dissolved in IPA containing OEBC and DIA, separately. Then, the both components were mixed well, and the resulting hydrogels were stored in airtight containers at room temperature prior to use.

2.2.2. *Evaluation of percutaneous absorption and skin irritation*

To evaluate the percutaneous absorption of experimental formulations, the test hydrogel was applied to rat abdominal skin. Blood samples were taken via the jugular vein at 1–8 h after topical application. The concentration of ketoprofen in the blood was analyzed, and the rate of penetration (R_p) of ketoprofen was estimated (Takayama and Nagai 1991).

Irritation evoked by the model formulations on rat skin was microscopically judged at the end of the absorption experiment. The site of application of each formulation was excised and fixed. The microscopic findings were graded as five levels of irritation from no change to a marked change including liquefaction of epidermis, edema of subepidermis, collagen fiber swelling, and inflammatory cell infiltration in both the dermis and hypodermis, as well as degeneration of skin appendages. The total irritation score (TIS) was obtained by summation of each irritation score and used as an index of skin damage caused by the application of ketoprofen hydrogel (Takayama and Nagai 1991).

Table: Experimental design and model formulations of ketoprofen hydrogels

Formulation	X_1	OEBC (%)	X_2	DIA (%)	X_3	IPA (%)
1	−1	0.42	−1	−1.06	−1	24.23
2	−1	0.42	−1	1.06	1	35.77
3	−1	0.42	1	3.94	−1	24.23
4	−1	0.42	1	3.94	1	35.77
5	1	1.58	−1	1.06	−1	24.23
6	1	1.58	−1	1.06	1	35.77
7	1	1.58	1	3.94	−1	24.23
8	1	1.58	1	3.94	1	35.77
9	−1.732	0	0	2.50	0	30.00
10	1.732	2.00	0	2.50	0	30.00
11	0	1.00	−1.732	0	0	30.00
12	0	1.00	1.732	5.00	0	30.00
13	0	1.00	0	2.50	−1.732	20.00
14	0	1.00	0	2.50	1.732	40.00
15	0	1.00	0	2.50	0	30.00
16	0	1.00	0	2.50	0	30.00

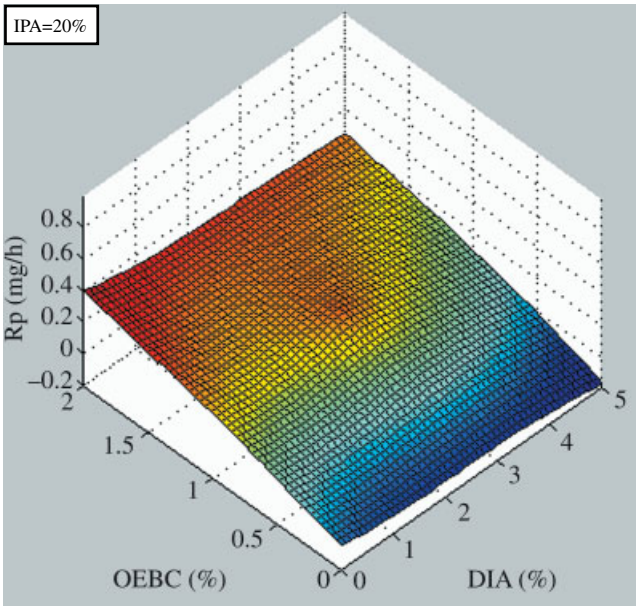
The amounts of ketoprofen, HPC and HEC were fixed at 3, 1 and 1%, respectively. The total amount of each hydrogel was adjusted to 10.00 g by addition of water

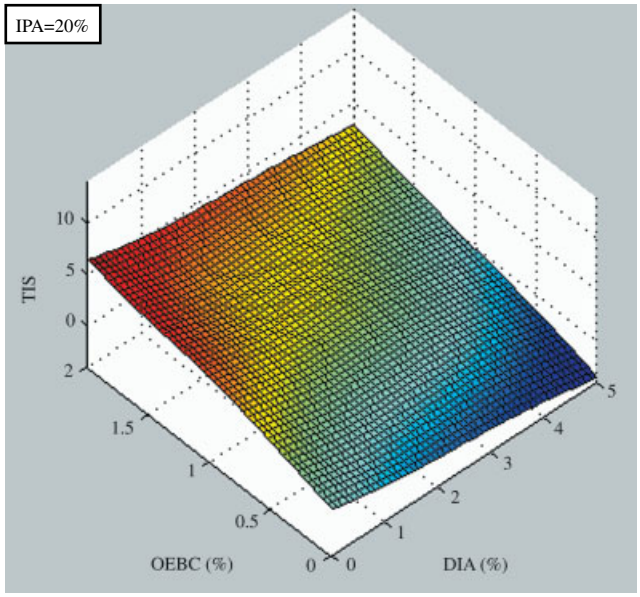
2.2.3. *Prediction of response variables*

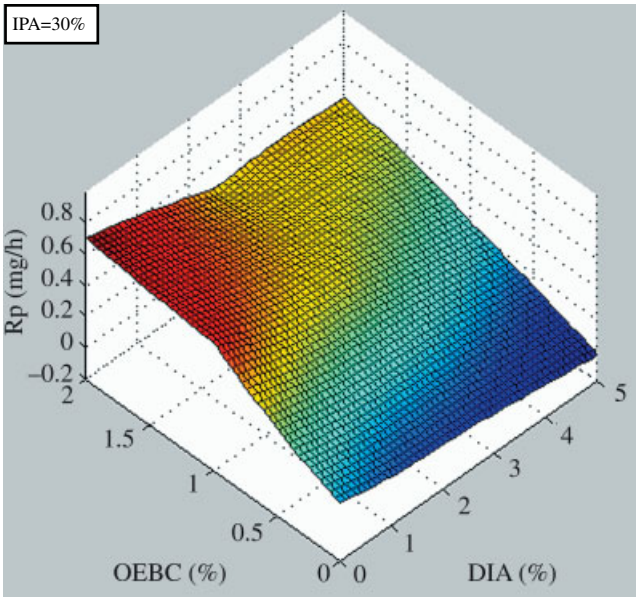
MSI was applied to the prediction of response variables such as R_p and TIS as a function of causal factors. The response surfaces generated by MSI are shown in Figs. 1 and 2, as a function X_1 (the amounts of OEBC), X_2 (the amounts of DIA) and X_3 (the amounts of IPA). The response surfaces generated by MSI clearly demonstrated the combined effect of OEBC and the other factors on both R_p and TIS values. Furthermore, the nonlinear relationship between the causal factors and the responses was represented well with the response surface predicted by MSI. Generally, the quantitative relationships between causal factors and response variables *in vivo* are thought to be complex and nonlinear. This may suggest that MSI is useful in cases when approximations of such relationships are required.

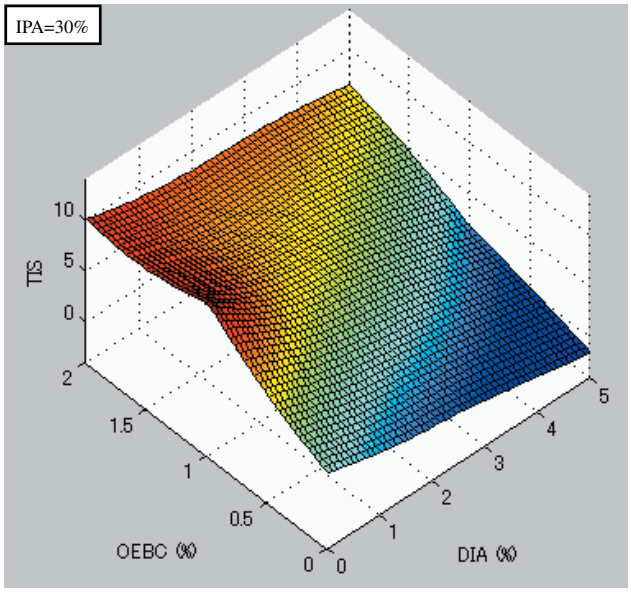
2.2.4. *Simultaneous optimization*

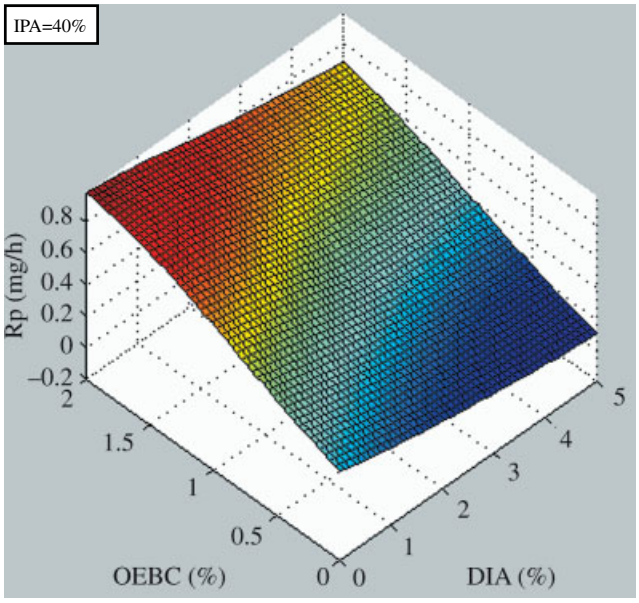
Simultaneous optimization was performed according to the Euclidian distance function above described. As an optimal value of factors, OEBC = 1.26%, DIA = 4.87% and IPA = 31.7% were predicted. The optimum formulation predicted by MSI exhibited the prominent activity on the











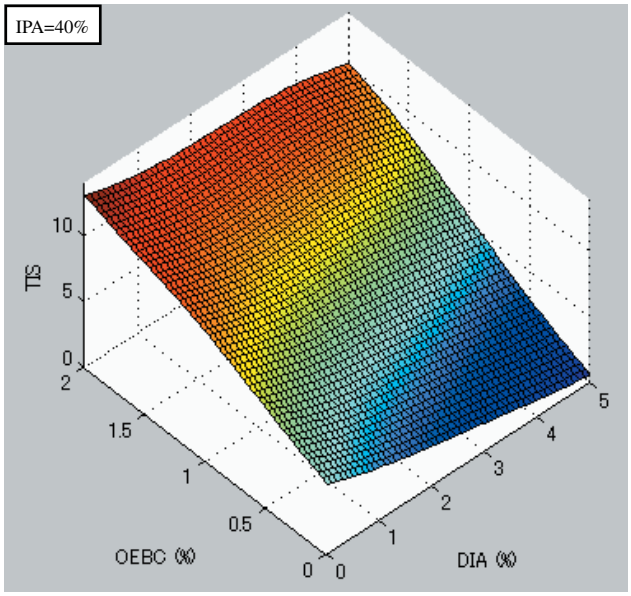


Fig. 1: Response surface of the rate of penetration (Rp) generated by the multivariate spline interpolation (MSI) as a function of the amounts of OEBC, DIA and IPA

Fig. 2: Response surface of the total irritation score (TIS) generated by the multivariate spline interpolation as a function of the amounts of OEBC, DIA and IPA

percutaneous absorption of ketoprofen (Rp = 341.6 μg/h) despite the finding that the skin damage was sufficiently low (TIS = 4).

In general, strong percutaneous absorption action can be obtained by increasing the concentrations of the chemical enhancers, but this increase often causes significant skin damage. However, the above findings clearly demonstrate that strong enhancement action as well as low skin damage can be attained by seeking the optimal combination of enhancers and other additives in the formulations. It is obvious that it would be impossible to reach the exact combination of causal factors using a normal analysis based on a one-factor-at-a-time experiment.

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