Journal of Advanced Scientific Research

Available online through http://www.sciensage.info

ISSN
0976-9595
Review Article

ARTIFICIAL NEURAL NETWORK (ANN) AND ITS APPLICATIONS IN THE FIELD OF PHARMACY WITH A SPECIAL FOCUS ON PHARMACEUTICAL PRODUCT DEVELOPMENT: A RECENT REVIEW

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ABSTRACT

Artificial Neural Network (ANN) is a new field and a machine learning method based on artificial intelligence (AI) which has recently been utilized to optimize pharmaceutical products. ANN usually makes highly complicated models into a simple and convenient numerical solution. The potential of ANN technique is its capacity to understand and measure complicated non-linear input output interactions and their ability to interpret ambiguous or slightly constricted structures. Description about the ANN includes the historical background, its different phases while product development and also its various types that can be employed in field of optimized pharmaceutical product development. Within the context of Quality by Design (QbD), ANN techniques can be employed for the creation of design space within the limits of all applied variable factors. The aim of this review paper includes the description about the ANN and all possible applications in the field of pharmaceutical product development.

Keywords: Artificial Neural Network (ANN), Artificial Intelligence (AI), Quality by Design (QbD), Pharmaceutical product, Optimization, Multi-Layer Perceptron (MLP).

1. INTRODUCTION

Artificial Intelligence (AI) is a well-known area of program designing that focuses for development of software fit for complicated, canny, counts like that the human mind regularly performs. It fuses many strategies, instruments and structures to mimic human techniques for obtaining intelligent and inductive information, mind development and handling problems. There are two rules for classifications of AI advancements. The first one fuses strategies and structures that have ability to copy human experience and make conclusion from a set of rules, for example, master frameworks. The second one consists of structures that model the manner in which the human mind works, for example Artificial Neural Network (ANN) [1].

2. TECHNICALITIES OF ARTIFICIAL NEURAL NETWORK

Artificial neural network (ANN) development consists of collection of digital techniques for showing and affirmation of the model that works very identical to working of human brain's neuron. The brain gains information from its experience. A natural neuron in the brain receives, goes with and performs a non-straight movement and after a while allows a choice based on the convincing outcomes from various external sources. ANN is a kind of numerical model that recreates the natural tactile structure and uses analogues consisting of typical adaptable neurons. Artificial neural networks (ANNs) are arithmetic/computative estimations executed through programming setups which separate facts corresponding to human mind abilities to learn, summarize and sort out the issues based on past experience. Like the brain structure, the framework of ANN contains a couple of dealing with parts or center points which are talented to remove nonlinear associations from the figures and apply these figures to intercede the results from fascinating conditions [2]. ANNs are based on nonlinear data planning units (pseudo neurons) and thus consider compelling confirmation of nonlinear concerns that are tested in measurable procedures for a fraction of the time. Another property of ANNs is their ability to manage multidimensional problems with tens of thousands of features and cases [3]. The ability of neural frameworks to handle complex data/yield links is crucial to their applications [4].

2.1. Advantages of ANN

- In ANN, entire network is used instead of database to store the information like traditional programming. Because of this benefit the network can continue its functioning even after some information got disappear or corrupted.
- ANN has the ability to produce results with incomplete information. After the training of ANN, the output can be produced by incomplete data. Thus, the importance of missing information is known based on their direct impact on the performance lose.
- There is no effect on data output even if one or more than one cells of ANN got corrupted, leads to the false tolerance of network.
- In ANN, the desired result can be produced by determining the examples of events and showing them to network in all aspects, in order to teach the network and ANN can learn about desired output. ANN can produce the output only by showing the event to network.
- It avoids immediate corruption of network. The network undergoes degradation relatively after getting slower over a time.
- ANN has the ability to see the event and learn them in all aspects. It can comment on the event and make decisions.
- It is multitasker and carries out more than one function at a time. It has numerical strength and the ability of parallel processing.

2.2. Disadvantages of ANN

- ANN needs processors for performing parallel processing. So, it depends on awareness of hardware or equipment.
- There is serious trust issue with ANN because it never gives any explanation or proof about the probing solution produced by it.
- Assessing the design of ANN is very difficult because there are no policies and rules available for that.
- It is difficult to show the problems to network as the numerical information is used to work with ANNs. User has to change the data into numerical values and then those values are introduced to ANNs. This has direct influence on network performance.
- In order to complete the training, the network is reduced to exact values of error on sample. Optimum result is not produced by this value.

2.3. Characteristic features of ANN

In ANN, data is collected by the framework consisting of learning system. Inter-neuron affiliation characteristics generally known as synaptic burdens are used for data collection [5]. ANNs have following outstanding qualities and properties:

1. Understanding of nonlinear data yield:ANNs can understand nonlinear data yield arranging genuinely from getting ready data.
2. Hypothesis:ANNs can logically implant input plans that are new to the framework. From a quantifiable perspective, ANNs can adequate the ideal limit. So, they can summarize to conditions that contrast from those in accumulated planning information.
3. Adaptivity:ANNs can thus modify their affiliation stacks, or even framework structure (number of centers or affiliation types) to propel them directly as regulators, markers, plan recognizers, bosses, and so on.
4. Adaptation to non-basic disappointment:The basic transformation to inside disappointment limit of ANNs originates from the way that the gigantic number of affiliations gives a great deal of redundancy. Each center exhibits self-governing of all others and each center point relies upon neighborhood information [6].

3. VARIOUS PHASES OF ANN

There are various phases through which ANN model works. They include training phase, working phase and testing and implementation stage which are further described below:

3.1. Training stage

The training method includes a task that includes adjusting the heaps of relationships between PEs for the ideal framework environment. The heaps are monitored until the error is restricted, taking into account the statistical model of structures. The framework may eventually stall out in local minima, where the batch is lower; in any case, the insistence is not actually refined. The ability will enable the framework to plan for a long iterative period by conducting an investigation affirmation [7].

Training techniques are operation methods for the improved weight plan, which can limit the standard errors between the components in the yield layer analyzed and the test results. Training is a long alternative approach and in an area minimum, ANN frequently slows down [8]. Then, the ANN gathers features (direct, plans, etc.) from a formerly given restricted course of action of models by operating a computation. As a disconnected stage and preparation set may be carefully constructed, this is frequently achievable [9]. In reality, framework training is a "learning process" and divided into the following categories:

3.1.1. Supervised learning

It involves partition into input-yield sets at the point where framework loads are operated using the established figures. The most widely used training method for ANNs is supervised learning method [10]. In supervised learning, the goal is to predict at least one objective quality given at least one set of information factors. Supervised training is a method of relapse that operates on knowledge sets of modeling techniques:data sources and practice set outputs. This form of organization is an assembly of neurons coated with a layer, the output layer, the information and the hidden layer among them that are completely interconnected. Neurons of the input image get information from a record containing information. Yield neurons therefore provide reaction of ANN towards input file. Only concealed nerve cell converses with various neurons [1].

3.1.2. Unsupervised learning

This implies the issue undertaken to discover covered structure in data that remains unlabeled. Because the models given to the understudy are not labeled, there is no bungle or prize sign to calculate a normal data arrangement [10]. In unsupervised learning, we assume that there is nobody to present the appropriate patterns when there is no teacher. In this, framework is given data sources yet not with wanted yields. The framework itself then should choose what highlights it will be used to compile the data. Self-association or variation is a term that is frequently used to describe this. Rivalry between neurons, co-activity, or both may be involved in self-organizing behavior.

3.1.3. Reinforcement learning

These steps, which vary from conventional applied training, are rarely adopted or not implemented in the appropriate input information/output yield sets [10]. Even if a teacher is present, this style of learning does not give the desired answers; instead, it merely conveys the information obtained in the form of output, which is either correct or inaccurate. A reward is given for a correctly computed answer, and a penalty is given for an incorrect answer. But again, reinforce learning still isn't a popular form of learning.

3.2. Working stage

This is the procedure in which the designed ANN is utilized to interact to unique circumstances (genuine world). It is an internet based stage and having the framework established, the ANN does not need to waste time more [9].

3.3. Testing and execution

It is the foremost important to assess validity of the prepared ANN model. The assessment is done by employing the data plans for which the ANN was not readied. All things considered, the ANN does not watch the data plans used for assessing and are remarkable according to what are used to set up the ANN. The ANN is pursued for simply the characteristics that are not employed in preparing. It is made in this way to determine whether the prepared ANN is capable of maintaining the decency of the nonexclusive exchange characteristics threshold situations. Preparing continues, iteratively if backpropagation is applied, until some foreordained proportion of a decent model is met. When the training of the model is excessively short, at that point, results predicted by the model might be poor. The training of the model continues for a really long period time, at that point retention or memorization of the results may turn into an issue. At the point when retention or memorization happens, the ANN will give the same results for the information utilized for training as a final, however will neglect to be prescient or predict the actual result while applying for the data that varies from that of the training data. We typically use a distinct arrangement of information or input data for training, referred to as a test design record, that is periodically applied during preparation to reduce retention or memorization [11].

4. VARIOUS TYPES OF ANN

Artificial neural framework accomplishes tasks easily as the same way how the biological brain neuron and framework work. A huge segment of the artificial neural frameworks will have some resemblance with continuously composite and common accomplices and are fruitful at their normal tasks such as division or characterization of any data. Various types of Artificial Neural Networks are explained below.

4.1. Feedback ANN

In feedback ANN, the yield returns into the framework to accomplish the best-made outcomes inside. The framework of this type of neural network in particular is highly complex in terms of its implementation. This category of artificial neural network tries to replicate the functionality of the human brain neurons that are capable of sending information in all possible forward and backward directions and accordingly initiates responses and as a result gives feedback at the end. The signals in Feedback Artificial Neural Network can travel in both directions using loops. It's a common feature of associative memories and optimization software. In other words, the network is also known as a recurrent/recursive network.

4.2. Feed Forward ANN

The framework of this neural network is comparatively less complex as Feedback ANN. The network algorithm consists of 3 layers of neurons namely:the input layer, the hidden layer and the output layer. The hidden layer is present among the input and output layer. There is no loop formation in this type of network which means that the signal once initiated travels in a unidirectional fashion. Based upon a weighed sum of its input, each processing element present in the network makes it computational. The original calculated values then turn out to be new input values for the next layer, and the process repeats until all three levels have been completed and the output has been determined. It is frequently used in data mining and incorporates perceptron and radial basis function networks. This network is also known as the non-recurrent network. It is therefore believed that more the number of hidden layers present between the input and output layer more will be the efficiency of the output generated.

4.3. Classification-Prediction ANN

This is a sort of feed-forward ANN that is applicable to information mining situations. The framework is designed to recognize explicit models and group them into unambiguous groups, which are then grouped into "novel models" that are new to the system. A computational diversion of a natural neural framework is an artificial neural framework. These are where neurons and electrical signals move between data, such as from the eyes or sensitive regions in the hand, and the psyche's yield, like as when reacting to light, contact, or temperature [12].

4.4. Multilayer Perceptron (MLP)

The word "multilayer" is utilized in light of the fact that this procedure is made by a few brain neurons organized in various layers. Every association among the information and concealed layers (or two unseen layers) is like a neural connection (natural partner) and the information is changed by a decided weight. In this way, a three-layer feed-forward structure has been created via a database based on input information, multiple hidden layers along with the output level (MLP element is sometimes referred to as feed-forward neural organization since this statistics channels mostly the forwarded manner). As such, the created yield of a layer is just utilized as contribution for the following layer. Supervised learning layer is a significant quality of feed-forward organizations. The significant error in the Multilayer Perceptron approach is the instruction/ training steps. The learning or training stage is the phase of pursuit intended for a range of weight tests aimed at removing the accumulated standard errors (trial x investigated facts). This stage is one of the slowest, and restricted achievement is not guaranteed. There are certain training estimates with MLP, for instance, Form Angle drop, quasi-Newton, Levenberg-Marquardt, and so on; however the back-propagation computation is perhaps the most utilized. To alter the intensity of layer associations, this framework employs the error projections of the yield/result level (estimate). Thusly, this calculation gives an assurance of least assembly layer. The key challenge for MLP is to decide on the most suitable design. In MLP, the number of layers and the quantity of hidden unity for each layer have a clear influence on the speed with which the learning exhibition unfolds [13-16]. Fig. 1 shows how the number of layers affects the brain organization's ability to recognize examples.

The increase in various layer proportions in MLP estimate is connected to the multidimensional magnitude of the problem to be handled. The complicated nature of example recognition of the brain organization increases as the number of covered / hidden layers increases [15]. Back propagation algorithm is a supervised learning approach used by MLP. For an MLP neural organization, the relationship between data sources and yields can be defined as follows [10]:

$$y_I = f0 \times \sum_{0-1}^{n0} b0 + \sum_{n=1}^{Nn} Wh0.fh \times bn + \sum_{i=1}^{N1} W1h \times 1 \quad .... \textit{Equation 1}$$

In this equation, y_i are systems essential information and yield, respectively; W_{ho} and W_{ih} ($I = 1, 2. . , N_i$; $o = 1, 2, 3, …, N_o$) consisting of loads of the associations among the information and concealed components, and among the covered up and yield values, individually. b_h and b_o are predispositions of shrouded components and yield values, and $f_o(\cdot)$ and $f_h(\cdot)$ are covered up also yield works individually. Inclinations are neurons that constantly have stable characteristics and serve to enable the predicted yields to travel securely (i.e., they can be supposed of as capacity blocks)[10].

Generally perceived, Multi-Layer Perceptron (MLP) artificial neural network depends on four crucial parts (Fig. 2):input/ data source layer, hidden layer/ unseen layer (s), output layer /yield layer, connections / relationships (weights). Every layer contains very few "center points" which indeed are artificial neurons related between layers by methods for "loads"-counterfeit neurotransmitters. The data stream is one direction since the commitment to the yield [3].

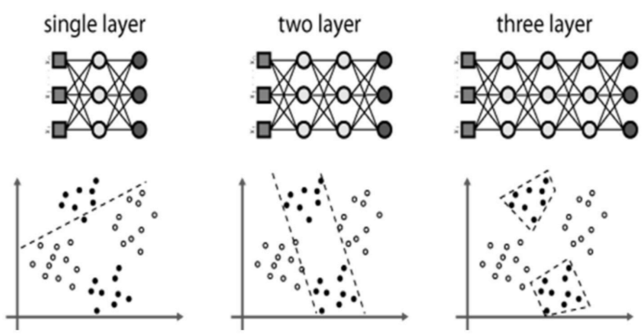

Fig. 1:Impact of the quantity of layers on the pattern recognition capacity of Multi-Layer Perceptron [17]

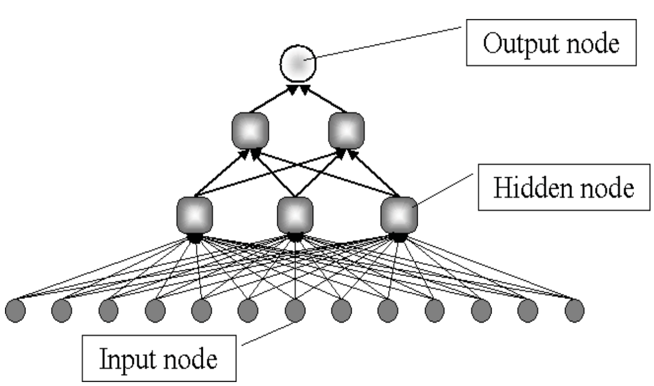

Fig. 2:Typical structure of MLP ANN [3]

5. WORKING PRINCIPLE OF AN ARTIFICIAL NEURAL NETWORK MODEL

The Artificial neural network models typically benefit from actuality, which is obtained by cycle/measure of preparation. The planning measure requires the necessary data for a prototypical neural organization. For a partner ANN model, in which input/yield information collections are provided to the model, training is handled. The steps of learning by the developed model of ANN are the route for changing the dependent of input components introduced to develop an ANN model. Training can be acquainted with the neural organization step by step (called gradual preparing) or as the entire information (called clump preparing) [18,19].

In the light of planning, each phase for the incremental training or in the wake of preparing the entire preparation set for the batch training, the dependency on each element is refreshed. The strategy employed to change the dependence factor is known as training algorithm. The training of ANN model is done through interactive process of giving input to training data collections to create model and altering the dependence of every factor. Each interactive process involves two steps, a feed forward steps and the back-propagation steps.

Data to be trained is presented in feed forward step. The processing nodes in the model processes the input data sets on the basis of randomly assigned weigh to the input factors. It then processes the input data on the basis of sigmoid function to calculate the output. Predicted output/yield can be achieved from the output layer of the model. The error in the output is calculated in back propagation step by comparing the predicted value to that of the desired output. After calculating the error, the weight adjustment is done for the all-input data. This interactive training is done till the error is minimized or reach the value set by the model creator [20].

6. PREDICTABILITY OF THE DEVELOPED ANN MODEL

Developed model of ANN can be utilized to foresee the reaction, for example, release profiles of drugs by giving a bunch of related information in the form of input variables. The information sources can be from different manufacturing aspects, for example, amount of polymer, drug loading, and so forth, and different processing factors. The capacity of prediction or optimization of a very much prepared ANN model can answer 'imagine a scenario in which' questions, for example, 'what will be the effect on drug release profile if we decrease the polymer amount in sustained release formulation? But, this could be a lengthy and more time taking to enhance the plan and formulation variables to acquire an ideal detailing by investigating all the potential blends of preparations and factors involved in formulations. Genetic algorithms (GAs) in combination of prepared neural organization model could be the answers for enhancement of sustained release types of preparations [21].

The approach of optimization utilized by developed ANN model for finding the arrangements that yield the fewer mistakes depends on the various methods such as desirability function technique or simplified distance function technique. GAs in combination with ANN frames a circle dependent on the estimation capacity of ANN and the misuse capacity of GAs. ANN anticipated yield results dependent on the new sources of information produced by GAs and compared with the objective yields. This cycle proceeds until the ideal or close ideal solution (optimized process or formulation variables) for a bunch of target yield are obtained. Thus, this circle gives an amazing asset for the optimization of sustained release formulations.

For illustration, if we know the manufacturing factors, the release of an optimized formulation can be acquired from the GA programming through a developed artificial neural model. As of now, several softwares have given single programming bundles, which incorporate both the GA and Neural Model for applications of optimization and predictions. Example of single bundled software/programming include Chem (AI WARE, Inc., Cleveland, OH), Neuro Solutions (Neuro Dimension, Gainesville, FL), and Neural Works Predict (Neural Ware, Carnegie) [20].

7. POSSIBLE APPLICATIONS OF ANN IN PHARMACEUTICAL FIELD

7.1. Identification of patterns and analysis of analytical data

The ANNs can identify designs from a set of complex analytical data. When the spectrum of a unknown sample is known, the concentration of unknown sample can be determined with the help of ANN. Agatonovic-Kustrin et al. analyzed diffuse reflectivity Infra-red spectral and X-ray deflection with artificial neural networks as a knowledge device to establish a simple, delicate and quick technique intended for the subjective and measurable monitoring of ranitidine-HCl [22]. In another study, Madden et al. utilized ANN to predict retention times for anions in linear gradient elution ion chromatography with hydroxide eluents. It also helped the advancement strategy for determination of ideal angle conditions for anion separations [23].

7.2. Pre-formulation studies

Preformulation studies are important part before actual development of a stable, safe and effective pharmaceutical dosage form. ANN model can be utilized in that pre-formulation studies for efficiently predicting drug-excipient interaction and excipient characterization. In one such study, Ebube et al. used ANN technique for efficient characterization of the physicochemical properties of amorphous polymers with less prediction error [24].

7.3. Optimization of pharmaceutical formulations

By using RSM and polynomial equation, optimization of pharmaceutical formulation generally limited to low level of factors that may leads to poor prediction of optimized formulations. For overcoming these disadvantages of response surface methodology, multi objective ANN model can be employed. The error less optimization with the help of ANN model have been reported by various researchers [21,25]. A comprehensive discussion of this topic is further given in next section.

7.4. Pharmacokinetics and pharmacodynamics

Important pharmaceutical applications such as estimation of clearances, amount of distribution of a variety of structurally diverse compounds, and amount attached to plasma proteins can be efficiently predicted by ANN model [26]. The scope of the ANN provides an option to screen complex connections between the drug product and the physiological systems that are generally pharmacodynamically (PD) regulated. In one such research, a pharmacodynamic model was utilized to assess the dose of HMG-Co-Areductase inhibitors using the ANN model [27].

7.5. *IVIV* correlations

For drug industry, *in vitro-in vivo* correlations (IVIVC) remain enormous tool in reducing bioequivalence assumptions which are intended to give adverse effects. The developed *In vitro-in vivo* correlation model based on ANNs can be a good predictive instrument that overcomes a portion of the obstacles linked with old classical regression models, basically that gives an earlier definition of the multiple regressions model [28].

7.6. Quantitative Structure Activity Relationship (QSAR)

QSAR associations connect chemical or natural behaviors with framework or properties identifiers of blends. All QSAR studies depend on the main idea of a physical and chemical limit associated with organic activities. Computational techniques, like the ANN model, will estimate the physicochemical identifiers and topological boundary. A new dynamical approach for estimating the antimicrobial activities of quinolone derivative products on the basis of their chemical configurations had been developed by Jaen-Oltra et al. [29].

7.7. Structure Retention Relationship (SRR) methodology

Anticipating chromatographic conduct from atomic structure is one of the structure-retention activity techniques. Them and its co-workers utilized the ANN model in the quantitative structure-inclination of phenyl thiocarbamyl amino acid subsidiary elution retention relationship [30]. Retention time was used to determine the relationship between chromatographic behavior of solute with pH and mobile phase quantity [1].

7.8. Prediction of Protein structure and functions

ANN can be employed for area identification related to domains of protein, its grouping forecast of enzyme groups, framework characterization of DNA/RNA and protein. The outcomes are important for the further investigation to know the connection between the structure and capacity of proteins which may likewise give data with respect to plan and the expectation of protein tertiary structure. For the analysis of dynamics in protein sequence, six feedback and six hidden nodes comprising ANN models with sigmoid function might be used [31].

7.9. Prediction of skin permeability of various drugs

Lim and his coworkers introduced a model for a complex molecular compound to predict the human tissue permeability (log K p) by utilizing a calculation based on mixture of molecular orbital (MO) and the formation of the artificial neural network model. The creation of an artificial neural network model by Degim and its co-workers predicted skin permeability of multiple molecules [32] and the results were compared with multiple regression models, as performed by Pugh et al. 33].

7.10. Diagnosis of disease

Precise diagnosis is the basis of successful treatment approach for complicated diseases. Based on medical biochemical evidence, ANN can be efficiently utilized fordetection of acute myocardial infarction, forecasting of cardiovascular risk, pregnancy-induced hypertensive disorders, Parkinsonian tremor, detection of benign focal liver disease, analysis and detection of AIDS, urological oncology, analysis of Alzheimer's disease, and diagnosis of cancers [34-40].

8. LITERATURES ON ANN BASED PHARMACEUTICAL PRODUCT OPTIMIZATION

ANN is an emerging area and has been utilized for optimization of pharmaceutical formulations and produced encouraging outcomes. Table 1 gives few such literatures that describe the main highlights of the research work and usefulness of ANN with respect to pharmaceutical product development.

Table 1:Applications of ANN in optimization of pharmaceutical formulations

S. No.	Highlights of work done	ANN model/software	Reference
1.	This paper provides information on optimization strategies for the creation of a SR matrix tablet formulation containing metformin HCl 500 mg with optimised *in vitro* release profile through ANN employing the MLP framework.	Multi-layer Perceptron/ STATISTICA Neural Network software	[8]
2.	A developed artificial neural network and required pharmacokinetics parameter profiling were used by the author to develop controlled-release pharmaceutical formulation with consistent behaviour in *in-vitro* parameter and also in *in-vivo*.	Chem version 4.6 developed by AI Ware, Inc., Cleveland, OH)	[41]

3.	This research demonstrates the use of a two-level back propagation neural network for the investigation and optimization of diclofenac sodium dissolving from sustained release matrix tablets.	Two-level back propagation type of Artificial Neural Network.	[42]
4.	The theophylline-containing controlled-release tablet formulation was developed using a simultaneous optimization strategy that included the use of an artificial neural network (ANN).	This formulation was optimized by partitioned ANN	[43]
5.	The GRNN (Generalized Regression Neural Network was included in the production of aspirin-containing extended-release tablets.	Generalized regression neural network (GRNN)	[44]
6.	The goal of this study was to use the quality by design (QbD) method and an artificial neural network to develop a sustained release direct compressible tablet containing alfuzosin (ALF) hydrochloride (HCl).	Artificial neural network	[45]
7.	The goal of this work was to improve the rosuvastatin-containing self-nanoemulsifying drug delivery system (SNEDDS) formula and examine its physicochemical properties.	Experimental design of D-optimal experimental developed by JMP 15 software	[46]
8.	The goal of this work was to formulate, optimise and analyze transdermal terbutaline sulphate (TBN)-loaded bilosomes (BLS) in gel form through artificial neural network (ANN) modelling compared to traditional oral TBN solution and free TBN-loaded transdermal gel in place to evade hepatic first-pass metabolism.	Feed-forward ANN models	[47]
9.	The release of diclofenac sodium (DS) topical matrix patches and the kinetics of ex-vitro skin permeation were both estimated using the artificial neural network (ANN) model.	Generative Adversarial Network (GAN) of Machine learning	[48]
10.	The goal of this study was to develop a thermosetting hydrogel containing lamotrigine for intranasal delivery to control and treat generalised epilepsy.	Multi-Layered Perceptron (MLP)	[49]
11.	This research primarily focused on the production of NSAID gelatin nanoparticles that were systematically delivered using the design quality principle and artificial neural networks (ANNs).	Feed-forward (FF) back-propagation with CCD.	[50]
12.	This study highlights the affects of the key development factors on tablet printability. It also included the optimization and forecasting of prolonged drug release using a designed artificial neural network from cross-linked polymeric consisting of ibuprofen printlets.	STATISTICA 7.0 Neural Net-works software (Stat SoftInc., Tulsa, OK, USA.)	[51]
13.	An accurate pharmacogenomic algorithm was utilized for estimation of effective and safe dose of warfarin.	ANN model, consisting of the 'Visual Gene Developer' version 1.4	[52]
14.	An optimal pH-Dependent Mesalamine Matrix Tablet was estimated using Artificial Neural Network (ANN) approaches.	Multilayer perception (MLP)	[53]
15.	This research consists of the use of ANN in the test composition of drug based on QbD, where ingredient provisions were specified by correlating their role during the in vivo study. An ANN model consisting of five hidden neurons with one hidden layer was built and was verified leveraging an arbitrary holdback of 33% of the database. For all the three selected responses, the model determines	MLP (multi-layer perceptron) composed of more than 1 layer	[54]

	the significant formulation, with R^2 estimates more than 0.94 for entire reactions, for both the preparation and the approval databases. The developed artificial neural network model accurately predicted the *in-vitro* disintegration, by error of nearly five percent.		
16.	This research consists of optimization of the composition of diclofenac sodium matrix based adhesive patches containing various chitosan concentration rations (CTS) and kappa carrageenanan (KC). The developed matrix film was casted on the membrane backed by polyvinyl alcohol and characterized by thickness, flatness, folding endurance, tensile strength, bio adhesion, drug content, moisture content, uptake of moisture, *in-vitro* release parameters and *in-vitro* skin infusion tests. Artificial Neural Network was used for formulation optimization and prediction of drug release and *ex vitro* permeation kinetics.	Generative Adversarial Network (GAN) of Machine learning	[48]
17.	In this study, the impact of development and various process variables on the *in-vitro* release of prednisone via a multiple unit pellet framework was analysed. Four definition and cycle factors such as microcrystalline cellulose fixation, amount of sodium starch glycolate, spheronization time and expulsion speed were explored and the drug discharge, required aspect ratio and obtained result were checked through the prepared ANN model.	A multi-layer perceptron (MLP) using back propagation (BP) and the Broyden-Fletcher-Goldfarb-Shanno (BFGS) learning method.	[55]
18.	The influence of seven variables, i.e., polymerization time, loading time, stirring rate, sorbent quantity, desorption time, absorption of initiator and ratio of monomer to template were investigated for molecularly imprinted polymer (MIP) production. Central composite design (CCD), Plackett-Burman design (PBD), ANN, and genetic algorithm were employed to optimise selected variables. The factors which have most impact on the responses were studied by using the CCD and received data was employed for the developed model training of ANN.	A three-layer feedforward ANN with a hyperbolic tangent function in the hidden layer and a linear function in the output layer. Bayesian control back propagation was done by the learning method	[56]
19.	This research work explored the use of Genetic Algorithm and ANN for the optimization of triacylglycerol acylhydrolase production using agro-residue as substrate. The optimization of this developed model employed that the enzyme production can be increased up to ~88.52 % at temperature 35°C, liquid-solid ratio is 1.5, pH 7 and incubation time 120 hrs. The ANN and GA based proposed optimized developed model helped in scale-up studies of enzyme production without any problem.	The Feed-Forward-Back Propagation (FFBP) algorithm along with CCD data	[57]
20.	The research work involved the use of Artificial Neural Network Organizations (ANNs) to predict biophysical parameters of therapeutic monoclonal antibodies, such as melting temperature (Tm), aggregation beginning temperature tags, and interaction boundary kD as functions of pH and salt fixation from the amino acid constituent. The developed ANNs were built using standard beginning phase screening datasets that produced high forecast/prediction values. It was suggested that by keeping the ANNs simple by merely using the amino acid composition resulted good broad applicability, robustness and interpretability.	Feedforward network consisting of one layer which was hidden or not discovered and one output layer.	[58]

21.	This study highlights the development of an optimized essential oil-based liquid vaporiser formulation consisting of essential oils like citronella and eucalyptus oils through ANN and other algorithmatic method. The effectiveness of the optimized formulation was examined across 2 significant mosquito species employing a Peet-Grady Chamber. The optimized formulation showed release of essential oils up to 450 hrs at room temperature.	Feed-forward back-propagation (FFBP) ANN	[59]

9. FUTURE PROSPECTS

It is very difficult to understand pharmaceutical processes. Their factors are affected by concentration and a huge number of control parameters. Modern technologies now offer the chance for a massive volume of data of different sorts to be created. If, at the very same time, technologies can't resolve the associated issues of evaluating, implementing and generating features from the dataset, such database system might be meaningless. AI, advancements presently in use and upcoming, will assist researchers with these challenging tasks:incorporating variable knowledge, describing what's been happening on, analyzing and finally predicting what is going to happen in a particular circumstance. As explained above, Artificial Neural Network can be employed for the various applications for the research related to pharmaceutical product development. As pointed out in this research article, when independent factors are given into the framework, artificial neural networks combined with genetic algorithms may predict the combination of inputs that would yield the optimal strategy. Also, in the ability to create non-linear relationship between the data (where source or category as well as of unfinished sets of data), neural network techniques have remarkable benefits over other frameworks, without needing specific user expertise. In practice, to accurately engage neural systems, the operator does not have to have a broad specific context. In addition, by introducing new data (inputs and/or outputs) to the dataset, the gathered information through neural networks could be simply enhanced providing extra opportunities to consider and develop improved pharmaceutical formulations.

10. CONCLUSION

Historically, ANN model is based upon the challenge to model the approach of data processing by a biological brain which has very different scenario as compared to basic statistical modelling methods. It has some limitations in spite of many genuine advantages. The applications of ANN method requires some in-depth knowledge to obtain accurate outcomes, as is the case with classic statistical modelling techniques. The important characteristic of ANN methods and their types are discussed in this review paper which may be utilized in future to formulate best formulation which will help to reduce all over cost of the formulation.

Conflict of Interest

There is no conflict of interest with respect to the content of this article.

11. ACKNOWLEDGEMENT

Authors would like to acknowledge Department of Pharmaceutical Sciences & Technology, Maharaja Ranjit Singh Punjab Technical University (MRSPTU), Bathinda, India for providing necessary infrastructure for this work.

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