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Optimization and Evaluation of Time-Dependent Tablets Comprising an Immediate and Sustained Release Profile Using Artificial Neural Network

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The aim of this work was to optimize time-dependent tablets using artificial neural network (ANN). The time-dependent tablet consisted of a tablet core, which contained sustained release pellets (70% isosorbide-5-mononitrate [5-ISMN]), immediate release granules (30% 5-ISMN), superdisintegrating agent (sodium carboxymethylstarch, CMS-Na), and other excipients, surrounded by a coating layer composed of a water-insoluble ethylcellulose and a water-soluble channeling agent. The chosen independent variables, i.e., X_1 coating level of tablets, X_2 coating level of pellets, and X_3 CMS-Na level, were optimized with a three-factor, three-level Box-Behnken design. Data were analyzed for modeling and optimizing the release profile using ANN. Response surface plots were used to relate the dependent and the independent variables. The optimized values for the factors X_1–X_3 were 4.1, 14.1, and 29.8%, respectively. Optimized formulations were prepared according to the factor combinations dictated by ANN. In each case, the observed drug release data of the optimized formulations were close to the predicted release pattern. An in vitro model for predicting the effect of food on release behavior of optimized products was used in this study. It was concluded that neural network technique could be particularly suitable in the pharmaceutical technology of time-dependent dosage forms where systems were complex and nonlinear relationships often existed between the independent and the dependent variables.

Keywords artificial neural network; response surface method; time-dependent tablets; isosorbide-5-mononitrate

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INTRODUCTION

The development of controlled release dosage forms with desired in vitro dissolution and in vivo bioavailability characteristics is often challenging because complex nonlinear relationships can exist between the independent formulation variables and the dependent drug release rate. As is well known, a response surface method (RSM) has widely been used for screening acceptable pharmaceutical formulations. However, prediction of pharmaceutical responses based on the second-order polynomial equation commonly used in an RSM is often limited to low levels, resulting in poor estimations of optimal formulations (Takayama et al., 2003). The recent availability of artificial neural network (ANN) software has provided a tool to assist in the iterative process of formulation development. ANN is a learning system based on a computational technique that can simulate the neurological processing ability of the human brain (Achanta, Kowalski, & Rhodes, 1995). It is very useful in modeling of systems where relationship between independent and dependent variables is not well known. ANN consists of a number of processing elements (artificial neurons) that are interconnected, forming input and output layers and one or more hidden layers (Figure 2). In recent years, pharmaceutical scientists have started using the ANN technology in fields such as pharmacokinetic–pharmacodynamic studies (Gobburu & Chen, 1996; Gobburu & Shelver, 1995), process development (Murtoniemi, Yliruusi, Kinnunen, Merkku, & Leiviska, 1994), in vitro–in vivo correlations (Parojčić, Ibrić, Djurić, Jovanovic, & Corrigan, 2006), and product development (Ebube, McCall, T., Chen, Y, & Meyer, 1997; Takahara, Takayama, & Nagai, 1997).

The back-propagation type of ANN is the one most often used in practice.

It is not always desirable that a controlled release formulation has a zero- or first-order release. Oral dosage forms with pulsed release kinetics have become the growing interest in recent years, and pharmaceutical scientists have displayed considerable ingenuity in the development of time-controlled drug delivery systems to address the emerging chronotherapeutic requirements. Various approaches to time-dependent delivery systems for oral application have been studied (Gothoskar, Joshi, & Joshi, 2004; Matsuo, Arimori, Nakamura, & Nakano, 1996; Schultz & Kleinebudde, 1997) . In this study, the time-dependent tablet consisted of a tablet core, which contained sustained release pellets (70% isosorbide-5-mononitrate [5-ISMN]), immediate release granules (30% 5-ISMN), superdisintegrating agent, and other excipients, surrounded by a coating layer composed of a water-insoluble ethylcellulose and a water-soluble channeling agent. It was designed to combine the advantages of a lag time (t_{lag}) and a once-daily nitrate with features such as fast onset and long-lasting action. Although the immediate release dose of 30% of the drug is available with a lag time of 4.5–5 h after intake, the maintenance dose (70% of 5-ISMN) is released in a sustained manner.

The objective of this study was to use the back-propagation neural network (BPNN) technique for the optimization of 5-ISMN release from time-dependent tablets. The dosage forms were technologically very sophisticated systems with complicated relationships between the independent variables (e.g., coating level of tablets) and the dependent variables (e.g., cumulative release). ANN was recognized as a potentially useful technique for this study. The optimized products were used to investigate the in vitro simulation of food effect in the biorelevant media and were then characterized by scanning electron microscopy (SEM).

MATERIALS AND METHODS

Materials

5-ISMN was purchased from Shanghai New Asiatic Pharmaceuticals Co., Ltd (Shanghai, China). Ethyl cellulose was purchased from Luzhou Northen Pharmaceutical Excipient Co., Ltd. (LuZhou, Sichuan, China) Avicel PH302, sodium carboxymethylstarch (CMS-Na), and nonpareil beads (Microcrystalline cellulose spheres, Celphere CP305) were freely supplied by Asahi Kasei Corporation (Shanghai, China), Hydroxypropylmethylcellulose (HPMC) (Methocel E5, manufactured by Dow Chemical Co., Midland, MI, USA) by Coloron (Shanghai, China), and diethyl phthalate (DEP) by Sinopharm Chemical Reagent Co., Ltd (Shanghai, China). Other excipients were of standard pharmaceutical grade. Water used in all experiments was deionized and distilled.

Design of Experiments

In this study, based on single-factor experimental results, coating level of tablets, coating level of pellets, and the level of core disintegrating agent CMS-Na were identified as the three important factors responsible for the cumulative percentage of 5-ISMN released. Therefore, a three-factor, three-level, Box-Behnken design was used to generate factor combinations by using a statistical software Design-Expert® version 7 (Stat-Ease, Inc., Minneapolis, MN, USA). It was suitable for investigating the quadratic response surfaces, thus enabling optimization of a process with a small number of experimental runs (15 runs) (Figure 1). Table 1 summarizes the factors, their levels, and responses.

Artificial Neural Network

NeuroShell 2 Release 4.0 (Ward Systems Group, Inc., Frederick, MD, USA) was used in this study. The input data obtained from Box-Behnken design and the responses obtained from dissolution studies were used for training and testing the ANN. BPNN was used in modeling and optimization of these dosage forms. The model training parameters chosen were: number of hidden layers, 2; number of nodes in the first hidden layer, 6; number of nodes in the second hidden layer, 8; learning rate, 0.5; momentum, 0.1; and learning algorithm, back propagation (Figure 2). Of the 15 experimental data sets listed in Table 2, 3 formulations that were representative of the range of release profiles were randomly chosen as test data by the software, whereas the data of the remaining 12 formulations were used as the initial training data for the ANN model development.

To compare the performance of the models, we computed the following indexes: A statistic that is widely used to determine how well a regression fits is the coefficient of determination (or multiple correlation coefficient), R^2. R^2 represents the fraction of variability in y that can be explained by the

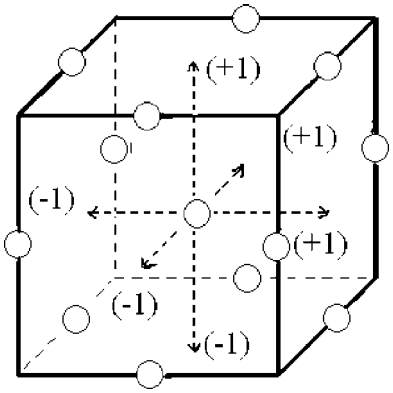

FIGURE 1. A Box-Behnken design for three factors. (–1) low level of factor; (+1) high level of factor.

TABLE 1
Box-Behnken Design: Factors and Response

Factors	Level Used			Responses
	–1	0	1	
X_1 = coating level of tablets (%)	3	5	7	$Y_1 = t_{lag}$[a] h
X_2 = coating level of pellets (%)	10	15	20	Y_2 = % of drug released in (t_{lag} + 1) h
X_3 = CMS-Na level (%)	26.7	33.3	40	Y_3 = % of drug released in (t_{lag} + 4) h
				Y_4 = % of drug released in (t_{lag} + 8) h
				Y_5 = % of drug released in (t_{lag} + 12) h

[a]t_{lag} is defined as the time from initial dosing to 10% of drug released.

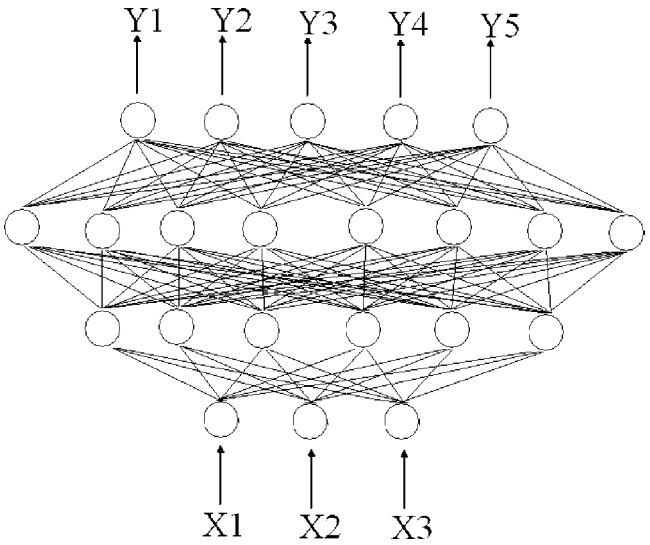

FIGURE 2. Structure of a 3–6–8–5 BPNN composed of three input units, two hidden layers (six neurons, eight neurons) and five output units.

variability in x, i.e., how close the points are to the line. The equation for R^2 is

$$R^2 = 1 - \frac{SSE}{SS_{YY}}$$

where

$$SSE = \sum (y - \hat{y})^2 \qquad SS_{YY} = \sum (y - \bar{y})^2 \tag{1}$$

In which is the actual value, $\hat{y}$ the predicted value of y, and the $\bar{y}$ mean of the y values.

Consequently, a perfect fit is obtained when $R^2 = 1$, and there is no fit when $R^2 = 0$. For each of the responses the best possible correlation coefficient (r) was also computed. This coefficient r is given by the quality of the response measurements and is defined as follows:

$$r = \frac{SSxy}{\sqrt{SS_{xx} SS_{yy}}} \tag{2}$$

where

$$SS_{xy} = \sum XY - \frac{(\sum X)(\sum Y)}{n}$$

$$SS_{xx} = \sum x^2 - \frac{(\sum x)^2}{n}$$

$$SS_{yy} = \sum y^2 - \frac{(\sum y)^2}{n}$$

where n represents the number of patterns, x refers to the set of actual outputs, and y refers to the predicted outputs. This is a statistical measure of the strength of the relationship between the actual vs. predicted outputs. The coefficient can range from –1 to +1. The closer r is to 1, the stronger the positive linear relationship, and the closer it is to –1, the stronger the negative linear relationship. When r is around 0, there is no linear relationship. (Extracted from NeuroShell 2 Help, (C) Ward Systems Group, Inc.)

Preparation of Coated Pellets

Two-hundred grams of non-pareil beads (Celphere CP305) was used as initial cores to achieve 40% drug loading by a fluidized-bed coater MP1® (Niro Inc., Aeromatic-Fielder AG, China). 5-ISMN was mixed with distilled water, and hydroxypropyl cellulose solution (HPMC E5, 2% wt/wt) was used as the binder. Opadry II® (85G68918 white) as seal coating was applied to drug-loaded beads primarily to avoid the leaching of drug into sustained release coating. After spraying the required amount of seal coating, pellets were dried in the fluid bed, collected in a tray, and dried again at 40°C overnight to ensure the evaporation of residual water.

TABLE 2
Box-Behnken Design: Factors and Responses

				Response									
				Y_1		Y_2		Y_3		Y_4		Y_5	
Runs	X_1	X_2	X_3	E	P	E	P	E	P	E	P	E	P
F1	0	0	0	5.2	5.2	34.9	34.1	54.8	51.2	75.5	71.5	87.5	87.7
F2	–1	0	–1	4.8	4.2	38.0	36.4	58.0	57.9	78.2	77.0	90	89.4
F3	1	0	–1	8.7	8.1	43.7	45.7	84.5	84.3	99.0	98.6	101.2	100.4
F4	–1	0	1	1.9	2.1	35.7	37.3	57.0	58.8	75.0	75.3	89	88.8
F5	–1	–1	0	3.4	3.1	44.0	44.6	82.3	80.2	98.6	96.9	100.3	101.2
F6	0	1	1	4.2	4.4	33.4	31.2	46.2	43.1	57.5	56.8	65.2	64.9
F7	1	–1	0	7.3	7.8	46.0	45.3	83.1	83.0	99.3	97.8	100	100.3
F8	0	0	0	5.2	5.2	31.5	34.1	50.2	51.2	71.7	71.5	85.3	87.6
F9	0	0	0	5.3	5.2	32.8	34.1	52.5	51.2	72.8	71.5	90	87.6
F10	1	1	0	7.5	6.7	31.2	32.3	47.3	47.5	59.2	59.1	68	68.1
F11	0	–1	–1	6.5	6.2	32.0	33.3	50.0	49.6	72.0	69.9	85	84.8
F12	–1	1	0	3.0	2.0	31.6	31.2	43.1	43.1	56.8	56.8	64.5	67.7
F13	1	0	1	5.7	5.7	36.5	36.9	57.1	58.6	78.7	79.5	97.1	93.5
F14	0	–1	1	4.2	4.3	38.6	37.5	60.0	60.3	80.0	81.7	92	94.6
F15	0	1	–1	6.3	6.7	33.3	32.4	47.9	48.0	58.6	59.8	67	68.7

Randomized runs and the responses (experimental [E] and predicted [P] values for chosen outputs).

TABLE 3
Process Parameters for the Isosorbide-5-Mononitrate (5-ISMN) Layering and Sustained Release Coating of Layered Pellets

Process Parameter	5-ISMN Layering	Seal Coating	Sustained Release Coating
Inlet temperature (°C)	55	45	32
Product temperature (°C)	40–45	35–40	35
Nozzle diameter (mm)	0.8	0.8	0.5
Atomization pressure (bar)	2.0	2.0	1.0
Spray rate (*g*)	3–5	2˜4	3

The sustained release coating consisted of 50 g/L EC, stearic acid, and DEP (15% of EC, wt/wt) as a plasticizer in ethanol solution. The coating method, nozzle diameter, and air volume were similar to those of drug loading. Coating weight gain achieved was 10, 15, or 20% (wt/wt). The process parameters are listed in Table 3.

Tableting

Micronized NaCl, CMS-Na, and 5-ISMN were sieved through an 80 mesh screen, separately, prior to their use as core materials. Then, drug and excipients were blended. Finally, the mixture of drug and excipients were blended with coated pellets (2:1 wt/wt). All the tableting experiments were performed by using a reciprocating press (Rimek, mini press-II SF, Indian) with a flat-faced punch and a die. Each tablet with average weight of 300 mg containing 100 mg of coated pellets was weighed and manually filled in the die. The diameter and hardness of core tablets were 9 mm and 5 kg, respectively.

Tablet Coating

The core tablets were coated in a conventional rotating coating pan. For the coating process, the rotation speed was adjusted to 36 r/min with the coating pan set at an angle of 45°; nozzle size was 0.8 mm; inlet air temperature was 35°C; and tablet bed temperature was 25°C. The coating solution was sprayed onto

the tablets at a flow rate of 0.8 mL/min. The coating solution was 50 g/L EC in ethanol which contained DEP (10% of EC, wt/wt) as plasticizer, micronized lactose as channeling agent, and iron oxide red as pigment. Coating weight gain achieved was 3, 5, and 7% (wt/wt), respectively.

In Vitro Drug Release

Dissolution studies were carried out with paddle method at a rotation speed of 100 r/min, and 500 mL of distilled water at 37°C was the medium ($n = 6$). Samples were collected at predetermined time points and analyzed for 5-ISMN content using high-performance liquid chromatography (HPLC, Shimadzu, Japan) at 220 nm, and the cumulative release amounts of 5-ISMN were calculated over the sampling times.

In Vitro Simulation of Food Effect

Biorelevant media have been developed to simulate the fasted and fed states. It has been observed that biorelevant media can provide a more accurate simulation of pharmacokinetic profiles than simulated gastric or intestinal fluids. Food effect studies were respectively carried out in the Fasted State Simulated Intestinal Fluid (FaSSIF) and Fed State Simulated Intestinal Fluid (FeSSIF). FaSSIF and FeSSIF were prepared as per preparation instructions for the biorelevant media developed by Dr. Dressman's group (Kostwicz, Brauns, Becker, & Dressman, 2002) (Table 4). Release conditions study and sample assay were performed as for dissolution studies above. Optimized formulation was used in this study.

Scanning Electron Microscopy

The nature of the coated surface of an optimized formulation and its cross section were scanned using an environmental SEM (Philips XL 30 ESEM, Eindhoven, Holland). Beads and tablet were loaded on the copper sample-holder and sputter-coated with carbon followed by gold. The topography of the whole beads, surface of tablet, and cross sections of beads and tablet were examined for the integrity of coated film.

RESULTS AND DISCUSSION

Release Behaviors

Release behaviors of 5-ISMN from pellets and tablet 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. Figure 4 shows rupture course of time-dependent tablets during 5 h in distilled water. Table 2 summarizes the experimentally observed percentages of 5-ISMN released in 20 h of dissolution study.

Artificial Neural Network

Training

Three causal factors corresponding to different values of coating level of tablets (X_1), coating level of pellets (X_2), and CMS-Na level (X_3) were used as each node of the input layer in the BPNN.

Responses were used as output layer:

Y_1—lag time, Y_2—% of 5-ISMN released after (t_{lag} + 1) h, Y_3—% of 5-ISMN released after (t_{lag} + 4) h, Y_4—% of 5-ISMN released after (t_{lag} + 8) h, and Y_5—% of 5-ISMN released after (t_{lag} + 12) h.

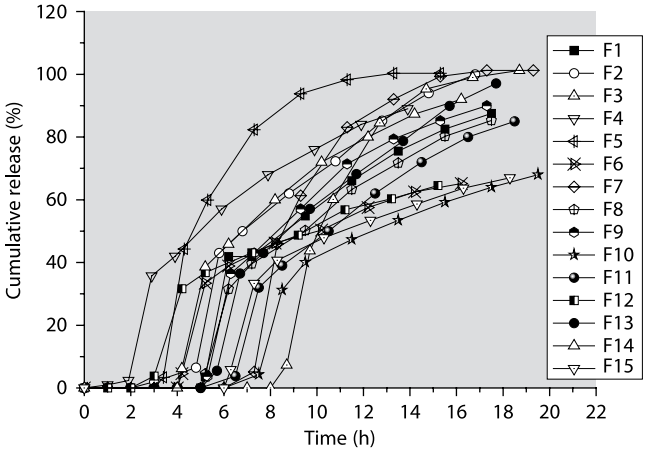

FIGURE 3. In vitro mean dissolution profiles of 15 formulations based on experimental design.

TABLE 4
Preparation Instructions for the Biorelevant Media

Fed State Simulated Intestinal Fluid (FeSSIF)		Fasted State Simulated Intestinal Fluid (FaSSIF)	
Sodium taurocholate	15 mM	Sodium taurocholate	3 mM
Lecithin	3.75 mM	Lecithin	0.75 mM
NaOH (pellets)	4.04 g	NaOH (pellets)	0.174 g
Glacial acetic acid	8.65 g	$NaH_2PO_4.H_2O$	1.977 g
NaCl	11.874 g	NaCl	3.093 g
Purified water qs.	1000 mL	Purified water qs.	500 mL
Media has a pH of 5.00 and an osmolality of about 670 mOsmol/kg		Media has a pH of 6.50 and an osmolality of about 270 mOsmol/kg	

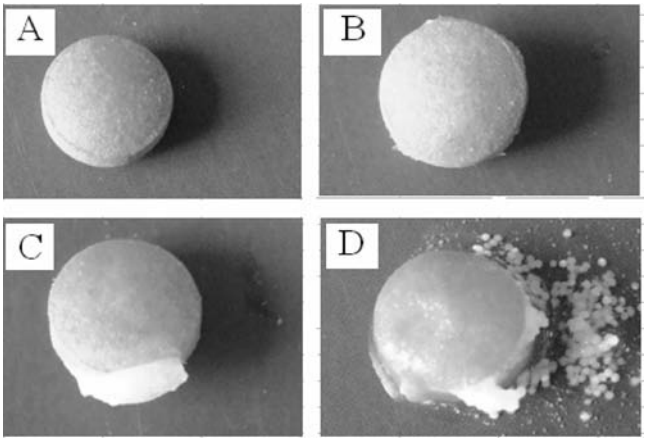

FIGURE 4. Rupture sequence of time-dependent tablets with a swelling layer and a rupturable ethylcellulose coating in purified water. (a) $t = 0$ min; (b) $t = 4$ h (start of rupture); (c) $t = 4.5$ h (rupture); and (d) $t = 5$ h (complete rupture).

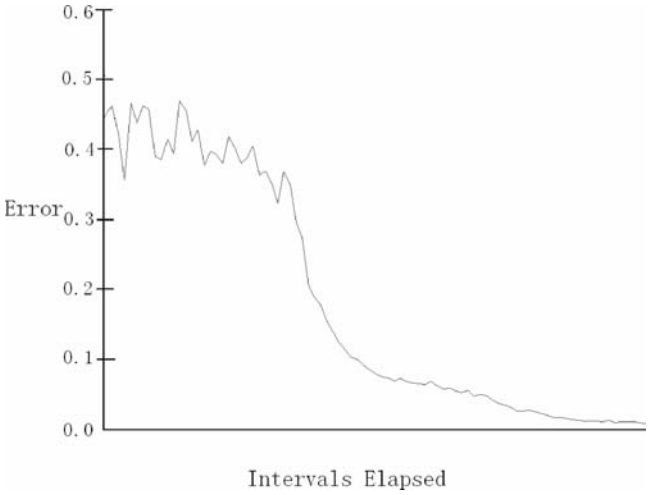

FIGURE 5. Back-propagation test set average error graphed against intervals elapsed.

A set of outputs and causal factors was used as learning data and fed into a computer. Modeling parameters were selected by trial and error. To select the optimum BPNN model, different numbers of nodes were compared. Finally, a 3-6-8-5 BPNN was used in modeling and optimization of the time-dependent tablet (Figure 2). An increase in the number of learning epochs would improve the reduction of the average test error. However, no appreciable decrease in average test error was observed when number of epochs was increased from 10,000 to 20,000, and here, the number of epochs was kept at 15,000 for all the models. Models were evaluated by minimum average training error, minimum average test error, coefficient of determination R^2, and correlation coefficient r (Table 5).

The model's predictive results were compared with the actual output values. R^2 values depict the percentage of response variability accounted for the model. We can see from Table 5 that there was a high and significant R^2 between independent variables (e.g., coating level of tablets) and dependent variables (e.g., cumulative release). The R^2 value of 0.90 and above for all the models in this study suggested an adequate modeling. The ANN modeling was particularly good for Y_3, Y_4, and Y_5 where the R^2 values were 0.9828, 0.9821, and 0.9803, respectively, and correlation coefficient r values were 0.9918, 0.9952, and 0.9909, respectively.

During training, a sharp decrease in test error was observed as it approached the maximum number of epochs (Figure 5). Generally speaking, if there is little or no change in the minimum average error for either the training set or the testing set, learning may be complete (if using calibration). Figure 6 shows the plot of experimental values against predicted values for the dependent variables. This plot shows that most of the points fell on the straight line of $y = x$, indicating that the predicted results were close to experimental results.

TABLE 5
Statistical Calculations Made for Each Output

Output	Y_1	Y_2	Y_3	Y_4	Y_5
R^2	0.9790	0.9736	0.9828	0.9821	0.9803
r^2	0.9608	0.9592	0.9837	0.9905	0.9819
Mean squared error	0.157	1.496	2.061	2.537	2.704
Mean absolute error	0.264	0.509	0.9483	1.141	1.296
Min. absolute error	0.011	0.400	0	0	0.065
Max. absolute error	0.869	2.738	3.071	3.574	3.832
Correlation coefficient r	0.9802	0.9794	0.9918	0.9952	0.9909
Minimum average training error	0.0001010				
Minimum average test error	0.0025035				

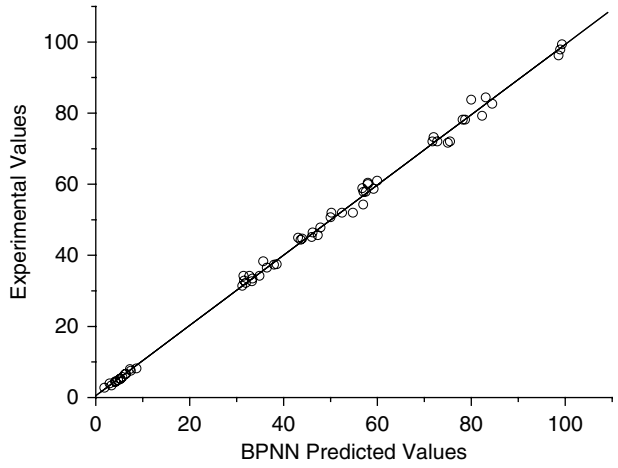

FIGURE 6. BPNN predicted vs. experimental values of dependent variables for all the data.

TABLE 6
Response After Optimization Procedure

Responses	Predicted	Observed	Residuals
Y_1	4.7	4.5	0.2
Y_2	35.0	36.4	–1.4
Y_3	54.0	54.8	–0.8
Y_4	76.2	78.2	–2.0
Y_5	95.0	98.7	–3.7

Optimization

Optimization of a time-dependent tablet was performed according to the generalized distance function method (Khuri & Conlon, 1981). Factors Y_1–Y_4 were targeted for the theoretical values as constraints (Table 6), and Y_5 was maximized. The optimized values for the factors X_1–X_3 were 4.1, 14.1, and 29.8%, respectively. Figure 7 shows the three-dimensional response surface and two-dimensional contour plot on lag time. Clearly, coating level of the tablet (X_1) had positive effect on lag time. As the coating level of tablet increased, the lag time had a tendency to increase. On the contrary, as CMS-Na level (X_3) increased, the lag time decreased, but coating level of pellet (X_2) had no significant effect on the lag time. Increasing coating weight gain increased the physical barrier between the drug in

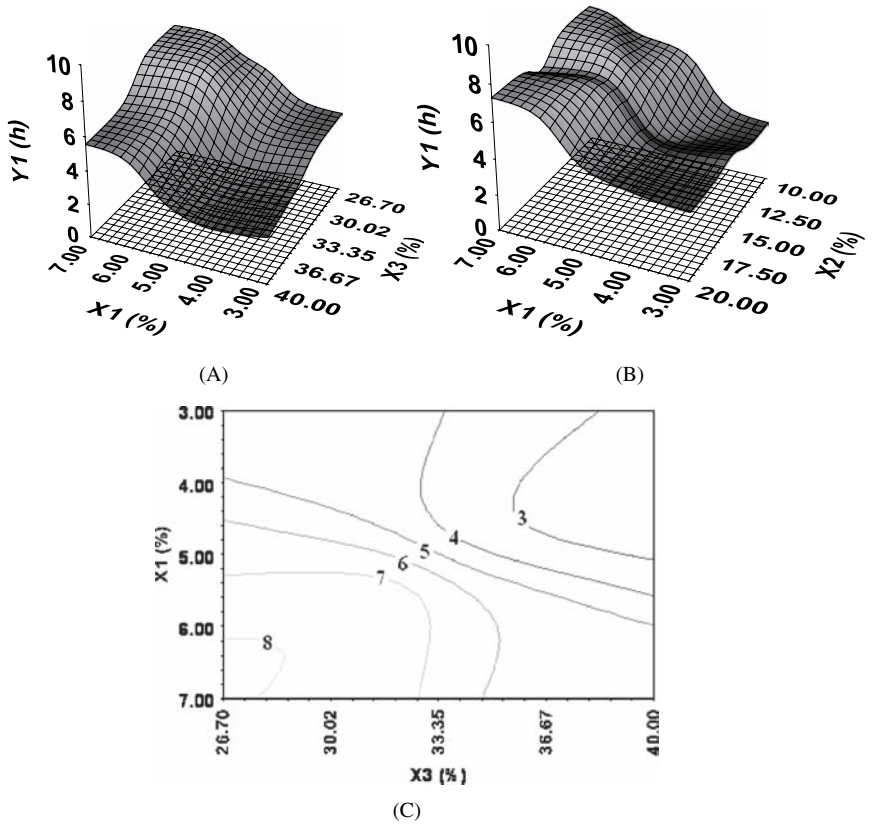

FIGURE 7. Predicted response surface of lag time (Y_1) of isosorbide-5-mononitrate (5-ISMN). (A) Three-dimensional response surface of coating level of tablet (X_1) and CMS-Na level (X_3). Coating level of pellets (X_2) was fixed at 15 wt.%. (B) Three-dimensional response surface of X_1 and X_2. X_3 was fixed at 33.3 wt.%. (C) Two-dimensional contour plot of X_1 and X_3. X_2 was fixed at 15 wt.%.

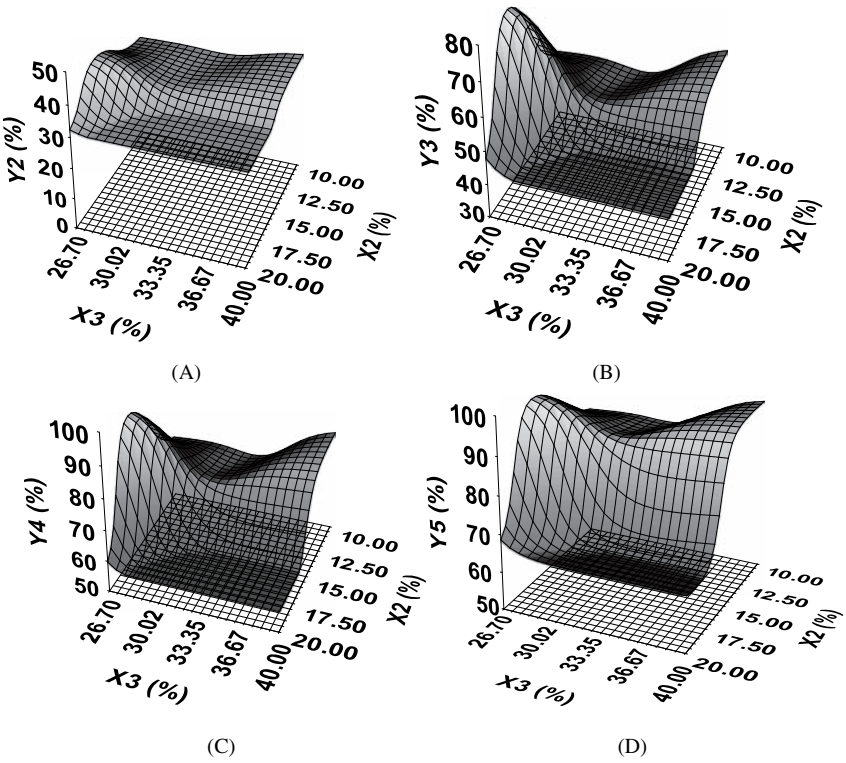

FIGURE 8. Response surfaces of the influence of the percentage of X_2 and X_3 on percentage of isosorbide-5-mononitrate (5-ISMN) released after (A) (t_{lag} + 1), (B) (t_{lag} + 4), (C) (t_{lag} + 8), (D) (t_{lag} + 12), predicted using the BPNN. X_1 was fixed at 5 wt.%.

the tablets and the dissolution medium, and that produced an increase in the lag time of drug release. Response surfaces of the effect of coating level of tablet, coating level of pellet, and CMS-Na level on the percentage of 5-ISMN dissolved after (t_{lag} + 1), (t_{lag} + 4), (t_{lag} + 8), and (t_{lag} + 12) h of testing, predicted using BPNN, are presented in Figure 8A–D. An increase of coating level of pellet resulted in a decrease in the percentage of 5-ISMN dissolved after (t_{lag} + 1) to (t_{lag} + 12) h because of reduced dissolution medium permeation. The influence of CMS-Na level seemed to have been negligible.

To check the validity of the optimization procedure, a new batch of tablets with the predicted levels of formulation factors was prepared. Simultaneously, the predicted levels of formulation factors were fed into the trained BPNN to produce an output. Table 6 summarizes the predicted and observed responses for the optimum formulation. It was observed that the optimized formulation prepared according to computer-determined levels ensured a release profile that was close to the predicted values.

Difference factor (f_1) and similarity factor (f_2) have been proposed to assess the similarity of the two in vitro dissolution profiles (FDA, 1997) or one dissolution profile predicted by the ANN model and the other obtained from physical experiments (Costa, Sousa, Pais, & Formosinho, 2003; Li, Rauth, & Wu, 2005) for controlled release formulations. The US Food and Drug Administration considers two dissolution profiles to be similar if the difference factor (f_1) is between 0 and 15 and the similarity factor (f_2) is between 50 and 100 (FDA, 1997). The difference factor, f_1, and the similarity factor, f_2, are defined in the following two equations, respectively (Moore & Flanner, 1996).

$$f_1 = \frac{\sum_{t=1}^{n} |R_t - T_t|}{\sum R_t} \times 100 \tag{3}$$

$$f_2 = 50 \times \log\left\{\left[1 + \frac{1}{n}\sum (R_t - T_t)^2\right]^{-0.5} \times 100\right\} \tag{4}$$

where R_t and T_t are the percentages of drug released from the reference formulation and the test formulation, respectively, at time t, and n is the number of sampling time points. In this study, release profiles predicted by the BPNN coincided well with the experimental values (f_1 = 3.45, f_2 = 81.46, r^2 = 0.9985) (Figure 9).

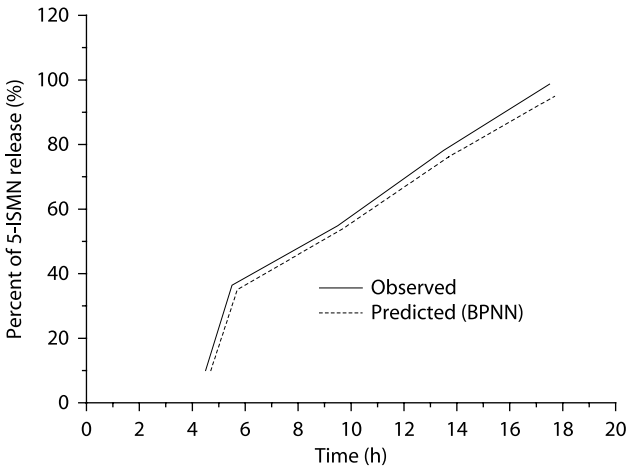

FIGURE 9. Predicted and experimentally observed isosorbide-5-mononitrate (5-ISMN) release from optimal formulation.

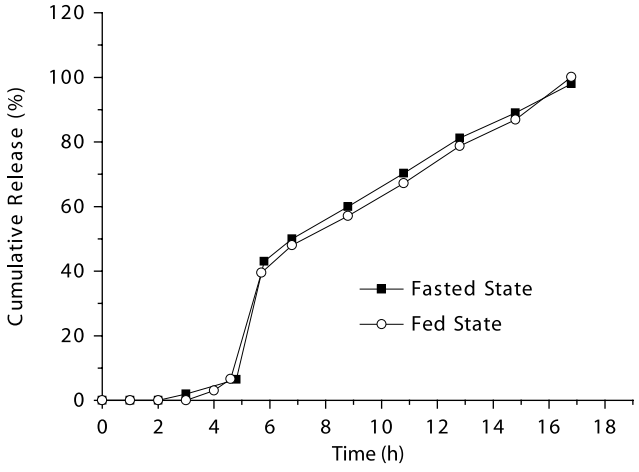

FIGURE 10. Release behavior of isosorbide-5-mononitrate (5-ISMN) from the optimized tablets in the fasted and fed states ($n = 6$).

In Vitro Simulation of Food Effect

When dissolution testing is used to forecast the in vivo performance of a drug, it is critical that the in vitro test mimic the conditions in vivo as closely as possible. Biorelevant in vitro dissolution testing is useful for qualitative forecasting of formulation and food effects on the dissolution and availability of orally administered drugs (Kostwicz, Brauns, Becker, & Dressman, 2002). It has been observed that biorelevant media can provide a more accurate simulation of pharmacokinetic profiles than simulated gastric fluid or simulated intestinal fluid (Dressman & Reppas, 2000; Nicolaides, Symillides, Dressman, & Reppas, 2001). Figure 10 suggests that there was no significant difference in release behavior between fasted and fed states (f_2 = 71.33). Release behavior of the optimized formulation could remain invariable when taken with or without food. In other words, when taken concomitantly with food, the drug did not release faster following the fat content of food, which has instructive significance for future in vivo work.

Scanning Electron Microscopy

SEM pictures of the optimized beads are given in Figure 11. The outer surface of coated pellets appeared as a smooth, homogenous coat that may facilitate the prevention of rapid water penetration and achieve a zero-order drug release profile. The cross section showed the core of inert beads (Celphere CP305) and the EC coating layer. The outermost section showed the uniform and intact coating layer of controlled release membrane. Figure 12 shows the cross section and the surface of the tablet. It could be seen that lactose particles as channeling agent were dispersed uniformly in the EC coating film. Continuous and homogeneous film coating contributed to keeping the lag time invariable for the same formulation.

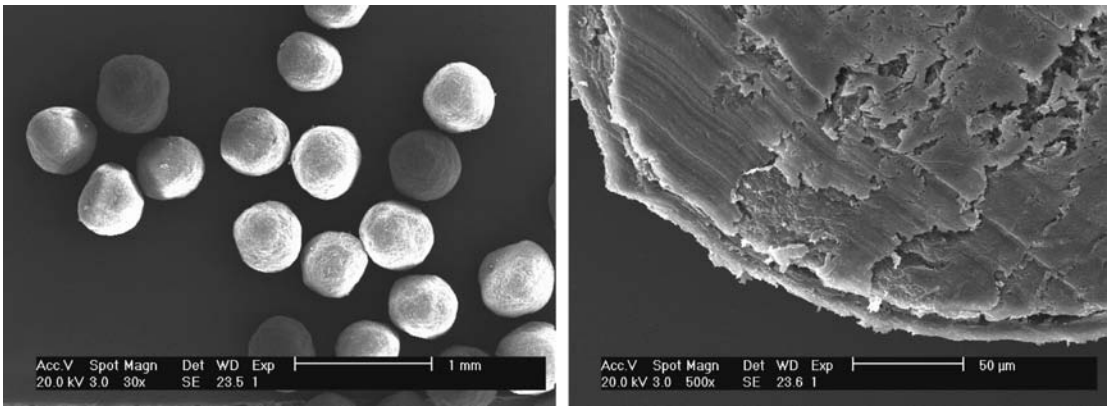

FIGURE 11. Scanning electron microscopy pictures of coated beads and its cross section.

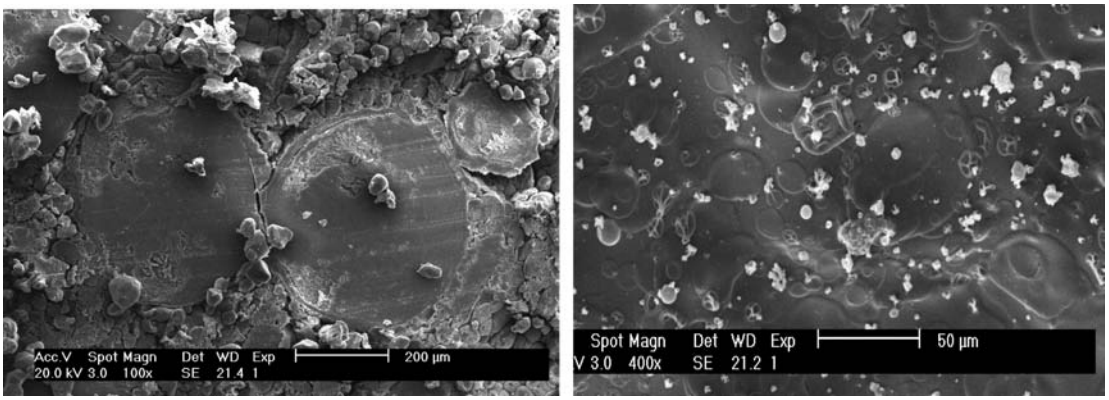

FIGURE 12. Scanning electron microscopy pictures of the tablets and its cross section.

CONCLUSION

This work has illustrated the potential for an ANN to assist in the development of complex dosage forms. The method can be used to achieve a desired in vitro dissolution profile. The two- and three-dimensional visualization of relations between independent and dependent variables proved to be a useful tool in studying pharmaceutical systems. The difference between observed and predicted dissolution profile of optimized batch was within the experimental error limits. The satisfactory prediction of drug release for optimal formulations by the BPNN in this study has clearly shown the applicability of a BPNN in modeling time-dependent tablet formulation. The superiority of the BPNN type of neural network in handling nonlinear data makes it suitable for the formulation problem.

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