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GENERALIZED ARTIFICIAL NEURAL NETWORK MODELLING AND ITS APPLICATION IN PERFORMANCE PREDICTION OF SUSTAINED RELEASE MONOLITHIC TABLETS

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ABSTRACT: Artificial Intelligence is the simulation of human intelligence. From delivering simple groceries to doorsteps to solving the toughest task in scientists' lab, it is surrounding human life in all the means. So how can the Pharma industry be untouched in the case of AI?! Artificial Neural Network (ANN) is a type of AI used to solve non-linear problems and predict the output for given input parameters from the training values. In this research work, such generalized ANN is developed to predict drug release from the sustained-release monolithic tablet. It is trained by the backpropagation method under supervised learning. This developed model is evaluated on the basis of RMSE, similarity and dissimilarity factors and can predict the output with the best achieved average error ~0.0095 and R^2 0.9953. Such ANNs can be the best combination of experience and intelligence, which can eliminate tedious lab works that can be cost-effective and time-effective.

INTRODUCTION: Artificial Intelligence is an area of computer science dedicated to improvise and simplify our routine and difficult life hacks as well as definitely bringing some revolutionary changes in various fields. AI has entered to almost all fields, so Pharma field [1]. Continuous development of new pharmaceutical formulation besides regular troubleshooting in the existed formulation is a very crucial task for pharmaceutical industries. The performance of pharmaceutical products relies upon multiple factors, and it is not possible to predict product performance in complex formulation development.

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One has to rely on empirical outcomes to understand the product performance along with experience of decades to select appropriate ingredients along with processing conditions to, even, find starting step of right pathway to develop successful formulation. Traditionally, formulators use empirical method or statistical methods. However, such statistical methods can help in case of screening only and can mislead in the case of complex formulation development. For example, in case of numbers of formulation affecting factors more than five, very profound numbers of experiments are required to be performed [2, 3, 4]. So it becomes important to work in a smarter way by combining experience of ages and today's smart technology. Even ANN is becoming very handy in current pandemic condition from recognizing pattern of virus spread to predicting COVID report by pattern recognition and also effect of this pandemic on economy of world [5, 6, 7].

In such cases AI can be a helping hand. By using AI some models can be developed which actually mimic the biological brain and such models are called Artificial Neural Networks (ANN). They simulate the brain, learn, solve problems and draw conclusions. According to Dr. Robert Hecht-Nielsen, the inventor of one of the first neurocomputers "ANN is a computing system made up of number of simple, highly interconnected processing elements, which process information by their dynamic state response to external output" [8]. In Pharma field ANN model can be used at various stages of formulation and development of controlled release matrix tablet-like optimization of formulations and manufacturing processes [9, 10, 11].

What is ANN?? There are problem categories that cannot be formulated as an algorithm. Problems that depend on many subtle factors, for example the purchase price of a real estate which our brain can (approximately) calculate. Without an algorithm a computer cannot do the same. Therefore the question to be asked is: *How do we learn to explore such problems?* Exactly – we *learn*; a capability computer does not have. Humans have a brain that can *learn*. Computers have some processing units and memory. They allow the computer to perform the most complex numerical calculations in a very short time, but they are not adaptive all the times [12].

Artificial neural networks (ANNs) technology is a group of computer methods for modelling and pattern recognition, functioning similarly to the neurons of the brain. It is a computational system inspired by the Structure Processing Method Learning Ability of a biological brain. In the brain, inputs are received by biological neurons from external resources, they are combined (performing a non-linear operation) and then a decision is made based on the final results. There are many types of neural networks exists but all are having same basic principle i.e. to receive input, process them and execute the output [13]. ANNs are a type of "mathematical model" that simulates the biological nervous system and draws on analogues of adaptive biological neurons. **Table 1** shows terminologies comparison between Biological Neural Network (BNN) and artificial Neural Network (ANN). A major advantage of ANNs compared to statistical modelling is that they do not require rigidly structured experimental designs and can map functions using historical or incomplete data.

TABLE 1: COMPARISON OF TERMINOLOGIES BETWEEN BNN AND ANN

Biological Terminology	Artificial Neural Network Terminology
Neuron	Node/ Unit/ Neuron
Synapse	Connection/ Edge/ Link
Synaptic Efficiency	Connection Strength/ Weight
Firing Frequency	Node Output

ANNs are known to be a powerful tool to simulate various non-linear systems and have been applied to numerous problems of considerable complexity in many fields, including engineering, psychology, medicinal chemistry, and pharmaceutical research. They are good recognizers of patterns and robust classifiers, with the ability to generate when making decision based on imprecise input data [17, 14].

General Applications of ANN: [15, 16, 18, 19]

1. Pattern Classification Applications

- Speech Recognition and Speech Synthesis
- Classification of radar/sonar signals
- Remote Sensing and image classification
- Handwritten character/digits Recognition
- ECG/EEG/EMG Filtering/Classification
- Credit card application screening
- Data mining, Information retrieval

2. Control, Time series, Estimation

- Machine Control/Robot manipulation
- Financial/ Scientific/ Engineering Time series forecasting.
- Inverse modelling of vocal tract

3. Optimization

- Travelling sales person
- Multiprocessor scheduling and task assignment

4. Real World Application Examples

- Real Estate appraisal
- Credit scoring
- Geochemical modelling
- Hospital patient stay length prediction
- Breast cancer cell image classification
- Jury summoning prediction
- Precision direct mailing
- Natural gas price prediction
- In drug discovery: Quantitative Structure-Activity Relationship (QSAR), Quantitative

Structure Toxicity Relationship (QSTR), Virtual Screening (VS)

Applications of ANN in Pharmaceutical Product and Process Development: [20, 21, 22]

- In the modeling and optimization of pharmaceutical formulations
- In minimization of the capping tendency of tableting process optimization.
- In the prediction of the in-vitro permeability of drugs
- Optimizing emulsion formulation
- Determination of factors controlling the particle size of nanoparticle.
- ANN in tablet manufacturing.
- Investigation of the effects of process variables on derived properties of spray-dried solid dispersion.
- Quantitative structure Property relationship and Molecular Modeling.
- Molecular de novo design and combinatorial libraries.
- Validation of pharmaceutical processes.
- Modeling the response surface in HPLC
- Structure Retention Relationships in Chromatography.
- Pharmacokinetics.

Artificial Neural Network Structure: As biologically inspired computational model, ANN is capable of simulating neurological processing ability of the human brain. An average human brain contains about 100 billion neurons, with each neuron being connected with 1000-10,000 connections to others [23].

A single neuron consists of three major parts **Fig. 1**

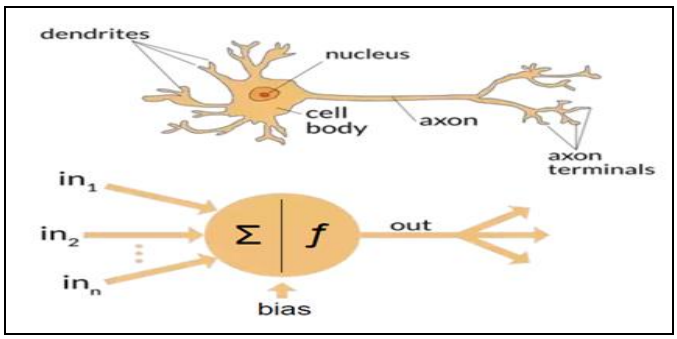

FIG. 1: A BIOLOGICAL AND AN ARTIFICIAL NEURON. (Via https://www.quora.com/What-is-the-differences-between-artificial-neural-network-computer-science-and-biological-neural-network)

- Dendrites (fine branched out threads)- carrying signals into the cell
- The cell body- receiving and processing the information
- The axon (a single longer extension) - carries the signal away and relays it to the dendrites of the next neuron or receptor of a target cell. The signals are conducted in an all-or-none fashion through the cells.

The arrangement of neurons to form layers and the connection pattern formed within and between layers is called network architecture.

Simulating BNN there are 3 layers in ANN which are as follows [24]

- ✓ **Input Layer:** It contains those units (artificial neuron) which receive input from the outside world on which network will learn, recognize, or otherwise process.
- ✓ **Hidden layer:** These units are in between the input and output layer. The job of the hidden layer is to transform the input into something that the output unit can use in some way. The hidden layer may be different for different types of networks.
- ✓ **Output layer:** It contains units that respond to the information about how it learns any task. An output layer depends on the outcome of the problem. The hidden layer then links to an output layer receives connections from hidden layers. It returns an output value that corresponds to the prediction of the response variable. The active nodes of the output layer combine and change the data to produce the output values.

Fig. 2 shows the basic architecture of ANN.

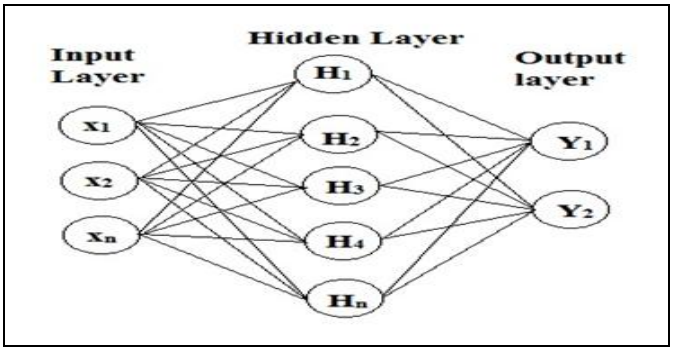

FIG. 2: ARCHITECTURE OF ANN

Weight and Activation Function: Weight is a parameter of the network that transforms input data within the hidden layer. The training mode of model begins with arbitrary values of the weights - they might be random numbers – and proceeds iteratively. Each iteration of the complete training set is called an epoch. In each single epoch the network adjusts the weights in the direction so that to reduces the error. As the iterative process of incremental adjustment continues, the weights gradually converge to the locally optimal set of values. Many epochs are usually required before training is completed. So, generally, weights are parameters selected by the network itself to reduce error while learning. Activation functions are mathematical equations that determine the output of a neural network. This function is attached to each neuron in the network and determines if it should be "fired" or not depending on whether neuron's input is relevant for model's prediction. There are different types of activation functions like Sigmoid, Hyperbolic Tangent, Softmax, Softsign, Rectified Linear Unit, Exponential Linear Unit, *etc*.Types of ANN models can be classified into various categories based on different parameters [25, 26, 27,] which are shown in **Table 2**:

TABLE 2: TYPES OF ANN MODEL BASED ON VARIOUS PARAMETERS

Parameter	Types
Based on their function	Prediction Neural Network / Nonadaptive Network Clustering Neural Network / Feature Extracting Network Association Neural Network
Based on nature of weights	Fixed, Adaptive
Based on learning	Feed forward, Recurrent
Based on Memory unit	Static, Dynamic
Based on development of networks	Single layer, Multi-Layer
Miscellaneous	Hopfield network ,Stochastic neural network ,Modular neural network, Radial basis function neural network, Kohonen self-organizing neural network, Convolutional neural networks, Boltzmann machine network, Long Short-Term Memory Units (LSTMs)

How does a Model *"learn"*? The learning process is human intelligence. This ability permits us to acquire various skills and expertise in numerous fields with reference to changing environments.

Our reactions rather say outputs in different - different conditions are totally based on some previous experiences or inputs.

So, implementing these learning capabilities in machines and predicting the outputs by them is the central goal of Artificial intelligence. Based on the topology, the connection of ANN could be feedback and feed-forward [28, 29].

Feedback or Recurrent ANN Model: There are cycles in the connections. The feedback model first decreases error between predicted output and real output, and after that, it gives the final output.

In such ANN models, each time an input is presented, the ANN model must iterate for a potentially long time before it produces a response.

Feedback ANN models are usually more difficult to train than feed-forward ANN models. Here the network learns by Backpropagation or Delta rule.

Feedforward ANN Model or Acyclic Network: the connections between the nodes do not form cycles. Feedforward network works on the bases of randomly assigned weigh values and apply the activation function and gives the output [30].

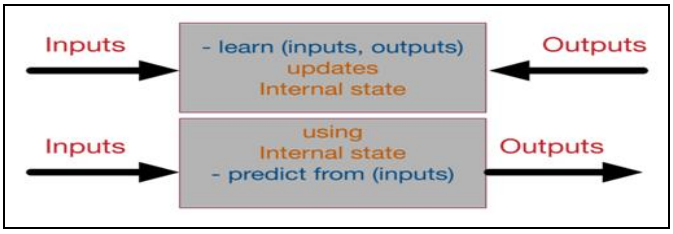

FIG. 3: FEEDBACK AND FEED-FORWARD MODELS

METHOD:

ANN Model Development: [31, 32] In this research work model is developed to predict drug release from SR monolithic tablet by using backpropagation supervised learning method which not possible by other simple statistical methods [33]. ANN model can learn the latent relationship between the causal factors (formulation variables) and response (*in-vitro* release characteristics) [34]. Artificial model development includes a number of operations like training, validation or testing. Such operations are as follows stepwise:

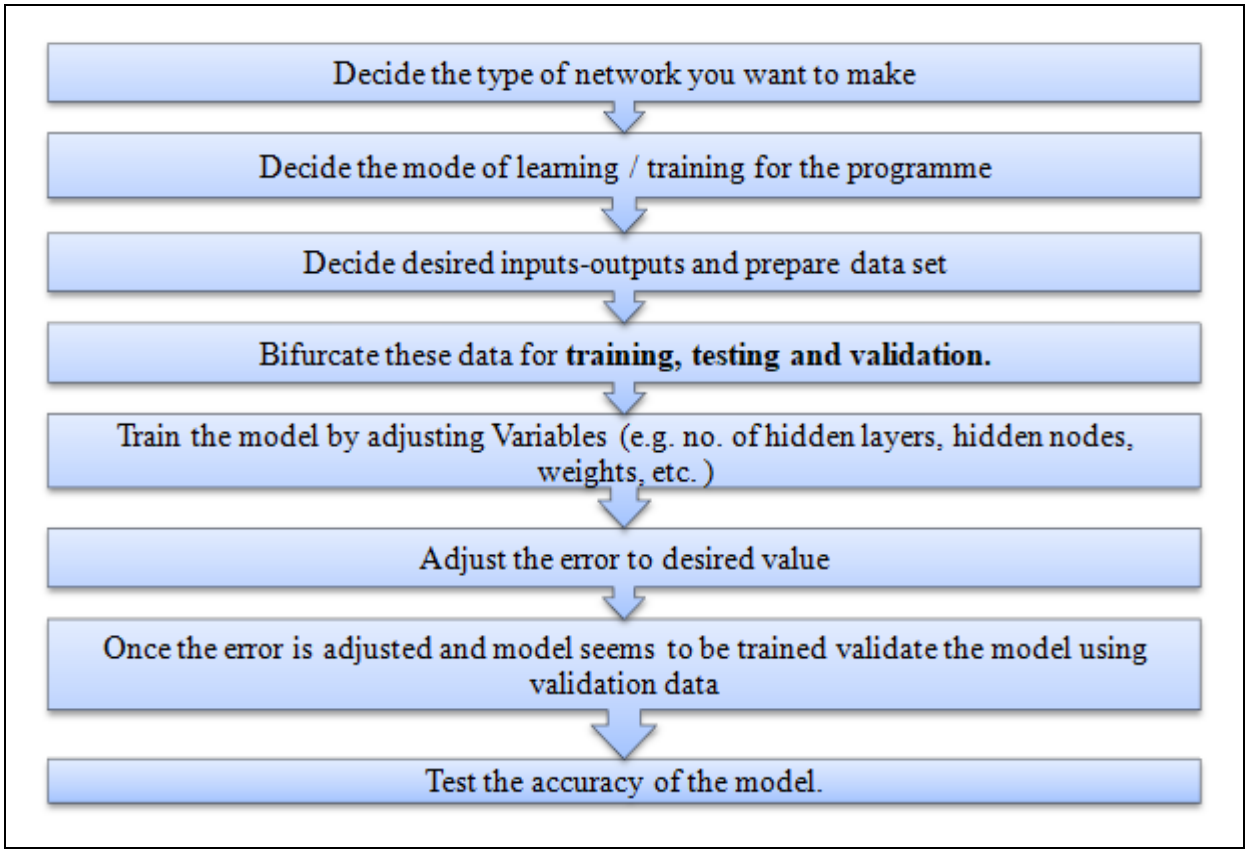

FIG. 4: HIERARCHY OF ANN MODEL DEVELOPMENT

As per hierarchy, we can select the type of network on the basis of the problem we want to solve. The present study aims to develop ANN model which a formulator can be used in the prediction of the SR tablet performance. Because of which there will be the elimination of course trial and error methods and even it can be useful instead of other statistical methods where there is number of runs that have to be performed because of a large number of dependent factors.

Data Gathering: Formulators have to develop their own data set to develop their own ANN model [35]. Model will be trained by data on principle of generalization [36]. Present study involves retrieval and compilation of data over experiments and granted patents pertaining to pharmaceutical formulation. This huge pool of data will be utilized for development of ANN model. Compilation of data from granted patents will vanish the need to perform number of experiments. Granted patents provide authenticated data, *per se.* However, data will be validated randomly by developing formulation from a collected data set. For these data set, data were developed and collected having selection criteria like Sustain release Monolithic tablets. From the total of 101 data collected. These formulation data contain characteristics of drugs and excipients like mol. Wt of the drug, log P and solubility of the drug as well as factors which can affect the dissolution profile of the formulation like pH of dissolution medium, USP apparatus number, RPM, drug to polymer ratio, total weight of tablet, *etc*. This data will be used as input nodes for the network, and the network will predict the performance of SR monolithic. Tablets in the form of time required to release 10%, 50%, and 80% release of the drug from formulations as output nodes [37, 38]. Data should be selected as such as it does not overfit or underfit the model.

Data Splitting: Generally 3 data set (training, validation, testing) splitting technique is used. Here we have used the software JUSTNN version 4.0b. This requires 2 set of data *i.e.* training and testing. From these dataset itself the software will learn for its validation and for tuning hyper-parameters to fit the best model with least error. The accuracy of the test set shows the prediction ability of unknown data and this strategy is widely adopted in machine learning [39, 40]. So, here 79 data were used for training and remaining was kept as testing dataset.

IFS: In various formulation problems, a large range of variables are available to train the network, but it is very much hard to define which of them are most relevant or useful [41]. This situation can be more confusing when there is interdependence or correlations between any of the variable. ANN can be used to rank which of the various formulation and processing variables are most critical in influencing the output parameter of interest because of its unique ability in spotting pattern in data. So the network is designed by considering the input feature selection. Input feature Selection is generally used to cop up with large number of irrelevant input features which may confuse the network unnecessarily during learning. The objective of IFS are manifold, the important ones being (1) to avoid overfitting and improve model performance, (2) to provide faster and more cost effective models, (3) to gain a deeper insight into the underlying process of data generation.

The software itself contains the feature of IFS on bases of which we can perform this task. Software suggested importance of inputs in this manner: Polymer 1 viscosity > Drug: Polymer 2 ratio > Drug Amount > Log P> Polymer 3 viscosity > Mol. Wt of drug > USP Apparatus > Tab wt > RPM > Drug: Polymer 1 ratio > pH of medium > Polymer 2 viscosity > Water solubility of drug > pKa > Drug: Polymer 3 ratio Following "remove one at a time" strategy and evaluating each model on bases of RMSE.

Comparison between actual outcome and predicted outcome is compared by means of root mean square error (RMSE). More the error is the dissimilarity between two results. So poor and less accurate the prediction is. So our target should be to decrease the RMSE [42, 43]. RMSE can be calculated by using following equation:

$$RMSE = \sqrt{(1 / N\sum (Predicted - Observed)^2)}$$

Where "PREDICTED" is the predicted value from the models, "OBSERVED" is the observed value from the experiments, and "N" is the total number of test cases.

Training and Optimization of Learning Variables: The training dataset contains total of 79 data which is been trained with different learning variables. Choosing the correct variables like learning rate and momentum will help weight adjustment. Setting right learning rate could be the biggest task, if learning rate is too small algorithm might take long time to converge [44]. On the other hand, choosing large learning rate could have opposite effect, algorithm could diverge also the large values of momentum will influence the adjustment in the current weight to move in same direction.

This ANN network contained 1 hidden layer with 3 hidden nodes. The finalized Network after IFS was trained for further learning variables. Variables like Learning rate and Momentum were studied at 3 different levels. Targeted error was set below 0.01 within 10% of range of given validation data. So total of 3 models were trained for 3 different values.

Evaluation Criteria: Generally, in machine learning, correlation coefficient of determination are usually adopted as evaluation metrics for regression problems. The correlation coefficient generally indicates a linear relationship between 2 variables and gives the correlation between predicted and observed value. However, this cannot be that useful in the prediction of pharmaceutical product performance. In pharmaceutics, a good dissolution profile prediction model should have less than 10% error [45]. Following USFDA credibility or we can say accuracy of final model can be evaluated on basis of similarity (f2) and dissimilarity factors (f1) [46, 47, 48].

The $f1$ factor (eq.1) calculates the percent difference between the two dissolution profiles at each time point and is a measurement of relative error between the two profiles:

$$f1 = (\sum nt = 1\ [Rt - Tt] / \sum nt = 1\ Rt) * 100 \text{.....1}$$

where n is the number of time points, R_t is the mean dissolution value for the reference product at time t and T_t is the mean dissolution value for the test product at that same time point. The $f1$ value is equal to zero when the test and reference profiles are identical and increases as the two profiles become less similar.

The $f2$ factor (eq.2) is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the

percent dissolution between the two profiles. The *f*2 value is equal to 100 when the test and reference profiles are identical and exponentially decrease as the two profiles becomes less similar.

$$f2 = 50 * \log10 [100 /1+ (\sum nt = 1(Rt - Tt\ 02 / /n....2$$

Where R_t and T_t are the percent (%) drug got into solution at every time point for the reference and test product, respectively.

According to the guidelines issued by regulatory authorities *f*1 values upto 15 (0-15) and *f*2 values greater than 50 (50-100) ensures the "sameness" or "equivalence "of the two profiles. Values less than 50 may be acceptable if justified.

Testing: Finalized Model was tested for its accuracy by using remained Testing dataset. The model ultimately predicts the value, which can be compared in form of *f*1 and *f*2 which must have to fulfill guidelines of regulatory authorities [49, 50].

RESULTS AND DISCUSSION: Deep learning requires a huge number of the dataset from which it structures algorithms in layers to create an "artificial neural network" that can learn and make intelligent decision on its own.

TABLE 3: COMPARISON OF NETWORKS FOR IFS ON BASES OF RMSE

	Observed value	Predicted value	RMSE
Network A	1.36	2.2806	1.338144
(Without removal of any input)	5.18	5.6155	
	7.49	9.572	
Network B	1.36	1.6672	0.630322
(Removal of D:P3 ratio)	5.18	4.6353	
	7.49	8.3849	
Network C	1.36	1.6995	0.604847
(Removal of D:P3 ratio+ pKa)	5.18	4.6116	
	7.49	8.3019	
Network D	1.36	0.7903	1.338549
(Removal of D:P3 ratio+ pKa+ solubility	5.18	5.4318	
of drug)	7.49	9.7232	

Here total of 101 data used to train and test the model. Inputs were optimised by using IFS method. From the table 3 it can be concluded that up to removal of 2 features RMSE is decreasing but further removal leads to increase in RMSE suggesting the previous one as a best fit. So the finalized model which is selected for training is having 13 input nodes and 3 output nodes.

TABLE 4: VARIABLE OPTIMIZATION OF FINAL NETWORK C

Variables	Network C1	Network C2	Network C3
Learning rate	0.01	2.5	5
Momentum	0.05	0.6	0.9
Epochs	480801	9038600	114201
Target error	0.01	0.01	0.01
Average error	0.009504	0.013350	0.2413
RMSE	0.5062	1.3367	2.6335

After performing IFS method, final model C was further studied for different learning variables for optimization as shown in **Table 4**.

From these 3 models, Network C1 was optimized on the bases of RMSE as it is having the least RMSE among all, indicating the best fit model, which would be further go for testing and evaluation.

This strategy of similarity and dissimilarity was adopted because it would be useful to paramount the predictive ability of the trained network and to verify whether the network could be used to speculate unseen data within the dataset. Below **Table 5** shows the comparison of predicted and observed values and their evaluation in the form of *f*1 and *f*2 by using the remaining 22 test datasets.

TABLE 5: TESTING OF ANN ON BASES OF *f*1 AND *f*2

S. no.	Observed Value	Predicted Value	*f*1	*f*2
1	2.9106	2.1558	2.888	96.85
	11.672	12.6761		
	20.3986	20.4187		
2	5.821	5.7879	2.36	98.58
	9.875	10.5044		
	15.987	16.1385		

3	1.8543	1.8736	6.768	98.24
	6.7413	7.4654		
	10.832	10.7662		
4	1.5221	1.88	6.447	97.56
	6.6992	7.488		
	10.7212	10.7957		
5	0.5341	0.4394	0.149	99.96
	5.4998	5.5201		
	10.412	10.4619		
6	0.4672	0.1645	2.854	98.68
	5.9843	5.4987		
	12.5647	12.8103		
7	0.7549	0.2833	1.463	99.11
	6.2876	6.3092		
	10.98	11.1662		
8	0.2656	0.1519	3.349	97.65
	8.6951	8.7006		
	12.9875	13.8308		
9	2.3111	2.4388	1.662	99.51
	6.6782	6.5611		
	10.3168	9.9853		
10	0.7065	0.6377	1.374	99.89
	5.778	5.778		
	10.256	10.0948		
11	0.4311	0.3229	5.645	98.03
	5.9753	6.3312		
	9.9842	10.6617		
12	0.3468	0.287	1.728	97.34
	6.11	5.3704		
	9.003	9.5353		
13	1.0178	0.1864	4.754	97.45
	8.6431	8.3403		
	16.4569	16.3494		
14	0.2543	0.1992	0.072	100.97
	8.0543	8.7134		
	12.4511	13.8401		
15	1.0322	0.153	3.333	97.5
	8.6733	8.7134		
	13.7842	13.8401		
16	0.6742	0.1869	1.742	99.15
	8.9765	9.0108		
	11.5235	11.6078		
17	3.8648	3.8806	0.743	99.93
	8.6835	8.7424		
	14.5883	14.7149		
18	7.1298	7.2526	1.429	99.2
	14.8975	15.3526		
	23.7854	23.8623		
19	0.9923	1.8356	2.4774	97.38
	6.2113	5.9159		
	9.3145	9.1753		
20	0.6322	0.4742	1.75	98.69
	4.993	5.5753		
	10.1734	10.0255		
21	6.7611	7.2985	4.826	94.9
	14.953	15.4364		
	22.8639	23.9944		
22	0.6419	0.255	11.56	95.97
	5.7124	4.6392		
	8.1648	7.9467		

Satisfying regulatory norms, values of testing data are falling within range *i.e. f*1 is between 0-15 and *f*2 is within 50-100 except one which ensures the "sameness" or "equivalence "of the two profiles with average error ~0.0095. A regression plot was constructed for predicted value and the observed value of drug releases at various sampling points

using the test dataset to obtain a squared correlation coefficient (R^2) and slope.

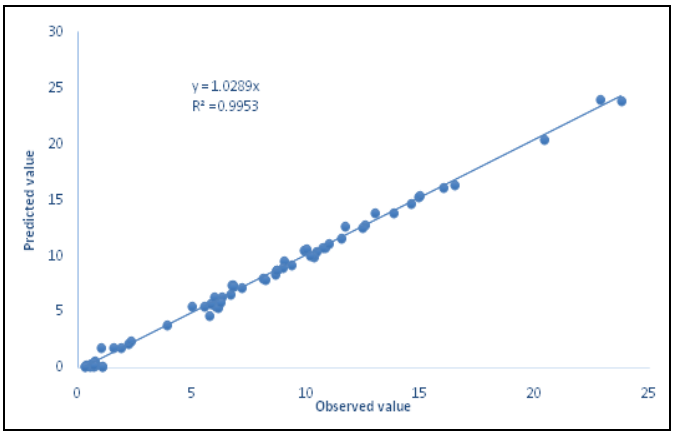

FIG. 5: REGRESSION PLOT OF ANN MODEL FOR PREDICTED AND OBSERVED VALUES

The ANN model developed above that must yield a regression plot with a slope and R^2 both being closest to value 1.0 then it is considered as the optimum model. Considering these 2 criteria *i.e. f*1 and *f*2 and squared correlation coefficient (R^2) this developed model can be said satisfying in norms of accuracy and regulatory guidelines.

CONCLUSION: In this work, a generalized artificial neural network is successfully developed for drug release prediction of SR monolithic tablet. The networks were rigorously trained and optimized for various variables and also tested for enough data to exhibit reliable prediction behaviour with best achieved average error ~0.0095 and R^2 0.9953. It also satisfactorily fulfils USFDA guidelines for comparison of 2 dissolution profiles adding acceptability credits to our model. A lengthy and tedious work like Pharmaceutical formulation development can be simplified by using various statistical methods, but it can be furthermore lightened by using today's smart methods like ANN development. A once-developed model can further be used to predict the product performance eliminating the requirement of tedious physical practicals. ANN is the perfect combination of experience of ages and intelligence of present, which must be explored more and more in the pharmaceutical world.

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