ARTIFICIAL INTELLIGENCE IN PHARMA PROCESSING

Shalini Tripathi, Gurvinder Singh, Rajesh Kumar, Pardeep Kumar Sharma*
Department of Pharmaceutical Sciences, Lovely Professional University, Phagwara, Punjab, India.

Abstract: In 2002, certain amendments were proposed by food and drug administration in cGMP (current good manufacturing process) to modernize and improve the regulations for drug manufacturing and quality. Considering the amendments International Conference of Harmonization (ICH) developed Q8 guideline for pharmaceutical development which is based on the concept of Quality by Design (QbD). QbD is a systematic approach to pharmaceutical development with pre-defined objectives of designing manufacturing processes and developing manufacturing formulation of prescribed quality and offers better understanding of critical process. Later Q9 (Quality Risk Management) and Q10 (Pharmaceutical Quality System) guideline was introduced based on Q8. Pharmaceutical manufacturing is a complex process including multi variable interaction between process condition and raw material which is important for processing and defining the quality of the end product. This developed an urge in the researchers of employing design of experiment (DoE) to link CQAs (Critical Quality Attributes) to process parameters and API and excipient attributes and to define the design space. Artificial Intelligence can establish relationship between process parameters and various formulations in more understandable way while saving huge amount of money and time. Genetic algorithms, neural network are the technologies growing rapidly in pharmaceutical quality control processing.
Artificial neural network is a data processing and learning machine which is inspired by the functioning of human brain. Human brain works slow but potential to perform complex tasks that computer is unable or might take long time to perform. ANN consists of artificial neurons (connected parallel) and weighs also called synaptic strength that helps to emulate the nervous system. Neural networks have capability of establishing the relation between the input and output data without prior assumptions or knowledge about the given data set that makes it suitable for regression and classification tasks which plays a vital role in many biomedical applications. Conventional methods for analysing the data is linear but neural network are non-linear (inherently) that makes it practicable for preparing models of complex data accurately. Hence, ANN can be used to solve many problems in biomedical and healthcare sector.
This review article aims on demonstrating the successful and innovative application of Artificial Neural Network in the pharmaceutical industries.

Index Terms: **Artificial Intelligence, Artificial Neural Network, Genetic Algorithms, Neural Network Model**

1. INTRODUCTION

Pharma Industries are undergoing revolutionary changes and struggling with various challenges comprising the need to accelerate processing operations to fulfil the demand and tackling the global competition, and incorporation of PAT (process analytical technologies) and QBD (quality by design) principles in analytical and process development to meet the guidelines provided by Food and Drug Administration (FDA) [4]. Pharmaceutical manufacturing is a complex process including multi variable interaction between process condition and raw material which is important for processing and defining the quality of the end-product. This developed an urge in the researchers of employing design of experiment (DoE) to link CQAs (Critical Quality Attributes) to process parameters and API and excipient attributes and to define the design space. [1] Statistical methods and thinking plays a vital role to encounter such issues.
Nowadays, Avant-grade instrumental analysis is being used in broad range of pharmacy such as analysis of raw material, quality of the product, developing new dosage form using advanced manufacturing technique with desired drug release profile and process optimization. These techniques not only reduce the time of analysis, but also broadens study range and helps in exploring the new area. Operations being used in pharmaceutical industries require regressive analysis and implementation of curve suitable to pre-existing data [2]. In such analysis, single variable (dependent) is analysed in relation to various independent variable. But adept application of advanced, computerized and automatic instrumental analysis technique leads to collection of enormous volume of multiple dimensional data-base in real time which makes the data interpretation more complex majorly when relation between the variables (being investigated) is non-linear [9].
Statistical tools and concepts have been implemented successfully in many sectors such as automobile and chemical industries but in case of pharmaceutical industries they exhibit unique challenges. Many pharma industries vacillate to invest in large-scale manufacturing and quality check prior marketing approval of drug due to high risk of product failure. It requires approximately 12 to 15 year to get approved and mostly the drugs fail in confirmatory phase (phase 3 trials) [4]. Hence, process understanding and quality enhancing initiatives are required to compete for potential money and time loss during manufacturing and quality control processing that calls for statistic-based approaches in pharmaceutical industries.
Artificial Intelligence is a flourishing branch of computer science evolved with problem solving application in multiple ways in industries as well as life science by the aid of programming. Artificial intelligence (AI) identifies problem, processes the functional information and provides various methods to solve it. It does the analysis based on application and designing of new algorithms for interpreting, learning and analysing the data. It includes branches like machine learning, pattern recognition, clustering, similarity-based methods and statics which shows a promising future for pharma industries [3]. Pharmaceutical industries are discovering innovative and new strategies to use powerful AI technologies to tackle some major problems faced by pharma industries. In pharma industries use of AI refers to the algorithms leading to automation to

carry out the tasks which typically depend on human intellectual capabilities [3]. Artificial Intelligence can establish relationship between process parameters and various formulations in more understandable way while saving huge amount of money and time. Genetic algorithms, neural network are the technologies growing rapidly in pharmaceutical quality control processing [8]. There are two emerging categories of AI that is involved in further advancements:

- System and methods that imitates human experiences and finds conclusion by using certain set of rules for example expert system.
- System that mimics the functioning of human brain for example ANN (Artificial Neural Network) [7].

Expert systems are also called 5th generation of computers or knowledge-based system, that is an extended version of conventional computing. The concept of knowledge-based system is logical thinking that provides guide for decision making and prediction during the uncertain and vague circumstances and mostly helpful in diagnosis.

3.6. Similarity Between Biological Neuron and Artificial Neuron

Artificial neural network is a data processing and learning machine which is inspired by the functioning of human brain (processing information and learn with experiences via suitable learning examples) and not from programming. Human brain works slow but has potential to perform complex tasks that computer is unable or might take long time to perform [8]. The brain is brilliant in recognizing patterns and neural network also acquire data and knowledge by recognising the relation and pattern within the given data. For example, if we see an apple, we recognise that it is an apple due to the neurons that have previously experienced similar patterns and learned to connect that pattern with description 'apple'. Moreover, human brain consists of billions of interconnected neurons that helps to recognize and learn infinite number of possible input pattern [7].

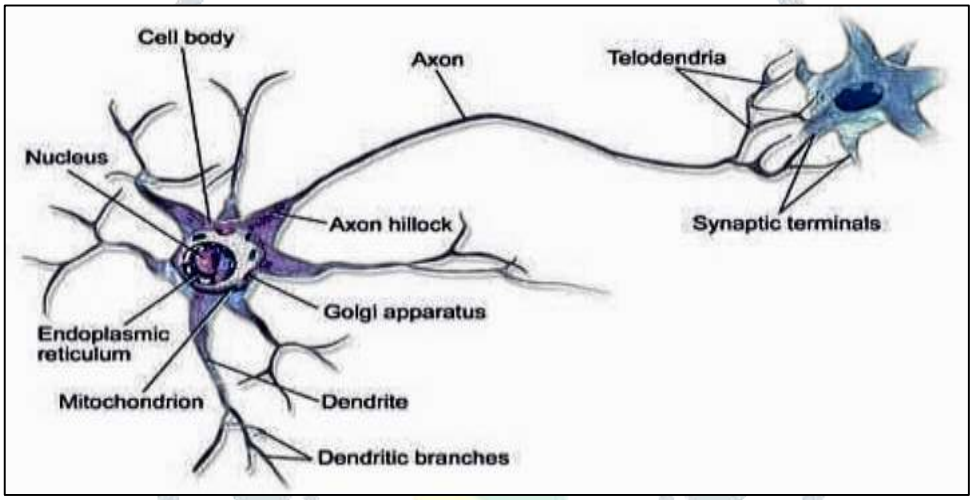

Figure 1- Structure of Neuron

On an average human brain consists of hundred billion of interconnected neurons made up of cell body including nucleus (controls cell activity), dendrites (transfer the signals into the cell), and axon (carry the signal away from the cell). The generated impulse passes through axon towards the synapse and is transferred to other neurons. That leads to formation of an organized network and helps in sending and receiving the impulse and results in quick-witted brain that has ability to learn, predict and recognise [7]. ANN consists of artificial neurons (connected parallel) and weighs also called synaptic strength that helps to emulate the nervous system. Neural networks have capability of establishing the relation between the input and output data without prior assumptions or knowledge about the given data set that makes it suitable for regression and classification tasks which plays a vital role in many biomedical applications. Conventional methods for analysing the data is linear but neural network are non-linear (inherently) that makes it practicable for preparing models of complex data accurately. Hence, ANN can be used to solve many problems in biomedical and healthcare sector [8]. This project aims on demonstrating the successful and innovative application of Artificial Neural Network in the pharmaceutical industries.

2. ARTIFICIAL NEURAL NETWORK

Artificial neural network (ANN) is a structured data processing system that operate by imitating the computational potential of the nervous system and deals with fuzzy circumstances containing irrelevant input data [2]. ANN is made up of neurons and weights also called synaptic strength. Neural network is a phrase that does not emphasis on the word 'neural' but on 'network'. Artificial neurons are networked or connected plays vial role instead how each neuron functions [10]. Nevertheless, ANN have functional resemblance to biological neurons but are more simplified and hence the similarity between biological neuron and artificial neuron is merely superficial. ANN can be described as a black box using parallelly connected arithmetic units to process the multiple input data to give the useful output. Interestingly, ANN can be applied to describe both linear and nonlinear relations in the given data set, but works is more efficient when the data exhibit nonlinear relation. Initially, it's difficult to identify the type of relation (linear or nonlinear) existing, which necessitate the use of certain statistical methods for data interpretation parallel to ANN [10].

2.1. Goals of ANN in analytical chemistry are:

- Selecting the useful information from the large volume of pre-existing data
- Separation of unknown set of samples from pre-defined classes
- Identifying the measurement space of the sample
- Preparation of models (direct as well as inverse) to predict the behaviour of unknown quantitatively

2.2. Artificial Neuron

The concept of artificial neuron was introduced by Pitt and McCulloch in 1943. Artificial neuron also known as node or unit is the functional unit of ANN, exhibiting following functions:

- Receiving the impulse or signals
- Multiplying or amplification of the signals using appropriate weights (connection strength)
- Sums up the amplified signals and passes via an activation function.
- Gives the processed output to other nodes [2].

Nodes accepts various signals (x_i) from neighbouring nodes and process them in pre-determined way and based on the processed output, the next neuron (j) decides whether to give the output (y_j) or not. If the output signal is triggered it can be in different form for example 0 and 1 (while dealing with binary) or can exhibit a real value (value in between 0 and 1). The nodes calculate the result from the matrix-dimensional vector (input) X, f(X) is consisting of 2 parts, first estimates the 'net input' whereas, the second part transfers the net input in a nonlinear fashion to produce the output 'y'. Calculation of net input is a linear combination of various variables, x_1, x_2, x_3, --x_i--x_m ($\sum x_i$), multiplied with constant (w_{ji}) know as weights and can be calculated using equation (1). Whereas the 2nd function is used to transfer the signals via axon to the dendrites of another neuron.

$$Net_j = \sum_{i=1}^{m} w_{ji}\, x_i + w_{j0} = w_j x + b \qquad \text{-------(Equation 1)}$$

Where, Net_j = Net input
w_{ji} = weights (coefficient)
w_{j0} or b = bias (weight having input signal +1)

Netj is used further for transfer function

$$y_j = out_j = 1/\{1 + \exp[-\alpha_j (Net_j + \theta_j)]\} \qquad \text{--------(Equation 2)}$$

Weights (w_{ji}) in nodes resembles the synaptic strength between the axons transferring the signals and receiving dendrites and hence decides what part of the received signals will be transmitted further [10].

The brain gains the knowledge by constantly adapting the synapses of various input signals and hence providing better results i.e., gives appropriate response to the body. Similarly, the nodes (artificial neurons) in ANN adapts the synapse strength by repetitive adaptation of weights in nodes depending on the difference between the obtained output (y_j) and desired output (t_j). The transfer function can be represented in three ways:

- Binary threshold function
- Sigmoidal function
- Radial function

The type of transfer chosen for one neuron is applied to all the neuron regardless of the network pattern. Weights and variables that directs the positioning of threshold value (θ_j) and slope (α_j) of transfer function are used as functional variables and not the parameters that changes during training and learning process. According to equation (2) θ_j is the parameter that defines the Net_j for which the node is highly selective, whereas α_j determines the slope of transfer function (except the threshold function) [10].

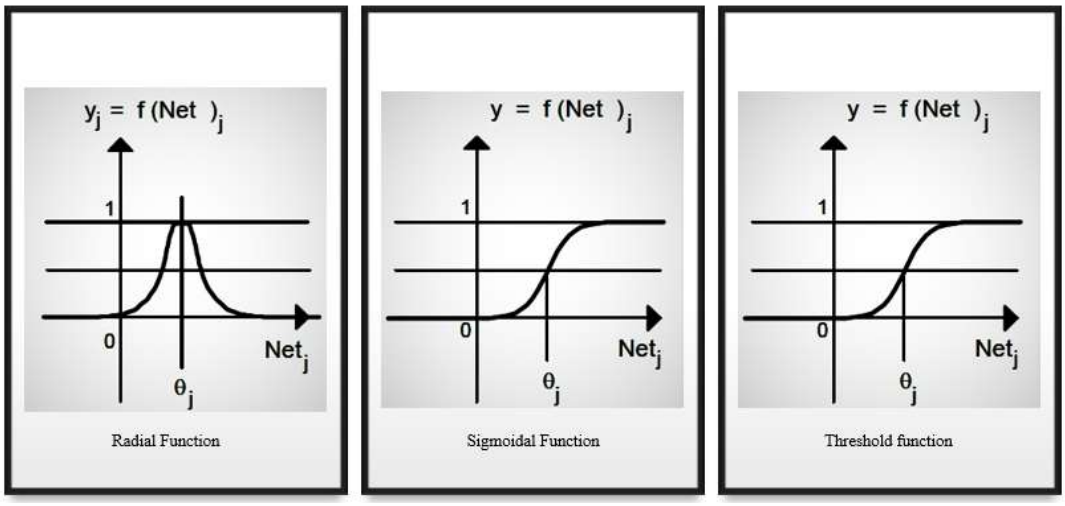

Figure 2- Different forms of transfer function.

2.3. Neural Network Model

When the number of artificial neurons is assembled, they lead to formation of network which can be stimulated by computer and the network is called Artificial Neural Network (ANN). Artificial neurons are arranged in specific pattern to form neural network model and till date various models have been proposed depending on the mode of operation and topology. According to Horne and Hush (1993), and Lippman (1987) every model follows seven concepts (majorly):

- Processing unit
- Activation function
- Network topology
- Transfer function
- Set of rules for continuous functional update of each neuron
- Information feeding system
- Learning and network modification methods

Widely used method is to arrange the nodes in series and forming layers consisting of the uppermost layer is called input layer and the final layer called output layer. Also, in some model intermediate layer is present between the input and output layer known as hidden layer (can vary in number) [2]. Where, the input units present in the input layer is equivalent to the number of independent variables and the output is proportional to the number of predicted values but there is no such rule to determine the number of optimum hidden unit(s) or layer(s). Neural network with lesser hidden unit than the required lead to insufficient input and output mapping, while overloading lead to generalization of the data. Hence it become necessary to use appropriate number of hidden layer(s) and are determined based on hit and trial method [2].
The training rules used for learning process in ANN are specifically of two type:

- Supervised
- Unsupervised

In supervised training, for every input there exist a corresponding known output and the weights are adjusted by utilizing the known input-output sets and after completion of training procedure, an output is produced in response to unknown input. Although in unsupervised method of training the weight adjustment is done in accordance to input pattern (without any known correlated output), also, the network is trained for classification of the analogous input into various categories. Such learning rules are effective in situations where known output does not exist [2]. Neural network model permits the what if approaches and investigates them in all possible ways and more effective when combined with other technologies such as genetic algorithms and fuzzy logics. Fuzzy logics are widely used when the desired properties are contradictory e.g. hard but quickly disintegrating tablets. Neuro-fuzzy logic is an innovative approach to combine the abilities of ANN (i.e. learn from data) and fuzzy logics (i.e. simplification of complex data) more efficiently that ease the information mining, also provides functional rules and guides for future work [12].

3. APPLICATION OF ANN IN PHARMACEUTICAL PROCESSING

Artificial neural network model is a promising tool for analysing the process parameter in correspond to current parameters when the situation becomes out of hand while processing and helps in enhancing the quality of product while taking care of the process. Some cases have been listed below where ANN has proved its potential.

3.6. Prediction of Size of Polymeric Nanoparticle and Surface Area of Microspore:

Polymeric nanoparticle has various advantages with respect to drug administration and drug targeting, but the preparation of polymeric nanoparticle includes multiple variables or factors that determines the character of final product. Hence, multiple batches are prepared to acquire nanoparticle with desired properties, which is time consuming and requires lots of

effort. Since, the level of a particular variable is changed (keeping other variables constant) [14]. Traditional statistical techniques are poor in prediction and calls for an effective method.

A study conducted by Ne´ vine Rizkalla and Patrice Hildgen emphasize that ANN can be used as a potential tool in combination with genetic algorithm and polynomial regression analysis in predicting the two relevant properties: surface area of micropore and nanoparticle (NP) size to acquire the desired drug release fashion from the PLA (polyacetic acid) nanoparticle. Two ANN models used were:

- Neuro-shell 1 Predictor: The Neuro Shell 1 utilises pre-determined black box (i.e. feed-forward network) and genetic algorithm is used to find the suitable weights to obtain better output.
- Neuro-Solution 1: It helps to determine the topology of the neural network, learning algorithms, quantity of hidden nodes and iteration, and transfer function. NeuroSolutions1 consist of two software Excel D AND Neural-Builder D for data processing and determining the configuration of the model, respectively.

Table 1- Experimental Design Used for the Modelling Study and NP Size Experimental Data

Batch Number	Polymer Concentration (%w/v)	Pressure	PVA Concentration (%w/v)	NP Size (nm)
1	5	5000	0.1	295.3
2	5	5000	0.5	225.5
3	5	5000	1	141.3
4	5	10000	0.1	214.5
5	5	10000	0.5	177
6	5	10000	1	137.8
7	5	15000	0.1	229
8	5	15000	0.5	178.1
9	5	15000	1	128.2
10	5	20000	0.1	205.4
11	5	20000	0.1	176.3
12	5	20000	1	152.4
13	7.5	5000	0.1	387
14	7.5	5000	0.5	197.1
15	7.5	5000	1	169.8
16	7.5	10000	0.1	343.3
17	7.5	10000	0.5	197
18	7.5	10000	1	158.1
19	7.5	15000	0.1	290.6
20	7.5	15000	0.5	196.8
21	7.5	15000	1	153.2
22	7.5	20000	0.1	413.6
23	7.5	20000	0.5	188.5
24	7.5	20000	1	173.4
25	10	5000	0.1	545.2
26	10	5000	0.5	211.8
27	10	5000	1	192.6
28	10	10000	0.1	502.2
29	10	10000	0.5	194.4

30	10	10000	1	183.5
31	10	15000	0.1	437.9
32	10	15000	0.1	219.4
33	10	15000	1	178.9
34	10	20000	0.1	500.2
35	10	20000	0.5	214.9
36	10	20000	1	178

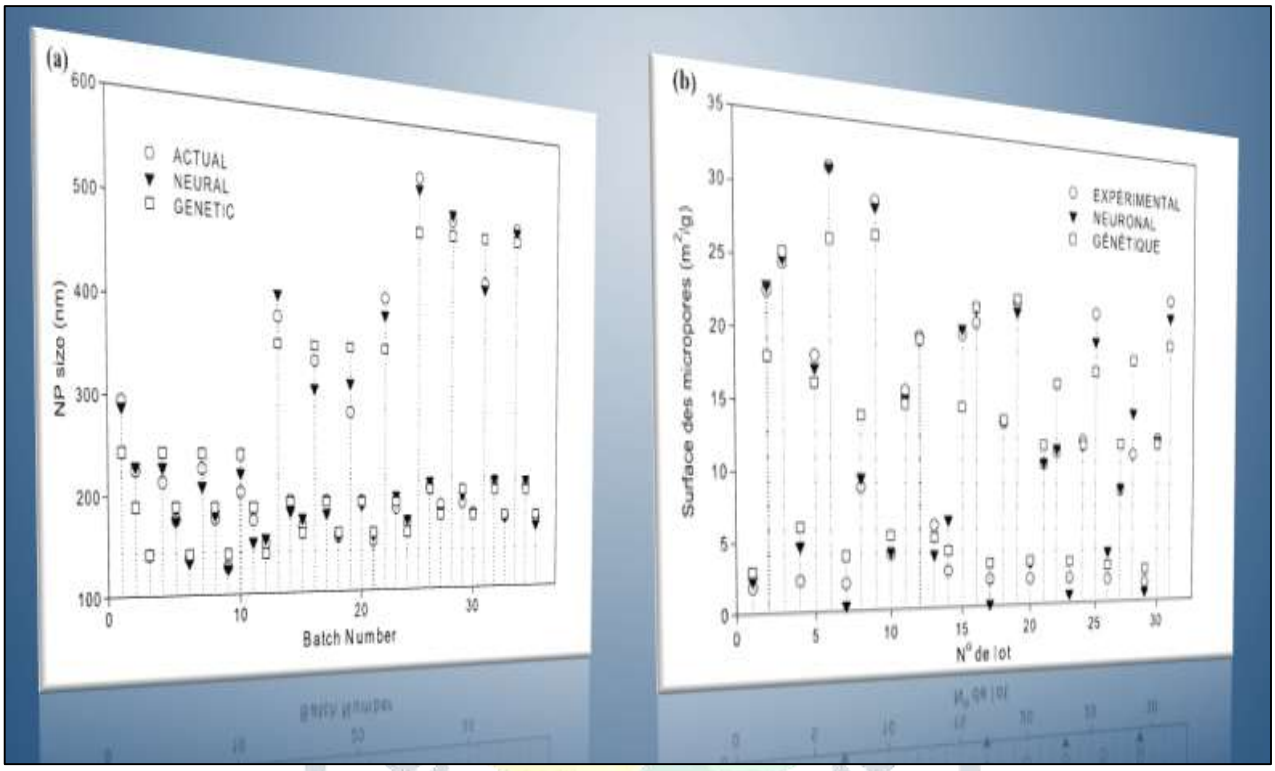

Figure 3- Comparison between Predicted and actual data: (a) Nanoparticle size; (b) Microspore surface area

The results obtained from each ANN model was then analysed and compared with the results obtained from polynomial regression analysis. The predicted output acquired from ANN models were nearer to experimentally obtained values than the output obtained from PR analysis. Besides, the results produced by Neuro-Solution network shows that utilization of flexible programme instead of black-box is more beneficial as it enables the use of various parameters to different problems appropriately [14].

3.6. Molecular Modelling and QSAR (Quantitative Structure Activity Relationship)

For the first time Louis Hammett established the relation between the electronic properties of organic bases and acids with their corresponding reactivity and equilibrium constant. After that, many attempts were made to develop a mathematical model to correlate the structures. It is believed that molecular structure of a compound is responsible for its biological activity, this is forming the base of QSAR modelling. QSAR help in describing the physico-chemical properties of a compound such as electronic properties, topology, solubility etc. Determination of such properties experimentally require lot of time with high error risk. In QSAR firstly the chemical structure is represented mathematically which are then used determine the best suited descriptor subset which encode for the properties being investigated. Investigation of every possible combination is time consuming and calls for evolution of better computational method. Genetic Algorithm is a computational model that optimises the data by selecting and recombining process to produce appropriate output (sample points). The function of GA is enhanced when coupled with Artificial Neural Network. As soon as the descriptor subset is determined the descriptor mapping is done by non-linear computation via neural network with respect to desired property [7].
In recent studies the ANN based QSAR model was used to predict and explore every possible pharmacological potential of analogues of capsaicin (not attained so far) by analysing their structure. The structure of Capsaicin can be divided into 3 regions:

- Region A- Base structure is benzene and can be substituted with various groups including methoxy, hydroxy etc
- Region B- Connects region A to C and is responsible for bonding interactions and integrity of structure. The length can increase unto 5 atoms.
- Region C- It is an end tail (composite of B and C). It can be aliphatic as well as aromatic in nature depending upon the components. The sub-structures present in this region is responsible for the lipophilic character [19].

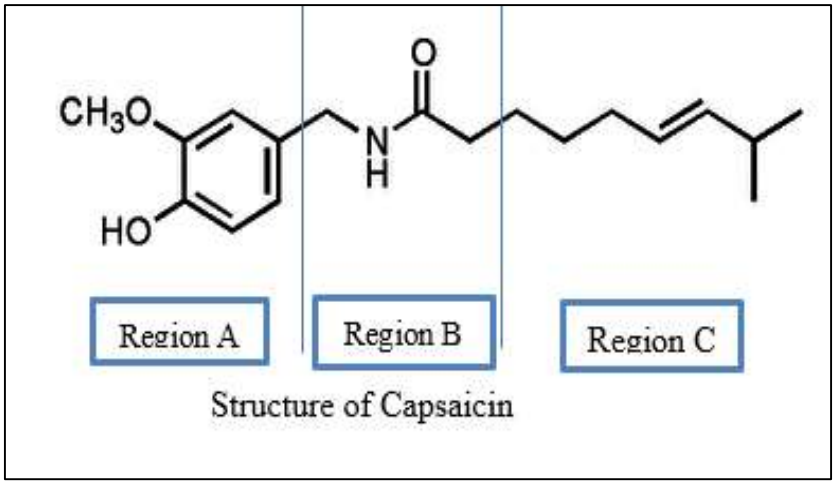

Figure 4- Structure of Capsaicin

A 3 layered back propagation neural network Bioactive net was used to carry out the study. The ANNs were designed in such a way that for every ANN model the input layer (exhibiting input parameters) was having different number of nodes or neurons, with hidden layer consisting of 2 nodes and a single node in output representing the measured activity in the form of logEC50 value. During the training and learning period the results were cross validated for accurate results. The trained ANNs were further used for final prediction of biological activity [19].

Table 2- Training procedure

Method to obtain output	Inverse scaling
Transfer function used	Sigmoidal
Learning Cycle	Varying in between 7000-20000

ANN for the analysis of whole compound representing 103 compounds was trained using 34 input parameters. It classified active compound (58/60) and inactive compounds (36/43) appropriately [19].

Table 3- Result Obtained where RT-Mean correlation (during training), SET-Standard deviation/ error between predicted and known activity (during training), RCV- Mean correlation (during cross-validation), SECV- Standard error (during cross-validation), RCV* and SECV*- indicates the values when outlier compounds (inappropriately classified) were removed.

Region	RT	SET	RCV	SECV	Accuracy%	RCV*	SECV*
Region A	0.984	0.254	0.899	0.617	89	0.97	0.351
Region B	0.99	0.194	0.93	0.519	96	0.945	0.474
Region C	0.954	0.457	0.827	0.856	93	0.894	0.647
Whole Compound	0.961	0.42	0.854	0.796	91	0.926	0.571

QSAR based ANN model classified 91% of the Capsaicin activity precisely. Moreover, the 8 compounds which were not used during training purpose, 7 of them were correctly classified. This shows that ANN has exceptional potential to predict the biological activity of the compound by analysing their structure and physico-chemical descriptors [19].

3.6. Induction Hardening Process:

Induction heating or hardening is a process in which utilises the heat induced when a high frequency alternating current is passed through the metallic surface under the appropriate electro-magnetic condition and lead to hardening of metallic surface (i.e. During the whole process at first transforms the upper most layer is transformed to austenite (at above750° C) and then due to quenching (at pre-determined rate) austenite is transformed to martensite. This makes the steel more brittle [17].

Martensite

Tempering

Allow the structure to relax to an equilibrium state
Which is hard and strong but not brittle.

Honeywell Sensing and Control conducted the design of experiment (DOE) in which they investigated 4 parameters i.e., coil height (it is the distance from the part to coil channel), part temperature (time at which the metal part leaves the channel), motor speed (distance via which the metal travels the coil), and quenching distance (distance from carousel to quenching solution). These four parameters are mainly responsible for the hardness of metal and there exist a non-linear relation between part temperature and motor speed. Hence neural network can be used for investigation and for the sake of same an automated closed loop ANN framework was developed. The network was consisting of 2 backpropagation networks and Brain-Maker software was used. The prediction network was designed in such a way that there were two input layer, three hidden and one output layer with 30 set of data for training and 15 for the testing purpose and 5% tolerance limit was determined during training procedure [17].

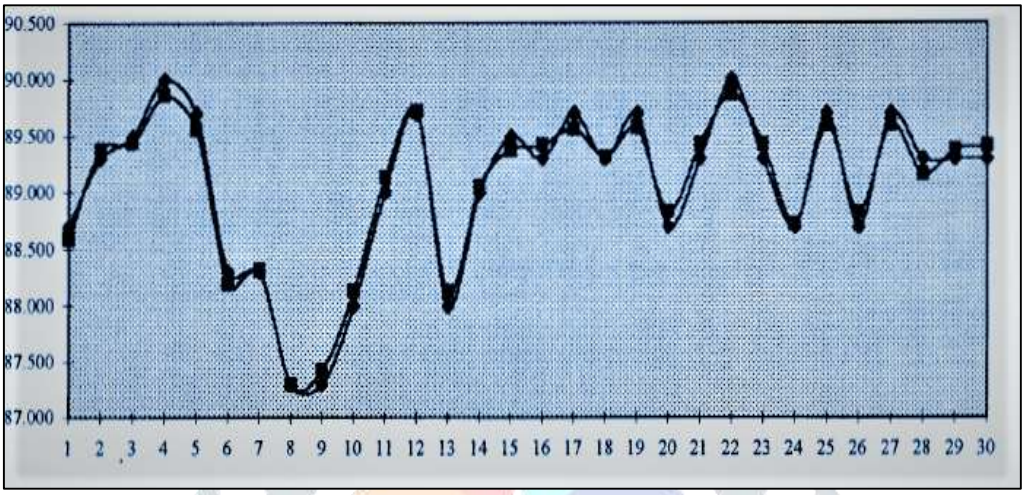

Figure 5- Predicted data (trained) -■Predicted hardness versus ●Actual Hardness (using backpropagation ANN method)

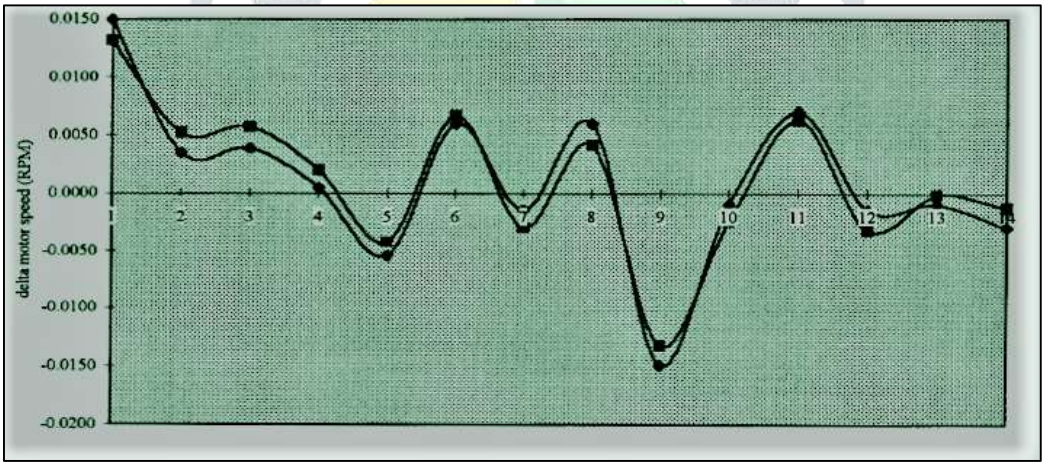

Figure 6- Predicted data (trained)-■Predicted motor speed versus ●Actual motor speed (using Feedback neural network)

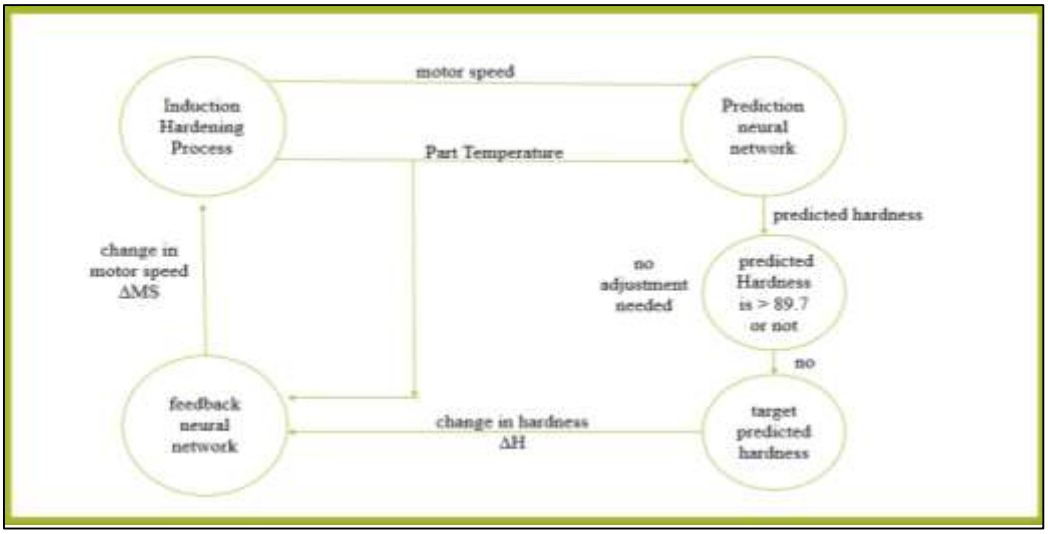

Figure 7- Automated ANN Process Control System

Use of such process presents two significant benefits:

- Enhanced product quality
- In hand control of the process.

The results show that the ANN can be used to predict and investigate design the experimental models of manufacturing processes where the relationship is non-linear.

3.6. Determination of Pharmacokinetic Parameters:

Most of the leading drug molecules recognised for clinical trial are unable to make it to the market. The new competitive drug molecule being introduced in the market should exhibit high potential, selectivity and economical (though-out the process) then the already available drugs. But the problem is high risk of failure during the clinical trials which may be either due to lack of human efficiency or pharmacokinetic parameters (ADME). It is observed that in many cases the poor ADME is the cause of drug failure. Hence, it necessitates the identification of problems that might occur before going for expensive drug development phases further [23]. Moreover, the drug choice and dose is determined by pharmacodynamic and pharmacokinetic parameters and lack of such information which may lead to lack of desired pharmacological effect. ANN possess great potential to predict the pharmacokinetic parameters due to its non-linear way of dealing with complex data. A study was conducted using ANN in which the multiple pharmacokinetic properties of 20 cephalosporins by analysing their QSPkR (quantitative structural-pharmacokinetic relationship).
Cephalosporins collected (20) were classified into validation and working subset and 133 descriptors were produced for every molecule based on their structure. The generated descriptors were used as inputs for the neural network models. During the study correlation (linear dependence of one descriptor on another) was determined and it was observed that the predicted behaviour of the drug molecule was close to the ones experimentally calculated. Further, the sensitivity report showed that the influence or effect of descriptor on an output does not depend on its effect on others e.g. effect of molar volume on clearance (CL), renal clearance CLR, unchanged drug fraction excreted via urine (fe), volume (V). Whereas, had negative on drug fraction bound (fb) to plasma and half-life ($T_{1/2}$).
Mathematically,
Half-life ($T_{1/2}$) = ln2.V/CL
According to above equation for every negative impact on half-life there must be a corresponding impact on (V) but this do not happen. As all the descriptors have different influence on every pharmacokinetic parameter [23].

3.6. ANN for Analysis of Active Pharmaceutical Ingredients:

ANN can be used for qualitative as well as quantitative analysis multivariate calibration of data related to the APIs and raw material generated with an aid of advanced analytical technologies such as chromatography, spectroscopy etc. Such analysis helps in determination and identification of API from the mixture of compounds. In pharmacy the crystalline form and nature of API, purity, and stability determines the solubility, shelf-life, bioavailability, density and vapor pressure of the compound. Due to this, various attempts have been made to find the appropriate technique to identify and analyse various crystalline forms from the mixture of component [26-29]. During the investigation it was found that neural network can be used to quantify, characterise and identify the crystalline form of the drug being investigated on the basis of appropriate data generated while processing via modern technologies such as Raman spectroscopy, DRIFT spectral pattern, attenuated total reflectance (FTIR- spectral pattern), X-ray diffraction pattern and with the help of neural network models it was demonstrated that the signals produced by the mentioned analytical method were proportional to the quantity of crystalline drug forms occurring in the sample. Additionally, the complex and lengthy procedure was simplified and made easy to perform with the help of ANN models [26-29].
ANN models as supporting methods are also applicable in various analytical techniques such as high-performance liquid chromatography (HPLC), UV-visible spectrophotometry, fluorescence spectra [43] etc. A study was conducted to use the

ANN in HPLC technique for response-surface modelling for the separation of methyclothiazide and amiloride. Where, percentage of methanol (in mobile phase) and pH were considered as input (independent variables) and capacity factor was the output. The analysis was done by 2 ways:

- Neural network-based analysis (via backpropagation)
- Regression Analysis

From the study it was observed that the predicted output responses obtained from ANN models were more accurate when compared to the responses from regression analysis [25].

3.7. ANN in Optimization and Evaluation Modified Released Drug Delivery System:

Modified released drug delivery system has many significant benefits over conventional mode of drug delivery such as reduced dose frequency and side effects, prevents dose fluctuation, localised delivery of the drug. The conditions required to maintain the drug release rate (in-vivo) for the modified release is complex and full of challenges. In 2002 dynamic ANN model was used to determine the drug release profile from the controlled drug released system [32]. Similarly, a study was conducted for designing a formulation space for optimizing the drug release profile as well as mechanical properties of matrix released tablets by using dynamic neural network [31].

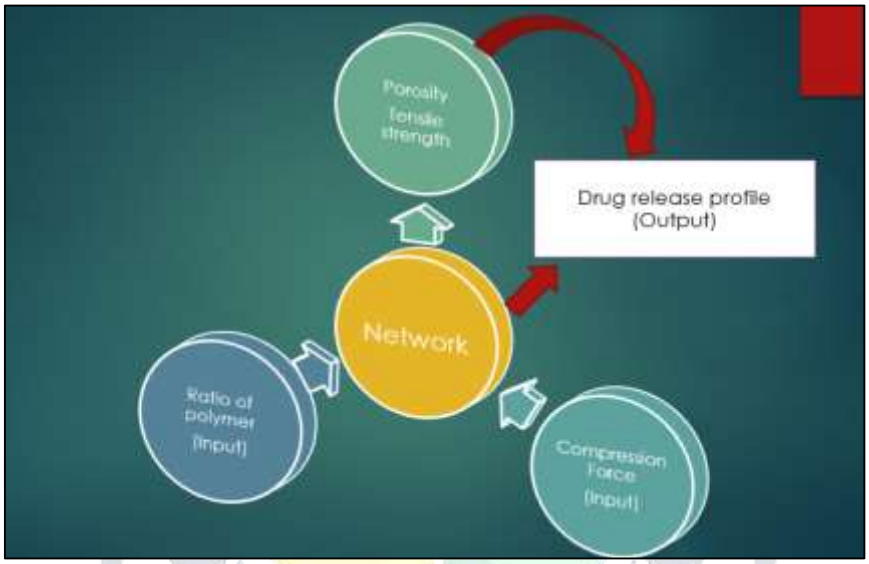

Figure 8- Representation of Input-Output for optimization of matrix tablet

The main objective of the study was to find out the correlation between the input and output variables. Four dissolution models were prepared for predicting the dissolution time in in-vitro conditions and it was observed that all the four ANN models gave the reasonable and positive prediction result.

4. CONCLUSION

This review article emphasise that Artificial Neural Network is an innovative approach which can be used as a powerful tool in finding the solution of complex problems that are encountered during the processing in pharmaceutical industries. Till date lots of work and experiments have been conducted to explore the potentials of artificial neural network. Neural network when combined with other machine learning programmes including genetic algorithms, fuzzy logics, SOM (self-organizing maps) etc then the network becomes more efficient. The major limitation of ANN models is that they require high volume of data set as the predictions made by neural network depends upon amount of available data and needs to be trained before the use but with appropriate training and learning process it shows positive and useful results. Additionally, it reduces the risk of process failure, time of experimentation and analysis, and benefits economically. It can be used to analyse any kind of data set where the non-linear relationships exist between the input and output data sets and leads to simplification of complex process. The exceptional recognising and robust ability to Classify make is promising tool presenting high potential in the field of pharmaceutical processing.

REFERENCES

[1]. Alfassi, Z. B., Boger, Z., & Ronen, Y. (2005). Artificial Neural Networks – Unlikely but Effective Tools in Analytical Chemistry [E-book]. In Statistical Treatment of Analytical Data (1st ed., pp. 172–262). Oxford, UK: Blackwell Science.

[2]. Teran, C. K., & Grotewold, D. (1996). Process optimization and control system that plots inter-relationships between variables to meet an objective (United States Patent 5521814). Washington, DC: U.S. Patent and Trademark Office.

[3]. Krishnaveni, C., Arvapalli, S., Sharma, J. V. C., & K, D. (2019). ARTIFICIAL INTELLIGENCE IN PHARMA INDUSTRY-A Review. International Journal of Innovative Pharmaceutical Sciences and Research, 7(10), 37–50.

[4]. Peterson, J. J., Snee, R. D., McAllister, P. R., Schofield, T. L., & Carella, A. J. (2009). Statistics in pharmaceutical development and manufacturing. Journal of Quality Technology, 41(2), 111-134.

[5]. Aksu, B., Paradkar, A., de Matas, M., Özer, Ö., Güneri, T., & York, P. (2012). Quality by design approach: application of artificial intelligence techniques of tablets manufactured by direct compression. AAPS PharmSciTech, 13(4), 1138-1146.

[6]. Davenport, T., & Kalakota, R. (2019). The potential for artificial intelligence in healthcare. Future healthcare journal, 6(2), 94.

[7]. Agatonovic-Kustrin, S., & Beresford, R. (2000). Basic concepts of artificial neural network (ANN) modeling and its application in pharmaceutical research. Journal of pharmaceutical and biomedical analysis, 22(5), 717-727.

[8]. Begg, R., Kamruzzaman, J., & Sarkar, R. (2006). Neural networks in healthcare: potential and challenges. Igi Global.

[9]. Sable, P., & Khanvilkar, V. V. (2018). Pharmaceutical Applications of Artificial Intelligence. Int. J. Pharma. Res. Health Sci, 6, 2342-2345.

[10]. Zupan, J. (1994). Introduction to artificial neural network (ANN) methods: what they are and how to use them. Acta Chimica Slovenica, 41, 327-327.

[11]. Basheer, I. A., & Hajmeer, M. (2000). Artificial neural networks: fundamentals, computing, design, and application. Journal of microbiological methods, 43(1), 3-31.

[12]. Ibrić, S., Đurić, Z., Parojčić, J., & Petrović, J. (2009). Artificial intelligence in pharmaceutical product formulation: neural computing. CICEQ-Chemical Industry and Chemical Engineering Quarterly, 15(4), 227-236.

[13]. M. Ankith, SP Teja Surya, N. Damodharan (2018). ARTIFICIAL NEURAL NETWORKS: FUNCTIONINGANDAPPLICATIONS IN PHARMACEUTICAL INDUSTRY. International Journal of Applied Pharmaceutics, 10(5), 28–33.

[14]. Rizkalla, N., & Hildgen, P. (2005). Artificial neural networks: Comparison of two programs for modeling a process of nanoparticle preparation. Drug development and industrial pharmacy, 31(10), 1019-1033.

[15]. Sabzian, H., Kamrani, E., & Hashemi, S. M. S. (2018). A Neural Network Model for Determining the Success or Failure of High-tech Projects Development: A Case of Pharmaceutical industry. arXiv preprint arXiv:1809.00927.

[16]. Almhdi, K. M., Valigi, P., Gulbinas, V., Westphal, R., & Reuter, R. (2007). Classification with artificial neural networks and support vector machines: application to oil fluorescence spectra. EARSeL eProceedings, 6(2), 115-129.

[17]. Saikin, S. K., Kreisbeck, C., Sheberla, D., Becker, J. S., & Aspuru-Guzik, A. (2019). Closed-loop discovery platform integration is needed for artificial intelligence to make an impact in drug discovery.

[18]. Stich, T. J., Spoerre, J. K., & Velasco, T. (2000). The application of artificial neural networks to monitoring and control of an induction hardening process. Journal of Industrial Technology, 16(1), 1-11.

[19]. Hosseini, M., Maddalena, D. J., & Spence, I. (1997). Using artificial neural networks to classify the activity of capsaicin and its analogues. Journal of chemical information and computer sciences, 37(6), 1129-1137.

[20]. Holzinger, A., Langs, G., Denk, H., Zatloukal, K., & Müller, H. (2019). Causability and explainability of artificial intelligence in medicine. Wiley Interdisciplinary Reviews: Data Mining and Knowledge Discovery, 9(4), e1312.

[21]. Turner, J. V., Cutler, D. J., Spence, I., & Maddalena, D. J. (2003). Selective descriptor pruning for QSAR/QSPR studies using artificial neural networks. Journal of computational chemistry, 24(7), 891-897.

[22]. Vamathevan, J., Clark, D., Czodrowski, P., Dunham, I., Ferran, E., Lee, G., ... & Zhao, S. (2019). Applications of machine learning in drug discovery and development. Nature Reviews Drug Discovery, 18(6), 463-477.

[23]. Turner, J. V., Maddalena, D. J., Cutler, D. J., & Agatonovic-Kustrin, S. (2003). Multiple pharmacokinetic parameter prediction for a series of cephalosporins. Journal of pharmaceutical sciences, 92(3), 552-559.

[24]. Wesolowski, M., & Suchacz, B. (2012). Artificial neural networks: theoretical background and pharmaceutical applications: a review. Journal of AOAC International, 95(3), 652-668.

[25]. Agatonovic-Kustrin, S., Zecevic, M., Zivanovic, L. J., & Tucker, I. G. (1998). Application of artificial neural networks in HPLC method development. Journal of pharmaceutical and biomedical analysis, 17(1), 69-76.

[26]. Kachrimanis, K., Rontogianni, M., & Malamataris, S. (2010). Simultaneous quantitative analysis of mebendazole polymorphs A–C in powder mixtures by DRIFTS spectroscopy and ANN modeling. Journal of pharmaceutical and biomedical analysis, 51(3), 512-520.

[27]. Ibrić, S., Djuriš, J., Parojčić, J., & Djurić, Z. (2012). Artificial neural networks in evaluation and optimization of modified release solid dosage forms. Pharmaceutics, 4(4), 531-550.

[28]. Goh, W. Y., Lim, C. P., Peh, K. K., & Subari, K. (2002). Application of a recurrent neural network to prediction of drug dissolution profiles. Neural Computing & Applications, 10(4), 311-317.

[29]. Petrović, J., Ibrić, S., Betz, G., & Đurić, Z. (2012). Optimization of matrix tablets-controlled drug release using Elman dynamic neural networks and decision trees. International journal of pharmaceutics, 428(1-2), 57-67.

[30]. Kolisnyk, T. Y., Ruban, O. A., Fil, N. Y., & Kutsenko, S. A. (2018). Application of an Artificial Neural Network for Design of Sustained-Release Matrix Tablets Containing Vaccinium Myrtillus Leaf Powder Extract.

[31]. Fahmy, R., Kona, R., Dandu, R., Xie, W., Claycamp, G., & Hoag, S. W. (2012). Quality by design I: application of failure mode effect analysis (FMEA) and Plackett–Burman design of experiments in the identification of "main factors" in the formulation and process design space for roller-compacted ciprofloxacin hydrochloride immediate-release tablets. Aaps Pharmscitech, 13(4), 1243-1254.

[32]. Aksu, B., & Mesut, B. (2015). Quality by design (QbD) for pharmaceutical area. İstanbul Üniversitesi Eczacılık Fakültesi Dergisi, 45(2), 233-251.

[33]. Luo, J., Hu, J., Fu, L., Liu, C., & Jin, X. (2011). Use of artificial neural network for a QSAR study on neurotrophic activities of Np-tolyl/phenylsulfonyl L-amino acid thiolester derivatives. Procedia Engineering, 15, 5158-5163.

[34]. Sutariya, V., Groshev, A., Sadana, P., Bhatia, D., & Pathak, Y. (2013). Artificial neural network in drug delivery and pharmaceutical research. The Open Bioinformatics Journal, 7(1).

[35]. Sabzian, H., Kamrani, E., & Hashemi, S. M. S. (2018). A Neural Network Model for Determining the Success or Failure of High-tech Projects Development: A Case of Pharmaceutical industry. arXiv preprint arXiv:1809.00927.

[36]. Ramesh, A. N., Kambhampati, C., Monson, J. R., & Drew, P. J. (2004). Artificial intelligence in medicine. Annals of The Royal College of Surgeons of England, 86(5), 334.

[37]. Vyas, M., Thakur, S., Riyaz, B., Bansal, K. K., Tomar, B., & Mishra, V. (2018). Artificial intelligence: the beginning of a new era in pharmacy profession. Asian J Pharm, 12(2), 72-76.

[38]. Parojčić, J., Ibrić, S., Djurić, Z., Jovanović, M., & Corrigan, O. I. (2007). An investigation into the usefulness of generalized regression neural network analysis in the development of level A in vitro–in vivo correlation. European journal of pharmaceutical sciences, 30(3-4), 264-272.

[39]. Almhdi, K. M., Valigi, P., Gulbinas, V., Westphal, R., & Reuter, R. (2007). Classification with artificial neural networks and support vector machines: application to oil fluorescence spectra. EARSeL eProceedings, 6(2), 115-129.

[40]. Dearden, J. C., & Rowe, P. H. (2015). Use of artificial neural networks in the QSAR prediction of physicochemical properties and toxicities for REACH legislation. In Artificial neural networks (pp. 65-88). Springer, New York, NY.

[41]. Landin, M., & Rowe, R. C. (2013). Artificial neural networks technology to model, understand, and optimize drug formulations. In Formulation Tools for Pharmaceutical Development (pp. 7-37). Woodhead Publishing.

[42]. Nagy, B., Petra, D., Galata, D. L., Démuth, B., Borbás, E., Marosi, G., ... & Farkas, A. (2019). Application of artificial neural networks for Process Analytical Technology-based dissolution testing. International journal of pharmaceutics, 567, 118464.

[43]. O'Connor, T., & Lee, S. (2017). Emerging technology for modernizing pharmaceutical production: continuous manufacturing. In Developing Solid Oral Dosage Forms (pp. 1031-1046). Academic Press.

[44]. Das, M. K., & Chakraborty, T. (2016). ANN in Pharmaceutical Product and Process Development. In Artificial Neural Network for Drug Design, Delivery and Disposition (pp. 277-293). Academic Press.

[45]. Gupta, M. K., Gupta, S., & Rawal, R. K. (2016). Impact of artificial neural networks in QSAR and computational modeling. In Artificial Neural Network for Drug Design, Delivery and Disposition (pp. 153-179). Academic Press.