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Generalization of a Prototype Intelligent Hybrid System for Hard Gelatin Capsule Formulation Development

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ABSTRACT

The aim of this project was to expand a previously developed prototype expert network for use in the analysis of multiple biopharmaceutics classification system (BCS) class II drugs. The model drugs used were carbamazepine, chlorpropamide, diazepam, ibuprofen, ketoprofen, naproxen, and piroxicam. Recommended formulations were manufactured and tested for dissolution performance. A comprehensive training data set for the model drugs was developed and used to retrain the artificial neural network. The training and the system were validated based on the comparison of predicted and observed performance of the recommended formulations. The initial test of the system resulted in high error values, indicating poor prediction capabilities for drugs other than piroxicam. A new data set, containing 182 batches, was used for retraining. Ten percent of the test batches were used for cross-validation, resulting in models with $R^2 \geq 70\%$. The comparison of observed performance to the predicted performance found that the system predicted successfully. The hybrid network was generally able to predict the amount of drug dissolved within 5% for the model drugs. Through validation, the system was proven to be capable of designing formulations that met specific drug performance criteria. By including parameters to address wettability and the intrinsic dissolution characteristics of the drugs, the hybrid system was shown to be suitable for analysis of multiple BCS class II drugs.

KEYWORDS: in silico modeling, capsule formulation, artificial neural networks, expert systems, low solubility drugs.

INTRODUCTION

Artificial Intelligence

The use of artificial intelligence, such as artificial neural networks (ANNs) and expert systems, provides an opportunity to systematically approach formulation in an efficient manor. ANNs are computer-based programs that attempt to simulate some features of the biological brain such as learning, generalizing, or abstracting from experience.[1] ANNs are parallel information processing systems that can develop adaptive responses to environmental information.[2] ANN models, such as back propagation learning networks, may be viewed simply as multiple nonlinear regression models. The experimental data and information generated may be transformed relatively easily into knowledge that can be used in the construction of domain specific rules by the formulator.

There are several advantages to using ANNs. Unlike statistics-based analysis, these programs do not require experimentally designed data. Incomplete or historical data can be used successfully to train ANNs. These programs can also model nonlinear and discontinuous functions. In spite of these advantages, there are disadvantages to using this type of modeling. The model generated is very specific and is dependent on experimental conditions. The ability of the program to successfully model the relationships hidden in the data is dependent on the quality of the data used to train the system. Overtraining of the ANN is also possible, resulting in "memorized" patterns instead of derived relationships.

An expert system is a computer program that emulates expert thought to solve significant problems in a particular domain of expertise. These intelligent computer programs use knowledge and inference procedures to solve problems. A unique characteristic of these problems is that they are often difficult enough to require significant expertise for their solutions. The knowledge necessary to perform at such an expert level as well as the inference procedures used are often thought of as a model of the expertise of the best practitioners of that given field.[3]

The use of expert systems (ES) presents several advantages. Well-functioning ES can facilitate an increased distribution of expertise in a given field and present a new communication channel for this knowledge. Moreover, the system provides protection of this knowledge by establishing a coherent and durable existence that can easily be accessed, modified, and updated. This knowledge base can serve as a valuable training aid for novices, allowing experts involved in training to focus on other issues. ES also

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provide for more consistent approaches to resolution of problems.[3] On the other hand, these systems suffer from such limitations as lacking creativity in problem resolution. ES can only deal with issues that have been anticipated and included in the knowledge base.

Artificial intelligence is not a newcomer in the arena of pharmaceutical sciences. ANNs have been used to predict dissolution profiles and for formulation optimization.[4-10] Their use has also been employed in predicting model granulation and tablet characteristics based on material and process variables[11] as well as in estimating the aqueous solubility of structurally related drugs.[12] ANNs have been used to assess in vitro-in vivo correlations[13] and parameters such as crushing strength and disintegration time have been optimized.[14] In preformulation, ANNs have been used to characterize the physiochemical properties of amorphous polymers.[15]

ES have been used to recognize complex relationships between formulation variables and in vitro drug release.[16] They have also been used in the area of solid dosage development, especially in the areas of tableting and film coating.[3] ES have also been applied to troubleshooting pharmaceutical processing equipment, such as rotary tablet presses.[17] Prototype ES have been developed for the use in formulary decision making[18,19] as well as selecting the most appropriate pharmaceutical powder mixer.[20]

Capsugel's expert system (CES) for formulation support is a centralized system incorporating worldwide industrial experience to support formulation of powders in hard gelatin capsules.[21] The most serious limitation is that the CES provides only a suggested formulation. The system provides no guidance or assurance that the predicted formulation will meet any particular dissolution, content uniformity, and/or weight variation requirement within user specified limits. It was hypothesized by Guo et al that the development of a hybrid system linking the current expert system to an ANN would effectively address this limitation and provide a facilitated way of generating new rules based on "learning." The development of such a hybrid system that integrated an ANN with an ES could take advantage of the strengths of both the ANN and the ES while avoiding the weaknesses of either. By combining both of these systems, the knowledge of an ES can be used to design a formulation that could subsequently be optimized by the ANN. The concept of an expert network (EN) has been proven viable on a small scale by Guo et al using piroxicam as a model drug.[19]

Biopharmaceutics Classification System

The work of Amidon et al resulted in a scientific method to identify drugs based on their solubility and permeability.[22,23] The biopharmaceutics classification system (BCS), introduced in 1995, consists of 4 drug categories: class I, class II, class III, and class IV. Class II drugs demonstrate high permeability but are poorly soluble. These compounds have the potential for enormous therapeutic success; however, absorption and, hence, the effectiveness may be limited by the rate of dissolution of the drug. Owing to solubility issues, the dissolution behavior of class II compounds is one of the most critical variables for this category of substances. In contrast to class I and class III, multipoint dissolution specifications are recommended for class II drugs. In addition, a complete characterization of the entire dissolution profile may be necessary to ensure quality control.[24]

The widely understood and studied drugs carbamazepine, chlorpropamide, diazepam, ibuprofen, ketoprofen, naproxen, and piroxicam were used as model drugs in this project. These drugs were selected because of their low solubilities and high permeabilities. These drugs were classified as BCS class II drugs based on their dissolution rate-limited absorption behavior. Owing to their low solubility, it was important to characterize the properties of the drugs that were associated with solubility and wettability. The intention of this project was to provide a more systematic approach to capsule formulation of BCS class II compounds by expanding the prototype EN for use in the analysis of multiple BCS class II drugs.

Materials and Methods

Materials

The following drugs were used as received from the suppliers: carbamazepine *United States Pharmacopeia (USP)* (lot RF1355, Spectrum Chemicals, Gardena, CA); chlorpropamide *USP* (lot 7812B, ICN Biomedicals, Aurora, OH); diazepam BP (lot RD0991, Spectrum Chemicals); ibuprofen *USP* (lot SE0196, Spectrum Chemicals); ketoprofen *USP* (lot RC0730, Spectrum Chemicals); naproxen (lot E2JA099, courtesy of Syntex Pharmaceuticals, Clarecastle, Ireland); and piroxicam (lot C21P903, courtesy of Pfizer Inc, Groton, CT).

The following materials were used as received from the suppliers: anhydrous lactose (lot 60679, Quest International, Hottman Estates, IL); citric acid (lot RT0330, Spectrum Chemicals), croscarmellose sodium NF (Ac-Di-Sol, lot T226N, courtesy of FMC Biopolymer, Newark, DE); cyclohexane (lot 000696, Fisher Scientific, Fair Lawn, NJ); fumed silica dioxide (Cab-O-Sil M-5P, lot 1J079, Cabot Corp, Billerica, MA); hydrochloric acid (lot 993660, Fisher Scientific; lot 43169, EMD, Gibbstown, NJ); hard gelatin capsules (lot 590311, courtesy of Capsugel, Greenwood, SC); microcrystalline cellulose (Emcocel 90M, lot E9B0B17, courtesy of PenWest Pharmaceutical, Patterson, NY); potassium

citrate (lot QU0707, Spectrum Chemicals); potassium phosphate, monobasic (lot RP0462, Spectrum Chemicals; lot L49147, JT Baker Chemicals, Phillipsburg, NJ); and potassium phosphate, dibasic (lot PX0482, lot SM1234, lot SS0455, Spectrum Chemicals; lot 7080KAHA, Mallinckrodt, St Louis, MO); sodium lauryl sulfate (Stepanol, lot 1-354 87, Stepan Co, Northfield, IL); and sodium stearyl fumarate (Pruv, lot 305-01X, Mendell, Patterson, NJ).

Aqueous Solubility

Aqueous solubility was determined using the shaker-flask method. Two grams of neat drug was added to 50 mL of reagent grade water and was shaken for 24 hours at 25°C ± 1°C. Filtered samples were analyzed spectrophotometrically at the wavelength of maximum absorption for each drug. Each sample was analyzed in triplicate.

Contact Angle

Augustine Scientific (Newbury, OH) determined contact angles using the sessile-drop method. One gram of neat drug was compressed at 500 psig in a lab-scale Carver press. Ten drops of pure distilled water of volume 1 μL were placed on each compact surface and analyzed using a Kruss Drop Shape Analysis System (model DSA10, Kruss GmbH, Hamburg, Germany). The contact angles reported are the mean of 10 determinations.

Specific Surface Area

Single-point BET determinations of specific surface area were conducted by the Materials Analysis Laboratory at Micromeritics Inc (Norcross, GA) using nitrogen. Most actives were degassed at 100°C. Ibuprofen (IBU) was degassed at 60°C and ketoprofen (KET) was degassed at 80°C owing to their melting points being below 100°C.

Intrinsic Dissolution Rate

A quantity of 250 (± 1) mg of drug was compressed at an average compression force of 1000 lbs for 3 minutes to make nondisintegrating compacts using intrinsic dissolution rate (IDR) dies and a Carver Press (model 4687, Sterling Inc, Menomonee Falls, WI). The surface area of the compacts was 0.950 cm^2. Compacts were tested in 900 mL of media maintained at a temperature of 37°C ± 1°C in a VanKel VK7000 (VanKel Industries, Edison, NJ) dissolution system fitted for IDR die attachments and were rotated at 100 rpm. Samples were analyzed with recirculation every 2 minutes over a time period of 1 hour and analyzed using an in-line Shimadzu spectrophotometer (model UV160U, Shimadzu, Kyoto, Japan) at the maximum absorbance wavelength for each active tested. The flow rate used was one mL/min. Based on the dissolution profiles obtained, the intrinsic dissolution rate was calculated using the following equation[9]:

$$G = \frac{dw}{dt} * \frac{1}{S} \quad (1)$$

where G is intrinsic dissolution rate (mg/min/cm^2); dw is the change in drug dissolved (mg); dt is the change in time (minutes); and S is the surface area of the compact (cm^2). The cumulative amount dissolved was plotted vs time for each vessel. The linear region of this plot ($R^2 \geq 0.95$) was determined using linear regression. The slope of the linear region was taken as dw/dt.

Encapsulation

Hard gelatin capsules were manufactured using a capsule filling simulator. Fifteen-gram batches were blended for 10 minutes without lubricant. Lubricant was added and the batches were mixed for an additional 3 minutes. A size 1 tamping piston was used to compress 200 mg of formulated batch at 100 to 120 N using a laboratory scale Carver Press (model 4687, Sterling Inc). Compression force was monitored using a load cell (model 13, Sensotec, Columbus, OH), strain gauge conditioner (model 2160, Measurements Group Inc, Raleigh, NC), and digital oscilloscope (model 310, Nicolet Instrument Corp, Madison, WI). Twenty-five capsule plugs were formed and pushed into the empty capsule bodies (ConiSnap Gelatin Capsules, lot 590311, Capsugel) and closed by hand.

Dissolution

Dissolution testing was performed using a VanKel VK 7000 dissolution apparatus with a Shimadzu UV spectrophotometer (model UV-160). UV cells with a path length of 1 cm were used (model 175, Hellma, Plainview, NY). Automated sampling with recirculation was performed every 5 minutes for 45 minutes at a flow rate of 1 mL/min. A quantity of 900 mL of appropriate medium was maintained at 37°C ± 1°C for each capsule tested. The weakly acidic drugs (naproxen [NAP], KET, chlorpropamide [CHL]) were tested in 0.1 M pH 6.8 potassium phosphate ($K PO_4$) buffer using *USP* apparatus II (paddles) with a rotation speed of 50 rpm. Capsules were deterred from floating using capsule sinkers (model 0500-0473, Epoxy Capsule Weights, Distek, North Brunswick, NJ). The weakly basic drugs (carbamazepine [CAR], diazepam [DIA]) were tested in 0.1 N HCl using *USP* apparatus I (baskets) with a rotation speed of 100 rpm. The percentage dissolved values at 10, 30, and 45 minutes reported are the average of 6 determinations.

Table 1. Physiochemical Properties of the Model BCS II Drugs*

	Contact Angle (°)†	Specific Surface Area (m^2/g)	Aqueous Solubility (mg/mL)†	Intrinsic Dissolution Rate ($mg/min/cm^2$)†
CAR	93.3° (0.2)	0.5924	0.039 (0.001)	0.054 (0.004)
CHL	106.7° (0.3)	0.7107	0.049 (0.001)	0.038 (0.008)
DIA	101.5° (0.3)	0.1397	0.015 (0)	0.002 (0.001)‡
IBU	98.8° (0.3)	0.1892	0.035 (0)	0.015 (0.002)§
KET	67.5° (0.2)	2.3045	0.036 (0.001)	0.035 (0.003)
NAP	105.7° (0.4)	0.3486	0.006 (0)	0.008 (0.001)‡
PIR	90.4° (0.3)	0.7264	0.010 (0.001)	0.003 (0.0003)‡

*CAR indicates carbamazepine; CHL, chlorpropamide; DIA, diazepam; IBU, ibuprofen; KET, ketoprofen; NAP, naproxen; and PIR, piroxicam.
†Reagent grade water
‡Run time = 6 hours
§Run time = 3 hours

Results and Discussion

Model Drugs

Table 1 includes the results of the determination of aqueous solubility, contact angle, specific surface area, and aqueous intrinsic dissolution rate. The contact angles for these drugs are all in the range of 90° to 100° with the exception of KET having a value of 68°. Drugs that are conducive to wetting generally have low contact angles. These values, along with the low values for aqueous IDR and aqueous solubility supported the selection of these drugs as models for the low solubility BCS class II drugs. The marginal values for the specific surface areas of these drugs, with the exception of KET, indicated that wetting of these drugs was problematic due to the limited surface area available for contact with the solvent.

Expert Network

System design and architecture

A rule-based ES was developed and integrated with an ANN. Several assumptions were made in the development of the model ES for simplification purposes: (1) only directly fillable formulations will be considered (ie, granulation is outside of the scope of this program); (2) all excipients are compatible with the active ingredients; (3) a simplified blend uniformity model can be applied; and (4) diluents can be simplified to microcrystalline cellulose/lactose (MCC/LAC) blends (low dose, more LAC; high dose, more MCC). The ES was used as the decision module and the ANN served as the prediction module. These components were connected using 2 information exchange paths to form a loop. These systems, along with a control module (CM), formed the 3 major components of the hybrid EN. The flowchart detailing the functions and interrelationships of the 3 major components of the hybrid EN are detailed in Figure 1.

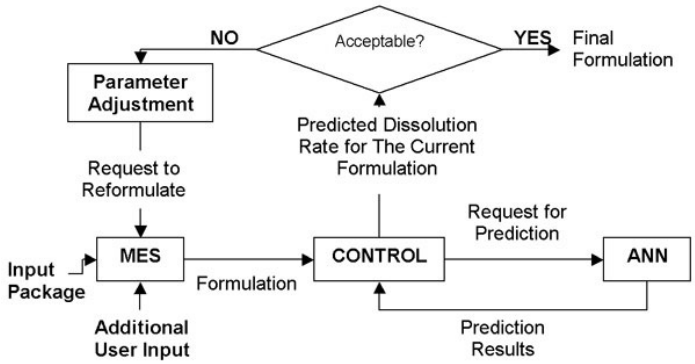

Figure 1. Overview of the Prototype Expert Network

Based on information provided by the user in the input package, the ES recommended a capsule-based formulation for the drug of interest. The CM transmitted the recommended formulation to the ANN, where the ANN predicted the dissolution performance of the recommended formulation. The ANN then returned the predicted dissolution performance to the CM. The user was then allowed to compare the predicted results with the target dissolution properties for the formulation. If the dissolution performance was not acceptable, the CM provided guidance to improve the dissolution and sent the new information to the ES for reformulation. The CM guided the optimization process until a satisfactory formulation was achieved or the optimization cycle was terminated by the user.

ANN

The ANN used in the prediction module was a back propagation learning system that computed output based on

Table 2. ANN Architecture Parameters

Input layer	7
Output layer	3
Hidden layer	12
Activation function	Sigmoid
Slope	0.1
Learning rate	0.02
Error limit	0.00001
Maximum number of iterations	30 000

Table 3. Initial Test of Expert Network*

	CAR	CHL	DIA	KET	NAP
Diluent	F-InSol	F-InSol	F-InSol	F-InSol	F-InSol
% Diluent	72	67	82	82	69
% Glidant	1	1	1	1	1
% Disintegrant	0.5	0.5	0.5	0.5	0.5
% Lubricant	8	8	8	4	8
% Wetting agent	0.1	0.1	0.1	0.1	0.1
Q10	20.3	67.3	86.8	94.8	85.1
Q10 Predicted	52.3	52.2	53.1	48.4	52.7
Q10 Error	-32	15.1	33.7	46.4	32.4
Q30	40.3	98.9	98.3	97.5	98.2
Q30 Predicted	68.6	68.8	67.8	70.8	68.1
Q30 Error	-32	15.1	33.7	46.4	32.4
Q45	50.6	98.8	97.8	98	99.2
Q45 Predicted	73.4	73.8	71.9	78.8	72.6
Q45 Error	-32	15.1	33.7	46.4	32.4

*CAR indicates carbamazepine; CHL, chlorpropamide; DIA, diazepam; IBU, ibuprofen; KET, ketoprofen; NAP, naproxen; and F-InSol, blend of 75% anhydrous lactose and 25% microcrystalline cellulose.

the forward pattern established by the training. The training of the back propagation network involved 3 stages: the feed forward of the input training pattern, the calculation of the output and back propagation of the associated error, and the adjustment of the weights associated with the variables. After training, the ANN computed the outputs using the feed forward method. By increasing or decreasing the weight associated with a given variable, the effect of that variable on the model developed was altered to reduce the error between the calculated values and the actual data. Variables found to be insignificant in the model were weighted less. Variables that contributed significantly to the model were weighted more.

The optimization of several ANN training parameters was the key to the success of the program. These parameters included the number of hidden layers, number of hidden nodes, type of training function, training time, training rate, and training slope. Different combinations of these parameters were evaluated to determine the optimum values for training to provide minimal system error for the predictions. For this study, the maximum system error allowed was 0.00002. The optimized ANN parameters used are listed in Table 2. A sigmoid function with a learning rate of 0.02 and maximum iterations of 30 000 was used for training. Sufficient training time along with a complimentary training rate ensured that the program would develop models for the data that it was presented. Seven input nodes were used to model the 7 input variables (% LAC, % disintegrant, % lubricant, % wetting agent, specific surface area (SSA), contact angle, and IDR). Three output nodes represented the 3 output variables, Q10, Q30, and Q45.

Table 4. Box-Behnken Experimental Design*

Batch	%LAC	%ADS	%SSF	%SLS	Batch	%LAC	%ADS	%SSF	%SLS
1	55	12	0.85	1	15	10	12	0.85	0.55
2	55	8	0.85	0.55	16	10	8	0.2	0.55
3	55	4	1.5	0.55	17	10	4	0.85	0.55
4	55	4	0.2	0.55	18	100	8	0.85	0.1
5	10	8	1.5	0.55	19	55	12	1.5	0.55
6	100	4	0.85	0.55	20	55	4	0.85	1
7	100	8	0.2	0.55	21	55	8	0.2	1
8	55	8	0.85	0.55	22	100	8	1.5	0.55
9	55	12	0.85	0.1	23	55	8	0.2	0.1
10	10	8	0.85	0.1	24	55	8	1.5	0.1
11	55	8	0.85	0.55	25	100	8	0.85	1
12	55	4	0.85	0.1	26	55	12	0.2	0.55
13	100	12	0.85	0.55	27	100	8	0.85	1
14	55	8	1.5	1					

*%LAC indicates percentage of lactose in the MCC/LAC blend; %ADS indicates the percentage of disintegrant (Ac-Di-Sol); %SSF indicates the percentage of lubricant (sodium stearyl fumarate); and %SLS indicates the percentage of wetting agent (sodium lauryl sulfate).

Table 5. ANN Training Data Set Variables

182 Experimental Batches
3 Responses
Q10
Q30
Q45
7 Independent Variables
% Lactose in MCC/LAC blend (10%, 55%, 100%)
% Disintegrant (4%, 8%, 12%)
% Lubricant (0.2%, 0.85%, 1.5%)
% Wetting agent (0.1%, 0.55%, 1%)
Specific surface area (m^2/g)
Contact angle (^{o})
Intrinsic dissolution rate ($mg/min/cm^2$)

Twelve hidden nodes were used. The number of hidden layers and nodes per layer were dependent on factors such as the number of input and response variables as well as the number of samples and the required prediction accuracy.

Data Analysis

Initial test of hybrid system

The capacity of the initial hybrid system to accurately predict the dissolution performance of model BCS class drugs other than PIR was tested before any modifications to the system were made. Input data for CAR, CHL, DIA, KET, and NAP were processed by the ES, and recommended formulations for each drug were manufactured. Dissolution testing was performed on these formulations to determine the experimental Q10, Q30, and Q45 values. These values were then compared with the predicted values generated by the hybrid system. The results of these tests are listed in Table 3.

The system recommended a filler system of 75% LAC and 25% MCC (F-InSol). The recommended formulations for each model drug are listed in Table 3. The differences in the values for predicted vs actual are included in the table as the error values. As evidenced by the high error values, the initial system was not very successful in predicting the dissolution performance of drugs other than PIR. Based on these results, retraining of the ANN was conducted using a new training data set.

ANN training

In order to form the causal associations between the formulation parameters and dissolution performance, the ANN was trained using experimental data. To ensure sufficient prediction power, it was extremely important to include sufficient experimental data from well-designed experiments. For this research, a Box-Behnken experimental design (Table 4) was used to develop a data set for the variables drug, excipient levels, and dissolution performance in the most efficient manner. The quality of the training data and the number of batches used dramatically affected the prediction power of the ANN. The variables and levels used in the training set data are listed in Table 5. In total, 182 batches were included in the training set data.

Table 6. ANN Training Model Statistics

Q10				
Source of Variation	**Sum of Squares**	**Degrees of Freedom**	**Mean Squares**	**Computed f ratio**
Model	100938.846	109	926.044461	51.365618
Error	973.538386	54	18.028489	
Total	100857.607	163		
Train set R^2	99.03474			
Test set R^2	69.053528			
Q30				
Source of Variation	**Sum of Squares**	**Degrees of Freedom**	**Mean Squares**	**Computed f ratio**
Model	66676.8402	109	611.714131	72.094966
Error	458.181267	54	8.484838	
Total	66788.0279	163		
Train set R^2	99.313977			
Test set R^2	70.236563			
Q45				
Source of Variation	**Sum of Squares**	**Degrees of Freedom**	**Mean Squares**	**Computed f ratio**
Model	53297.3053	109	488.966103	139.130902
Error	189.779332	54	3.514432	
Total	53231.717	163		
Train set R^2	99.643484			
Test set R^2	88.278314			

Table 7. ANN Validation Results

	% Lac	% Disint	% Lub	% Wetting Agent	SSA (m^2/g)	Contact Angle (°)	IDR (mg/min/cm^2)	Q10	Q10 Pred	Q10 Err	Q30	Q30 Pred	Q30 Err	Q45	Q45 Pred	Q45 Err	Pattern Error
B13	10	12	0.85	0.55	0.592	93.3	0.057	15.9	12.3	3.6	38.8	26.6	12.2	47.8	47.1	0.7	80.5
B22	55	8	1.5	0.1	0.592	93.3	0.057	21.0	9.8	11.2	39.3	51.9	−12.6	46.1	54.4	−8.3	177.1
B44	55	8	1.5	0.1	0.711	106.7	1.154	97.2	91.2	6.0	98.2	98.3	−0.1	98.4	99.4	−1.1	18.5
B48	55	8	0.85	0.55	0.140	101.5	1.265	75.9	73.5	2.4	94.1	95.1	−1.0	98.0	97.8	0.2	3.4
B52	100	8	0.2	0.55	0.140	101.5	1.265	83.5	45.4	38.1	97.8	98.2	−0.5	96.7	97.7	−1.1	728.3
B57	100	12	0.85	0.55	0.140	101.5	1.265	83.7	80.6	3.0	99.0	98.0	1.0	97.9	96.9	1.0	5.6
B65	100	8	1.5	0.55	0.140	101.5	1.265	80.1	81.1	−1.0	96.7	98.2	−1.5	96.1	92.9	3.2	6.7
B78	10	8	0.85	0.1	2.304	67.5	1.511	96.8	101.8	−5.0	98.2	100.0	−1.8	98.4	92.2	6.2	33.2
B90	55	8	1.5	0.1	2.304	67.5	1.511	92.3	86.3	5.9	97.6	91.0	6.6	98.4	98.7	−0.3	39.3
B104	100	12	0.85	0.55	0.348	105.7	0.434	86.2	90.5	−4.3	98.0	97.5	0.5	99.5	100.0	−0.5	9.6
B128	100	5	1.5	1	0.161	90.4	0.033	76.2	83.9	−7.7	86.5	91.3	−4.8	88.9	88.5	0.5	41.7
B144	50	5	1	0.5	0.246	90.4	0.033	67.1	66.7	0.4	80.7	82.2	−1.5	85.2	86.9	−1.7	2.7
B156	0	4	0.9	0.6	0.277	90.4	0.033	63.7	66.7	−3.1	92.0	78.9	13.1	97.7	86.6	11.1	151.8
B165	100	8	0.9	0.6	0.277	90.4	0.033	81.7	90.9	−9.2	98.8	91.9	6.8	100.0	96.7	3.3	71.1
B167	0	4	0.6	1	0.277	90.4	0.033	64.1	61.0	3.1	84.2	81.3	2.9	89.9	78.8	11.1	70.6
B174	0	6	0.8	0.3	0.277	90.4	0.033	69.9	45.7	24.2	92.1	79.5	12.7	97.0	88.4	8.6	410.4
B176	0	6	0.2	1.1	0.277	90.4	0.033	70.9	72.2	−1.3	89.1	69.6	19.6	94.6	87.5	7.1	217.5
B179	0	9	0.2	0.7	0.277	90.4	0.033	75.7	85.4	−9.8	93.1	68.0	25.2	97.9	91.1	6.8	387.8

*Lac indicates the percentage of lactose in the MCC/LAC blend; [% Disint] indicates the percentage of disintegrant (Ac-Di-Sol); [% Lub] indicates the percentage of lubricant (sodium stearyl fumate); SSA - specific surface area; IDR - intrinsic dissolution rate; Pred - Predicted; and Err - Error.

ANN validation

Validation of the ES was conducted to assess predictability and functionality. Ten percent of all available batches were randomly selected to serve as batches for validation and were not included in the training. The program was trained under optimal conditions and then used to predict the dissolution performance of the validation batches. The predicted dissolution was then compared with the experimentally determined dissolution data for these batches. Model statistics were determined during the training and are listed in Table 6. The target R^2 value was ≥70%. The system was extremely accurate in modeling the training set data, resulting in R^2 values > 99%. The system was successful in modeling the test data with increasing predictive capabilities as the amount of drug dissolved increased. Based on the training parameters chosen, the system error and R^2 value indicate that the model determined by the ANN was very predictive of the dissolution behavior of the model drugs.

The results for the validation batches are shown in Table 7. The predicted percentage drug dissolved was compared with the actual dissolution values and the error calculated. Considering the normal variability of real dissolution data, percentage error values ≤ ±10% for the comparison data were acceptable. Based on the data included in Table 6, it was determined that the ANN had a reasonable capability of modeling the relationship among the formulation parameters and dissolution performance.

The other facet of validation was assessing the ability of the EN to recommend a formulation based on sound design criteria and predict the dissolution performance accurately. The system should be able to perform these functions for drugs not included in the training as well. To determine the competence of the system in terms of these criteria, recommended formulations were manufactured and tested for the model drugs included in the training set. This information was used to investigate the accuracy of the system

Table 8. Expert Network Validation Results*

	Q10 Pred	Q10	Q10%error	Q30 Pred	Q30	Q30%error	Q45 Pred	Q45	Q45%error
CAR	21.2	20.3	-4.2	40.8	40.3	-1.2	48.3	50.6	4.8
CHL	94.8	67.3	-29.0	99	98.9	-0.1	99.5	98.8	-0.7
DIA	80.3	86.8	8.1	95.8	98.3	2.6	97.3	97.8	0.5
IBU	77.2	87.4	13.2	93.3	97.5	4.5	96.3	97.8	1.6
KET	91	94.8	4.2	97.2	97.5	0.3	97.9	98	0.1
NAP	87.3	85.1	-2.5	97.6	98.2	0.6	99	99.2	0.2
PIR	20.1	92.1	358.2	40.8	96.8	137.3	47.5	97.4	105.1

**CAR indicates carbamazepine; CHL, chlorpropamide; DIA, diazepam; IBU, ibuprofen; KET, ketoprofen; NAP, naproxen; and PIR, piroxicam.

predictions. Input data for IBU, a drug not included in the training, was processed by the EN, and a recommended formulation was also manufactured and tested to determine if the system was capable of adequately formulating and predicting performance of drugs not included in the training.

The results of the external validation are shown in Table 8. The moderate success of the system can be attributed to the increased error in prediction at Q10 for CHL, IBU, and PIR. The result of 13.2% for IBU may not be considered extremely significant since the acceptance criteria is 10%. CHL and PIR showed significant deviations from the 10% acceptance criteria. The system was able to predict the behavior at Q30 and Q45 with much greater success (%error $\leq$ 10%) for all drugs with the exception of PIR. One factor that may have contributed to this lack of predictability for PIR was the fact that the experimental values for the input data for PIR were close to the values used for CAR. The system may have treated both drugs as one and made its predictions based on the patterns learned for CAR instead of PIR. The addition of another variable in the training set to further distinguish between drugs would overcome this issue. The results were somewhat promising in that the system was able to predict the performance of IBU with some success. It was also encouraging that the prototype EN was expanded to include several other BCS class II drugs along with the initial drug, PIR.

CONCLUSION

From this research, the EN was expanded to include several other BCS class II drugs. Through validation, the EN was proven to be capable of recommending formulations for the model drugs that met specific drug performance criteria. By including parameters to address wettability and the intrinsic dissolution characteristics of the drugs, the EN was expanded to include multiple BCS class II drugs.

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