JOURNAL OF PHARMACEUTICAL SCIENCE AND BIOSCIENTIFIC RESEARCH (JPSBR)

(An International Peer Reviewed Pharmaceutical Journal that Encourages Innovation and Creativities)

A Review Literature and Optimization of Controlled Drug Delivery System Using Artificial Neural Network

Nitin S. Parmar[1, 2]*, Sahilhusen I. Jethara[1, 2,] Alpesh D. Patel[2], Mukesh R. Patel[2]

1 Research scholar, Gujarat Technological University, Gujarat, India

2 Shri B. M. Shah College of Pharmaceutical Education & Research, Modasa-383315, Gujarat, India

ABSTRACT:

Artificial neural network (ANN) operation is based upon the simulation of biological neural process abilities in the human brain. In past statistic formulation optimized by response surface methodology (RSM) is one of the techniques that have been employed to develop and formulate controlled release dosage forms but limitations to the RSM technique another technique called artificial neural networks (ANN) has recently gained wide popularity in the development of controlled release dosage forms. In this review articles most powerfully technique ANN has been optimized the formulation in controlled release drug delivery systems. Artificial neural networks (ANNs) are biologically inspired computer programs designed to simulate the way in which the human brain processes information. ANNs gather their knowledge by detecting the patterns and relationships in data and learn (or are trained) through experience, not from programming. In this review, the basic ANN structure, the development of the ANN model and an explanation of how to use ANN to design and develop controlled release drug delivery systems are discussed. The behaviour of a neural network is determined by the transfer functions of its neurons, by the learning rule, and by the architecture itself. The weights are the adjustable parameters and, in that sense, a neural network is a parameterized system. In addition, the applications of ANN in the design and development of controlled release dosage forms are also summarized in this review. The potential applications of ANN methodology in the pharmaceutical sciences range from interpretation of analytical data, drug and controlled release dosage form design through bio-pharmacy to clinical pharmacy.

KEY WORDS: Artificial neural network, Controlled-release formulations, Drug delivery systems, Computer, Network architecture

Article history:
Received 10 Feb 2015
Accepted 26 Feb 2015
Available online 01 May 2015

Citation: Parmar N S, Jethara S I, Patel A D, Patel M R. A Review Literature and Optimization of Controlled Drug Delivery System Using Artificial Neural Network. **J Pharm SciBioscientific Res**. 2015. 5(3):306-314

For Correspondence:

Mr. Nitin S. Parmar

Department of Pharmaceutics,
Shri B. M. Shah College of Pharmaceutical Education and Research, College Campus,
Modasa -383315, Gujarat, India

Email: np4601@gmail.com

(www.jpsbr.org)

INTRODUCTION:

First implemented in the early 1960's, neural network only began to develop significantly in the mid 1980's with the introduction of new neural network architecture and advances in processing technologies. Since then, neural networks have been successfully used in variety of areas such as finance, retail, manufacturing, energy, health, telecommunications and security. The potential applications of artificial neural network (ANN) methodology in the pharmaceutical sciences range from interpretation of analytical data, drug and dosage form design through biopharmacy to clinical pharmacy. [1]

The application of artificial neural networks (ANNs) in the field of pharmaceutical development and optimizing of controlled release dosage forms has recently become a topic of discussion in the pharmaceutical literature. 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. 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. Artificial neural networks systems appear very attractive from the economic as well as from the process development and scale-up points of view in controlled release systems. [2, 3]

Artificial neural networks (ANN) are computer programs that are designed to simulate some functions of the human brain using different learning algorithms, which can learn from experience. Based on the topology, the connection of ANN could be feed-forward and feed-back. In a feed-forward ANN model, the connections between the nodes do not form cycles. In some feed-back ANN models, each time an input is presented, the ANN model must iterate for a potentially long time before it produces a response. Feed-back ANN models are usually more difficult to train than feed-forward ANN models. ANN attempts to simulate some of the neurological processing ability of the biological brain such as learning and drawing conclusion from experience. Therefore, the problems handled by ANN can be quite varied like pattern recognition, pattern association and modeling and optimization application. Artificial neural networks (ANN) are an alternative approach to the statistical methodology of RSM. RSM works well for the low dimensionality or for approximating simple functions. However, there are limitations for this polynomial approach. RSM may only be practically suited to one dependent variable or a low order polynomial. To optimize problems that involve multiple responses, an appropriate response surface model for each response variable needs to be built first. [4, 5] Then, a set of independent variables that optimize all the responses or keep them in the desired ranges need to be obtained. A comparison between ANN and RSM is made in table 1.

Table 1: Comparison of RSM and ANN

Item	Response Surface Methodology	Artificial Neural Network (ANN)
Function Regression	Quadric equation Least square	Sigmoid equation Adaptive learning paradigm specific
Cost Function	Mean squared error (MES) (Training data only)	Mean squared error (MES) (Both Training and test data)
Stop criterion	Minimization of MSE (Training data only)	Minimization of MSE (Test data only)

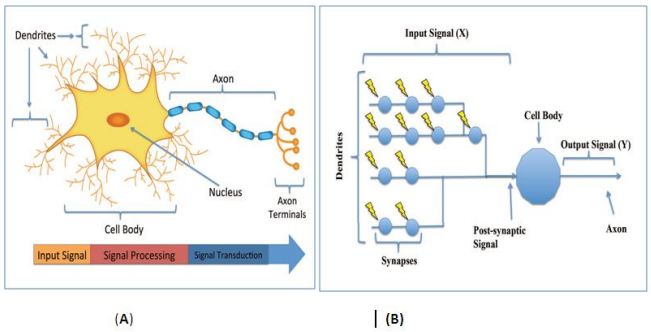

Figure 1: Conceptual structure of a biological neuron. (A) Schematic representing structure of biological neuron. Branched out dendrites receive the signal. **(B)** The input signals, represented by lightning bolts stimulate the dendrites in the synapses.

NEED AND BENEFITS OF ANN

Various types of formulation and process variables relating to effectiveness, safety and usefulness need to be optimized simultaneously while developing pharmaceutical formulations. A response surface method (RSM) has often been applied to optimize the formulation variables. The optimization procedure based on RSM includes statistical experimental designs, multiple regression analysis, and mathematical optimization algorithms for seeking the best formulation under a set of constrained equations. When the theoretical relationship between the response variables and casual factor are not clear, multiple regression analysis can be applied for the prediction of response variables on the basis of a second order equation.

The prediction of pharmaceutical responses based on second order polynomial equation, however is often limited to low levels, resulting in the poor estimation of optimal formulations. To overcome this limitation of factorial design (FD), artificial neural network (ANN) was incorporated. [6, 7]

ADVANTAGES OF ANN OVER CONVENTIONAL STATISTICAL TECHNIQUE [7, 8]

- ANN accurately predicts results when the response variables are highly non-linear.
- A neural network also keeps in check the curse of dimensionality problem that bedevils attempts to model nonlinear functions with large number of variables.
- Neural networks are more accommodating to sparse and noisy data than statistical modeling packages. Therefore, literature or historic data can also be used for training.
- No prior knowledge of the underlying statistical nature of the problem is required.
- Neural Network has a unique ability of spotting a pattern

- In data. Therefore, it can be used to rank formulation variables that are most critical in influencing the parameters of interest.
- Once trained, neural networks are inherently fast and can lead to saving in both time and cost of product development.
- An ANN model, unlike statistical models operates upon the experimental data without data transformations.
- ANN requires no assumption to be made about the nature or significance of interconnections between formulation components or the relationship between the ingredients and properties of the formulation.

DISADVANTAGES OF ANN [9]

- The major disadvantage of ANN is that, they are by nature black boxes; the relationship that the network finds cannot be expressed easily in mathematical form. The
- primary risk in developing a model is that of overtraining, a situation in which the neural network starts to reproduce the noise specific to a particular sample in the training data, which may cause it to lose its ability to predict accurately. This disadvantage can be removed as mentioned earlier by performing network validation.
- ANN requires the use of sophisticated software's whereas the (response surface methodology) RSM can be done using the earliest software such as EXCEL.

REVIEW OF WORK DONE IN ANN

Some of the ANN formulations for controlled drug delivery system are presented in Table 2.

Table 2: Formulations optimization by ANN in the Literature

Field	Application	Author	Types of ANN	Software use
Preformulation	The physiochemical properties of amorphous polymers	Nkere KE	MLBP	CAD : Chem
	A novel preformulation tool to group microcrystalline celluloses	Josephine LP	RBF	Visual Basic 5.0 language
	Prediction of drug stability	Svetlana I	GRNN	STATISTICA
Tablet	The bimodal drug delivery	Ghaffari A	MLP - FFN	CPC X
	Diclofenac Sodium Extended Release	Branka I	MLP	STATISTIA
	Aspirin Extended Release Tablets	Svetlana I	GRNN	STATISTIA
	Nimodipine controlled release tablet formulation	Panagiotis B	FFBP	SNNS
	The sustained release formulations	Junichi Takahara	MLP	Kalman filter algorithm
	Time-Dependent Tablets Comprising an Immediate and Sustained Release	Huijun Xie	BPNN	Neuro Shell 2 Release
	Diclofenac sodium dissolution from sustained release formulations	Zupancic D	BPNN	The SRC Computer company
	Metformin HCl 500mg Sustained Release Matrix Tablets	Uttam M	MLP	STATISTICA
	Salbutamol Sulfate Dissolution from Sustained Release Matrix Formulations	Faith C	BPNN	Matlab® R 2008a

	Porosity osmotic pump tablets for salvianolic acid	Wen-Jin X	BPNN	Visual Basic 5.0 language
	A Pharmaceutical formulation is composed of several formulation factors and process variables.	Anand P	RBF	HSOL algorithm
	Crushing Strength and Disintegration Time of a High-Dose Plant Extract Tablet	K. Rocksloh	MLP	Camo A/S, Trondheim, Norway
Beads	Prediction of Dissolution Profiles of Acetaminophen Beads	Yingxu P	MLP	NeuroShell® Predictor, Release 2.1
Microspheres	preparation of controlled release acrylic microspheres	N. YUÈ KSEL	MLP	NeuroShell Easy Predictor,
Powders	Modeling properties of powders	Eyal Z	BP and RBF	Visual Basic 5.0 language
	Modeling of powder flow.	Kachrimanis	BPNN	SNNS
Pellets	Matrix-controlled release theophylline pellet	Kok KP	MLP	The NEURAL program
Transdermal	The effect of O-ethylmenthol (MET) on the percutaneous absorption of ketoprofen.	Takayama K	MLP	Kalman filter algorithm
	The transdermal delivery of melatonin	Karunya KK	MLP	Visual Basic 5.0 language
Liposomes	The optimizing formulation parameters for cytarabine liposomes	Narayanaswamy S	MLP	Visual Basic 5.0 language
Hydrogel	Ketoprofen hydrogel formula containing o-Ethyl-3- butylcyclohexanol as percutaneous absorption enhancer.	PAO-CHU W	MLP	Program MULTI
	ketprofen hydrogel formula containing o-Ethylmenthol as a percutaneous absorption enhancer.	Junichi T	MLP	The computer program ANNOP
Emulsion	Paclitaxel Carried by PEGylated Emulsions	Tianyuan Fan,		ANN and ALCORA
	Optimizing the fatty alcohol concentration in the formulation	Jayaram K.	MLP	NeuroShell 2
Gelisphere	Textural profiling and statistical optimization of crosslinked calcium-alginate-pectinate-cellulose Acetopthalate gelisphere matrices.	Viness P	MLP	Neuro Solutions Version 4.2
Granules	Sustain release granules of indomethacin	Takayama K		Visual Basic 5.0 language
Pharmaco - kinetics	Modeling the pharmacokinetics and pharmacodynamics of unique oral hypoglycemic agent	Sam HH	MLP	NeuroShell Predictor™

	Pharmacokinetic parameter prediction from drug structure	Joseph VT	MLP	STATISTICA
	Neural network predicted peak and trough Gentamicin concentrations.	Michael EB	MLP	Program NONMEM
	Quantitative structure- pharmacokinetic relationship for drug distribution properties	YAP CW	GRNN	MLFN Algorithm
QSAR Analysis	A QSAR study of some cyclobutenediones as CCR1 antagonists by	Shahlaei M	MLP - BP	Visual Basic 5.0 language
	QSAR study of oxazolidinone antibacterial agents	ZOU C	BPNN	Matlab 6.5
	QSAR Study of Anti-HIV Activity for a Large Group of HEPT Derivatives	Jalali-Heravi M	MLP	FORTRAN 90
	QSAR Study on Neurotrophic Activities of N-p-Tolyl/phenylsulfonyl L-Amino Acid Thiolester Derivatives	Jin L	MLFF - BP	MATLAB
	QSAR for predicting rejection of neutral organic compounds by polyamide nanofiltration and reverse osmosis membranes	Yangali-Quintanilla V.	MLP	MATLAB 2007b
	Artificial neural networks and genetic algorithms in QSAR	Stefan PN	PNN	Neuro Shell and STATISTIA
	QSAR study of antiplatelet agents	Alan R. Katritzky	MLP	CO DESSA PRO
Spectro-scopy analysis	UV Spectroscopy	Balamurugan C	MLP - FF	UV neural

OUTLINE OF ARTIFICIAL NEURAL NETWORK (ANN) [10]

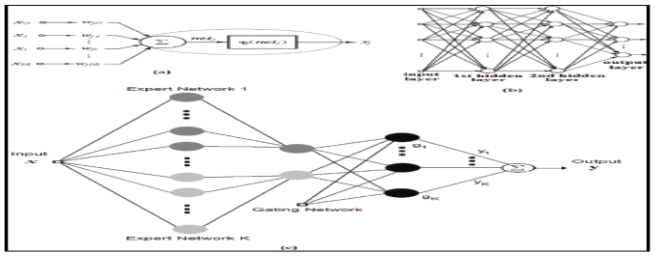

Figure 2: (a) Nonlinear model of an artificial neuron; (b) FNN configuration with two hidden layers; (c) Extended modular neural network configuration with K experts

a) Basic Structure or network architecture of artificial neural network

A neural network can consist of many neurons and the method by which neurons are organized is called as "network architecture". ANN consists of mostly three types of layers.

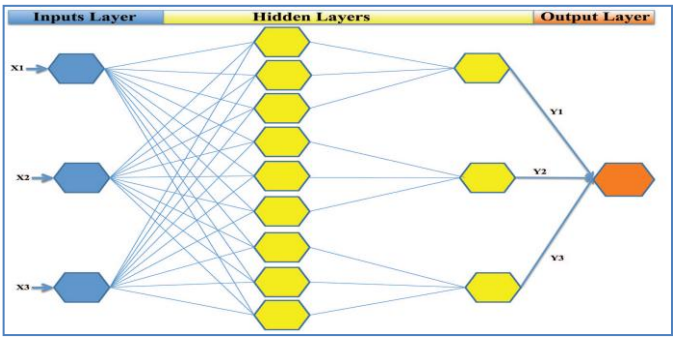

Figure 3: Typical structure of artificial neural networks. x represent input value of causal factors; n, number of causal factors; y, output value of responses; m, number of responses.

- **Input layer**

Input layer to the neural network is the conduit through which data is presented to neural network.

- **Hidden layer**

Hidden layers refer to one or more layers of neurons that are arranged between the input and output layer. Though these layers do not directly interact with the external environment these layers have tremendous influence on the final output and hence on the network performance.

- **Output Layer**

Output layer of the neural network is what actually presents the results to the user. [10-12]

b) Network architectures

- Single layer feed forward networks
- Multilayer feed forward networks
- Recurrent networks
- Back propagation networks

c) Types of ANN

- Multilayer Perceptrons (MLP)
- Radial Basis Function Networks (RBF)
- Probabilistic Neural Networks (PNN)
- Generalized Regression Neural Networks (GRNN)

The optimization of POT was performed according to the generalized distance function method as per following equation 1.

$$S = \left[\sum \left(\frac{FD_t - FO_t}{SD_t} \right)^2 \right]^{1/2} \quad \text{--- [1]}$$

Where;

Sis the distance function generalized by the standard deviation,

SD$_t$, of the observed values for each response variable,

FD$_t$ is the optimum values of each response optimized individually over the experimental region and

FO$_t$ is the simultaneous optimum value.

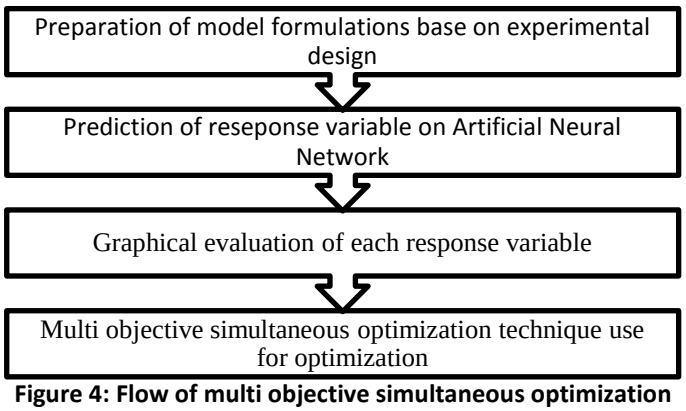

Figure 4: Flow of multi objective simultaneous optimization technique

The simultaneous optimum can be estimated by minimizing *S* under the restriction of the experimental region. [20] Flow of multi objective simultaneous optimization technique is incorporating ANN in figure 4.3.

For every pair of observed/predicted drug release profile for optimal formulation, difference (f_1) and similarity (f_2) factors were calculated. According to the US Food and Drug Administration's guide for industry, generally $f_1$values up to 15 (0—15) and $f_2$values greater than 50 ensures sameness of the 2 curves.

Dissimilarity factor f_1 and similarity factor $f_2$were determined using the equation 2 and 3 as given below.

$$f_1 = \{ \sum_{t=1}^{n} |R_t - T_t| \div \sum_{t=1}^{n} R_t \} \times 100 \quad \text{---------- [2]}$$

$$f_2 = 50 \log\{ [1 + 1/n \sum_{t=1}^{n} w_t (R_t - T_t)^2]^{-0.5} \times 100 \}$$

----------[3]

Where;

n is the number of time points,

w_t is an optional weight factor,

R_t is the reference assay at time point **t** and

T_t is the test assay at time point **t**.

The f_2 value between 50 and 100 suggests that dissolution profiles are similar. The f_2 value of 100 suggests that the test and reference profiles are identical and as the value becomes smaller, the dissimilarity between releases profiles increases. The f_1 describes the relative error between two dissolution profiles.

SOFTWARE'S TO USE IN ANN

A large number of software for ANN is now commercially available. These programs are now being used widely and are gaining more and more acceptance in Pharmaceutical sector. Examples of such software based on ANN, which have been used to design or study different dosage forms are enlisted below.

Table 3: Software's use in ANN

Software	Description	Ref.
MATLAB R2012a (The Mathwork's , Natick , MA, USA , 2012)	Neural Network Toolbox™ provides tools for designing, implementing, visualizing, and simulating neural networks. Neural networks are used for applications where formal analysis would be difficult or impossible, such as pattern recognition and nonlinear system identification and control.	[21]
CAD/Chem v5.0 (AI Waare, Inc., Cleveland, OH)	It is Microsoft windows based software. 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.	[22]
STATISTICA 10 (Stat soft, USA, 2012)	STATISTICA Automated Neural Networks contains a comprehensive array of statistics, charting options, network architectures, and training algorithms; C and PMML (Predictive Model Markup Language) code generators. The C code generator is an add-on.	[23]
Stuttgart Neural Network Simulator (SNNS 4.2, 2012)	Currently the following network architectures and learning procedures are included: • Back propagation (BP) for feed forward networks • Counter propagation • Quick prop • Back percolation 1 • RProp • Generalized radial basis functions (RBF) • Cascade Correlation • Recurrent Cascade Correlation • Dynamic LVQ • Back propagation through time (for recurrent networks) • Quick prop through time (for recurrent networks) • Self-organizing maps (Kohonen maps) • TDNN (time-delay networks) with Back propagation • Jordan networks • Elman networks and extended hierarchical Elman networks • Associative Memory	[24]
Pythia – The Neural Network designer	A Neural Network has two phases, commonly referred to as the "Training phase" and the "Reproduction phase". During the training phase sample data containing both – inputs and desired outputs – are processed to optimize the network's output, meaning to minimize the deviation.	[25]

Neuro solutions© 6.07 (Neuro Dimension, Inc, USA)	Neuro Solutions is leading edge neural network development software that combines a modular, icon-based network design interface with an implementation of advanced learning procedures, such as Levenberg-Marquardt and backpropagation through time. Some other notable features include C++ source code generation, customized components through DLLs, neuro-fuzzy architectures, and programmatic control from Visual Basic using OLE Automation. We recommend that you also download a free evaluation copy in order to gain a full understanding of the software. Once you've gone through the extensive set of live demos, you can try building and training a neural network with your own data.	[26]
BrainMaker v3.7	Brain Maker Neural Network Software lets you use your computer for pharmaceutical science, business and marketing forecasting, stock, bond, commodity, and futures prediction, pattern recognition, medical diagnosis, sports handicapping... almost any activity where you need special insight. The menu at the left contains short articles about a few of our customers and their applications of Brain Maker.	[27]
NeuralWorks Professional II/PLUS (NeuralWare, USA)	Neural Works® Professional II/PLUS is the world standard for comprehensive neural network development environments. Professional II/PLUS is available for UNIX, Linux, and Windows operating systems on a variety of hardware platforms; data and network files are fully interchangeable. The Professional II/PLUS package contains comprehensive documentation that address the entire neural network development and deployment process, including a tutorial, a guide to neural computing, standard and advanced reference manuals, and platform-specific installation and user guides.	[28]

CONCLUSIONS AND FUTURE PERSPECTIVES

ANN model and an explanation of how to use ANN to design and develop controlled release drug delivery systems are discussed. Overall the use of ANN offers a new dimension to pharmaceutical systems study because of its unique advantages, such as nonlinear processing capacity and the ability to model poorly understood systems. Applications of ANNs in the pharmaceutical field have been of increased interest due to their ability to model process that cannot be adequately represented using classical statistical methods. The scope of current uses that ranges from special perceptions to chemical properties, activity, diagnosis and toxicology indicates the true potential of ANNs in analyzing the data and making predictions. The ANNs do not need special computer as neural nets are described using mathematical models and implemented using ordinary computer software. The application of ANN in medical decision making has been immensely successful especially as it applies to disease diagnosis, classification and modeling. The ANNs are newly developed strategies as an alternative to conventional modeling techniques. The use of artificial neural network in pharmaceutical controlled release drug discovery is growing at a fast rate with very promising prospects. This exciting versatility allows ANNs be utilized almost in any area of science requiring analysis of large, variable, and/or multivariate data; thus, applications of ANNs are expected to continue expanding into many more disciplines. The application of ANN in the design and development of controlled release drug delivery systems will definitely increase in the near future as more user friendly and powerful ANN software packages are developed. In addition, the applications of ANN in the various controlled release system are also summarized.

Abbreviations

ANNs = Artificial neural networks
RSM = Response Surface Methodology
MES = Mean squared error
MLP = Multilayer Perceptrons
RBF = Radial Basis Function Networks
PNN = Probabilistic Neural Networks
GRNN= Generalized Regression Neural Networks

Conflict of Interest

The author declares no conflict of interest.

ACKNOWLEDGEMENTS

The author would like to thank Dr. A. D. Patel for his comments on this article.

REFERENCES

1. Boza A, De la C, Jordan G, Jauregui-Haza U, Aleman A, Caraballo I. Statistical optimization of a sustained release matrix tablet of lobenzarit disodium. Drug Dev. Ind. Pharm. 2000; 26: 1303–1307.

2. Montgomery DC. Response surface methods and other approaches to process optimization, in: Design and Analysis of Experiments, Wiley, New York, 2001, pp. 427–500.
3. Yongqiang L. Rational design of controlled release ion-exchange polymeric microspheres and polymer-lipid hybrid nanoparticles for the delivery of water-soluble drugs through a multidisciplinary approach Degree of Doctor of Philosophy Leslie Dan Faculty of Pharmacy University of Toronto. 2008.
4. Hinton G. Mental simulation. Nature. 1990; 347: 627-628.
5. Hinton GE. How neural networks learn from experience. Sci. Am. 1992; 267: 145-151.
6. Takahara J, Takayama K, Nagai T. Multi-objective simultaneous optimization technique based on an artificial neural network in sustained release formulations, J. Contr. Release. 1997; 49: 11-20.
7. Rowe RC, Colbourn EA. Neural computing in product formulations. Chem. Educator. 2003; 8: 1-8.
8. Takayama K, Fujikawa M, Nagai T. Artificial Neural Network as a novel method to optimize pharmaceutical formulations. Pharm. Res. 1999; 16: 1-5.
9. Plumb AP, Rowe RC, York P, Doherty C. The effect of experimental design on the modeling of a tablet coating formulation using artificial neural network. Eur. J. Pharm. Sci. 2002; 16: 281-288.
10. Leane MM, Cumming I, Corrigan OI. The use of artificial neural networks for the selection of the most appropriate formulation and processing variables in order to predict the in vitro dissolution of sustained release minitablets, AAPS Pharma Sci Tech. 2003; 4: 1-12.
11. Dondeti S, Kannan K, Mnavalan R. Insights into Artificial neural networks and its implications for Pharmacy – A Tutorial Review: part-2, Ind. J. Pharm. Educ. 2005; 39(1): 5-13.
12. Rowe RC, Robert RJ. Artificial intelligence in pharmaceutical product formulation: neural computing and emerging technologies, Pharm.Sci and Tech. Today, 1998, 1,200-205.
13. Cybenko G. Approximation by superpositions of a sigmoidal function Mathematics of Control, Signals, and Systems, 1989; 2(4): 303–314.
14. Rosenblatt, Frank. x. Principles of Neurodynamics: Perceptrons and the Theory of Brain Mechanisms. Spartan Books, Washington DC, 1961.
16. Chen S., Billings SA, Covan C, Grant P. Nonlinear systems identification using radial basis functions, International Journal of Systems Science. 1990; 21(12): 2513–2539.
17. Musavi M, Ahmed W, Chan K, Faris K, Hummels D. On the training of radial basis function classifiers. Neural Networks. 1992; 5: 595– 603.
18. Specht DF. Probabilistic Neural Networks for Classification, Mapping, or Associative Memory. IEEE International Conference on Neural Networks. 1998; 1: 525-532.
19. Specht DF. Enhancements to Probabilistic Neural Networks. International Joint Conference on Neural Networks. 1992; 1: 761-768.
20. Svetlana I, Milica J, Zorica D, Jelena P, Ljiljana S. The application of generalized regression neural network in the modeling and optimization of aspirin extended release tablets with Eudragit RSPO as matrix substance. Journal of Controlled Release 2002; 82: 213–222.
21. Khuri AI, Conlon M. simultaneous optimization of multiple responses represented by polynomial regression function. Techno metrics. 1981; 23: 363-375
22. The Math Works, Inc., 2006: MATLAB r2006b. The Math Works, Inc. Howard Demuth Mark Beale Neural Network Toolbox User's Guide Version 4 for Use with MATLAB.
23. www.chemstations.com
24. Robert N, John E IV, Gary M. The Handbook of Statistical Analysis and Data Mining Applications.
25. Andreas Z, Gunter M, Michael VS. Neural Network Simulator (SNNS) User Manual, Version 4.2 University of Stuttgart, University of Tubingen
26. Pythia – The Neural Network Designer © 2000 by Runtime Software. http://home.thep.lu.se/~torbjorn/Pythia.html
27. www.neurosolutions.com
28. www.calsci.com/BrainMaker.html
29. www.neuralware.com