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COMMUNICATION

Formulation Optimization Technique Based on Artificial Neural Network in Salbutamol Sulfate Osmotic Pump Tablets

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ABSTRACT

The aim of this study was to develop a formulation optimization technique in which an artificial neural network (ANN) was incorporated; 30 kinds of salbutamol sulfate osmotic pump tablets were prepared, and their dissolution tests were performed. The amounts of hydroxypropyl methylcellulose (HPMC), polyethylene glycol 1500 (PEG1500) in the coating solution, and the coat weight were selected as the causal factors. Both the average drug release rate v *for the first 8 hr and the correlation coefficient* r *of the accumulative amount of drug released and time were obtained as release parameters to characterize the release profiles. A set of release parameters and causal factors was used as training data for the ANN, and another set of data was used as test data. Both sets of data were fed into a computer to train the ANN. The training process of the ANN was completed until a satisfactory value of error function* E *for the test data was obtained. The optimal formulation produced by the technique gave the satisfactory release profile since the observed results coincided well with the predicted results. These findings demonstrate that an ANN is quite useful in the optimization of pharmaceutical formulations.*

Key Words: *Artificial neural network; Optimization; Osmotic pump; Salbutamol sulfate.*

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INTRODUCTION

Formulation factors and process variables have significant effects on the effectiveness, safety, and usefulness of pharmaceutical formulations. So, expertise and experience are required to design excellent formulations. Sometimes, the complicated relationship between causal factors and individual pharmaceutical responses brings difficulties to the researchers. In addition, there is a multiobjective optimization problem, that is, a desirable formulation should meet more than two requirements, making the formulation design even harder. The aim of this paper was to establish a formulation optimization technique in which an artificial neural network (ANN) was incorporated to solve the above-stated problems. An ANN is a learning system based on a computation technique; it attempts to simulate the neurological processing ability of the human brain (1). It has been applied to solving problems in pharmaceutical sciences recently (2–5). The complicate nonlinear relationship between causal factors and pharmaceutical responses can be grasped by iterative training with data obtained from experiments. The technique provided by this paper was validated by the application to the formulation design of salbutamol sulfate osmotic pump tablets.

ARTIFICIAL NEURAL NETWORKS IN GENERAL

A typical ANN consists of one input layer, one hidden layer, and one output layer (Fig. 1). Each layer has some units that correspond to neurons. The training procedure for the ANN often used is described as a two-step process: the feed-forward step and the back-propagation step. During the feed-forward step, each unit in the hidden layer sums its input and then applies the sigmoidal function to compute its output. The calculation processes are represented as the following equations:

$$S = \Sigma W_{ij} X_I$$

$$F(S) = 1/[1 + \exp(S)]$$

where W_{ij} is the weight of the connection between unit i in the current layer to unit j in the following layer, X_i is the output value from the previous layer or the value of the causal factors for the input layer, and S is the weighted sum. Therefore, $F(S)$ is conducted to the following layer as the output value. The units in the output layer do the same thing as the units in the hidden layer. The ultimate output of the output layer is regarded as the estimated release parameter. The error function E was calculated according to the following equation:

$$E = \frac{1}{2} \sum_{p=1}^{p} \sum_{j=1}^{m} (Y_{pj} - R_{pj})^2$$

where E is the value of total error, P is the number of the data, m is the number of the unit for the output layer, Y_{pj} is the jth pharmaceutical response for the pth data calculated from the ANN, and R_{pj} is the jth pharmaceutical response for the pth data determined in the experiments.

To make the ANN represent the nonlinear relationship well, some techniques are employed to make the error function smallest. In this paper, the first derivative method is used to minimize the error function in the back-propagation step. The calculations begin at the output layer and progress backward through the network to the input layer. The calculation process for the output layer can be summarized as follows:

$$\delta_j = (Y_j - R_j) f'(S_j)$$

For a hidden layer, the computation can be represented as the following equation:

$$\delta_j = [\Sigma(\delta_k W_{kj})] f'(S_j)$$

where δj is the error value of unit j, Y_j is the estimated result of the ANN, R_j is the result of the experiment, $f'(S_j)$ is the first derivative of the sigmoid function, δ_k is the error of unit k in the output number, and W_{kj} is the connection between units k and j. The connection weight adjustment is done as shown below:

$$\delta W_{jI} = \alpha R_i \delta_j$$

where α is the learning rate of the network. The training process continued for thousands of times until the ideal

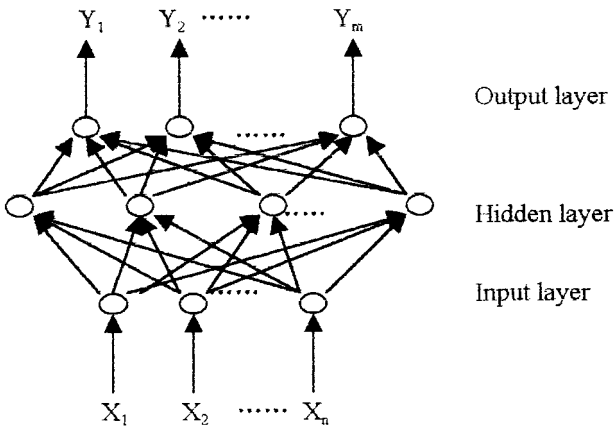

Figure 1. The structure of an artificial neural network.

value of E was obtained. By iterative training, the ANN system tends to obtain the nonlinear relationship between the causal factors and the pharmaceutical response and contribute to formulation optimization.

MATERIALS AND METHODS

Materials

Salbutamol sulfate was purchased from Lisheng Pharmaceutical (Tianjin, China). Hydroxypropyl methylcellulose (HPMC; the viscosity of 2% HPMC aqueous solution is 0.05Pa · s) was purchased from Ruitai Chemical Company, Limited (Shandong, China); polyethylene glycol 1500 (PEG1500; average molecule weight 1300–1700) was purchased from Shanghai Chemical Company, Limited (Shanghai, China); cellulose acetate (CA; acetyl content 39.8%) was generously supplied by Eastman Company, Limited (Kingsport, TN). Polyvinylpyrrolidone (PVP) was purchased from Kaiyuan Chemical (Henan, China); carboxymethyl cellulose sodium (CMC-Na) was purchased from Shenyang Chemical (Shenyang, China). The other chemicals used were analytical grade.

Preparation of the Salbutamol Sulfate Osmotic Pump Tablets

Salbutamol sulfate, CMC-Na, and PVP were mixed well in a polyethylene bag, 60% alcohol solution was added to make granules by passing through a sieve, and the granules were left to dry at 50°C for 12 hr. A tablet with a diameter of 7 mm was prepared by compressing the mixture.

According to the experimental design (Table 1), 20 formulations were prepared as training formulations, and 3000 tablets were coated by 2.4% cellulose acetate methylene chloride–ethanol (4:1) solution with different concentrations of HPMC and PEG1500. The coat weight was controlled by the volume of the coating solution that was consumed in the coating process. The coated tablet was dried at 40°C for 48 hr before a 0.4-mm orifice was drilled by laser on one side of the tablet. The coat weight was the mean value of tablet weight gain for 50 tablets.

Dissolution Test

The dissolution tests of salbutamol sulfate osmotic pump tablets were carried out using a paddle method.

Table 1

Experimental Design of Salbutamol Sulfate Osmotic Pump Tablets

Formulation	HPMC ($g \cdot 500\ ml^{-1}$)	PEG1500 ($g \cdot 500\ ml^{-1}$)	Coat Weight (mg)	r	V ($mg \cdot hr^{-1}$)
1	3.500	1.750	5.35	.9145	1.23
2	3.000	1.500	3.57	.9169	1.14
3	3.000	0	2.75	.7831	1.07
4	3.000	1.500	6.55	.9693	0.53
5	3.000	1.000	8.57	.9789	0.35
6	3.000	1.000	5.77	.9747	0.43
7	2.000	1.500	2.53	.5964	1.10
8	3.000	2.250	3.00	.8256	1.10
9	4.150	1.250	4.00	.8019	1.14
10	4.150	1.250	4.20	.7791	1.07
11	1.500	2.000	5.33	.9501	1.01
12	1.000	2.500	6.00	.9696	1.00
13	3.500	1.750	7.00	.9797	0.90
14	3.500	1.750	7.31	.9478	0.86
15	1.500	2.000	10.00	.9700	0.97
16	0	3.000	10.50	.8654	1.14
17	4.500	1.000	5.31	.9582	1.06
18	3.000	1.000	7.32	.9238	0.94
19	3.000	1.000	8.70	.9854	0.48
20	4.000	2.250	5.54	.9945	0.94

The amount of salbutamol sulfate released in 150 ml of water was measured at a paddle rotation speed of 50 rpm at 37°C. The amount of salbutamol sulfate released was determined by measuring the absorbance at 276 nm using an UV-260 ultraviolet spectrophotometer (Shimadzu Co., Tokyo, Japan). All the tests were performed with 6 tablets.

Computer Program

The computation was carried out on an IBM 80-586 personal computer. The program used for the formulation optimization into which the ANN was incorporated was written by us using Visual Basic 5.0 language. The data can be input through Microsoft Excel 97®, and the results together with the graph would also be given using a Microsoft Excel 97 interface.

RESULTS AND DISCUSSION

Release Behaviors of the Training Formulations

Table 1 shows the dissolution results of the training formulations. Since the osmotic pump tablets have an excellent zero-order release character, the tablets should release the same amount of drug in the same period. On the other hand, the drug release rate is also important concerning the ideal therapeutic effect. Both the average drug release rate v for the first 8 hr and the correlation coefficient r of the accumulative amount of drug released and time were selected as release parameters to characterize the release profile of the osmotic pump tablets.

Determination of Artificial Neural Network structure

Three causal factors corresponding to different levels of HPMC (X_1), PEG1500 (X_2) in the coating solution, and the coat weight (X_3) were selected as input factors. The output layer was composed of two units that represent r and v: Y_1 and Y_2, respectively. The training data composed of the causal factors and release parameters of the training formulations were fed into the computer. Another set of data, called the test data, was prepared and also fed into the ANN to validate the ability of the prediction of ANN (Table 2). All the data were converted into [0,1] before they were fed into the computer. After the training data were fed into the ANN, the error function E was calculated for training data. Then, the weights were regulated according to the method mentioned above, and the test data were put into the ANN. After the error function E was calculated for test data, a training process was completed. A three-dimensional diagram of the error function value E observed with the test data as a function of training times and number of units in a hidden layer is shown in Fig. 2.

It was found that 2 units in the hidden layer and 5000 iterative training processes were needed to obtain an excellent prediction of the response variables. The E value observed with the optimal ANN structure was 0.1165, while the optimal learning rate was 0.75.

Table 2

Test Data for the Artificial Neural Network Structure

Formulation	HPMC ($g \cdot 500\ ml^{-1}$)	PEG1500 ($g \cdot 500\ ml^{-1}$)	Coat Weight (mg)	r	v ($mg \cdot hr^{-1}$)
1	3.000	1.500	2.25	.9654	1.34
2	3.000	1.500	7.30	.8845	1.13
3	2.000	1.500	2.00	.6478	1.12
4	3.000	2.250	3.37	.7816	1.09
5	1.500	2.000	5.00	.8768	1.03
6	1.000	2.500	6.23	.9660	0.95
7	1.500	2.000	10.00	.9439	0.93
8	0	3.000	10.50	.9239	1.14
9	3.000	1.000	6.40	.9351	1.03
10	4.000	2.250	6.00	.9874	0.92

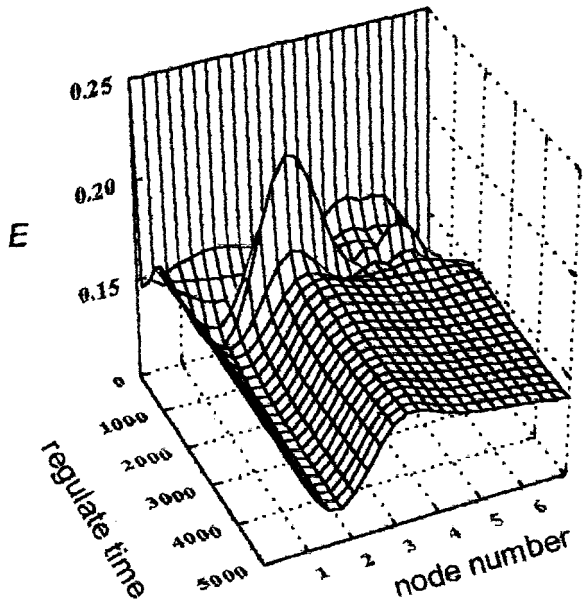

Figure 2. The graph of *E* as a function of training times and node number in the hidden layer.

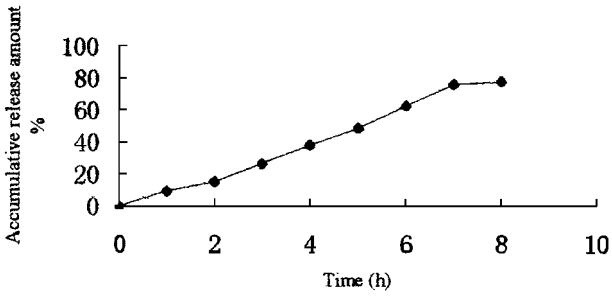

Figure 3. The results of dissolution tests for optimal formulation.

Formulation Optimization

The primary object of this paper was to find an optimal formulation that has excellent zero-order release character and an ideal drug release rate. After the ANN structure was determined, we estimated the release parameters for 1000 formulations to find the optimal formulation with the ideal release parameters. The optimal formulation provided by the technique was HPMC 3.6 g/500 ml, PEG1500 1.5 g/500 ml, with a tablet weight gain of 8.5 mg. The salbutamol sulfate osmotic pump tablets were prepared according to the optimal formulation, and their dissolution tests were performed. The results are shown in Fig. 3. From the results, we can see that the drug release rate was 0.9360 mg/hr, and the correlation coefficient was .9874. The results predicted by the computer were 0.9460 mg/hr and .9755, respectively. All the results showed that ANN was a useful tool for formulation design.

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