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Prediction of drug dissolution and hardness of indomethacin tablets using artificial neural networks and partial least-squares

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ABSTRACT

The prediction of drug dissolution and hardness of indomethacin tablets by modeling of formulation factor data has been reported. Because of several variables in tablet formulation and the presence of non-linear relationship between the amount of components and the amount of dissolved drug, partial least-squares (PLS) and artificial neural networks (ANN) techniques were used for the modeling. A validation set of simulated samples was employed for testing the accuracy and precision of the models and the performance of the models were shown in the values of the root mean square error in prediction (RMSEP). The RMSEP values for PLS model of tablet hardness was 0.84 and the RMSEP values for ANN model of drug dissolution was 1.83. The PLS technique was a useful tool in prediction of tablet hardness and the use of an ANN technique allowed the estimation of indomethacin tablets dissolution, which could not be adequately modeled by PLS.
Keywords: partial least-squares, artificial neural networks, indomethacin, dissolution, hardness

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INTRODUCTION

More recently, a group of methods known as 'multivariate data analysis', such as multiple linear regression (MLR), principal component regression (PCR) and partial least-squares (PLS), are capable of modeling hundreds of experimental data, and making it possible to estimate the response variables of interest simultaneously. Among them, PLS has found important applications in pharmaceutical science [1]. PLS is linear regression method that forms components (factors or latent variables) as new independent variables (explanatory variables) in a regression model. The components in PLS are determined by both independent variables and dependent variables. The model from PLS can be expected to have a smaller number of components without an appreciably smaller *r*-square value [2]. However, in the presence of substantial non-linearity, PLS tends to give large prediction errors and calls for more robust models such as artificial neural networks (ANN) [3].

Artificial neural networks are computer methods that simulate learning and generalization behavior of the human brain through data modeling and pattern recognition for complicated multidimensional problems. A significant difference between an ANN model and a statistical model is that the ANN can generalize the relationship between independent and dependent variables without a specific mathematical function. Thus, an ANN works well for solving non-linear problems of multivariate systems. The ANN has been used in a variety of disciplines, such as chemistry, chemical engineering, and pharmaceutical science [4-5]. It has also proved useful for resolving non-linearity problems.

Indomethacin ([1-(4-Chlorobenzoyl)-5-methoxy-2-methylindol-3-yl] acetic acid) is an effective analgesic and antipyretic for treatment of minor, non-inflammatory conditions in patients who are prone to gastric symptoms [6]. Thus, tablets containing indomethacin show analgesic, antipyretic and skeletal muscle relaxing actions. In this report, we study the possibility of the estimation of drug dissolution and hardness in tablet dosage form, which has difference proportions of various ingredients by PLS and ANN techniques. In our study, hardness can be estimated with PLS method, on the other hand, drug dissolution requires the use of an ANN since it is apparent non-linearity that cannot be adequately modeled by PLS.

MATERIALS AND METHODS

Materials

Indomethacin (Batch No.050814, China National chemical Imp. Exp. China) was use as received. Polyethylene glycol 4000 (lot no. 504907) and polyethylene glycol 400 (lot no. PO76049) were purchased from P. C. Drug Center Co.,Ltd., Thailand. Di-sodium hydrogen orthophosphate (lot no. 405300, Ajax Finechem, Australia), hydrochloric acid (lot no. E23W60, J. T. Baker, USA), potassium dihydrogen orthophosphate (lot no. E23W60, Ajax Finechem, Australia), sodium chloride (lot no. AF 407256, Ajax Finechem, Australia), sodium hydroxide (lot no. AF 310204, Ajax Finechem, Australia), were used to prepare the dissolution fluids. Xanthan gum (Xantural 75, lot no. 01-100, CP Kelco US., Inc. USA.), Edragit L 100 (lot no. 1200403005, Rohm GmbH Chemische Fabrick, Germany), ethyl alcohol

absolute (lot no. V5C933235C, Rohm GmbH Chemische Fabrick, Germany) and triethyl citrate (lot no. 0000078425, Vertellus, USA) were used as received.

Apparatus and Software

The hardness of the tablets was determined using a hardness tester (Pharmacist, USA, n=10). A test of drug release was undertaken in 900 ml phosphate buffer pH 6.2 using a dissolution apparatus (Erweka DT 70, Germany) with the basket method at 100 rpm. For drug release test in acid environment, 0.1 N HCl (pH 1.2) was use as dissolution fluid. In the case of the dissolution test with pH change, the drug released in 900 ml 0.1 N HCl was conducted for 1.5 h. Then the pH was increased to 6.2 and continued up to 8 h (1.5+6.5). The contents of indomethacin in sample were determined by measuring the absorbance at 323 nm (n=3) in a UV/Vis spectrophotometer (Perkin-Elmer, Germany).

The obtained data were processed by a Pentium IV computer having 512 MB for RAM (Windows XP operating system). The PLS was performed by PLS_Toolbox 2.0 [7] and the ANN was implemented in MATLAB software using the additional Neural Network Toolbox [8].

Calibration and validation set preparation

Artificial, a training set of 34 samples was built to be used as calibration set for PLS. This set was composed of 2 groups. Each group was prepared on different months in order to take into account the maximum possible variability on the data. The set of 34 samples was randomly divided into a training set (28 samples) and a monitoring set (6 samples). All tablet samples were prepared using the melting and mold technique with the stainless steel mold as described previously [9] and using 7:3 polyethylene glycol 4000: polyethylene glycol 400 as the drug carrier. The amounts of indomethacin, xanthan gum, talcum, and lactose were varied in the range of 25-300 mg, 0-25 mg, 0-55 mg and 0-55 mg, respectively. More over, the tablet size was varied from 8 to 16 and the rotary speed was varied from 25 to 150.

One set of five synthetic samples on each compound were prepared, randomly, using the same technique as calibration set, to validate the PLS model and ANN model.

RESULTS AND DISCUSSION

PLS modeling

In the case of PLS, a cross-validation method using leave one out, was applied to select the number of principal components (PCs). The cross-validation procedure consists of systematically removing one of the training samples in turn, and using only the remaining ones for construction of the latent factors and regression. The predicted concentrations were then compared with the actual ones for each of calibration samples, and the prediction residual error sum of squares (PRESS) was calculated. The PRESS was computed in the same manner, each time a new principal component was added to the PLS model. The method described by Haaland and Thomas [10] was used for selecting the optimum number of PCs. Two PCs were found suitable for PLS models of tablet hardness and drug

dissolution. The PLS models were established by PLS_Toolbox program with these optimum parameters. Table 1 shows the result obtained when applying each PLS model for tablet hardness and drug dissolution to the validation samples. The root mean square error in prediction (RMSEP) also was calculated to measuring the performance of each model.

Table 1 the obtained statistical parameters are good for tablet hardness, but those are poor for drug dissolution. In multivariate modeling, the simplest tool to detect the presence of non-linearity is the graphical tool. This method is to plot actual dissolution versus predicted dissolution, looking for curvatures in the residuals for the estimated dissolution. Figure 1 shows this kind of graphic, which predictions obtained by using a linear PLS model of dissolution show deviations from linearity. Thus, ANN technique could be used for the estimation of dissolution to handle this intrinsically non-linearity.

ANN modeling

When the presence of non-linearity was found and cannot be modeled by linear model such as PLS, one can apply ANN. Although ANN are also able to deal with a linear behavior and can often improve the results in comparison with a linear model, they are modeling techniques especially constructed to model non-linear information. In this application, the set of 34 samples was used as calibration set for ANN. This set was randomly divided into a training set (28 samples) and a monitoring set (6 samples). The ANN model was established by Neural Network Toolbox. This ANN model consisted of three layers of neurons or nodes, which were the basic computing units: the input layer with a number of active neurons corresponding to the input variables, one hidden layer with a number of active neurons, and the output layer with one active neuron corresponding to the scaled percentage of drug dissolution. The neurons were fully connected in a hierarchical manner, i.e. the outputs of one layer of nodes were used as inputs for the next layer and so on. The nodes in the input layer transfer the input data to all nodes in hidden layer. These nodes calculate a weighted sum of the inputs that is subsequently subjected to a non-linear transformation:

$$o_j = f[\sum_{i=1}^{I}(s_i w_{ij} + w_{bj})] \qquad (1)$$

where s_i is the input to node i in the input layer, I is the number of nodes in the input layer, w_{ij} (weights) are the connections between each node i in the input layer and each node j in hidden layer, w_{bj} is the bias to node j and o_j is the output of node j in hidden layer, and f is a non-linear function (in this work we have used the tan-sigmoid function).

$$f(x) = \frac{e^{x} - e^{-x}}{e^{x} + e^{-x}} \qquad (2)$$

The tan-sigmoid hidden layer is critical as it allows the network to learn non-linear relationships between inputs and outputs. Linear functions are used in both the input and output layers. The learning process was carried out through the back-propagation algorithm. The back-propagation network learns by calculating an error between desired and actual output and propagating this error information back to each node in the network. This back-propagation error is used to drive the learning at each node. The process of

changing the weight of the connections to achieve some desired result is called learning or adaptation.

In the present work the number of neurons in the hidden layer, momentum and learning rate were optimized. At this point, the mean square error (MSE) was calculated, each time a new node was added to the hidden layer at arbitrary learning rate, momentum and the number of iterations. The number of neurons at the hidden layer, which has the minimum MSE value, was selected as the optimum number. After this step, the learning rate was varies from 0.1 to 0.9, and for each learning rate the momentum was examined from 0.1 to 0.9. A total of 81 networks were designed in this way. Each network was trained with training set, but it was subsequently stopped before it learns idiosyncrasies present in the training data by searching the minimum MSE for the test set (monitoring set). Finally, the number of the neurons at the hidden layer with the use of optimized momentum and learning rate was determined. Figure 2 shows the stopping point, which was obtained at 6000 epochs for best ANN found for drug dissolution. The summary specifications for the network created for the modeling were listed in Table 2.

For accuracy studies, by recovery, five validation samples were determined. The recovery values of dissolution, obtained using ANN calibration model are shown in Table 3. They illustrate the reasonable good recovery values in most of the samples determined. Furthermore, ANN model offered better values of RMSEP, when comparing with PLS model.

Table 1 Actual and predicted values from the analysis of tablet hardness and dissolution when applying PLS model to the validation samples

Hardness (kg)			Dissolution (%)			Recovery (%)	
Actual	Predicted		Actual	Predicted		Hardness	Dissolution
16.68	16.74		22.93	57.74		100.35	251.81
24.30	25.99		31.25	44.40		106.95	142.08
26.40	27.36		34.13	45.25		103.62	132.57
16.46	17.65		92.79	76.78		107.21	82.75
16.46	17.56		100.72	95.83		106.65	95.14
Mean recovery						104.96	140.87
R^{2*}						0.989	0.830
RMSEP						0.84	14.10

*Square of correlation coefficient

Table 2 Artificial neural network specifications and parameters

Parameter	Specification
Input nodes	6
Hidden nodes	4
Output nodes	1
Learning rate	0.3
Momentum	0.7
Hidden layer transfer function	Tan-sigmoid
Output layer transfer function	Linear
Optimum number of iterations	6,000

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Table 3 Actual and predicted values from the analysis of drug dissolution when applying ANN model to the validation samples

Sample	Actual (%)	Predicted (%)	Recovery (%)
1	22.93	23.71	103.41
2	31.25	32.18	102.99
3	34.13	33.26	97.44
4	92.79	93.66	100.94
5	100.72	105.92	105.16
Mean recovery			101.99
R^2			0.998
RMSEP			1.83

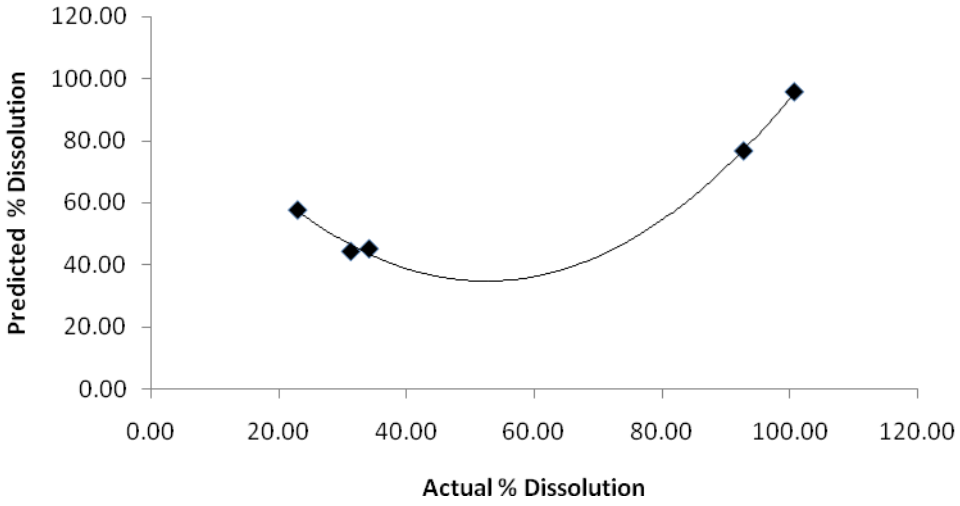

Fig. 1. Plot of actual vs. predicted dissolution obtained by applying PLS

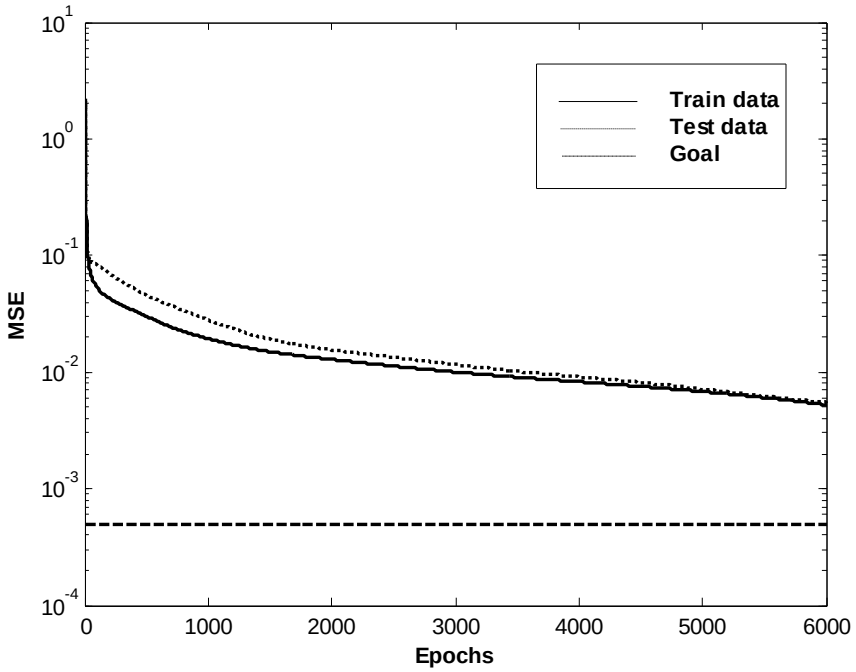

Fig. 2. Evolution of training and test errors versus the number of epochs for dissolution at learning rate 0.3 and momentum 0.7

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CONCLUSIONS

This work illustrated the potential of the estimation of drug dissolution and hardness in tablet preparations. A validation set of simulated samples was employed for testing the accuracy and precision of the models. Reasonably good recoveries were obtained with PLS for hardness and the use of an ANN allowed the estimation of drug dissolution, which could not be adequately modeled by PLS. According to RMSEP, the ANN model leads to 87% improvement of predictive ability for drug dissolution, when comparing with PLS model. It is concluded that artificial neural networks may be capable of giving superior performance for PLS technique, when non-linear response is present.

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