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Mini-Review

Artificial Neural Network as a Novel Method to Optimize Pharmaceutical Formulations

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One of the difficulties in the quantitative approach to designing pharmaceutical formulations is the difficulty in understanding the relationship between causal factors and individual pharmaceutical responses. Another difficulty is desirable formulation for one property is not always desirable for the other characteristics. This is called a multi-objective simultaneous optimization problem. A response surface method (RSM) has proven to be a useful approach for selecting pharmaceutical formulations. However, prediction of pharmaceutical responses based on the second-order polynomial equation commonly used in RSM, is often limited to low levels, resulting in poor estimations of optimal formulations. The aim of this review is to describe the basic concept of the multi-objective simultaneous optimization technique in which an artificial neural network (ANN) is incorporated. ANNs are being increasingly used in pharmaceutical research to predict the non-linear relationship between causal factors and response variables. The usefulness and reliability of this ANN approach is demonstrated by the optimization for ketoprofen hydrogel ointment as a typical numerical example, in comparison with the results obtained with a classical RSM approach.

KEY WORDS: artificial neural networks; response surface method; multi-objective optimization; polynomial equation; pharmaceutical formulation.

INTRODUCTION

A pharmaceutical formulation is composed of several formulation factors and process variables. Several responses relating to the effectiveness, safety, and usefulness must be optimized simultaneously. Consequently, expertise and experience are required to design acceptable pharmaceutical formulations. One of the difficulties in the quantitative approach for formulation design is understanding the actual relationship between causal factors and individual pharmaceutical responses. Another difficulty is a desirable formulation for one property is not always desirable for the other characteristics. This is called a multi-objective optimization problem.

A computer optimization technique, based on a response surface method (1), has proven to be a useful approach for selecting pharmaceutical formulations (2–10). The optimization procedure based on RSM includes statistical experimental designs, multiple regression analysis, and mathematical optimization algorithms for seeking the best formulation under a set of constrained equations. Composite experimental designs can be applied to prepare systemic model formulations which are composed of several formulation factors and process factors. Response variables of these model formulations are predicted quantitatively from the combination of these factors. In general, since theoretical relationships between response variables and causal factors are not clear, multiple regression analysis can be applied to the prediction of response variables on the basis of a second-order polynomial equation. Finally, optimization algorithms are applied for deciding the best formulation.

Unfortunately, prediction of pharmaceutical responses based on the polynomial equation is often limited to low levels, resulting in the poor estimation of optimal formulations. In order to overcome the shortcomings in RSM, a multi-objective simultaneous optimization technique incorporating an artificial neural network (ANN) has been developed (11,12). ANN is a learning system based on a computational technique which can simulate the neurological processing ability of the human brain (13). ANN has successfully been applied to solving various problems in pharmaceutical research such as product development (11,12,14), estimating diffusion coefficients (15), predicting the mechanism of drug action (16), and predicting

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ABBREVIATIONS: RSM, response surface method; ANN, artificial neural network; w_{pq}, weight matrix of ANN; α, shape parameter of sigmoidal function; N_{hidden}, number of hidden units; N_{sample}, number of data pairs; N_{input}, number of input units; N_{output}, number of output units; β, overdetermination parameter; X, factor vector; $F(X)$, objective function; $G_i(X)$, inequality constraint; $H_i(X)$, equality constraint; $T(X, r)$, transformed objective function; r, perturbation parameter; Φ_i, step function; $d_{1,2,3,\ldots,n}$, desirability function; D_{total}, geometric mean of desirability function; $S(X)$, distance function; SD_k, standard deviation of observed value for each response; $FD_k(X)$, individual optimum value of each response; $FO_k(X)$, estimated value of response in the same set of causal factors; MET, *O*-ethylmenthol; X_1, amount of ethanol; X_2, amount of MET; R_p, penetration rate; t_L, lag time; *TIS*, total irritation score.

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pharmacokinetic parameters (17–20). For instance, Hussain et al. (14) applied ANN to analyze the quantitative relationships between several formulation factors and release parameters in a hydrophilic matrix capsule system containing cellulose polymers. It was found that ANN predictions are more accurate than those predicted by polynomial equations.

The aim of this review is to describe the basic concept of the multi-objective optimization technique incorporating ANN (11,12,21). The usefulness and reliability of this ANN approach were also demonstrated by the optimization for ketoprofen hydrogel ointment as a typical numerical example (12).

ANN STRUCTURE

Theoretical details of a hierarchical ANN have been given elsewhere. Briefly, the general structure of ANN has one input layer, one or more hidden layers, and one output layer (Fig. 1a). Each layer has a few units corresponding to neurons. The units in neighboring layers are fully interconnected with links corresponding to synapses. The strengths of connections between two units are called "weights". In each hidden layer and output layer the processing unit sums its input from the previous layer and then applies the sigmoidal function to compute its output to the following layer according to the following equations:

$$y_q = \sum w_{pq} x_p \quad (1)$$

$$f(y_q) = 1/\{1 + \exp(-\alpha y_q)\} \quad (2)$$

where w_{pq} is the weight of the connection between unit q in the current layer to unit p in the previous layer, and x_p is the output value from the previous layer. $f(y_q)$ is conducted to the following layer as an output value. Alpha is a parameter relating to the shape of the sigmoidal function. Non-linearity of the sigmoidal function is strengthened with an increase in α. ANN learns an approximate non-linear relationship by a procedure called "training", which involves varying weight values. Training is defined as a search process for the optimized set of weight values which can minimize the squared error between the estimation and experimental data of units in the output layer. A back-propagation method with the steepest descent algorithm has been widely applied for training ANN (22). Training is a very long iterative process, and ANN often gets stuck in a local minima. Certain empirical techniques have been reported to improve the convergence of ANN in the global minima (13,23). Another essential approach is to use an extended Kalman filter algorithm for ANN training (24–26). We can greatly reduce the number of iterative training and avoid to a certain extent, ANN getting stuck in a local minima (24) by using the extended Kalman filter algorithm. Although multiple layers can be set between the input layer and the output layer, many ANNs consist of only one hidden layer (23). One layer is usually sufficient to provide adequate prediction even if continuous variables are adopted as the units in the output layer (27–29).

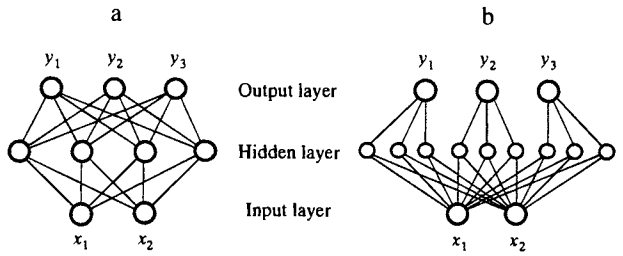

Fig. 1. Typical structures of hierarchical ANN. a, general ANN composed of two input units, four hidden units and three output units; b, partitioned structure of ANN composed of two input units, three hidden units and three output units. Every response (output unit) in the partitioned ANN can be estimated by the independent set of units in the hidden layer, although the same units in the hidden layer are used in common for the prediction of different responses in the case of general ANN.

In order to enable reasonable prediction of each response variable by ANN, Carpenter *et al.* (30) introduced an equation relating to the number of units in the input layer, the hidden layer and the output layer:

$$N_{hidden} = (N_{sample}/\beta - N_{output})/(N_{input} + N_{output} + 1) \quad (3)$$

where N_{hidden} is the number of hidden units, N_{input} is the number of input units, N_{output} is the number of output units and N_{sample} is the number of training data pairs. The constant β is the parameter relating to the degree of overdetermination.

Equation (3) can be rewritten as:

$$N_{sample} = \beta\{N_{hidden}(N_{input} + 1) + N_{output}(N_{hidden} + 1)\} \quad (4)$$

The unknown parameters associated with ANN are the weights of the network. Overdetermined ($\beta > 1$), exact determined ($\beta = 1$) and underdetermined ($\beta < 1$) approximations have more, an equal number, or fewer training data pairs than the number of unknown parameters associated with the approximation. For example, $\beta = 1.5$ would give a 50% overdetermined approximation. With an underdetermined approximation ($\beta < 1$), each output data point is fitted perfectly by iterative training, but the approximation may vary wildly between the output data points; i.e., the overtraining problem. Thus, the selection of $\beta > 1$ is usually recommended to enable reasonable prediction of each response variable adopted as the unit in the output layer. However, it may be possible to reduce the β value; i.e., $\beta \cong 1$, when statistical experimental designs are employed to prepare the model formulations, because the independency among the factors is highly ensured by using such designs (1).

In the general structure of ANN (Fig. 1a), the same units in the hidden layer are used for the prediction of different response variables. This may occasionally lead to poor estimation of some responses. To avoid this problem, Fujikawa *et al.* (31) developed a partitioned ANN in which every response could be estimated by an independent set of units in the hidden layers (Fig. 1b). This is equivalent to predicting each response variable independently by different ANN systems. In the optimization study for pharmaceuticals, model formulations are usually prepared according to statistical experimental designs in order to reduce the number of experiments. Hence, the number of data pairs available for ANN training is limited to low levels. This may often lead to the underdetermined approximation in the general ANN structure composed of plural units in the input, hidden, and output layers. On the other hand, the partitioned ANN is much easier to avoid the underdetermined approximation because $N_{output} = 1$ can be adopted in equations (3) and (4).

SINGLE-OBJECTIVE OPTIMIZATION

In general, the optimization problems of pharmaceutical formulations can be viewed in terms of minimization (or maximization) of the objective function, $F(X)$, under the following inequality and/or equality constraints:

$$G_i(X) \geq 0 \qquad i = 1, 2, 3, \ldots \tag{5}$$

$$H_j(X) = 0 \qquad j = 1, 2, 3, \ldots \tag{6}$$

where $G_i(X)$ is the inequality constraint and $H_j(X)$ is the equality constraint. In the case of a fully-trained ANN, $F(X)$ corresponds to the predicted value of response variable adopted as the unit in the output layer and X is a set of causal factors used as the units in the input layer. As it is difficult to solve the constrained optimization problem described above without any mathematical modifications, the constrained optimization problem is transformed to one that is unconstrained by adding a penalty function as follows:

$$T(X, r) = F(X) + r^{-1} \sum \Phi_i \{G_i(X)\}^2 + r^{-1} \sum \{H_j(X)\}^2 \tag{7}$$

$$\text{when } G_i(X) < 0,\ \Phi_i = 1;\ \text{when } G_i(X) \geq 0,\ \Phi_i = 0$$

where $T(X, r)$ is the transformed unconstrained objective function, r is a perturbation parameter ($r > 0$) of $T(X, r)$ and Φ_i is a step function by which the objective function, $F(X)$, is penalized. The second and third terms in equation (7) act as penalty functions because these values increase abruptly when the values of $G_i(X)$ are negative or the $H_j(X)$ values deviate from zero. The meaning of the perturbation parameter, r, and the means of obtaining a global optimum solution are described fully in a previous paper (5). The optimum solution is obtained as the point, $X(r)$, which gives the minimum value of $T(X, r)$ when the value of r is sufficiently close to zero.

MULTI-OBJECTIVE OPTIMIZATION

When the optimization problem includes several objectives, response variables should be incorporated into a single function in order to consider all responses simultaneously. Derringer and Suich (32) introduced general transformations based on the concept of desirability associated with a given response function. This transformation, a desirability function method, requires minimum and maximum acceptable value for every response. The individual response can be normalized to the desirability functions, $d_{1, 2, 3, \ldots, n}$, which have values inside the interval [0, 1] by using the distance between minimum and maximum acceptable values. The normalized functions are then combined into a multi-objective function, D_{total}, by means of the geometric mean of predicted values of each function:

$$D_{total} = (d_1 \times d_2 \times d_3 \times \cdots \times d_n)^{1/n} \tag{8}$$

The desirability function method has been widely applied to the development of pharmaceutical products (33–35) and the method has been useful for solving practical optimization problems. However, one of the basic shortcomings of this approach is the subjectivity in the selection of the minimum and maximum acceptable values for each response. Namely, improper values of minima and/or maxima may lead to inaccurate solutions for the optimum formulation. In order to avoid the problem of subjectivity in application of the desirability function method, we can employ another approach based on the generalized distance between the predicted value of each response and the optimum one that was obtained individually (7,36):

$$S(X) = (\sum [\{FD_k(X) - FO_k(X)\}/SD_k]^2)^{1/2} \tag{9}$$

where $S(X)$ is the distance function generalized by the standard deviation, SD_k, of the observed values for each response variable, $FD_k(X)$ is the optimum value of each response variable optimized individually over the experimental region and $FO_k(X)$ is the estimated value of all the responses given in the same set of causal factors, X. Substituting $F(X)$ in equation (7) with $S(X)$ in equation (9), the transformed function, $T(X, r)$, in the case of multi-objectives can be given as follows:

$$T(X, r) = (\sum [\{FD_k(X) - FO_k(X)\}/SD_k]^2)^{1/2} + r^{-1} \sum \{\Phi_i G_i(X)\}^2 + r^{-1} \sum \{H_j(X)\}^2 \tag{10}$$

when $G_i(X) < 0$, $\Phi_i = 1$; when $G_i(X) \geq 0$, $\Phi_i = 0$.

The simultaneous optimum solution is estimated as the point, $X(r)$, which gives minimum value of $T(X,r)$ when the value of r is sufficiently close to zero.

Table I. Experimental Design and Model Formulae of Ketoprofen Hydrogels Containing Various Amounts of Ethanol (X_1) and MET (X_2)

Formulation	X_1	Ethanol (%)	X_2	MET (%)
1	$\sqrt{2}$	50.0	0	1.50
2	$-\sqrt{2}$	20.0	0	1.50
3	0	35.0	$\sqrt{2}$	3.00
4	0	35.0	$-\sqrt{2}$	0
5	1	45.6	1	2.56
6	1	45.6	−1	0.44
7	−1	24.4	1	2.56
8	−1	24.4	−1	0.44
9	0	35.0	0	1.50
10	0	35.0	0	1.50
11	0	35.0	0	1.50
12	0	35.0	0	1.50

Note: The amounts of ketoprofen, carboxyvinyl polymer and triethanolamine were fixed at 0.30 g, 0.15 g and 0.20 g, respectively. The total amount of each hydrogel was adjusted to 10.0 g by the addition of water.

Table II. Experimental Values of Response Variables

Formulation	R_p (mg/h)	t_L (h)	*TIS*
1	1.45	0.900	17
2	0.468	0.626	4
3	1.84	0.190	16
4	0.00499	1.08	0
5	1.36	0.854	16
6	0.422	0.931	14
7	1.56	0.235	11
8	0.273	0.956	1
9	0.918	0.904	12
10	1.06	0.954	13
11	1.37	0.913	17
12	1.08	0.929	17

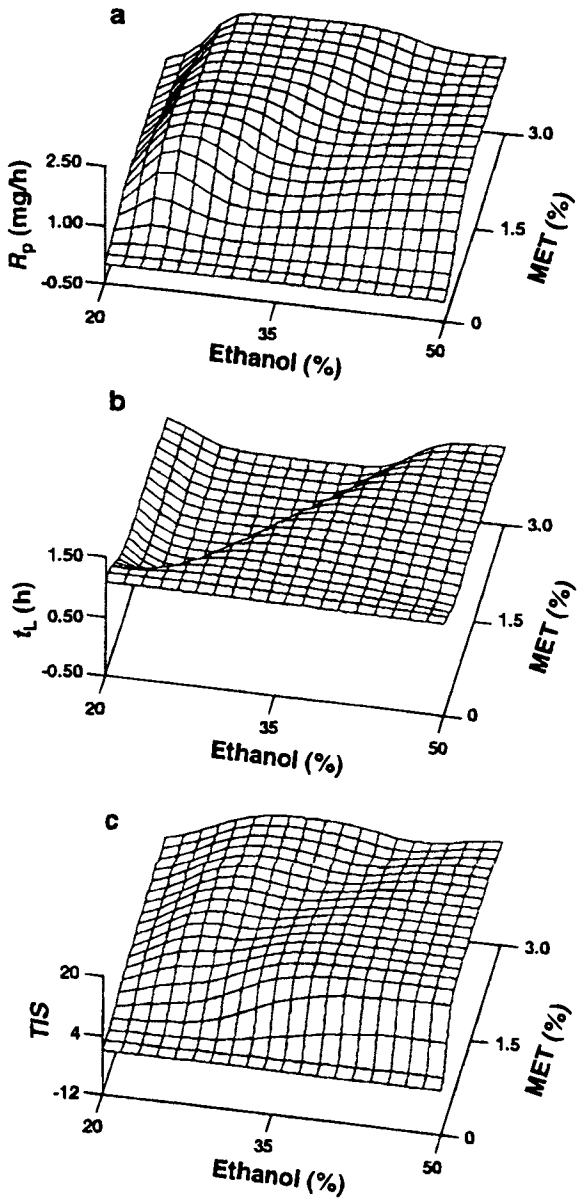

Fig. 2. Response surfaces of R_p, t_L and *TIS* predicted by ANN as a function of the amounts of ethanol and MET. a, R_p; b, t_L; c, *TIS*.

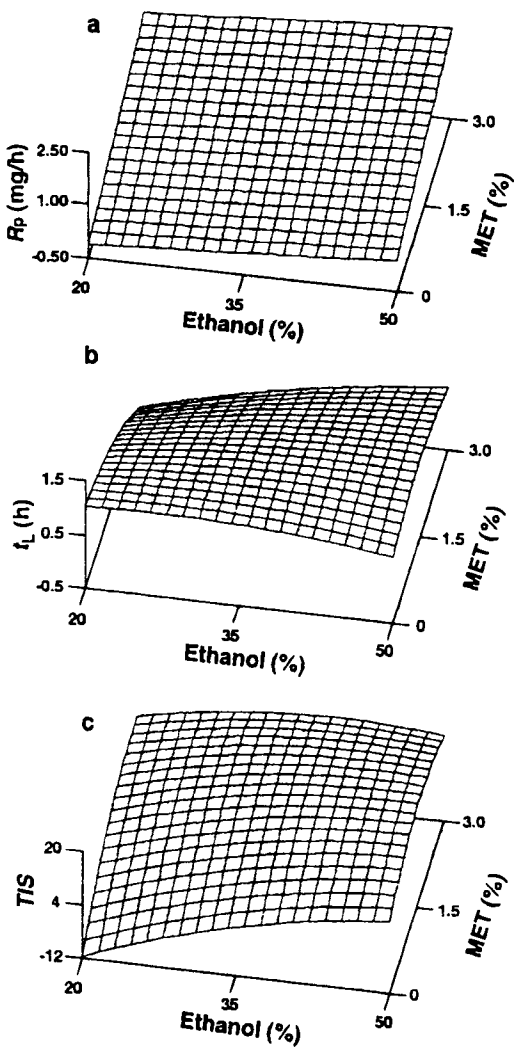

Fig. 3. Response surfaces of R_p, t_L and *TIS* predicted by second-order polynomial equation as a function of the amounts of ethanol and MET. a, R_p; b, t_L; c, *TIS*.

A NUMERICAL EXAMPLE

A transdermal therapeutic system requires drugs to penetrate the stratum corneum into the systemic circulation in sufficient concentrations for the desired therapeutic effect. To achieve this, an absorption enhancer is usually needed. Recently, Negishi *et al.* (37) synthesized *O*-alkylmenthol and *O*-acylmenthol derivatives and investigated their ability to enhance percutaneous absorption of ketoprofen from alcoholic hydrogels in rats *in vivo*. Among these compounds, *O*-ethylmenthol (MET) was the most promising compound, with the greatest promoting action and relatively low skin irritancy (37,38). We therefore applied the optimization technique described above to the design of a formulation for a ketoprofen hydrogel containing MET as an absorption enhancer (12).

The amounts of ethanol (X_1) and MET (X_2) in the hydrogels were selected as causal factors. A central composite spherical design with four center point replications was used for preparing the model formulations (Table I). The concentrations of ketoprofen, carboxyvinyl polymer and triethanolamine in the hydrogels were fixed at 3.0, 1.5 and 2.0%, respectively. An appropriate amount of water was added to adjust the total weight of the hydrogels. Pharmacokinetic parameters, the apparent penetration rate (R_p), and the lag time (t_L), of ketoprofen percutaneously absorbed from model formulations were determined in rats as prime response variables. The skin damage evoked by each formulation was microscopically judged and graded as the total irritation score (*TIS*) for skin safety factors (7). These response variables are summarized in Table II.

A set of causal factors and response variables was used as tutorial data for the partitioned ANN (12,31). According to equation (3), $N_{hidden} = 2$ was employed as the number of units in the hidden layer. Degree of overdetermination in this partitioned ANN structure ($N_{sample} = 12$, $N_{input} = 2$, $N_{hidden} = 2$, $N_{output} =$

Table III. Predicted and Experimental Response Variables for the Optimal Formula

Response	Predicted	Experimental[a]
R_p (mg/h)	1.45	1.21 ± 0.19
t_L (h)	0.264	0.713 ± 0.106
TIS	9.42	10.8 ± 1.0

[a] The mean ± *S.D.* of 4 determinations.

1) was estimated to be 33%. The extended Kalman filter algorithm was applied for training ANN (24). Figures 2 and 3 show the three-dimensional diagrams of each response variable as a function of X_1 (amounts of ethanol) and X_2 (amounts of MET). Nonlinear relationships between the causal factors and the response variables were well represented with response surface predicted by ANN (Fig. 2). On the other hand, the second-order polynomial equation exhibited relatively plain surfaces for all responses (Fig. 3). Further, polynomial equation analysis predicted negative values in the boundary region of the experimental limits, and were outside of physical reality (Fig. 3). Generally, the quantitative relationships between causal factors and response variables *in vivo* are thought to be complex and nonlinear. ANN seems to be more useful than polynomial equations in cases where approximations of such relationships are required.

Optimization of a ketoprofen hydrogel was performed according to the generalized distance function defined in equation (10) under the restriction of the experimental region ($2 \geq X_1^2 + X_2^2$; in coded form). The optimal values of individual response variables, $FD_k(\boldsymbol{X})$, were calculated before simultaneous optimization was carried out; i.e., the individual maximum R_p, the minimum t_L and the minimum *TIS* values, respectively. ANN training and the estimation of simultaneous optima were repeated several times and the results were fairly stable. The simultaneous optimal solution was estimated at 23% as ethanol and 2.2% as MET. The predicted and the experimental response variables for the optimal formulation are given in Table III. The observed results of R_p and *TIS* coincided well with the predictions although the result of t_L did not. The difference between the predicted and the experimental t_L value was about 30 min. In order to predict t_L more precisely, other experiments such as an *in vitro* permeation study are required. However, R_p and *TIS*, which are very significant for effectiveness and safety, were satisfactorily predicted.

In conclusion, the multi-objective simultaneous optimization technique incorporating ANN is useful for optimizing pharmaceutical formulae when predictions of pharmaceutical responses based on the second-order polynomial equations are limited to low levels.

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