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Modern optimization techniques in field of pharmacy

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ABSTRACT

The pharmaceutical formulation process is highly specialized and requires specific domain knowledge and often years of experience. Neural computing, machine learning, knowledge-based systems and expert systems, derived from research into artificial intelligence, can assist in the efficient formulation of products and increase productivity, consistency and quality. Modern optimization techniques called Artificial Neural Networks (ANNs) were used to predict formulation process. Artificial Neural Networks (ANN) is machine based computational techniques which attempt to simulate some of the neurological processing ability of the Human brain. This feature of ANN, to extract latent information from the data presented to them, proves them to be powerful tools for modeling and predictive purposes and offers great potential for applications in a variety of disciplines. An evaluation of the performance of ANN technology as compared to standard statistical modeling techniques published in 1iterature has also been made.

Keywords: Design of experiment, Response surface methodology, Artificial neural network (ANN), Artificial intelligence, Software's for ANN.

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INTRODUCTION

Pharmaceutical formulators often face the challenge of finding the right combination of formulation variables that will produce a product with optimum properties [1]. One of the difficulties in the quantitative approach for formulation design is due to difficulty in understanding the real relationship between causal factors and individual pharmaceutical responses. Optimization becomes more important for particulate delivery systems. The use of systemic experimental design along with mathematical optimization is time and cost efficient and more importantly assures the formulation quality. A pharmaceutical optimization problem usually has two objectives

(i) To determine and quantify the relationship between the formulations response and the independent variables.
(ii) To find the settings of these formulation variables that produces the best response values.

The procedure encompasses designing a set of experiments that will reliably measure the response variables, and determining the optimum value of the independent variables that produce the best response. Traditionally, formulators have favored the use of statistical techniques, such as a response surface methodology, in an investigation of the design space. However, optimization by such a method can be misleading and this is particularly true in the case of a complex formulation. Recent advances in mathematics and computer science have resulted in the development of two techniques that can be used to remedy the situation: neural networks (an attempt to mimic the processing of the human brain) and genetic algorithms (an attempt to mimic the evolutionary process by which biological systems self-organize and adapt) [2].

Ghaffari et al concluded that ANN shows superiority as modeling techniques for data sets showing non-linear relation for both data mining and prediction abilities between casual factor and pharmaceutical response by means of ieritative training of data obtain from designed experiment [3]. An artificial neural network is a mathematical model for information processing based on the biological nervous system, which has a natural propensity for storing experiential knowledge and making it available for use the main advantage of a neural network is its ability to approximate functional relationships, particularly nonlinear relationships. Neural networks have been applied to several classes of optimization problems and have shown promise for solving such problems efficiently. Most of the neural architectures proposed in the literature solve specific types of optimization problems. In contrast to these neural models, the network proposed here is able to treat several kinds of optimization problems using unique network architecture.

Different Experimental Methods

In an experiment, we deliberately change one or more process variables (or factors) in order to observe the effect; the changes have one or more response variables. The (statistical) design of experiments (DOE) is an efficient procedure for planning experiments so that the data obtained can be analyzed to yield valid and objective conclusions. DOE begins with determining the objectives of an experiment and selecting the process factors for the study. An Experimental Design is the laying out of a detailed experimental plan in advance of doing the experiment. Well-chosen experimental designs maximize the amount of "information" that can be obtained for a given amount of experimental effort. To study the effect of different factors, conditions and their interactions on the response observed in experiments [4]

- Experimental Designs can be defined as the strategy for setting up experiments in such a manner that the information required is obtained as efficiently and precisely as possible
- Factorial Designs are used in experiments where the effects of different factors or conditions on experiment results are to be elucidated

Choosing an experimental design

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A Set Objective.
B. Select process variable and levels.
C. Select Experimental Design.
    i. Completely randomized designs.
    ii. Randomized block designs.
        - Latin squares.
        - Graeco-Latin squares.
        - Hyper-Graeco-Latin squares.
    iii. Full Factorial designs.
        - Two-level full factorial designs.
        - Full factorial example.
        - Blocking of full factorial designs.
    iv. Fractional factorial designs.
        - A 2^{3-1} half-fraction designs.
        - How to construct 2^{3-1} designs.
        - Confounding.
        - Design resolution.
        - Use of fractional factorial designs.
        - Screening designs.
        - Fractional factorial designs summary tables.
    v. Plackett-Burman designs.
    vi. Response surface (second-order) designs.
        - Central composite designs.
        - Box-Behnken designs.
        - Response surface design comparison.
        - Blocking a response surface design.
    vii. Adding center points.
    viii. Improving fractional design resolution.
        - Mirror-image foldover designs.
        - Alternative foldover designs.
    ix. three-level full factorial designs.
    x. Three-level, mixed level and fractional factorial designs.

Advantages of Experimental Designs

- Factors and interactions are assessed with maximum efficiency.
- In absence of interaction they have maximum efficiency in estimating main effects.
- If interaction exists they are necessary to reveal and identify the interaction
- Conclusions apply to a wide range of conditions since factor effects are measured over varying levels
- Maximum usage data for calculation of main effects and interaction

Applications of Experimental Designs

- Drug-excipient compatibility
- Dissolution testing
- Granulation
- Tablet formulation
- Coating of tablets
- Extrusion-Spheronization

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- Solubility
- Microcapsule/nanoparticles/liposome formation
- Transdermal drug delivery systems

The independent variables x1, x2, etc. generally represent factors which influence the response E.g. response like tablet dissolution time which depends on several factors Amount of disintegrate ,Amount of drug, Amount of lubricant

Response surface methodology (RSM)

RSM can be defines as a statistical method that uses quantitative data from appropriate experiments to determine & simultaneously solve multivariate equations.

The response surface method (RSM) has widely been used for selecting acceptable pharmaceutical formulations which includes Statistical factorial experimental designs, Modeling between causal factors and response variables, Multi-objective optimization for seeking the best formulation under a set of pragmatic constraints, Composite experimental design can be applied for selecting rationale model formulations, which are composed of several formulation factors and process variables.

Compared with a normal analysis based on one-factor-at-a-time experiments, we can greatly reduce the number of experiments for the preparation of model formulations. Response variables of these model formulations are predicted quantitatively by the combination of causal factors. In a classical way, multiple regression analysis has been applied on the basis of a quadratic polynomial equation, since theoretical relationships between causal factors and response variables are not clear. Finally, multi- objective optimization algorithms are applied for applied for predicting the best formulation. Since prediction of pharmaceutical response based on the quadratic polynomial equation is often limited to low levels. This leads to the poor estimation of optimal formulation. To overcome the shortcoming of poor estimation based on quadratic polynomial application of an artificial neural network (ANN) has been investigated.

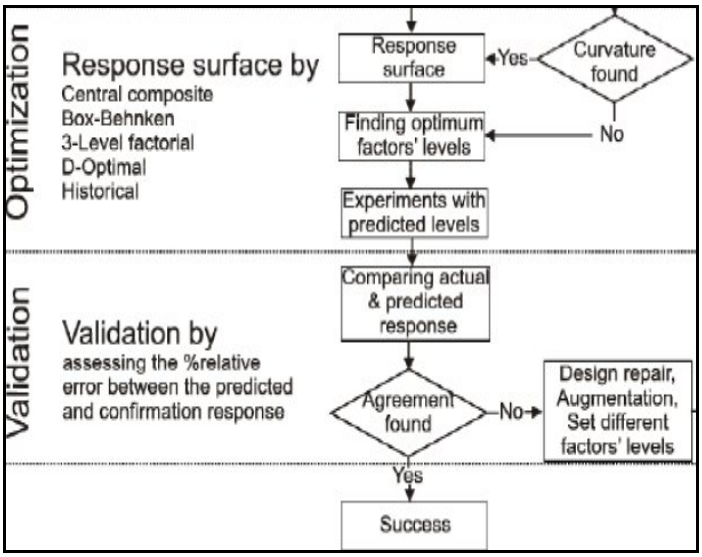

Figure 1: Process input and output flow chart with affecting variables (Black Box)

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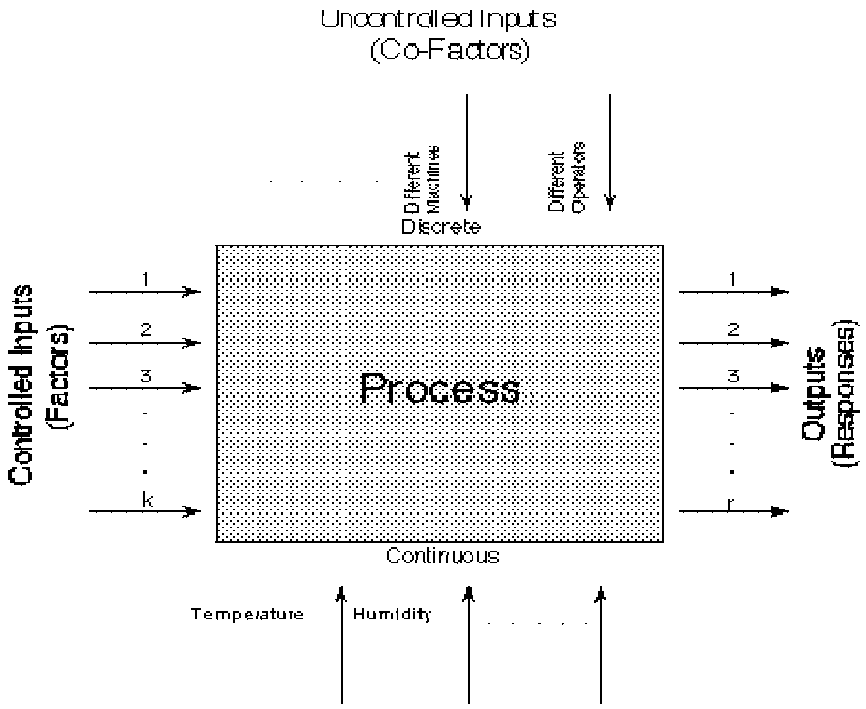

Figure 2: Optimization and Validation of design

Regression analysis

The targeted response parameters were statistically analyzed by applying one-way ANOVA at 0.05 levels in the Design-Expert® 6.0.5 demo version Software (Stat-Ease Inc., USA). and in also different software [5]. Individual response parameters can be evaluated using the F-test and quadratic models of the form given below were generated for each response parameter using the multiple linear regression analysis [6]

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_1 X_2 + \beta_4 X_1^2 + \beta_5 X_2^2 \quad \text{------ (1)}$$

where Y is the level of the measured response,

- b0 is the intercept,
- b1 to b5 are the regression coefficients,
- X1 and X2 stand for the main effects,
- X1X2 is the interaction between the main effects,
- X11 and X22 are the quadratic terms of the independent variables that were used to simulate the curvature of the designed sample space.

A backward elimination procedure was adopted to fit the data to the quadratic model. The quadratic models generated from the regression analysis were used to construct the 3-dimensional graphs, in which the response parameter Y was represented by a curvature surface as a function of X. The effects of independent variables on the response parameters were visualized from the contour plots. Numerical optimization using the desirability approach was employed to locate the optimal settings of the formulation variables to obtain the desired response [6]. An optimized formulation was developed by setting constraints on the dependent and independent variables. The formulation developed was evaluated for the responses and the experimental values obtained were compared with those predicted by the mathematical models generated.

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Uses of RSM:

- to determine the factor levels that will simultaneously satisfy a set of desired specifications
- to determine the optimum combination of factors that yield a desired response and describes the response near the optimum
- to determine how a specific response is affected by changes in the level of the factors over the specified levels of interest
- to achieve a quantitative understanding of the system behavior over the region tested
- to product properties throughout the region - even at factor combinations not actually run
- to find conditions for process stability = insensitive spot.

Limitations to RSM:

- large variations in the factors can be misleading (error, bias, no replication)
- critical factors may not be correctly defined or specified
- range of levels of factors to narrow or to wide --optimum cannot be defined
- lack of use of good statistical principles
- over-reliance on computer -- make sure the results make good sense

Artificial Neural Network & Artificial intelligence

Artificial intelligence is an interdisciplinary field which is often depicted as a tree with roots equating (for example, machine learning, problem solving, neural computing, computer vision, natural language processing, speech recognition, etc.) [2]. The fundamental processing unit of the brain is the neuron of which there are estimated to be in excess of 100 billion. The neurons are linked together by dendrites which serve to deliver messages to the neuron. Each neuron also has an output channel known as an axon by which signals can be transmitted unchanged or altered by synapses. These structures are able to increase or decrease the strength of the output signal and cause excitation or inhibition of a subsequent neuron.

Figure 4: A comparison of biological and artificial neurons

Biological	Artificial
soma	Node
Dendrites	inputs
Axons	outputs
Synapse	weights
Slow speed	Fast speed
Many neurons-10^9	Few neurons-10^2-10^3

Table 1: A comparison of biological and artificial neurons

In the artificial neural network the logic processing unit is the neuron which takes one or more inputs and produces an output. At each neuron every input has an associate weight that defines the relative importance of each input connected to the neuron. The neuron simply computes the weighted sum of all the inputs (the

summation function) and calculates an output to be forwarded to another neuron. A comparison of both the biological and artificial neurons is shown in Figure 4.

Both biological and artificial neurons behave as threshold devices. The biological neuron is generally quiescent until the output voltage rises above a threshold value. Once this has been exceeded the neuron is switched on and the output signal is generated. In artificial neurons the threshold activation is computed by means of the transformation function (also known as the transfer or activation function). The transformation function may be linear or non-linear, although the former will limit the neural network to implementation of simple linear functions e.g. addition and multiplication. Generally non-linear transformation functions are used allowing the neural network to implement more complex transformations and thus tackle a wider range of problems.

The process of formulation, whether for oral products, parentrals, or other pharmaceutical products, is complex and involves the interaction of many ingredient and process variables. As such, it is difficult to understand such systems, let alone develop useful models of them [7]. Statistics have the advantage of generating clearly expressed models, with associated confidence levels. However, for more than three or four inputs, they rapidly become unwieldy, so that the formulator is tempted to oversimplify the problem in order to model it.

Neural networks provide an alternative approach. Neural networks are mathematical constructs that are capable of learning for themselves, relationships within data. The network makes no assumptions about the functional form of the relationships, but simply tries out a range of models to determine one that will best fit to the existing data that are provided to it. As such, increasingly artificial neural networks (often referred to as ANNs) are used to model complex behavior in problems like pharmaceuticals formulation and processing. Neural networks for modeling in conjunction with genetic algorithms for optimization have proved very powerful, because it allows the formulator to develop a formulation to meet stringent often conflicting objectives.

Neural network

Neural networks provide an alternative to statistics for the task of developing models to fit to experimental data. Because the field developed independently from statistics, different terminology is often used for neural networks. Equivalent terms in statistics and neural networks are summarized in

Table 2: Comparison of Statistic and Neural Network

Statistics	Neural Network
Model	Network
Regression	Supervised learning
Interpolation	Generalization
Observation	Training set
Parameters	(Synaptic)Weights
Independent Variables	Inputs
Dependent Variables	Outputs
Ridge regression	Weight Decay

Fundamental mathematical processing unit is analogous to the mammal's neuron, and like a neuron they collect inputs, and process them to create an output signal. Provided the signal is sufficiently significant, the neuron then ''fires'' to produce an output to the next neuron in the assembly. Like mammalian neurons, these

mathematical neurons are useful only when they are interconnected in a network. Neural networks are under active investigation by the artificial intelligence community.

Early use of neural networks was inhibited because the time taken to ''train'' a model on early computers was prohibitive. Now, however, inexpensive fast PCs make neural computing very feasible and widely accessible, since generally it takes only a few minutes to develop a useful model. Partly as a result, the growth of the use of neural networks in formulation has been rapid over the past few years. As discussed later, they have had application for many different fields of pharmaceutical formulation and processing. For formulation problems, the inputs to the network are generally the ingredients, ingredient amounts, and processing conditions. The outputs consist of all measured responses that the formulator has collected. Simply expressed, an ANN is a collection of mathematical processing units (neurons), interconnected into a network that is capable of ''learning'' relationships within data. ANNs are data driven; that is to say, they require data from which they can learn, but they do not require any assumptions about the model to be learned.

Applications of ANN in Product Formulation Development [8]:

Tablets	The effect of experimental design on the Modeling of a tablet coating formulation using artificial neural network [9].
	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 [10].
	Artificial neural network and pharmacokinetics simulations in the design of controlled release dosage forms [11]
	neural network in the modeling and optimization of aspirin extended release tablets with Eudragit®RS PO as matrix substance [12]
	Formulation and optimization of theophylline controlled release tablet based on artificial neural networks [13]
Powders	Modeling properties of powders using artificial neural network and regression: the case of limited data [14]
	Artificial neural networking (ANN) and modeling of powder flow [11]
Pellets	Use of artificial neural networks to predict drug dissolution profiles and evaluation of network performance using similarity factor [15]

Liposomes	Artificial neural network as an alternative to multiple regression analysis in optimizing formulation parameters for cytarabine liposomes [23]
Hydrogel	Multiobjective simultaneous optimization based on artificial neural network in a ketprofen hydrogel formula containing o- Ethylmenthol as a percutaneous absorption enhancer [16]
Gelisphere	The advantages by the use of neural networks in modeling the fluidized bed granulation process [17]
Pharmacology	Modeling the pharmacokinetics and pharmacodynamics of unique oral hypoglycemic agent using neural network [18]
	Neural network predicted peak and trough Gentamicin concentrations [19]
Preformulation	Preformulation studies and characterization of the physiochemical properties of amorphous polymers using artificial neural network [20]
Pharmaceutical Chemistry	Artificial neural networks for pattern recognition in biochemical sequences. Design of a genome-wide siRNA library using an artificial neural network
biotechnology	Bioprocess supervision: neural networks and knowledge based systems
	Applying neural networks as software sensors for enzyme engineering

Software's Available to Handle ANN Problems:

A large number of integrated computer programs based on ANN are now commercially available. These programs are now being used widely and are gaining more and more acceptance in Pharma sector. (www.pharmainfo.net)Examples of such programs based on ANN, which have been used to design or study different dosage forms are enlisted below-

CAD /Chem, version 5.0 computer associates, Cleveland, OH) [20]	It is based on multilayer back propagation paradigm.
Phythia: version 1.0 [21]	Pythia uses back propagation method to detect hidden relationships in a set of patterns.
Neurosolutions© Neurosolutions 1994) [22]	This model was implemented within the software package as a generalized feed forward multilayer preceptron network.
Matlab 7.0	Contains neural network and fuzzy logic

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REFERENCES

[1] Arulsudar N, N Subramanian & RSR Murthy. J Pharm Pharmaceut Sci 2005;8(2):243-258.
[2] Raymond C Rowe and Ronald J Roberts. PSTT 1998;1(5).
[3] Ghaffari AH, Abdollah MR, Khoshyanad I, Bozchalooi S, Dagar A and Rafiee M. Int J Pharma 2006;327(1-2):126–138
[4] Bolton, Bon, Pharmaceutical statistics, Marcel Dekker 4th edition volume 135, New York pg. no -215-318
[5] Hagalavadi Nanjappa Shivakumar, Pragnesh Bharat Patel, Bapusaheb Gangadhar Desai, Purnima Ashok, Sinnathambi Arulmozhi. Acta Pharma 2007;269-285.
[6] Narendra C, MS Srinath and B Prakash Rao. In. J Pharm 2005;304:102–114.
[7]Elizabeth Colbourn, Ramyond C Rowe. neural computing and formulation optimization ,Encyclopedia of pharmaceutical technology, informa healthcare, taylor & Francis group, Psychology press .3rd edition,2006, pp 75-120
[8] http://www.pharmainfo.net/reviews/neural-computing-pharmaceutical-formulation
[9] Plumb AP, Rowe RC, York P, Doherty C. Eur J Pharm Sci 2006;16:281-288.
[10] Leane MM, Cumming I, Corrigan OI. AAPS PharmaSciTech 2003;4:1-12.
[11] Chen Y, McCall TW, Baichwall AR, Meyer MC. J Cont Release 1999;59:33-41.
[12] Ibric S, Jovanovic M, Djuric Z, Parojčič J, Solomun L. J Cont Release 2002; 82:213-222
[13]Takayama K, Morva A, Fuji-kawa M, Hattori Y, Obata Y, Nagai T. J Cont Release 2000; 68:175-186.
[14] Zolotariov E, Anwar J. J Pharm Pharmacol 1998; 50:190.
[15] Peh KK, Lim CP, Quek SS, Khoh KH. Pharm Res 2000; 17:1384-1388.
[16]Takahara J, Takayama K, Isowa K, Nagai T. Int J Pharmaceutics 1997;158:203-210.
[17]Murtoniemi E, Yliruusi J, Kinnuen P, Merkku P, Leiviska K. Int J Pharmaceutics 1994; 108:155-164
[18] Haidar SH, Johnson SB, Fossler MJ, Hussain AS. Pharm Res 2002;19:87-91.
[19] Brier ME, Zurda JM, Arnoff GR. Pharm Res 1995;12:406-412.
[20] Ebude NK, Owusu-Ababio G, Adeyeye CM. Int J Pharmaceutics 2000;196:27-35
[21]Degim T, Hadgraft J, Ilbasmiş S, Özkhan Y. J Pharma Sci 2003;92:656-663.
[22] Borquin J, Schmidli H, Hoogevest PV, Leuenberger H. Eur J Pharm Sci 1998;6:287-300
[23] Subramanian N, Yajnik A and Murthy RSR. AAPS Pharm Sci Tech 2003;5:1-9