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RESEARCH PAPER

Prediction of Drug Content and Hardness of Intact Tablets Using Artificial Neural Network and Near-Infrared Spectroscopy

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ABSTRACT

The purpose of this study was to predict drug content and hardness of intact tablets using artificial neural networks (ANN) and near-infrared spectroscopy (NIRS). Tablets for the drug content study were compressed from mixtures of Avicel® PH-101, 0.5% magnesium stearate, and varying concentrations (0%, 1%, 2%, 5%, 10%, 20%, and 40% w/w) of theophylline. Tablets for the hardness study were compressed from mixtures of Avicel PH-101 and 0.5% magnesium stearate at varying compression forces ranging from 0.4 to 1 ton. An Intact Analyzer™ was used to obtain near infrared spectra from the tablets with varying drug contents, whereas a Rapid Content Analyzer™ (RCA) was used to obtain spectral data from the tablets with varying hardness. Two sets of tablets from each batch (i.e., tablets with varying drug content and hardness) were randomly selected. One set of tablets was used to generate appropriate calibration models, while the other set was used as the unknown (test) set. A total of 10 ANN calibration models (5 each with 10 and 160 inputs at appropriate wavelengths) and five separate 4-factor partial least squares (PLS) calibration models were generated to predict drug contents of the test tablets from the spectral data. For the prediction of tablet hardness, two ANN calibration

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models (one each with 10 and 160 inputs) and two 4-factor PLS calibration models were generated and used to predict the hardness of test tablets. The PLS calibration models were generated using Vision® software. Prediction of drug contents of test tablets using the ANN calibration models generated with 10 inputs was significantly better than the prediction obtained with the ANN calibration models with 160 inputs. For tablets with low drug concentrations (less than or equal to 2% w/w), prediction of drug content was better with either of the two ANN calibration models than with the PLS calibration models. However, prediction of drug contents of tablets with greater than or equal to 5% w/w drug was better with the PLS calibration models than with the ANN calibration models. Prediction of tablet hardness was better with the ANN calibration models generated with either 10 or 160 inputs than with the PLS calibration models. This work demonstrated that a well-trained ANN model is a powerful alternative technique for analysis of NIRS data. Moreover, the technique could be used in instances when the conventional modeling of data does not work adequately.

Key Words: *Artificial neural network; Drug content; Hardness; Near-infrared spectroscopy; Tablets*

INTRODUCTION

Artificial neural networks (ANNs) 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 dependant variables without a specific mathematical function. Thus, an ANN works well for solving nonlinear problems of multivariate and multiresponse systems. Figure 1 shows a typical ANN model.

The ANN has been used in a variety of disciplines, such as chemistry and chemical engineering. For example, the ANN technique has been applied to several analytical methods, such as inductively coupled plasma–atomic emission spectroscopy (1), nuclear magnetic resonance (2), high-performance liquid chromatography (3), and mass spectroscopy (4).

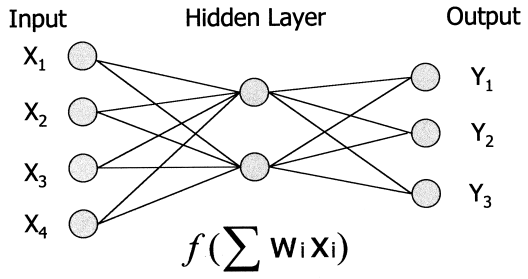

Figure 1. A schematic diagram of the ANN model.

Recently, pharmaceutical scientists have also started using the ANN technique in fields such as pharmacokinetic-pharmacodynamic studies (5–7), process development (8), in vitro–in vivo correlations (9), and product development (10–13). Achanta et al. discussed the fundamental principles of ANN technologies and their potential applications in the pharmaceutical sciences in detail (14).

Another powerful technique that is rapidly gaining importance in many areas of pharmaceutical research is near-infrared spectroscopy (NIRS). This is because of rapid nondestructive sample analysis (both qualitative and quantitative) of pharmaceutical raw materials and dosage forms. Forbess and Shukla (15) recently reviewed the use of NIRS for qualitative analysis of pharmaceutical raw materials and dosage forms. Examples of studies in which quantitative analysis has been performed using the NIRS technique include end-point determination during mixing of powders (16), determination of the degradation rate of a drug in intact tablets (17), prediction of drug dissolution from intact tablets (18), and evaluation of an active ingredient in intact film-coated tablets (19). The technique has also

been used to distinguish between different types of intact placebo tablets and drug-loaded tablets (20,21). Recently, the technique was used to determine the extent of formaldehyde-induced cross-linking in soft gelatin capsules (22) and determination of water uptake (23). In our laboratory, the NIR technique has been used to simultaneously determine the following in intact tablets: Avicel® type and crushing strengths of intact tablets compressed from three different types of Avicel products, lubricant concentration and crushing strengths of intact tablets (24), and drug content in intact tablets (25).

A review of literature showed that only one article describing the use of ANN to evaluate the near infrared spectral data has been published thus far (26). However, the use of ANN to evaluate NIRS data in predicting drug content and hardness of intact tablets has not been reported in the literature. Hence, the objective of this study was to (1) demonstrate the use of ANN technique to evaluate the NIRS data and predict drug content and hardness of intact tablets and (2) compare the results obtained from the use of ANN technique with a conventional NIRS data treatment technique such as the partial least squares (PLS) calibration models.

MATERIALS AND METHODS

The following materials were used in the study: Avicel PH-101 (FMC, Inc., Princeton, NJ), theophylline (Spectrum Chemical Company, Gardena, CA), and magnesium stearate (Mallinkrodt Specialty Chemicals, Chesterfield, MO).

Formulations with Varying Drug Contents and Tablet Hardness

Varying Drug Contents

Tablets weighing 300 mg were compressed from blends of Avicel PH-101 and varying concentrations of theophylline (0%, 1%, 2%, 5%, 10%, 20%, and 40% w/w) at 0.6 ton using an 18-station Elizabeth-Hata HT-AP 18SS-U/l.b. tablet press (Elizabeth-Hata International, Inc., North Huntington, PA). The tablet press was equipped with standard 3/8-inch concave punches and dies. Magnesium stearate (0.5% w/w) was used as a lubricant. The actual drug contents of tablets were determined using an ultraviolet-visible (UV-Vis) spectrophotometer (model Lambda 3B, Perkin-Elmer Corp., Norwolk, CT).

Varying Tablet Hardness

Tablets with varying hardnesses were compressed from blends of Avicel PH-101 and 0.5% magnesium stearate at 0.4, 0.6, 0.8, and 1.0 ton using the 18-station Elizabeth-Hata HT-AP 18SS-U/l.b. tablet press. The tablet press was equipped with standard 3/8-inch concave punches and dies. The weight of each compressed tablet that was used in the study was approximately 300 mg. Hardness of each tablet was determined using a tablet tester (PharmaTest model PTB 311, SITCO, Englishtown, NJ).

Near-Infrared Spectroscopy

For the drug content study, 10 tablets were randomly selected from each batch of tablets with different drug contents. The tablets were scanned from 900 to 1900 nm using the Intact Analyzer™ transmittance module (Foss NIRSystems, Inc., Silver Spring, MD).

For the hardness study, 10 tablets were randomly selected from each batch of tablets compressed at varying compression forces. Both sides of each tablet were scanned from 1100 to 2500 nm using the Rapid Content Analyzer™ (RCA) module (Foss NIR Systems). The spectra from the two sides of each tablet were then averaged, and the resulting spectral data were used for generating calibration models.

Artificial Neural Networks and Model Optimization

Commercial ANN software based on Microsoft Windows, NeuroShell 2 (Ward System Group, Inc., Frederick, MD), installed on a Pentium 166-MHz personal computer, was used throughout the study. This software allows the user to select the number of hidden layers, hidden layer nodes, iterations used during model training, learning algorithm, and transfer functions. The trained ANN model is also able to provide values of input strengths, which indicate the significance of the effect of each input on the output (predicted) data.

When each set of data such as drug content or tablet hardness is presented to the ANN network, NeuroShell 2 computes the error between the actual data and the ANN predicted output data. In the present study, the input data for determination of drug content was the actual drug content data determined from UV analysis, whereas the input

data for determination of tablet hardness were the actual tablet hardness values determined by the hardness tester. The total error (sum of error squares) for each value is the sum of the squares of the differences between the actual and the ANN predicted (output) data. This error was used as a measurement for selection of the optimal ANN architecture, and the ANN architecture with the lowest error was selected as the calibration model.

Two ANN models with different numbers of inputs were used for this study. The first ANN model had 160 inputs selected from NIR absorbances at 160 individual wavelengths that were equally spaced from 700 to 1400 nm for the drug content study and 1100 to 2500 nm for the tablet hardness study. For the second ANN model, the absorbance values of only 10 individual wavelengths (selected from the same NIR absorbances range) that showed the highest input strengths were selected as inputs for the model. Either tablet drug content (% w/w) or hardness (Kp) was used as the ANN model output.

Artificial Neural Network Model Training

It is important to train the ANN model adequately prior to its selection. Hence, training of the ANN calibration models used in this study was performed by first removing 10% of the spectral data set (validation data set) from the entire data set. This validation data set was later used for validating the architecture of the selected ANN models. Appropriate ANN calibration models with either one or two hidden layers were generated from the remaining 90% of the spectral data. The number of hidden layer nodes for the calibration models was varied from 10 to 100 for the architecture with one hidden layer or from 6 to 50 for the architecture with two hidden layers. The architecture of the ANN model that yielded the least sum of error squares (i.e., error between the actual values and the predicted values of the validation data set) was selected as the optimal ANN calibration model.

Table 1 shows the ANN models used for predicting the drug content and tablet hardness for the study. Spectral data from one drug concentration or tablet compression force were left out and used as the prediction set for the optimized ANN calibration model.

Partial Least Squares Data Analysis Techniques

Prediction of Drug Content

Five PLS calibration models were generated from the second derivative spectra obtained from the Intact Analyzer. The correlation coefficients,

Table 1

Artificial Neural Network (ANN) Models Used for Prediction of Drug Content or Tablet Hardness

	Batch Used for ANN Model Training (Drug Concentration, % w/w)	Batch to be Predicted (Drug Concentration, % w/w)	Number of Hidden Layer Nodes			
			160 Inputs		10 Inputs	
			1st HL	2nd HL	1st HL	2nd HL
Drug content study	0, 2, 5, 10, 20, 40	1	80	N/A	80	N/A
	0, 1, 5, 10, 20, 40	2	11	30	11	20
	0, 1, 2, 10, 20, 40	5	10	N/A	11	11
	0, 1, 2, 5, 20, 40	10	6	20	9	30
	0, 1, 2, 5, 10, 40	20	6	6	17	17
	Batch Used for ANN Model Training (Compression Force, ton)	Batch to be Predicted (Compression Force, ton)	Number of Hidden Layer Nodes			
			160 Inputs		10 Inputs	
			1st HL	2nd HL	1st HL	2nd HL
Hardness study	0.4, 0.8, 1.0	0.6	55	70	20	10
	0.4, 0.6, 1.0	0.8	55	70	20	10

HL, hidden layer; N/A, not applicable.

Table 2

Standard Errors of Calibration and Prediction for the Partial Least Squares (PLS) Calibration Models Generated from the Second Derivative Spectral Data

Type of Calibration Model	Theoretical Drug Content of Tablets[a] Used for Generating Calibration Models (% w/w)	Theoretical Drug Content of Prediction Set Tablets[b] (% w/w)	Standard Error of Calibration (%)	Correlation Coefficient (r)	Standard Error of Prediction (%)
PLS transmittance calibration model	0, 2, 5, 10, 20, 40	1	0.1923	0.999	0.2095
	0, 1, 5, 10, 20, 40	2	0.1899	0.999	0.0949
	0, 1, 2, 10, 20, 40	5	0.1761	0.999	0.1369
	0, 1, 2, 5, 20, 40	10	0.1692	0.999	0.1781
	0, 1, 2, 5, 10, 40	20	0.1656	0.999	0.1969

[a]10 tablets with each drug content were used to generate the calibration models.
[b]10 tablets with each drug content were used in the prediction set.

standard errors of calibration (SEC), and standard errors of prediction (SEP) of the PLS models are listed in Table 2. The criteria for selecting the calibration models were based on the mean squared error of cross-validation performed by the Vision™ software (Foss NIRSytems). The number of factors used for all the PLS calibration models was four. The wavelength range of the spectral data used to generate the PLS calibration models was 700 to 1200 nm. The spectral region above 1200 nm was not included in the analysis of the spectral data because of interference in the spectra.

Each PLS calibration model was generated from the spectral data of 10 tablets at all but one drug content level. Then, 10 tablets were randomly selected from the omitted drug content level to serve as the prediction (test) set. This was done to make the calibration models rugged and eliminate the bias that may arise during the prediction of drug content if the spectral data for the tablets in the prediction set were included in the calibration model.

Prediction of Tablet Hardness

Two PLS calibration models were generated from the second derivative spectral data obtained using the RCA. The criteria for selecting the calibration models were based on the mean squared error of cross-validation performed by the Vision software. The number of factors used for all the PLS calibration models was four. The wavelength range of the spectral data used to generate the PLS calibration models was 1100 to 2500 nm.

Each PLS calibration model was generated from the spectral data of 10 tablets at all but one hardness level. Then 10 tablets were randomly selected from the omitted hardness level to serve as the prediction (test) set. This was done to make the calibration models rugged and eliminate the bias that may arise during the prediction of tablet hardness if the spectral data for the tablets in the prediction set were included in the calibration model.

The correlation coefficients, SEC, and SEP of the PLS calibration models are depicted in Table 3.

RESULTS AND DISCUSSION

Generally, selection of an optimal ANN architecture is still a trial-and-error method. Comparison of the prediction from the ANN models with various architectures using test data helps the user find an appropriate ANN calibration model that gives the least prediction errors. Figure 2 and Table 4 are two examples of sum of error squares between the actual and predicted values for the test data set as a function of number of nodes in the hidden layer for an architecture with one or two hidden layers. Thus, for example, for the validation of 1% drug content, the ANN model with one hidden layer and 80 nodes was selected based on the prediction errors from test data. Likewise, for validation of 2% drug content, the model with two hidden layers and 11 nodes in the first hidden layer and 20 nodes in the second hidden layer was selected. This process was continued until the optimal ANN model architectures used for each

Table 3

Standard Errors of Calibration and Prediction for the Four-Factor Partial Least Squares (PLS) Calibration Models Used to Predict Tablet Hardness

Compression Force of Tablets Used for Generating Calibration Models[a] (Ton)	Compresssion Force of Tablets Used as the Prediction Set Tablets[b] (Ton)	Standard Error of Calibration (*Kp*)	Correlation Coefficient (*r*)	Standard Error of Prediction (*Kp*)
0.2, 0.4, 0.8, 1.0	0.6	0.3528	0.998	0.4772
0.2, 0.4, 0.6, 1.0	0.8	0.4455	0.996	0.5394

[a]10 tablets from a batch compressed with each compression force were used to generate the calibration models.
[b]10 tablets compressed either at 0.6 or 0.8 ton were used in the prediction set.

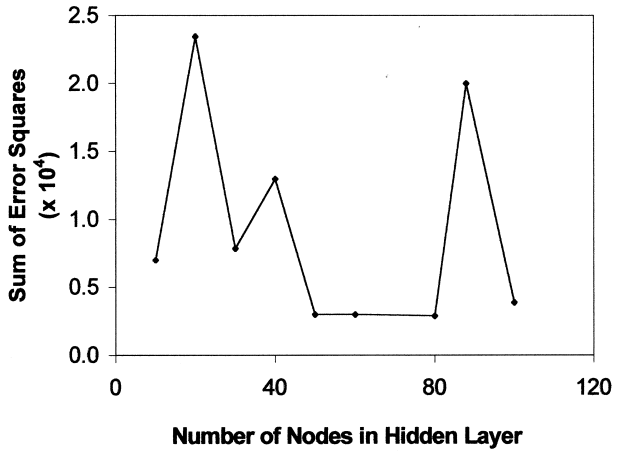

Figure 2. Sum of error squares between the experimental and predicted values for validation data set as a function of number of nodes in the hidden layer for a one-hidden layer architecture. (The validation data were from the batch of 1% drug content. Training and test data for the ANN model were from the batches of 0%, 2%, 5%, 10%, 20%, and 40% w/w drug content.)

prediction data set were determined. The results are listed in Table 1.

Figure 3 shows a plot of input number versus input strengths measured at 160 different equally spaced wavelengths. It is obvious from the figure that the input strengths at certain wavelengths are considerably greater than at others. This could be related to the second overtone of CH and RNH_2 groups and third overtone of RNH_2 and $RNHR'$ groups present in the chemical structure of theophylline. Hence, the 10 inputs with the greatest input strengths at 10 wavelengths ranging from 810 to 1282 nm as shown in Fig. 3 were selected to build the ANN calibration models, and these models were used to predict the drug content of the intact test tablets.

Interestingly, a similar plot of input number versus input strengths plotted from spectral data of tablets used for the tablet hardness study did not show any particular trend (Fig. 4). This is because tablet hardness is a physical characteristic of a tablet. Hence, a distinct wavelength in the spectra, which could be used as a measure of tablet hardness, could not be identified. The ANN calibration models generated to predict the hardness of tablets compressed at either 0.6 or 0.8 ton provided identical input strength patterns. The 10 inputs with the greatest input strengths (at 10 wavelengths ranging from 1212 to 2110 nm, as shown in Fig. 4) were selected as the inputs of the second ANN calibration model.

Figure 5 shows the prediction results of tablet drug contents using different calibration models, namely, ANN models with 160 and 10 inputs and PLS. Prediction of drug content of intact tablets was better with the 10-input ANN calibration models than with the 160-input ANN calibration models. At the lower drug contents (i.e., 1% and 2% w/w), the ANN calibration models gave a more accurate prediction than the PLS calibration models. However, the prediction of drug contents of tablets with greater than or equal to 5% w/w drug content was better with the PLS calibration models than with the two ANN calibration models.

For the prediction of hardness of tablets compressed at 0.6 ton, both the ANN calibration models predicted tablet hardness more accurately and precisely than the four-factor PLS calibration models. However, for tablets compressed at 0.8 ton, the ANN calibration model generated with 160 inputs was best able to predict tablet hardness (Fig. 6).

Table 4

Sum of Error Squares for the Test Data from Artificial Neural Networks (ANN) Models with Two Hidden Layers

		Number of Nodes in 2nd Hidden Layer				
		6	11	20	30	50
Number of nodes in 1st hidden layer	6	0.0000496	0.0000367	0.00023	0.0001107	0.0003727
	11	0.0008973	0.0001164	0.000027	0.0001407	0.0003094
	20	0.000057	0.0003912	0.0001016	0.0001576	0.0001521
	30	0.0005341	0.0003699	0.0001606	0.0002751	0.0000487
	50	0.0002035	0.0000635	0.0003002	0.0002425	0.000404

Validation data were from the batch of 2% w/w drug content. Training and test data for the ANN model were from the batches of 0%, 1%, 5%, 10%, 20%, 40% w/w drug content.

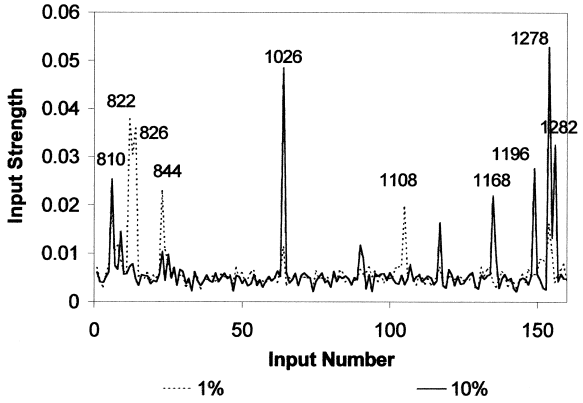

Figure 3. Input strengths of each input wavelength for the prediction of tablet drug content (ANN model with 160 inputs). The numbers in the graph indicate wavelengths.

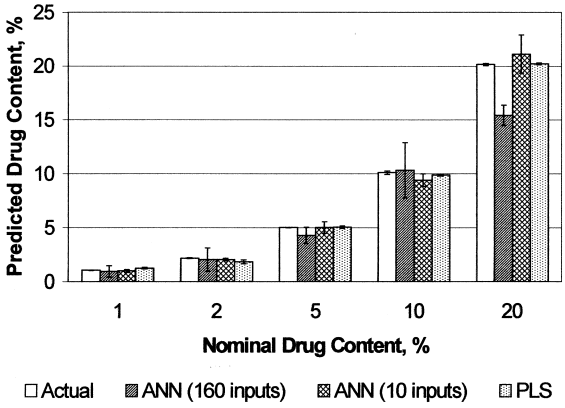

Figure 5. A comparison of predicted drug contents using ANN and PLS calibration models.

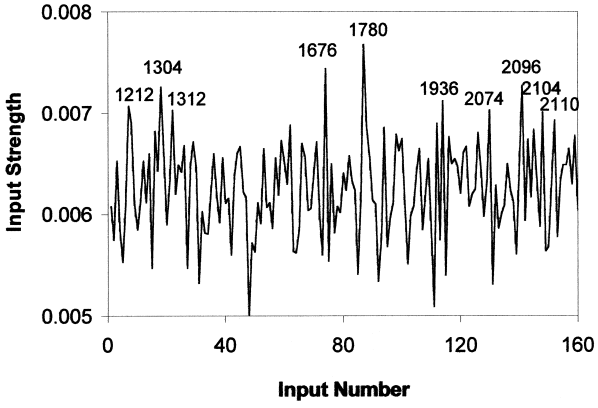

Figure 4. Input strengths of each input wavelength for the prediction of tablet hardness (ANN model with 160 inputs). The numbers in the graph indicate wavelengths.

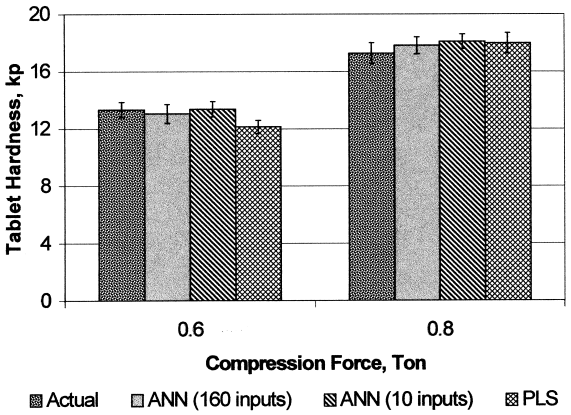

Figure 6. A comparison of predicted tablet hardness using ANN and PLS calibration models.

CONCLUSION

This work illustrated the potential for the use of artificial neural networks to model NIRS data. The study also revealed that selecting more inputs for an ANN calibration model does not always result in better prediction. Last, ANN is a promising alternative technique for NIRS data analysis and is comparable to the conventional NIRS data treatment techniques such as PLS.

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