Artificial Neural Networks in Optimization of Pharmaceutical Formulations
Manoj Kumar Ananthu¹, Pavan Kumar Chintamaneni¹, Shakir Basha Shaik², Reshma Thadipatri³, Nawaz Mahammed¹*

¹Department of Pharmaceutics, Raghavendra Institute of Pharmaceutical Education and Research (RIPER)-Autonomous, Ananthapuramu, Andhra Pradesh, India
²Department of Pharmaceutical Analysis, Raghavendra Institute of Pharmaceutical Education and Research (RIPER)-Autonomous, Ananthapuramu, Andhra Pradesh, India
³Department of Pharmaceutical Quality Assurance, Raghavendra Institute of Pharmaceutical Education and Research (RIPER)-Autonomous, Ananthapuramu, Andhra Pradesh, India

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*Corresponding author: Nawaz Mahammed

Abstract
Artificial Neural Network is a computer program based on the simulation of Neurons of human brain. During the past, statistical methods like RSM (Response Surface Methodology) other statistical methods are used for the development of modified release formulations (controlled release & sustained release formulations). Due to the drawbacks of the statistical methods another technique is Artificial Neural Network. ANN has an emerging field in the development of modified release formulations (CR & SR). This review article containing the optimized formulations of different modified release formulations by ANN and also the structure of Artificial Neural Network (ANN), different optimized formulations are developed by using ANN are discussed. ANN helps in emerging field in the optimization of pharmaceutical formulations. ANN are learning according to the different sets of data given to the neural networks. The functioning of the Artificial Neural Network identified according to the given output data of the formulations. ANN is a very powerful tool in the pharmaceutical industries, academics, research institutes to develop new formulations.

Keywords: Artificial neural network, Modified release formulations, Controlled Release & Sustained Release formulations, Computer, Response surface methodology, Network architecture.

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1. INTRODUCTION

Pharmaceutical formulations are dynamic structures in which various formulation and technique variables it might not be that readily understanding impact, the properties and performance characteristics. Pharmaceutical optimization is characterised as the application of systematic approaches to find, under a given set of conditions, the strongest mix of materials and/or process variables available that will contribute to the manufacture of a Pharmaceutical quality commodity Any time it is made, with predetermined and specified characteristics [1].

An alternative approach to the mathematical methods of RSM is artificial neural networks (ANN). For low dimensionality or for simple functions being approximated, RSM fits well. This polynomial form, however, has limitations. Basically, only one predictor variables or a small order polynomial can be suited to RSM. First an effective RSM for each dependent variable can be designed to maximise response surface problems [2, 3].

For this function, a computer optimization technique based on a reaction surface method (RSM) has been commonly used [4]. However, based on the second-order polynomial theorem, commonly used in RSM, the calculation of pharmaceutical responses often limited to low stages. The effect of this restriction may be the weak assessment of ideal formulations. We developed a multi-objective parallel optimization strategy to resolve the limitations in RSM in which an artificial neural network (ANN) was implemented [5-7]. ANN is a computer-based learning device that can mimic the human brain’s neurological processing ability [8].

The artificial neural network, first invented in the early 1960s, only started to expand progressively during the early-1980s along with launch for modern neural network modelling & developments with computer technology. Neural networks have since been used successfully in a number of fields, including banking, energy, health, retail, manufacturing, telecommunications and defence. Future uses of the Artificial Neural Network (ANN) In medicinal research methodology range from experimental analysis results, medication and dosage forms designed bio pharmacy to clinical pharmacy [9]. The use of artificial intelligence, such as artificial neural (ANN) networks, has been used in pharmaceutical sciences to generate and refine dosage forms in an increasingly growing area of knowledge discovery and data mining [10-15]. In recent years, the implementation of ANN in the field of pharmaceutical production has gained attention. The fundamental theory of simultaneously optimising many ANN-based pharmaceutical responses has previously been extensively developed [5-7].

Artificial neural networks (ANN) are computer systems programmed to use multiple learning algorithms to replicate the functions of the human brain, that can be learn from experience. Topological-dependent feed-forward and feed-back may be the link between ANN. The fields discussed by ANN, such as pattern recognition, pattern association, and simulation and optimization of algorithms, can also be very difficult to solve.

ANN is a digital tool that emulates the human brain’s intertwined neural processes and the human brain’s capacity to understand and overcome issues by pattern recognition [10]. Through modelling data and understanding patterns in dynamic multi-dimensional interactions is occurs in between input and output or target sets of data, ANN simulates the learning behaviour of the human brain. If an ANN has been licenced, responses for a given range of input conditions may be predicted and expected and can therefore be used to optimise both formulation and process variables in order to produce and deliver high-quality, secure and effective dosage forms [16].

2. Advantages & Disadvantages OF ANN

2.1. Advantages

- When the response variables are strongly nonlinear, ANN reliably forecasts outcomes.
- The dimensionality question curse also supervises a neural network which obscures attempts to model a large number of variables in nonlinear functions.
- Networks are more welcoming than mathematical simulation packages to fragmented and noisy knowledge. Therefore, for preparation, literature or historical evidence can also be used.
- It does not require any previous knowledge of the problem's underlying mathematical nature.
- The Neural Network has a special ability to recognise a pattern.
- They are efficient when fitted with neural nets but can leading to a decline in the timing and expense of product innovation.
- In comparison to mathematical simulations, an ANN model functions without data transformations on experimental data.
- ANN does not require any assumption as to the significance of the links between the materials of the formulation, as well as the properties of the formulations [7, 17].

2.2. Disadvantages

- The biggest limitation of ANN was how they are by default, computer systems; Interaction which network gets cannot readily represented as statistical format.
- In designing a model, the primary risk is overworking, a condition in when the neural net begins to replicate stimulus similar to a particular
section in the training data. The drawbacks could be eliminated if described above by conducting network inspection.

- ANN includes the use of specialised technologies, while RSM can carry out using earliest tools such as EXCEL (response surface methodology) [18].

3. **Artificial Neural Networks in Optimization of Pharmaceutical Formulations**

- The term Optimize is defined as to make perfect, effective, or functional as possible.
- It is the process of finding the best way of using the existing resources while taking in to the account of all the factors that influences decisions in any experiment as shown in table 1.

<table>
<thead>
<tr>
<th>Dosage Forms</th>
<th>Applications</th>
<th>Author Name</th>
<th>ANN Types</th>
<th>Software used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-formulation</td>
<td>The physiochemical characteristics of the Amorphous polymers</td>
<td>N K Ebube</td>
<td>Multi-Layer Back Propagation</td>
<td>CAD : Chem[19]</td>
</tr>
<tr>
<td>Pre-formulation</td>
<td>A new pre - formulation tool for microcrystalline cellulosis grouping</td>
<td>Josephine LP</td>
<td>Radial Basis Function Networks</td>
<td>Visual Basic 5.0 language [20]</td>
</tr>
<tr>
<td>Pre-formulation</td>
<td>The drug stability prediction</td>
<td>I. Svetlana</td>
<td>Generalized Regression Neural Networks</td>
<td>STATISTICA [21]</td>
</tr>
<tr>
<td>Tablets</td>
<td>The bi-modal delivery of drugs</td>
<td>A. Ghaffari</td>
<td>Multi-Layer Perceptron - FFN</td>
<td>CPC-X [22]</td>
</tr>
<tr>
<td>Tablets</td>
<td>Extended Release of Diclofenac Sodium</td>
<td>Branka I</td>
<td>Multi-Layer Perceptron</td>
<td>STATISTIA[23]</td>
</tr>
<tr>
<td>Tablets</td>
<td>Tablets of Aspirin Extended Release</td>
<td>Svetlana I</td>
<td>Generalized Regression Neural Networks</td>
<td>STATISTIA[24]</td>
</tr>
<tr>
<td>Tablets</td>
<td>CR(Controlled release) tablets formulation with Nimodipine</td>
<td>B. Panagiotis</td>
<td>FFBP</td>
<td>SNNS [25]</td>
</tr>
<tr>
<td>Tablets</td>
<td>Time-dependent tablets that provide rapid and continuous delivery</td>
<td>Huijun Xie</td>
<td>Back propagation networks</td>
<td>Neuro Shell 2 Release[26]</td>
</tr>
<tr>
<td>Tablets</td>
<td>Diclofenac sodium dissolution from preparations of continuous release</td>
<td>Zupancic D</td>
<td>Back propagation networks</td>
<td>SRC Computer company[27]</td>
</tr>
<tr>
<td>Tablets</td>
<td>Metformin HCl 500mg Sustained Release Matrix Tablets</td>
<td>Uttam M</td>
<td>Multi-Layer Perceptron</td>
<td>STATISTICA[28]</td>
</tr>
<tr>
<td>Tablets</td>
<td>Dissolution of Salbutamol Sulfate from Sustained Release Matrix Preparations</td>
<td>Faith C</td>
<td>Back propagation networks</td>
<td>Matlab® R 2008a [29]</td>
</tr>
<tr>
<td>Tablets</td>
<td>Porosity osmotic pump tablets for salvianolic acid</td>
<td>Wen-Jin X</td>
<td>Back propagation networks</td>
<td>Visual Basic 5.0 language [30]</td>
</tr>
<tr>
<td>Tablets</td>
<td>Several formulation factors and process variables comprise a pharmaceutical formulation.</td>
<td>Anand P</td>
<td>Radial Basis Function Networks</td>
<td>HSOL algorithm[31]</td>
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<td>Tablets</td>
<td>Crushing Strength and Disintegration Time of a High-Dose Plant Extract Tablet</td>
<td>K. Rocksloeh</td>
<td>Multi-Layer Perceptron</td>
<td>Camo A/S, Trondheim, Norway[32]</td>
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<td>Beads</td>
<td>Dissolution Profiles of Acetaminophen Beads Prediction</td>
<td>Yingxu P</td>
<td>Multi-Layer Perceptron</td>
<td>NeuroShell® Predictor, Release 2.1[33]</td>
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<td>Microspheres</td>
<td>Preparation of acrylic microspheres with controlled release</td>
<td>N. YUE KSEL</td>
<td>Multi-Layer Perceptron</td>
<td>NeuroShell Easy Predictor,[34]</td>
</tr>
<tr>
<td>Powders</td>
<td>Modeling properties of powders</td>
<td>Aykut Canakci</td>
<td>Back propagation &amp; Radial Basis Function Networks</td>
<td>Visual Basic 5.0 language[35]</td>
</tr>
<tr>
<td>Pellets</td>
<td>Theophylline pellet controlled-release matrix</td>
<td>Kok kp</td>
<td>Multi-Layer Perceptron</td>
<td>The NEURAL program[37]</td>
</tr>
</tbody>
</table>
4. ARTIFICIAL NEURAL NETWORK 'S Overview (ANN)

It is possible to make up a neural network of a huge number of neurons and the "network" is named the method by which neurons are coordinated. Architecture. ANN is mainly made up of three types of layers as Shown in figure-1.

<table>
<thead>
<tr>
<th>Topical Patches</th>
<th>The O-ethylmenthol (MET) effect on the absorption of ketoprofen percutaneously.</th>
<th>K.Takayama</th>
<th>Multi-Layer Perceptron</th>
<th>Kalman filter algorithm [38]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical Patches</td>
<td>Melatonin transdermal delivery</td>
<td>KK.Karunya</td>
<td>Multi-Layer Perceptron</td>
<td>Basic 5.0 language [39]</td>
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<tr>
<td>Liposomes</td>
<td>formulation parameters for the Optimization of cytarabine liposomes</td>
<td>S.Narayanaswamy</td>
<td>Multi-Layer Perceptron</td>
<td>Visual Basic 5.0 language [40]</td>
</tr>
<tr>
<td>Hydrogel</td>
<td>A preparation of ketoprofen hydrogel containing O-Ethylmenthol as a percutaneous enhancer of absorption.</td>
<td>Junichi T</td>
<td>Multi-Layer Perceptron</td>
<td>The computerrogram ANNOP [38]</td>
</tr>
<tr>
<td>Emulsion</td>
<td>Paclitaxel Emulsion Carried by PEGylation.</td>
<td>Tianyuan Fan</td>
<td>Probabilistic Neural Networks</td>
<td>ANN and ALCORA [41]</td>
</tr>
<tr>
<td>Emulsion</td>
<td>Optimizing the concentration of fatty alcohol in the formulation</td>
<td>Jayaram K.</td>
<td>Multi-Layer Perceptron</td>
<td>NeuroShell 2 [42]</td>
</tr>
<tr>
<td>Granules</td>
<td>Sustaining the release of indomethacin granules</td>
<td>K.Takayama</td>
<td>Multi-Layer Perceptron</td>
<td>Visual Basic 5.0 language [44]</td>
</tr>
<tr>
<td>Pharmacokinetics</td>
<td>Modeling of special oral hypoglycemic agents in pharmacokinetics and pharmacodynamics</td>
<td>Sam HH</td>
<td>Multi-Layer Perceptron</td>
<td>NeuroShell Predictor™ [45]</td>
</tr>
<tr>
<td>Pharmacokinetics</td>
<td>Prediction of pharmacokinetic parameters from the composition of drugs</td>
<td>Joseph VT</td>
<td>Multi-Layer Perceptron</td>
<td>STATISTICA [46]</td>
</tr>
<tr>
<td>Pharmacokinetics</td>
<td>The neural network predicted peak concentrations of Gentamicin and troughs.</td>
<td>Michael EB</td>
<td>Multi-Layer Perceptron</td>
<td>Program NONMEM [47]</td>
</tr>
<tr>
<td>Pharmacokinetics</td>
<td>Quantitative structure- pharmacokinetic relationship for drug delivery properties</td>
<td>YAP CW</td>
<td>Generalized Regression Neural Networks</td>
<td>MLFN Algorithm [48]</td>
</tr>
</tbody>
</table>

Fig-1: Artificial Neural Network
4.1. Input layer
The neural network entry layer is the direction in which neural network information is confronted.

4.2. Hidden layer
Hidden layers mean single or multiple neuron layers between the inputs and the inputs but that is all. Layers don't interact directly towards its outside environment. These layers have a significant effect on actual production. Thereby on the output of the network.

4.3. Output Layer
What currently occurs in the neural network output layer is what to the individual, the outcomes [49-51].

5. Network architectures [52]
5.1. Single layer feed forward networks
A single-layer perceptron network, containing one layer of output layer, is the most basic form of neural network; the inputs are supplied to the outputs directly by multiple weights. The simplest form of feed-forward network can be considered in this manner. Shown in figure – (2).

![Single Layer Feed Forward Networks](image)

Fig-2: Single Layer Feed Forward Networks

5.2. Multilayer feed forward networks
An integration of perceptron’s is a multi-layer feedback neural net where data and equations flow in one way from input and output data. There are several layers of perceptron’s in the neural net. The simplest neural net is a single input layer with a perceptron output layer. Shown in figure – (3).

![Artificial Neural Network](image)

Fig-3: Artificial Neural Network
5.3. Recurrent networks

Recurrent neural networks (RNNs) are common models with great success in various NLP tasks. But I have found only a few sources, in spite of their growing emergence, that discuss how RNNs function and how they can be implemented Shown in figure – (4).

![Recurrent Networks](image)

**Fig-4: Recurrent Networks**

5.4. Back propagation networks

Back-propagation is simply a way to replicate the total loss to the neuronal network in order to know how much loss each node is due to and update weight to minimise loss by giving lower weights and vice versa to nodes with higher error rates, Shown in figure – (5).

![Back Propagation Networks](image)

**Fig-5: Back Propagation Networks**

6. Types of ANN

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

The Porosity Osmotic Tablet (POT) optimisation was achieved in the following formula according to the common process of distance function 1.

\[
S = \sqrt{\sum \left(\frac{FDt - FOt}{SDt}\right)^2} \quad (1)
\]

Where:
- \(S\) = standard deviation widespread distance function,
- \(SDt\) = Values observed for each variable analysis,
- \(FDt\) = Optimal independently optimised values of each answer throughout the experimental field
- \(FOt\) = simultaneous optimum value.

Multi - objective simultaneous optimisation technology
It is possible to approximate the simultaneous optimum by minimising $S$ under the experiment area constraint [24]. ANN is included in the multi-objective optimization simultaneous optimization technique flow in Figure 4.3. Differential ($f_1$) and similarity ($f_2$) variables were measured for each pair of measured drug release profiles for optimum formulation. In general, $f_1$ values up to 15 (0-15) and $f_2$ value greater than 50 ensure the similarity of the 2 curves, as per the US Food and Drug Administration's industry guide. Dissimilarity factor $f_1$ and similarity factor $f_2$ is calculated using equations 2 and 3 as seen below:

$$f_1 = \left\{ \sum_{t=1}^{n} R_t - T_t + \sum_{t=1}^{n} R_t \right\} \times 100 \ldots \ldots 2$$

$$f_2 = 50 \log \left\{ 1 + \frac{1}{n \sum_{t=1}^{n} W_t(R_t - T_t)^2} \right\} - 0.5 \times 100 \ldots \ldots 3$$

Where:
- $n$ = Time points number.
- $w_t$ = Weight factor optional.
- $R_t$ = reference assay at time point $t$.
- $T_t$ = test assay at time point $t$.

The $f_2$ frequency between 50 & 100 indicates that there have been identical dissolution patterns. The $f_2$ value of 100 indicates that the trial and standard profiles are equivalent and the difference between release patterns rises as the value gets smaller. The relative error between two profiles of dissolution is defined in $f_1$.

### 7. ANN software’s

The massive amount for ANN technology is almost available widely. These systems have already commonly seen in pharmaceutical sector & will be gaining ever more popularity. Illustrations of these ANN-based applications used for the design or analysis of various formulations are described below as shown in table 2.

<table>
<thead>
<tr>
<th>Name of the Software</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>MATLAB (The Mathwork’s, Natick, MA, USA, 2012)</td>
<td>The Artificial Neural Toolkit offers neural network architecture, design, visualisation, and simulation software. For applications, systematic analysis is difficult, such as pattern recognition and nonlinear detection and regulation of structures, neural networks are used [4].</td>
</tr>
<tr>
<td>CAD/Chem v5.0 (AI Waare, Inc., Cleveland, OH)</td>
<td>It is Windows-based applications from Microsoft. This programme enables user to choose the numbers of hidden neurons, hidden nodes, model training iterations, learning algorithms and transition functions [53].</td>
</tr>
<tr>
<td>STATISTICA 10 (Statsoft, USA, 2012)</td>
<td>An extensive collection of statistics, marking options, network architectures, and training algorithms is included in STATISTICA Artificial Neural Networks; C and PMML code generators (Predictive Model Markup Language). An add-on is the C code generator [54].</td>
</tr>
</tbody>
</table>
| Stuttgart Neural Network Simulator (SNNS 4.2, 2012) | - The following network structures and mechanisms of learning are currently included:  
  - For feed forward networks, back propagation (BP)  
  - Reverse Transmission  
  - Swift prop  
  - Back percolation 1 |
CONCLUSION & FUTURE OUTLOOKS

The ANN model and the theory of how ANN can be used to help construct drug delivery pathways that are controlled have been clarified. Overall, because of its unique benefits, such as non-linear processing capability to model poorly understood structures, In the study of dosage forms processes, the using of ANN offers a modern function. Applications of ANN Model processes have more capability than conventional mathematical models in the pharmaceutical industry have become increasingly important. The spectrum of current applications, ranging from basic explanations of chemical properties, behaviour, anatomy, and epidemiology, indicates ANNs' true ability to recognise and forecast effects.

ANNs doesn’t require different devices, since neural systems are represented with scientific models and are applied via regular computer use. In particular, the usage of ANN to therapeutic choice formation has been very good in the fields of disease diagnosis, assessment and simulation. ANNs are a recently established technique when compared from marginal to predictable modelling techniques. The aid of the fake neural web in Sustained-release medication development have been increasing at a speed pace through same exciting possibilities. This unique flexibility permits ANNs to be used nearly in every field of learning involving investigation of bulky, parameter and multiple results; therefore, ANN implementations are expected to extend into several fields.

In manufacture & design of sustained release drug delivery systems, use of ANN will inevitably rise in forthcoming as user-friendly and successful ANN software systems are established. In count, various sustained release delivery, the implementations of ANN are also demonstrated.
Conflict of interest

The authors declare no conflict of interest, financial or otherwise.

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REFERENCES


44. Takayama, K., & Nagai, T. (1989). Novel computer optimization methodology for pharmaceutical formulations investigated by using sustained-release granules of...


