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RESEARCH PAPER

ARTIFICIAL NEURAL NETWORK AS TOOL FOR QUALITY BY DESIGN IN FORMULATION DEVELOPMENT OF SOLID DISPERSION OF FENOFIBRATE

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Optimization techniques are abundant in pharmaceutical industry. In general, all the required information should be obtained from as few experiments as possible. Conventional techniques such as response surface models or simplex optimization are often used. With the advent of the computer in the laboratory, a new class of optimization problems arose which could not be tackled with the standard methodologies. For these search type problems, new strategies such as simulated annealing (SA), genetic algorithms (GA) and artificial neural network are applied. Artificial neural network (ANN) is now become more efficient technique for the optimization of pharmaceutical formulation compared with the Multiple Linear Regression Analysis (MLRA). In the present investigation Self Organizing Featured Maps (SOFM) tool of ANN was implicated for the optimization of formulation of solid dispersion for fenofibrate. Solid dispersion was prepared using 3^2 full factorial design and the results obtained were evaluated using ANN for the optimization purpose. Solid dispersion was prepared using Poloxamer 407 as carrier and Lyophilization methods as method of preparation. Amount of Poloxamer 407 (X_1) and Lyophilization temperature (X_2) was selected as independent variable, angle of repose and $T_{90\%}$ was selected as dependent variables.Results of angle of repose and $T_{90\%}$ obtained by factorial analysis was choose as set of ANN training data and results of check point analysis for angle of repose and $T_{90\%}$ was choose as a set of test data for ANN. Both sets of data were trained using SOFM tool for ANN training using Software NEUROSOLUTION 6.31. Data was trained for satisfactory results.

Key words: ANN, Factorial Design, Poloxamer 407, Fenofibrate, Quality by Design.

INTRODUCTION

Artificial intelligence (AI) is the science and engineering of making intelligent machines, especially intelligent computer programs (Ahmadi Lakalayeh *et al* 2012). It is related to the similar task of using computers to understand human intelligence, but AI does not have to confine itself to methods that are biologically observable (Agatonovic-Kustrin and Beresford, 2000). Researchers in AI follow the algorithmic approach of creating computer program and try to capture the knowledge of an expert in some specific domain as a set of rules to create so-called expert systems (Aksu *et al* 2012). This is based on the hypothesis that the expert's thought process can be modeled by using a set of symbols and a set of logical rules. Using the algorithmic and symbolic approach, the digital computers solve problems that are difficult for humans. Artificial neural network

(ANN) is the most interesting branch of artificial intelligence and is most commonly used in medicine (Bourquin *et al* 1998; Arulsudar *et al* 2005; Gasperlin *et al* 2008; Anand *et al* 2009; Barmpalexis *et al* 2010).

Artificial neural networks (ANNs) - also called neurocomputing, connectionism or parallel distributed processing (PDP) - provide an alternative approach to be applied to problems where the algorithmic and symbolic approaches are not well suited (Hussain *et al* 1991; Husseini *et al* 2007). ANNs are inspired by the biological nervous systems, although they do not try to be realistic in every detail. Simply we can say that they are computer systems developed to mimic the operations of the human brain by mathematically modeling its neurophysiological structure and function (Ibrić *et al* 2003). The formal definition of an ANN was proposed by Hecht-Nielsen: An ANN is a parallel, distributed information processing structure consisting of processing elements (which can possess a local memory and can carry out localized information processing operations) interconnected *via* unidirectional signal channels called connections. Each processing element has a single output connection that branches into as many collateral connections as desired; each carries the same signal - the output signal (Jouyban *et al* 2004; Ivić *et al* 2010; Ioele *et al* 2011). The output signal of a processing element can be of any mathematical type desired. The information processing that goes on within each processing elements can be defined arbitrarily with the restriction that it must be completely local; that is, it must depend only on the current values of the input signals arriving at the processing element via impinging connections and on values stored in the processing element's local memory (Mendyk *et al* 2006; Leane *et al* 2003; Mandal *et al* 2008; Kikuchi and Takayama, 2009; Kikuchi and Takayama, 2010).

The artificial neural network (ANN) technique is a powerful non-linear mapping technique which is a mathematical system that simulates biological neural networks. It consists of processing elements (neurons, nodes) that are organized in the layers (Nelofer *et al* 2012; Mendyk *et al* 2013). There is always one input and one output layer and at least one hidden layer. Each layer of nodes receives its input from the previous layer or from the network input. The output of each node feeds the next layer or the output of the network. There are several types of neural networks, which are most frequently used in chemical and pharmaceutical applications (Sibanda *et al* 2004; Sadatsafavi *et al* 2005; Nettles *et al* 2010).

To the best of our knowledge, no information is available on the applications and the best utility of different network models with various activation functions in pharmaceutical formulation development. In the present study, an attempt was made to explore ANN models with proper activation function for the optimization and prediction of the best outputs in formulation development. Formulation of solid dispersion using Poloxamer 407 as carrier was optimized by Self organizing featured maps (SOFM) tool of ANN.

MATERIALS AND METHODS

Fenofibrate was obtained as gift sample from Cadila pharmaceuticals limited, Ahmedabad, India. PEG 600, Avicel PH 102, Aerosil 200 was purchased from BASF limited, Mumbai, India. All other solvents and excipients was used in the analysis was of analytical grade.

Preparation of solid dispersion

A 3^2 full factorial design was used to prepare different composition of solid dispersion containing fenofibrate and Poloxamer 407 as carrier molecule (**Table 1**). Poloxamer 407 and Fenofibrate were dissolved in a minimum amount of Chloroform. This solution was rapidly solidified by transferring small portions with a Pasteur pipette onto the inner surface of a cold flask rotating in a -50°C methanol bath. After a certain layer thickness was obtained, the flask was attached to the vacuum adapter of the lyophilizer. The solvent was sublimed under a pressure of 8-10 mmHg and condensed onto a -50°C/-60°C/-70°C condenser. After the solvent was completely removed, the powder residue appeared as a porous, light and fluffy mass. The lyophilized preparations were stored in a desiccator at room temperature. The pulverized mass was sifted through a #120 sieve, weighed, and transferred to amber colored Type-I glass vials, stored at 300°C±10°C. Amount of Poloxamer 407 (X_1) and Lyophilization temperature (X_2) were selected as variables for optimization of formulation using ANN. Angle of repose and Time to release 90% drug ($T_{90\%}$) was recorded as response.

In vitro dissolution study

An ELECTROLAB dissolution test apparatus type II (Paddle) at rotation speed of 50 rpm was used

for the study. Dissolution of the drug and solid dispersion was carried out on an equivalent of 100 mg of the Fenofibrate in 0.1 M SLS as dissolution media. The volume and temperature of the dissolution media were 900 ml and 37±0.2°C, respectively. After fixed time intervals, 5 ml of samples were withdrawn and replace the same fresh dissolution media so as to maintain sink condition. The samples were filters through 0.2 *μ*m filters and assayed using UV spectrophotometry at 290 nm. To increase the reliability of the observations, the dissolution studies were performed in triplicate.

Optimization of formulation using ANN

A three layer network with a different activation function was applied in this study. NeuroSolutions version 6.20 evaluation software was downloaded from NeuroDimension, Inc (www.nd.com). The independent variable X_1 and X_2 were used as inputs and the response recorded like angle of repose, $T_{90\%}$ were used as outputs or desired. Generally, the neural network methodology has several empirically determined parameters. These include: the number of iterations or epochs, the processing element, learning rate and momentum terms (Takayama *et al* 1999; Takayama *et al* 2000; Takayama *et al* 2004). The optimum values for ANN parameters were evaluated by obtaining those values, which yielded the lowest prediction errors. The Self-organizing feature maps (SOFMs) network model was selected from the customized new network. The different functions like TanhAxon, SigmoidAxon, LinearTanAxon, LinearSigmoidAxon, BiasAxon, LinearAxon, and Axon Functions were used to predict the output response.

Table 1. Formulation composition of solid dispersion as per 3^2 full factorial design

Batch	Actual value		Coded value	
	X_1	X_2	X_1	X_2
F1	40	-30	-1	-1
F2	40	-50	-1	0
F3	40	-70	-1	1
F4	80	-30	0	-1
F5	80	-50	0	0
F6	80	-70	0	1
F7	120	-30	1	-1
F8	120	-50	1	0
F9	120	-70	1	1
Level of factors				
Independent Factors	**Level**			
	Low (-1)		**Middle (0)**	**High (1)**
Amount of Poloxamer 407 (mg), (X_1)	40		80	120
Lyophilization Temperature (°C), (X_2)	-30		-50	-70

RESULTS AND DISCUSSION

***In vitro* dissolution study**

In vitro dissolution curve of batches F1 to F9 prepared using lyophilization method employing factorial design are shown in **Figure 1**. *In vitro* dissolution of fenofibrate showed only about 20% drug release. There was gradual increase in drug release from batch F1 to F9; which indicated that there was decrease in $T_{90\%}$. Batch F6, F7, F8, and F9 showed complete drug release in about 80 min, 60 min 50 min and 30min, respectively. It might be due to the presence of Poloxamer 407 and higher lyophilization temperature. As the amount of Poloxamer 407 was increased along with increase in lyophilization temperature simultaneously, the dissolution rate of drug was improved.

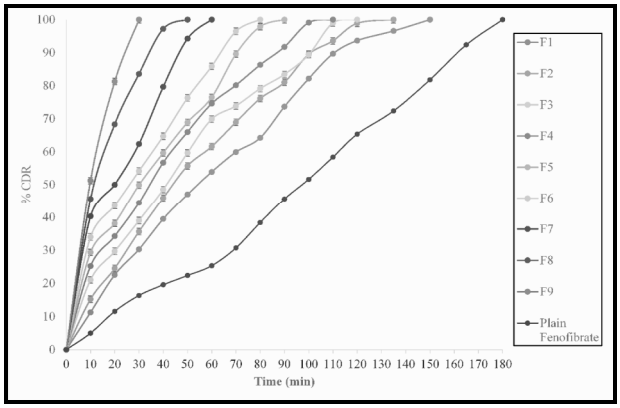

Fig. 1. *In vitro* drug release profile of batch F1 to F9 compared with plain fenofibrate

Batch F1, F2, F3 and F4 showed complete drug release in about 150 min, 135 min, 120 min and

110 min, respectively. It might be due to lower amount of Poloxamer 407 in the respective formulations. *In vitro* dissolution study indicated that Lyophilization temperature did not have marked effect on drug release alone but in combination with Poloxamer 407, marked effect on drug release was observed.

The results of dependent variable such as angle of repose and $T_{90\%}$ (time required for 90% drug release) of the batches were shown in **Table 2**.

Table 2. Results of experimental runs as per 3^2 full factorial design

Batch	Factors		Response	
	X_1	X_2	Angle of Repose (°)	$T_{90\%}$ (min)
F1	-1	-1	36.25±0.055	118.51
F2	-1	0	28.32±0.052	104.97
F3	-1	1	22.89±0.050	96.76
F4	0	-1	43.25±0.076	86.29
F5	0	0	32.98±0.057	72.76
F6	0	1	26.54±0.050	64.49
F7	1	-1	46.21±0.046	48.61
F8	1	0	33.65±0.023	37.66
F9	1	1	25.64±0.028	24.66

Optimization of formulation using ANN

The Self-organizing feature maps (SOFMs) network model was selected from the customized new network. The functions like TanhAxon, SigmoidAxon, LinearTanAxon, Linear SigmoidAxon, BiasAxon, Linear Axon, and Axon functions were used to predict the output responses.

Predictions MSE of various functions of SOFMs for training of data using 3^2 factorial design for preparation of fenofibrate solid dispersion were shown in **Figure 2, 3** for angle of repose and $T_{90\%}$, respectively.

The performance parameters like mean squared error (MSE), minimum absolute error, correlation coefficient and predicted output of the selected network models using various activation functions were presented in **Table 3** and **Table 4**.

Table 3. Testing performance of angle of repose (AR) for batch F8 using ANN function

Function/Parameter	Mean square error	Min Ab Err	r	Predicted AR
TanhAxon	4.565505236	0.795762301	1	36.4457623
SigmoidAxon	24.07375732	0.235431661	1	35.4145683
LinearTanAxon	3.097037142	1.178274025	1	36.8282741
LinearSigmoidAxon	401.7421086	14.05555556	1	21.5944444
BiasAxon	0.180464075	0.015031135	1	35.6650311
LinearAxon	0.748286470	0.777490635	1	36.4274906
Axon	1.047040887	0.470776763	1	37.0183753
Actual Angle of Repose = 35.65 for Batch F8				

Table 4. Testing performance of $T_{90\%}$ for batch F8 using ANN function

Function/Parameter	Mean square error	Min Ab Err	r	Predicted $T_{90\%}$
TanhAxon	18.45391436	0.110582009	1	37.5487701
SigmoidAxon	175.1005738	10.31448767	1	53.2738483
LinearTanAxon	35.05323373	2.448667537	1	29.6524492
LinearSigmoidAxon	186.7173568	11.60155265	1	53.1137589
BiasAxon	36.14497453	3.317004986	1	29.8307235
LinearAxon	38.97167440	5.836990974	1	31.8223612
Axon	48.17767768	2.665380842	1	28.2120721
Actual $T_{90\%}$ = 37.65 for Batch F8				

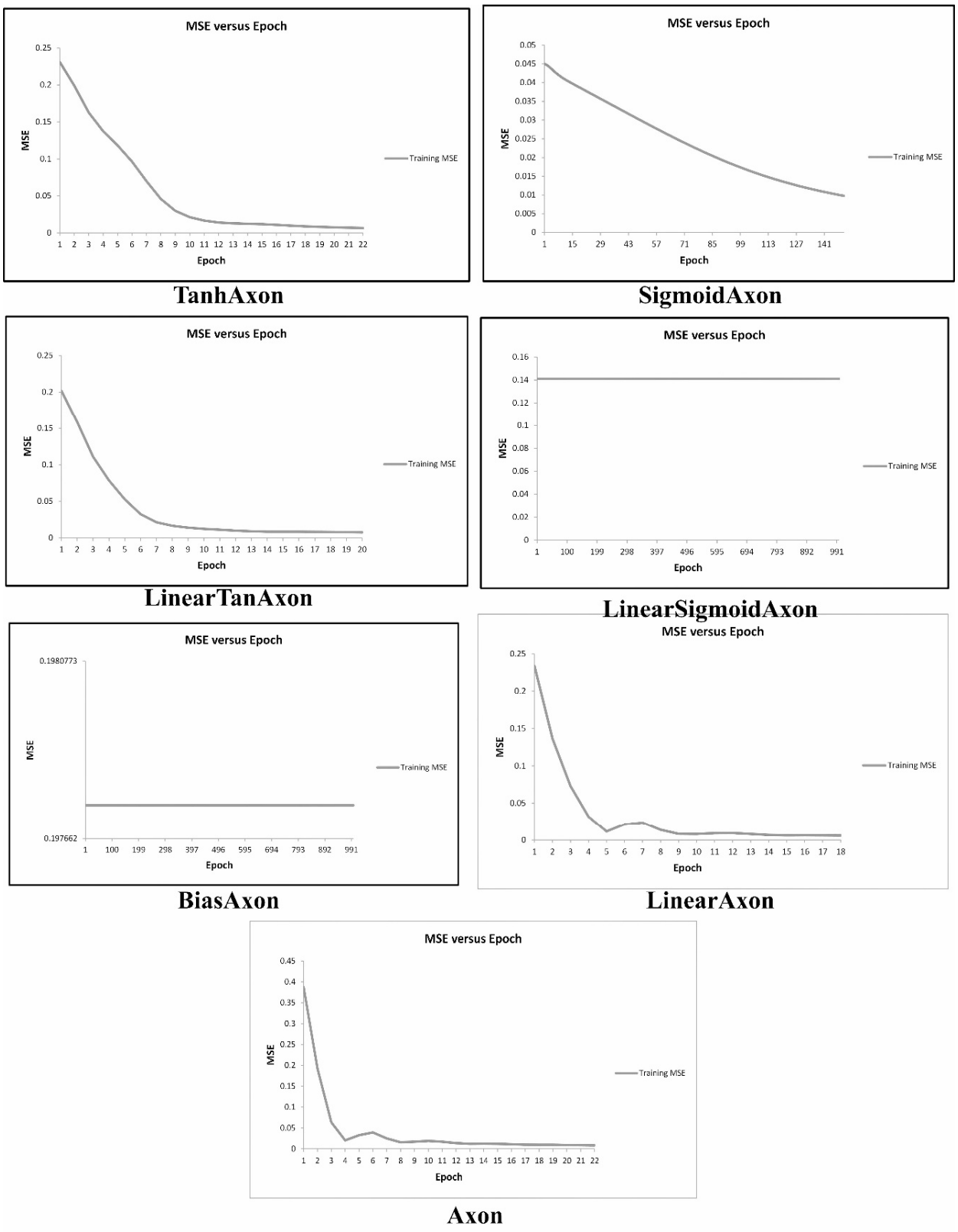

Fig. 2. Training of angle of repose results of 3^2 full factorial design with SOFMS function

The results indicated that the BiasAxon function using Self-organizing feature maps (SOFMs) network showed the least MSE and minimum absolute error for angle of repose and TanhAxon function using SOFMs network showed the least MSE and minimum absolute error for $T_{90\%}$. The predicted outputs for angle of repose and $T_{90\%}$ by using BiasAxon and TanhAxon function respectively, with selected Self-organizing feature maps (SOFMs) network were quite similar to the actual result.

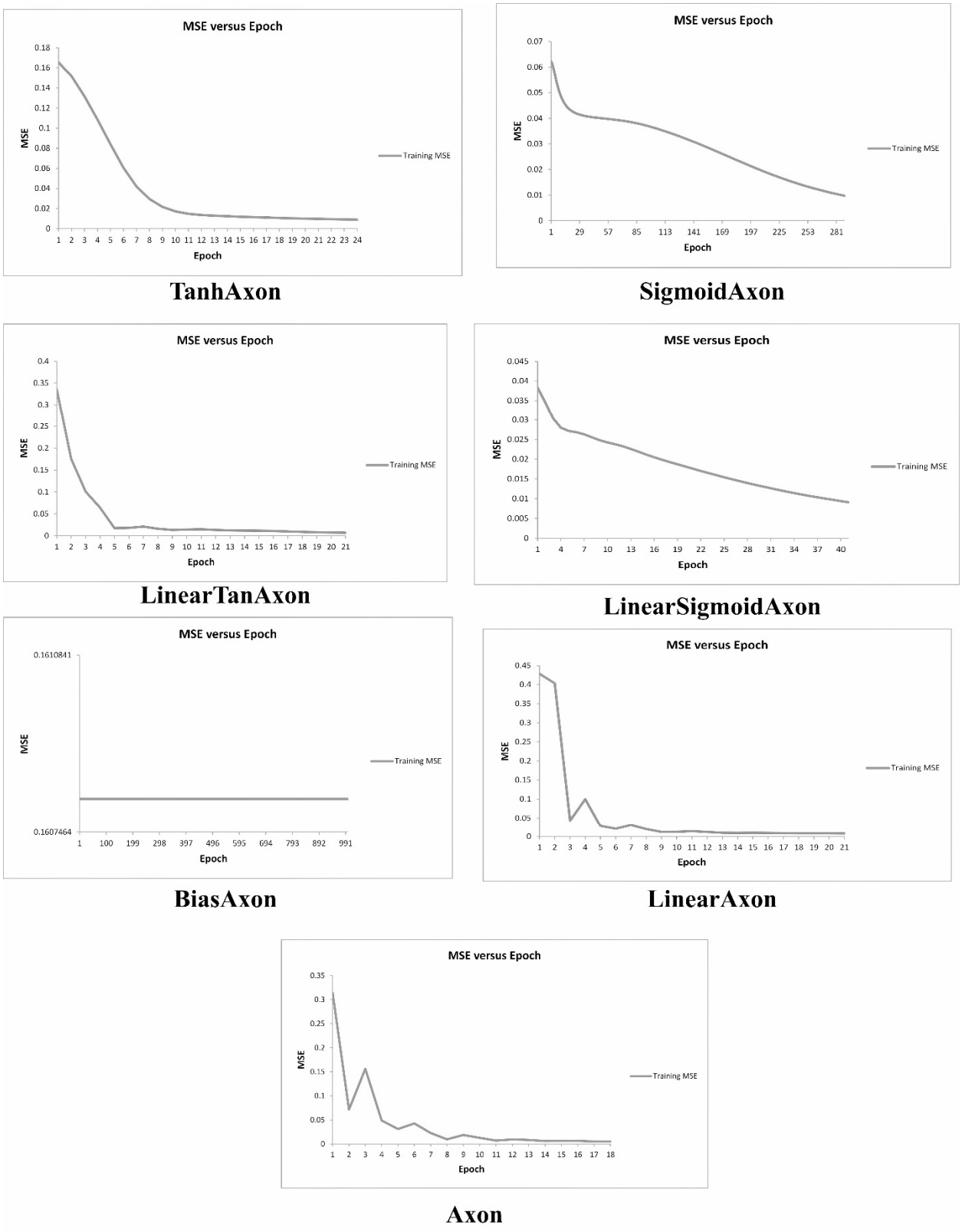

Fig. 3. Training of $T_{90\%}$ results of 3^2 full factorial design with SOFMs functions

CONCLUSION

Artificial intelligence (AI) is the science and engineering of making intelligent machines, especially intelligent computer programs. Artificial neural network (ANN) is the most interesting branch of artificial intelligence and is most commonly used in medicine. The artificial neural network (ANN) technique is a powerful non-linear mapping technique which is a mathematical system that simulates biological neural networks. In the present study, an attempt was made to explore ANN models with

proper activation function for the optimization and prediction of the best outputs in formulation development. The aim of the present work was to identify the proper function which is best fitting to predict the responses. The ANNs models provided relatively accurate calculations. Computation of descriptors is straight forward and by using a minimum number of experimental data, acceptable predictions could be achieved. It was concluded that the ANN models with proper optimized activation function might be used in pharmaceutical formulation development for theoretical prediction of responses within the factor space.

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