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Review Article

Artificial Neural Networks in Optimization of Pharmaceutical Formulations

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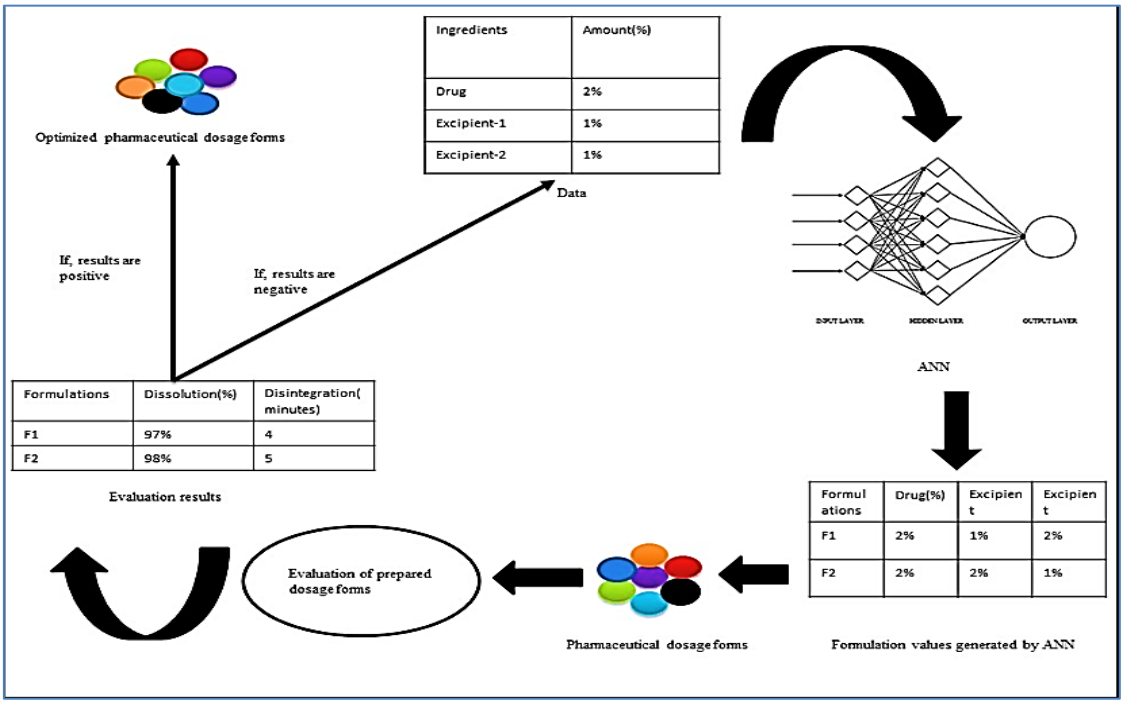
Abstract

Artificial Neural Network is a Computer program Based on 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 draw backs of 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 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 set 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.

GRAPHICAL ABSTRACT



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

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 non-linear, 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-1: Artificial Neural Networks in Optimization of Pharmaceutical Formulations

Dosage Forms	Applications	Author Name	ANN Types	Software used
Pre-formulation	The physiochemical characteristics of the Amorphous polymers	N K Ebube	Multi-Layer Back Propagation	CAD : Chem[19]
Pre-formulation	A new pre - formulation tool for microcrystalline cellulosis grouping	Josephine LP	Radial Basis Function Networks	Visual Basic 5.0 language [20]
Pre-formulation	The drug stability prediction	I.Svetlana	Generalized Regression Neural Networks	STATISTICA [21]
Tablets	The bi-modal delivery of drugs	A.Ghaffari	Multi-Layer Perceptron - FFN	CPC-X [22]
Tablets	Extended Release of Diclofenac Sodium	Branka I	Multi-Layer Perceptron	STATISTIA[23]
Tablets	Tablets of Aspirin Extended Release	Svetlana I	Generalized Regression Neural Networks	STATISTIA[24]
Tablets	CR(Controlled release) tablets formulation with Nimodipine	B.Panagiotis	FFBP	SNNS [25]
Tablets	controlled release drug delivery	Takahara	Multi-Layer Perceptron	Kalman filter algorithm[6]
Tablets	Time-dependent tablets that provide rapid and continuous delivery	Huijun Xie	Back propagation networks	Neuro Shell 2 Release[26]
Tablets	Diclofenac sodium dissolution from preparations of continuous release	Zupancic D	Back propagation networks	SRC Computer company[27]
Tablets	Metformin HCl 500mg Sustained Release Matrix Tablets	Uttam M	Multi-Layer Perceptron	STATISTICA[28]
Tablets	Dissolution of Salbutamol Sulfate from Sustained Release Matrix Preparations	Faith C	Back propagation networks	Matlab® R 2008a [29]
Tablets	Porosity osmotic pump tablets for salvianolic acid	Wen-Jin X	Back propagation networks	Visual Basic 5.0 language [30]
Tablets	Several formulation factors and process variables comprise a pharmaceutical formulation.	Anand P	Radial Basis Function Networks	HSOL algorithm[31]
Tablets	Crushing Strength and Disintegration Time of a High-Dose Plant Extract Tablet	K. Rocksloh	Multi-Layer Perceptron	Camo A/S, Trondheim, Norway[32]
Beads	Dissolution Profiles of Acetaminophen Beads Prediction	Yingxu P	Multi-Layer Perceptron	NeuroShell® Predictor, Release 2.1[33]
Microspheres	Preparation of acrylic microspheres with controlled release	N. YUÈ KSEL	Multi-Layer Perceptron	NeuroShell Easy Predictor,[34]
Powders	Modeling properties of powders	Aykut Canakci	Back propagation & Radial Basis Function Networks	Visual Basic 5.0 language[35]
Powders	Powder Flow Modeling.	Kachrimanis	Back propagation networks	SNNS[36]
Pellets	Theophylline pellet controlled-release matrix	Kok kp	Multi-Layer Perceptron	The NEURAL program[37]

Topical Patches	The O-ethylmenthol (MET) effect on the absorption of ketoprofen percutaneously.	K.Takayama	Multi-Layer Perceptron	Kalman filter algorithm[38]
Topical Patches	Melatonin transdermal delivery	KK.Karunya	Multi-Layer Perceptron	Basic 5.0 language [39]
Liposomes	formulation parameters for the Optimization of cytarabine liposomes	S.Narayanaswamy	Multi-Layer Perceptron	Visual Basic 5.0 language [40]
Hydrogel	Formulation of ketoprofen hydrogel incorporating o-ethyl-3-butylcyclohexanol as a percutaneous improver of absorption.	PAO-CHU W	Multi-Layer Perceptron	Program MULTI[11]
Hydrogel	A preparation of ketprofen hydrogel containing O-Ethylmenthol as a percutaneous enhancer of absorption.	Junichi T	Multi-Layer Perceptron	The computerrogram ANNOP [38]
Emulsion	Paclitaxel Emulsion Carried by PEGylation.	Tianyuan Fan	Probabilistic Neural Networks	ANN and ALCORA [41]
Emulsion	Optimizing the concentration of fatty alcohol in the formulation	Jayaram K.	Multi-Layer Perceptron	NeuroShell 2 [42]
Gelisphere	Cross-linked calcium-alginate-pectinatecellulose textural profiling and mathematical optimization Acetopthalate gelisphere matrices.	Viness P	Multi-Layer Perceptron	Neuro Solutions Version4.2[43]
Granules	Sustaining the release of indomethacin granules	K.Takayama		Visual Basic 5.0 language [44]
Pharmaco - kinetics	Modeling of special oral hypoglycemic agents in pharmacokinetics and pharmacodynamics	Sam HH	Multi-Layer Perceptron	NeuroShell Predictor™ [45]
Pharmaco - kinetics	Prediction of pharmacokinetic parameters from the composition of drugs	Joseph VT	Multi-Layer Perceptron	STATISTICA[46]
Pharmaco - kinetics	The neural network predicted peak concentrations of Gentamicin and troughs.	Michael EB	Multi-Layer Perceptron	Program NONMEM [47]
Pharmaco - kinetics	Quantitative structure- pharmacokinetic relationship for drug delivery properties	YAP CW	Generalized Regression Neural Networks	MLFN Algorithm [48]

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.

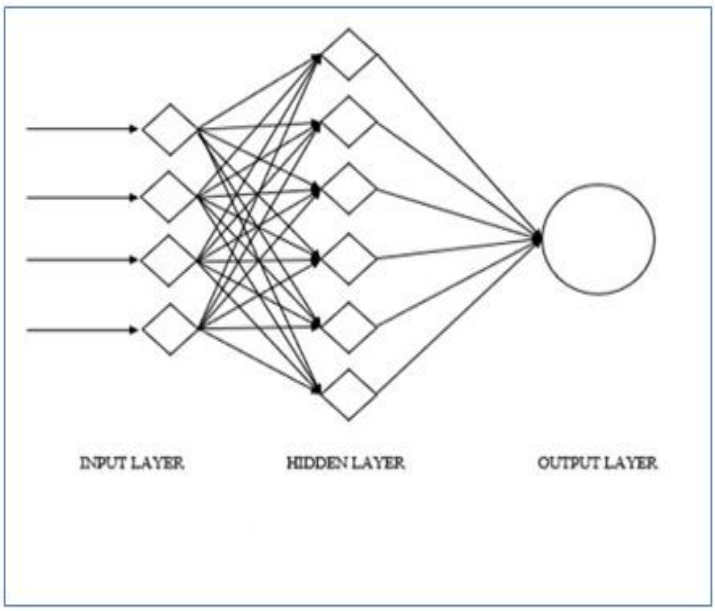


Fig-1: Artificial Neural Network

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).

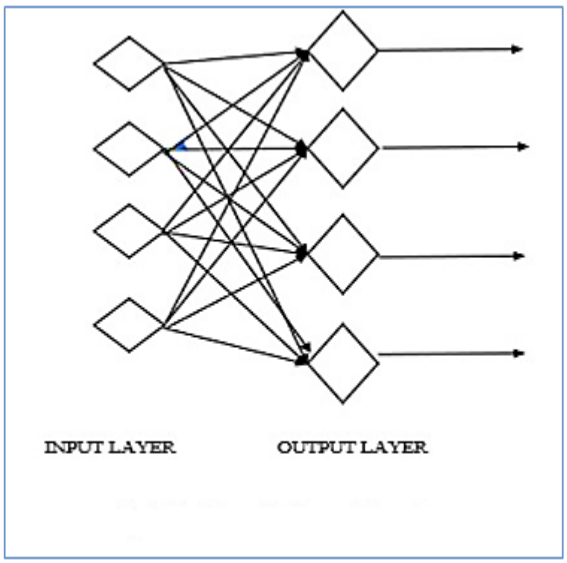


Fig-2: Single Layer Feed Forward Networks

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).

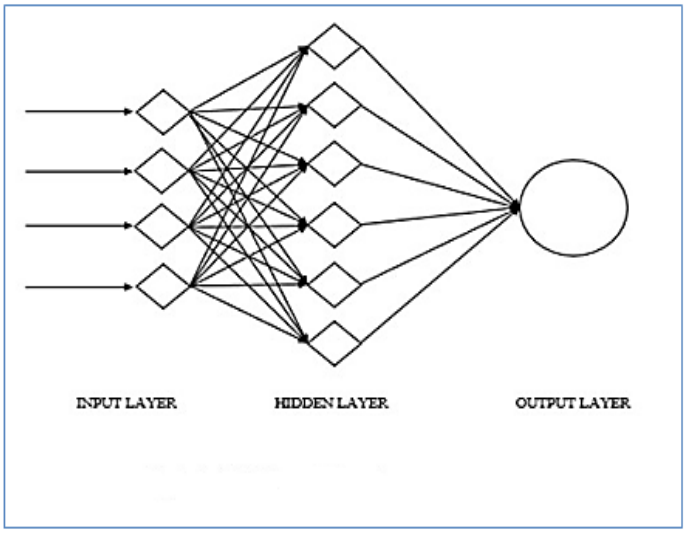


Fig-3: Artificial Neural Network

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).

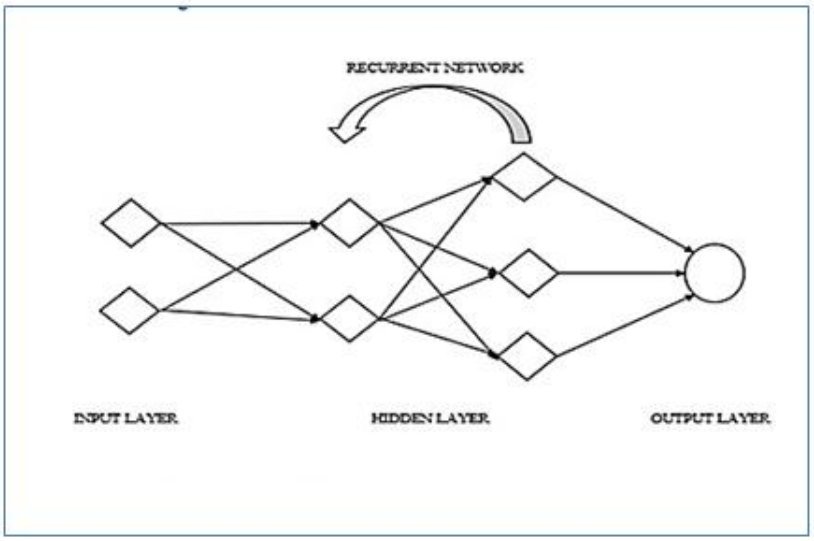


Fig-4: Recurrent Networks

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).

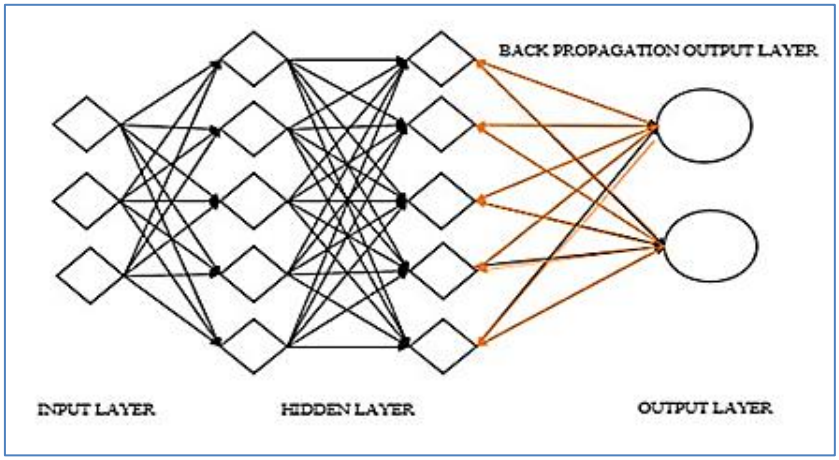


Fig-5: Back Propagation Networks

6. Types of ANN

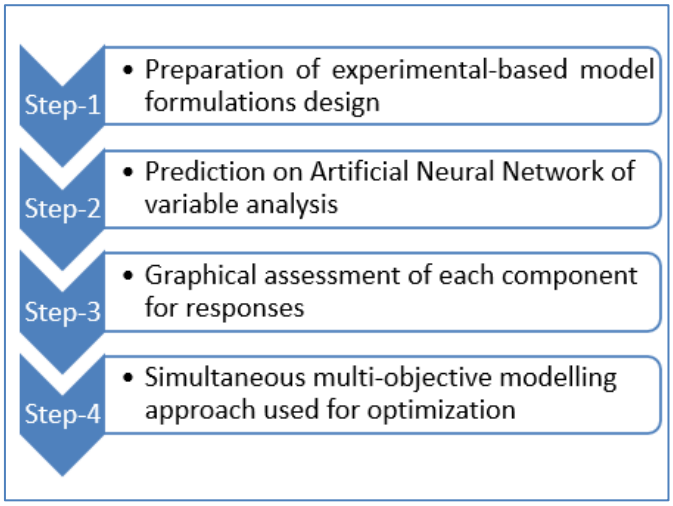
- Multilayer Perceptron's (MLP)
- Radial Basis Function Networks (RBF)
- Probabilistic Neural Networks (PNN)
- Generalized Regression Neural Networks (GRNN

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

$$S = [\Sigma \{\frac{FDt - FOt}{SDt}\}^2]^{1/2} \quad \_ (1)$$

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 (f1) and similarity (f2) variables were measured for each pair of measured drug release profiles for optimum formulation. In general, f1 values up to 15 (0-15) and f2 value greater than 50 ensure the similarity of the 2 curves, as per the US Food and Drug Administration's industry guide. Dissimilarity factor f1 and similarity factor f2 is calculated using equations 2 and 3 as seen below

$$f1 = \left\{ \sum_{t=1}^{n} \quad Rt - Tt \div \sum_{t=1}^{n} \quad Rt \right\} \times 100 \ldots\ldots\ldots 2$$

$$f2 = 50 \log \left\{ \left[1 + \frac{1}{n \sum_{t=1}^{n} Wt(Rt - Tt)\, 2} \right] - 0.5 \times 100 \right\} \ldots\ldots\ldots 3$$

Where;
n= Time points number.
wt= Weight factor optional.
Rt= reference assay at time point t.
Tt= test assay at time point t.

The f2 frequency between 50 & 100 indicates that there have been identical dissolution patterns. The f2 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 f1.

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-2: ANN SOFTWARE'S

Name of the Software	Description
MATLAB (The Mathwork's, Natick, MA, USA, 2012)	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].
CAD/Chem v5.0 (AI Waare, Inc., Cleveland, OH)	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].
STATISTICA 10 (Stat soft, USA, 2012)	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].
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

	• RProp • Modified functions of the radial base (RBF) • Correlation between cascades • Repeated Correlation of Cascade • Flexible LVQ • Back propagation with time (for recurrent networks) • Fast prop over time (for recurrent networks) • Maps for self-organizing (Kohonen maps) • TDNN with propagation by Back • Network with Jordan • Elman systems expanded Elman hierarchical networks • Adaptive Remembrance [55].
Pythia – The Neural Network designer	There are two steps of a Neural Network, usually referred to as the' learning process' as well as the' regeneration phase.' Sample data comprising all inputs and target outputs is analysed during the training period to maximise the performance of the network, which means reducing the variability [56].
Neuro solutions© 6.07 (Neuro Dimension, Inc, USA)	Neuro Technologies is the main programme for the development of neural networks that integrates a modular, icon-based interface for network architecture with the integration of innovative learning processes such as Levenberg-Marquardt and backpropagation over time. Some other noteworthy features also include generation of C++ source code, personalised components by DLLs, neuro-fuzzy designs, and programmatic management using OLE Automation from Visual Basic. In order to achieve a full understanding of the app, we suggest that you also download a free test copy. You should try creating and teaching a neural network with your own data after you've been through the comprehensive collection of live demonstrations [57].
BrainMaker v3.7	Brain Maker Neural Network Program helps you to use your software for medicinal research, predicting industry and sales, estimation of markets, shares, products, and futures, pattern recognition, medical diagnosis, sports disability... Nearly any job where you need unique insight. The menu on the left features brief papers about a couple of our clients and their Brain Builder software [58].
Neural Works Professional II/PLUS (NeuralWare, USA)	For detailed neural network production environments, Neural Works® Technical II/PLUS is the world standard. On a range of hardware architectures, Professional II/PLUS is available for UNIX, Linux, and Windows operating systems; data and network files are completely interchangeable. The Technical II/PLUS kit provides detailed documents covering the whole phase of neural network development and implementation, including a tutorial, a neural computation guide, basic and specialised reference manuals, and installation and user guides unique to the platform [59].

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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