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Artificial Neural Networks in the Modeling and Optimization of Aspirin Extended Release Tablets With Eudragit L 100 as Matrix Substance

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ABSTRACT

The purpose of the present study was to model the effects of the concentration of Eudragit L 100 and compression pressure as the most important process and formulation variables on the in vitro release profile of aspirin from matrix tablets formulated with Eudragit L 100 as matrix substance and to optimize the formulation by artificial neural network. As model formulations, 10 kinds of aspirin matrix tablets were prepared. The amount of Eudragit L 100 and the compression pressure were selected as causal factors. In vitro dissolution time profiles at 4 different sampling times were chosen as responses. A set of release parameters and causal factors were used as tutorial data for the generalized regression neural network (GRNN) and analyzed using a computer. Observed results of drug release studies indicate that drug release rates vary widely between investigated formulations, with a range of 5 hours to more than 10 hours to complete dissolution. The GRNN model was optimized. The root mean square value for the trained network was 1.12%, which indicated that the optimal GRNN model was reached. Applying the generalized distance function method, the optimal tablet formulation predicted by GRNN was with 5% of Eudragit L 100 and tablet hardness 60N. Calculated difference (f_1 2.465) and similarity (f_2 85.61) factors indicate that there is no difference between predicted and experimentally observed drug release profiles for the optimal formulation. This work illustrates th9e potential for an artificial neural network, GRNN, to assist in development of extended release dosage forms.

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INTRODUCTION

The application of artificial neural networks (ANNs) in the field of pharmaceutical development and optimizing of dosage forms has recently become a topic of discussion in the pharmaceutical literature.[1-5] Compared with classical statistical optimization techniques, such as response surface methodology, ANNs show superiority as a modeling technique for data sets showing nonlinear relationships, and thus for both data fitting and prediction abilities.[6-8]

ANN is a learning system based on a computational technique that can simulate the neurological processing ability of the human brain and can be applied to quantifying a nonlinear relationship between causal factors and pharmaceutical responses by means of iterative training of data obtained from a designed experiment.[9]

Matrix systems appear very attractive from the economic as well as from the process development and scale-up points of view in controlled release systems.[10,11] In our earlier studies,[12,13] the influence of various formulation variables on aspirin release from Eudragit matrices was investigated; the ratio of polymer as well as the compression pressure (influencing tablet porosity) were identified as the most important factors affecting drug release from matrix tablets.

The objectives of the present study were to model the effect of process and formulation variables on the in vitro release profile of aspirin from matrix tablets formulated with Eudragit L 100 as the matrix substance and to optimize the formulation by ANN.

GENERALIZED REGRESSION NEURAL NETWORK

The standard supervised network architectures (multilayer perceptrons and radial basis functions) infer a parameterized model (the weights forming the parameters) from available training data. The parameterized model (the network) is usually much smaller than the training data and can be executed quite quickly, although the time taken to train the model may be long. An alternative approach is to model the function more or less directly from the training data. This has the advantage that there is no need for training (or, at least, one can use "training" that is actually very simple, consisting of little more than changing the form in which the training data are held). Bayesian networks, often called generalized regression neural networks (GRNNs), are such methods. They have 4 layers (**Figure 1**): input, a layer of radial centers, a layer of regression units, and output. They were devised by Speckt,[14] who cast a statistical method of function approximation in a neural network form.[15,16] The radial layer units represent the centers of clusters of known training data. This layer must be trained by a clustering algorithm such as subsampling, K-means, or Kohonen training. The layer is typically large but not necessarily as large as the number of training cases. The regression layer must have exactly 1 unit more than the output layer. The regression layer contains linear units. There are 2 types of units in the regression layer: 1 type A unit for each output unit, and 1 type B unit. Type A units calculate the "desired" regression outputs for the cases; the type B unit calculates the probability density. The output layer performs a specialized function. Each unit simply divides the output of the associated type A unit by that of the type B unit in the previous layer. It is a special post synaptic function (PSP)-division. Regression networks train extremely rapidly.[17]

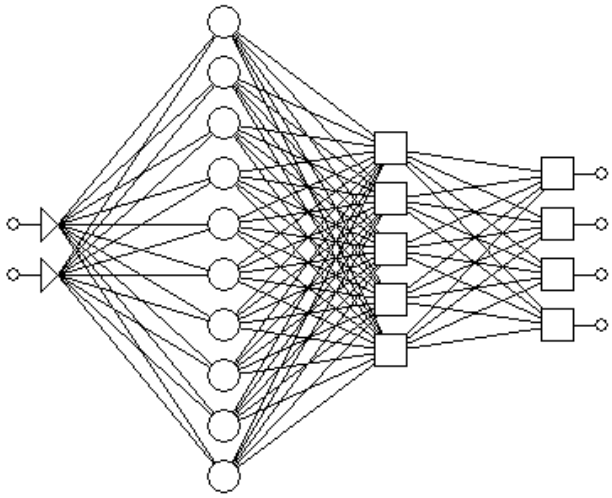

Figure 1. GRNN: 2 inputs in input layer, 10 radial units in hidden layer, 5 units in regression layer, and 4 units in output layer.

MATERIALS AND METHODS

Acetylsalicylic acid (ASA) was PhEur 1997 grade. Eudragit L 100 was kindly supplied by Rhom Pharma (Frankfurt, Germany). Avicel PH 112 (FMC Co, Philadelphia, PA), Aerosil 200 (Degusa, Frankfurt, Germany), Pruv (Mendell, London, UK), and talc (PhEur 1997) were used for model formulation. Tablets (325 mg ASA per tablet) were prepared with the direct compression method on an eccentric press (EKO Korsch, Berlin, Germany) using flat punches Ø 10 mm. Tablet hardness was measured by hardness tester Erweka TBH 28 (Heusenstamm, Germany) Tablet hardness values present average of 20 measurements. The amount of ASA and salicylic acid per tablet was assayed by high-pressure liquid chromatography analysis, according to the USP 23 monograph for aspirin extended release tablets. For all formulations, the content of salicylic acid was lower than 0.1%.

The dissolution study was performed in a rotating paddle apparatus (Erweka DT70, Heusenstamm), according to the USP drug release test for aspirin extended release tablets: Test 2 (water, 1000 mL, 30 rpm). The amount of aspirin released was determined by measuring the absorbance at 265 nm (Spectrophotometer GBC-UV, Dandenong, Australia). All the tests were performed with 6 tablets.

Design

Eudragit L 100 (chosen as the matrix substance) and compression pressure (expressed through tablet hardness) were screened out as the most important factors responsible for the cumulative percentage of aspirin released in 8 hours. Therefore a 2-factor spherical second-order composite experimental design was employed to generate factor combinations. **Table 1** summarizes the factors and their levels. Ten runs with 4 additional test points (T1, T2, T3, T4) were generated (**Table 2**). Test formulations (T1, T2, T3, T4, **Table 2**) were used for validation of ANN and testing the generalized abilities of ANN.

Table 1. Central Composite Design Factors

	Levels Used				
Factors	**–2.5**	**–1**	**0**	**1**	**2.5**
X_1: percentage of Eudragit L 100	2	2.58	4	5.41	6
X_2: tablet hardness (N)	25	35	57.5	80.4	90

Table 2. Experimental (E) and Predicted (P) Values for Chosen Outputs

	Y_1		Y_2		Y_3		Y_4	
	P	**E**	**P**	**E**	**P**	**E**	**P**	**E**
F1	47.00	47.03	74.66	74.69	92.61	92.62	103.4	103.4
F2	21.38	21.36	47.17	47.16	91.38	91.42	102.3	102.3
F3	13.81	13.81	21.61	21.61	33.95	33.94	47.49	47.48
F4	17.03	17.03	26.23	26.22	47.02	46.99	67.21	67.19
F5	14.06	14.06	21.81	21.81	32.86	32.85	49.55	49.54
F6	23.12	23.12	50.35	50.36	80.40	80.44	99.16	99.19
F7	17.02	16.66	30.08	29.81	49.79	49.87	67.44	68.76
F8	17.02	17.37	30.08	30.35	49.79	49.71	67.44	66.11
F9	14.47	14.46	26.46	26.44	42.44	42.41	62.08	62.06
F10	36.11	36.11	65.80	65.80	77.18	77.17	99.43	99.43
T1	14.08	12.96	23.62	20.86	37.46	33.36	53.55	56.24
T2	23.83	28.81	50.34	50.46	78.09	77.43	97.08	98.58
T3	37.39	22.06	62.46	49.21	78.91	69.30	94.45	93.37
T4	17.03	13.24	26.22	22.66	47.00	36.85	67.19	55.23

Computer Program

Commercially available STATISTICA Neural Networks software (StatSoft, Inc, Tulsa, OK was used throughout the study. GRNN was used in modeling and optimization of aspirin extended release tablets. In a GRNN model, it is possible to select (1) the number of units (nodes) in the second radial layer, (2) the smoothing factor (which controls the deviation of the Gaussian kernel function located at the radial centers), and (3) the clustering algorithm (eg, subsampling, K-means, Kohonen).

Initially, in the radial layer, the number of hidden units was varied from 1 to 10, using smoothing factor 0.1 and the K-means clustering algorithm. To select the optimal GRNN model, regression plots were constructed of the observed versus predicted responses for the 2 test formulations that were excluded from the 10-formulation data set. The GRNN model that yielded a regression plot with a slope and square coefficient (r^2) that were closest to a value of 1.0 was selected as the optimal GRNN model. A sum-squared error function was used in training the network. (The error is the sum of the squared differences between the target and actual output valued on each output unit.)

Learned GRNN was used for modeling, simulation, and optimization of the model extended release formulation in the following ways:

- Testing experimental points in experimental fields
- Searching for the optimal solutions
- Presenting response surfaces (or contour plots)

Figure 2 shows a typical flow of the GRNN-incorporated simultaneous optimization technique developed in this study. Factorial experimental design was applied when preparing systemic model formulations composed of 2 causal factors. The response variables of these model formulations are predicted quantitatively from a combination of these factors by means of GRNN. As is typical of optimization problems, the individual optima for different responses are not the same. Therefore, the response variables should be incorporated into a single function to consider all the responses simultaneously. For this purpose, the general transformation was based on the distance between the predicted values of each response and the optimized one that was obtained individually.[18] The simultaneous optimum can be estimated by the minimized generalized distance function under the restriction of the experimental region.

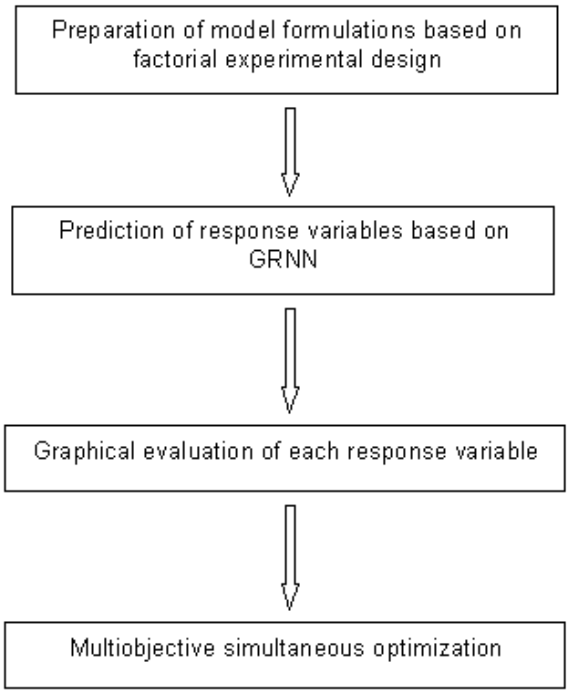

Figure 2. Flow of multiobjective simultaneous optimization technique incorporating GRNN.

RESULTS AND DISCUSSION

Release Behaviors

Release behaviors of ASA from the tablets are shown in **Figure 3**. A wide variation in these profiles among experiments was observed, indicating that dissolution was greatly affected by changes in the levels of causal factors. **Table 2** shows the experimentally observed percentages of ASA dissolved after 1, 2, 4, and 8 hours of dissolution study. The drug release rates vary widely, with a range of 5 hours to more than 10 hours for complete dissolution.

GRNN Structure

Two causal factors corresponding to different levels of Eudragit L 100 (X_1) and tablet hardness (X_2) were used as each unit of the input layer in the GRNN. Responses were used as 4 output layers

- Y_1: percentage of ASA dissolved after 1 hour
- Y_2: percentage of ASA dissolved after 2 hours
- Y_3: percentage of ASA dissolved after 4 hours
- Y_4: percentage of ASA dissolved after 8 hours

A set of outputs and causal factors was used as tutorial data (training runs F1-F10) and fed into a computer. Several training sessions were conducted with different numbers of units (1-10) in the second hidden (radial) layer to determine the optimal GRNN structure. Regression plots were constructed of predicted and observed responses for the 4 test formulations, and slopes and r^2 values were determined. **Figure 4** is a representative plot of the slopes and r^2 values for a GRNN model as a function of the number of hidden layer units. Based on the data shown in **Figure 4**, the optimized GRNN model consisted of 10 units in the radial hidden layer, since both the slope and r^2 approached 1.0. The learning period was completed when minimum root mean square (RMS) was reached:

$$RMS = [\Sigma(y_i^p - y_i^m)^2/n]^{1/2} \quad (1)$$

where y_I^p is experimental (observed) response, y_I^m is calculated (predicted) response, and n is number of experiments.

The selected GRNN structure was with 4 layers (**Figure 1**): the first layer with 2 input units and the second layer with 10 hidden units (with negative exponential activation function and radial PSP function). These units in the hidden layer were assigned using the K-means center assignment algorithm. A third

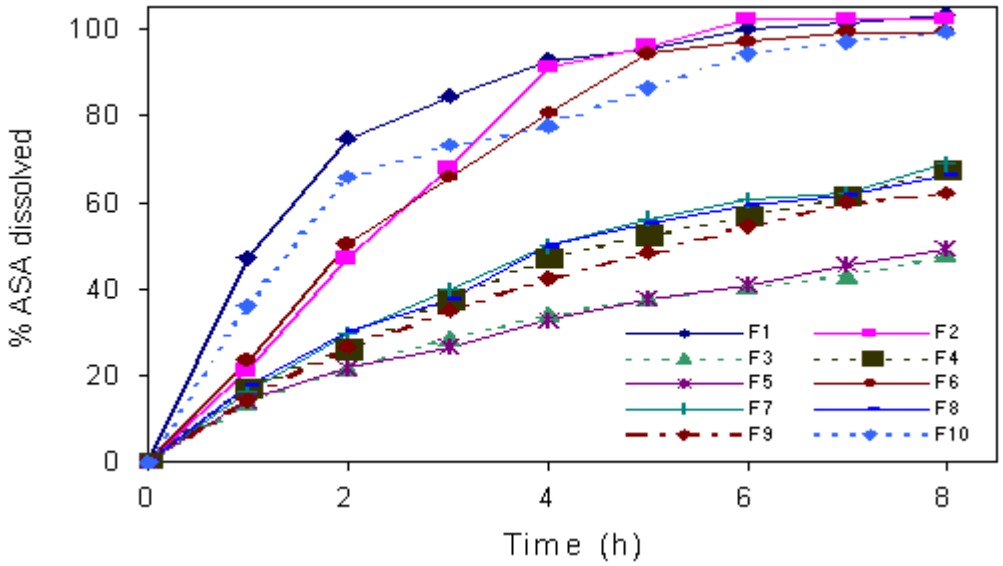

Figure 3. Release profiles of ASA from model formulations (formulation 1-10, Table 1); the mean of 6 determinations.

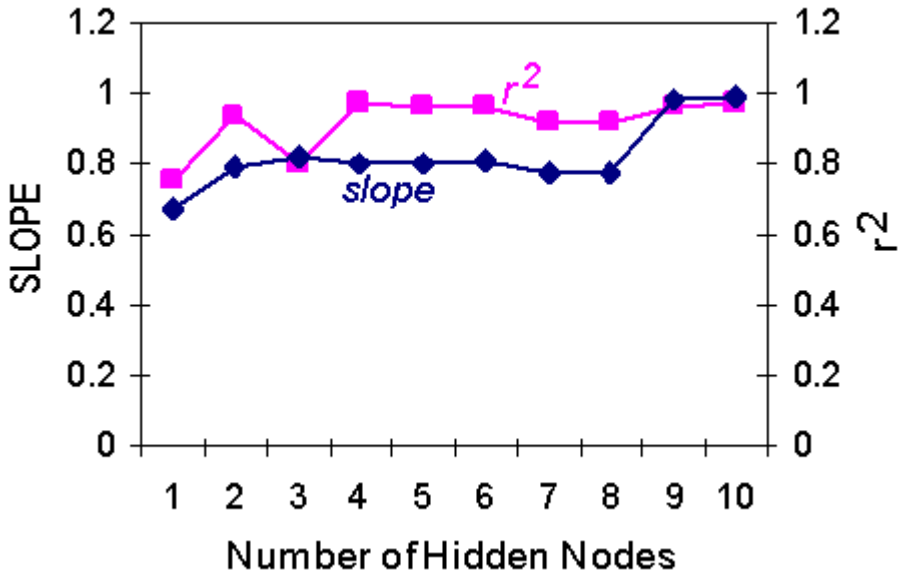

Figure 4. Plot of the regression slopes and squared correlation coefficients (r^2) for the 2 test formulations, as a function of the number of hidden layer units using a GRNN model with 1- to 10-layer units.

layer has 5 units (with linear activation and PSP function). The fourth layer has 4 output units (linear activation and division PSP function). Regression network training sets the weights on the third and fourth layers, which are used to estimate the regression curve.

Input values for test formulations (T1, T2, T3, T4, **Table 2**) were presented to GRNN when network training was completed.

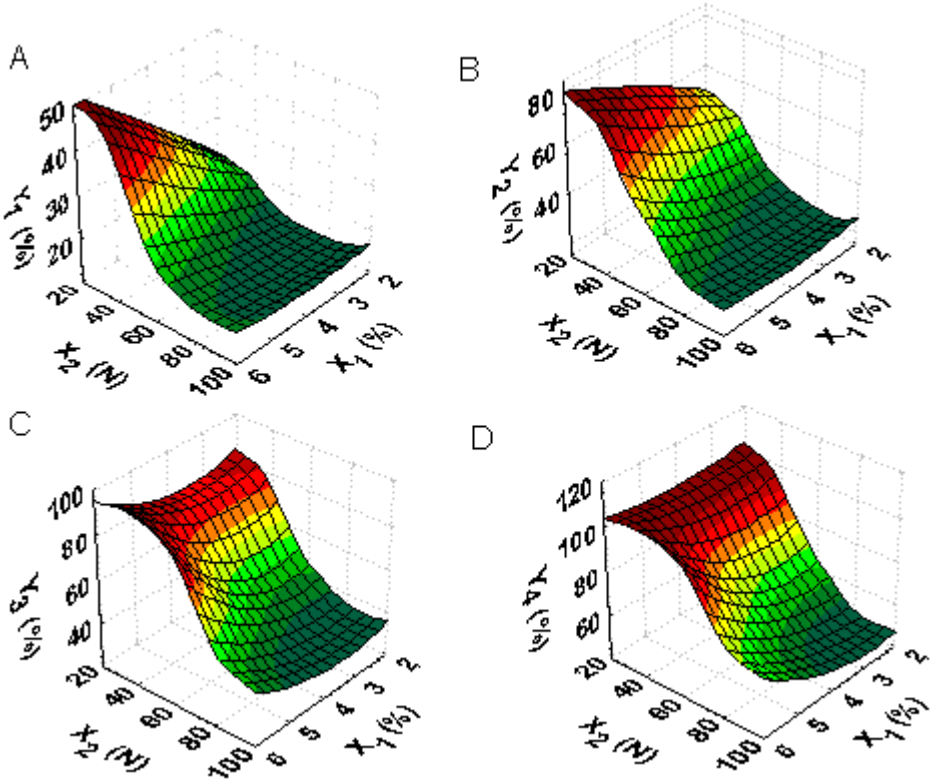

Figure 5. Response surfaces of the influence of the percentage of Eudragit L 100 and tablet hardness on the percentage of ASA released after (A) 1 hour, (B) 2 hours, (C) 4 hours, and (D) 8 hours, predicted using the GRNN.

Experimental and calculated values for training formulations (F1-F10) as well as test formulations are presented in **Table 2**. RMS reached after the training was 1.12%, which is an acceptable value.

Correlation plots were constructed for predicted versus observed values of drug release for test formulations. The GRNN model yielded a regression plot with squared coefficients (r^2) that were closest to a value of 1.0 (for all formulations >0.99), which indicate that the optimal GRNN model was reached.

Optimization

Response surfaces of the effect of ratio of Eudragit L 100 and tablet hardness on the percentage of aspirin dissolved after 1, 2, 4, and 8 hours of testing, predicted using GRNN, are presented in **Figure 5** (A-D) and corresponding contour plots in **Figure 6** (A-D). Bold red lines indicate pharmacopoeia limits. An increase of tablet hardness (ie, compression pressure) resulted in a decrease in the percentage of aspirin dissolved after 1 to 8 hours because of reduced tablet porosity. The influence of the percentage of Eudragit L 100 seems to have been negligible. This suggests that compression pressure acts as the controlling agent in the release of aspirin from the matrix tablets.

According to USP 23, after 1 hour of testing, aspirin extended release tablets have to release 15% to 40% of ASA, after 2 hours 25% to 60%, after 4 hours 35% to 75%, and after 8 hours more than 70%.

The optimization of the aspirin extended release tablets was performed according to the generalized distance function method.[18] Predicted optimal tablet formulation is with 5% of Eudragit L 100 and tablet hardness 60N. This tablet formulation was prepared, and in vitro release was performed

Experimental observed aspirin release from this optimal formulation, and the aspirin release predicted by GRNN, are presented in **Figure 7**. For every pair of experimental/predicted drug release profiles for test and optimal formulation, difference (f_1) and similarity (f_2) factors were calculated (**Table 3**). **Table 3** shows calculated regression coefficients (r^2) and slopes of regression curves of the observed versus predicted

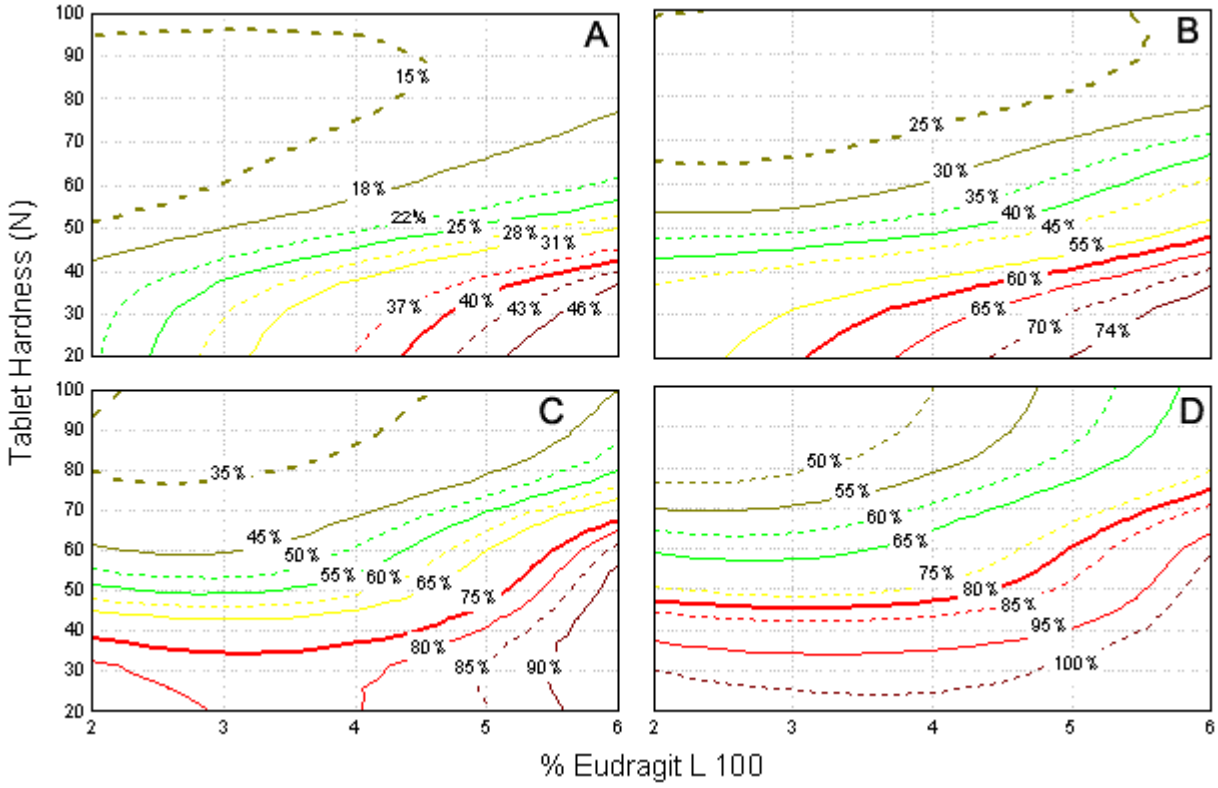

Figure 6. Contour plots of the influence of percentage of Eudragit L 100 and tablet hardness on percentage of ASA released after (A) 1 hour, (B) 2 hours, (C) 4 hours, and (D) 8 hours, predicted using the GRNN.

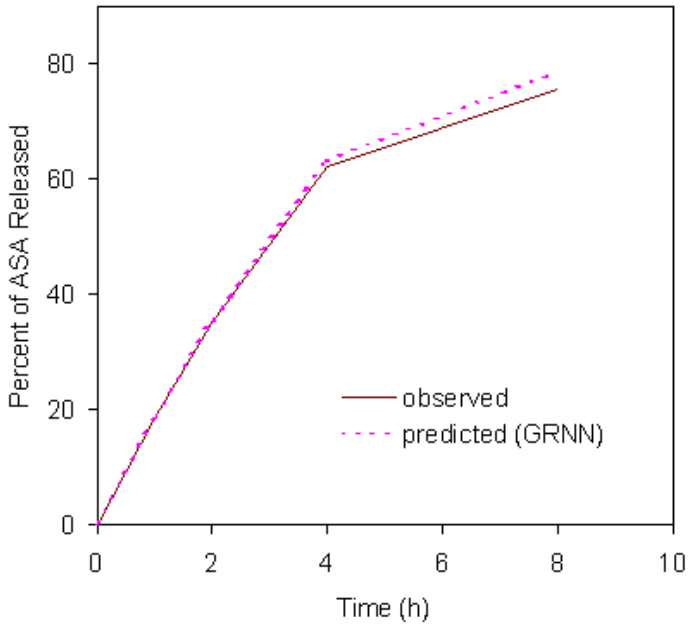

Figure 7. Predicted and experimental observed aspirin release from optimal formulation.

Table 3. Difference (f_1) and Similarity (f_2) Factors for Test and Optimal Formulations*

Profiles Predicted Using the GRNN	f_1	f_2	Slope	r^2
T1	4.286	75.870	1.0112	0.9876
T2	2.319	77.614	0.9963	0.9993
T3	5.670	71.120	0.9820	0.9970
T4	9.767	73.73	0.9602	0.9954
Optimal	2.465	85.61	1.0322	0.9997

*GRNN indicates generalized regression neural network.

release profiles. According to the US Food and Drug Administration's guides for industry,[19] generally (f_1 values up to 15 (0-15) and (f_2 values greater then 50 ensure sameness of the 2 curves. Release profiles predicted by the GRNN coincided well with the experimental values

The satisfactory prediction of the drug release for test and optimal formulations by the GRNN in this study has clearly shown the applicability of a GRNN to modeling extended release tablet formulation. The superiority of the GRNN in handling nonlinear data makes it suitable for the formulation problem.

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