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Spectrophotometric Analysis of Quaternary Drug Mixtures using Artificial Neural network model

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** This paper is dedicated to the memory of the late Sarmad B. Dikran. Deceased July 6, 2020;

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A Novel artificial neural network (ANN) model was constructed for calibration of a multivariate model for simultaneously quantitative analysis of the quaternary mixture composed of carbamazepine, carvedilol, diazepam, and furosemide. An eighty-four mixing formula where prepared and analyzed spectrophotometrically. Each analyte was formulated in six samples at different concentrations thus twenty-four samples for the four analytes were tested. A neural network of 10 hidden neurons was capable to fit data 100%. The suggested model can be applied for the quantitative chemical analysis for the proposed quaternary mixture.

Keywords: artificial neural network, simultaneous spectrophotometric analysis, quaternary mixture, carbamazepine, carvedilol, diazepam, furosemide

Carvedilol (CAV), Diazepam (DIA) and Furosemide (FUR) are different classes of medications that are used in combination for management of high blood pressure and heart diseases. CAV [(2RS)-1-(9*H*Carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy) ethyl] amino] propan-2-ol], nonselective beta-blocker/ alpha-blocker drug, commonly applied to control hypertension and treatment of congestive heart failure and cardiac arrhythmia [1, 2]. DIA [7-chloro-1- methyl-5-phenyl-1,3-dihydro-2*H*-1,4- benzodiazepin-2-one] is a drug used to manage a variety of medical situations like anxiety and status epilepticus [1, 3]. FUR [4-Chloro-2-[(furan-2-ylmethyl) amino] - 5-sulfamoyl benzoic acid], a loop diuretics, commonly used in the management of hypertension, fluid buildup as well as edema [1,4]. CAB [5*H*-dibenzo [*b*, *f*] azepine-5-carboxamide], antiseizure drug, mainly used to treat epilepsy and neuropathic pain [1, 4]. The chemical structures [1] of CAB, CAV, DIA and FUR are shown in Figure (1).

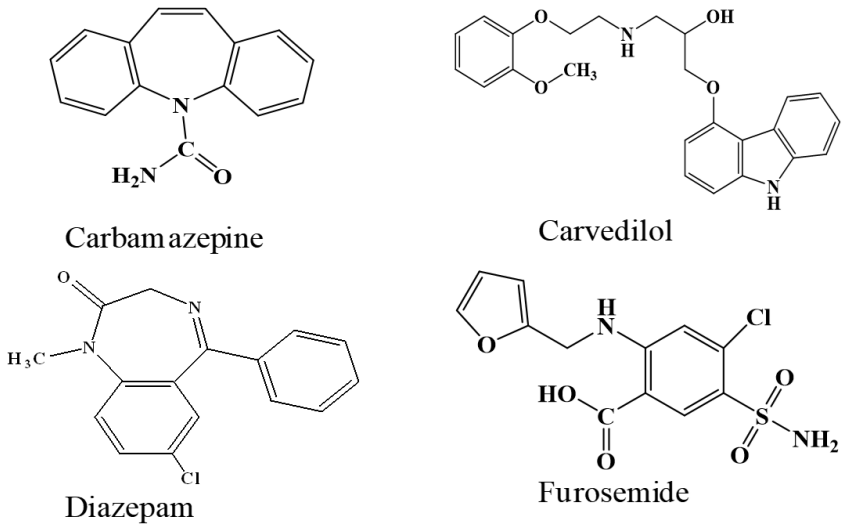

Figure 1: Chemical structures of studied drugs.

Literature survey reveals several conventional analytical techniques including HPLC [5-8], FT-IR [9], flow injection analysis [10,11], GC-Mass [12,13], voltammetry [14,15], spectrofluorimetry [16], and spectrophotometry [17-19] for individual or simultaneous quantification of the cited drugs in bulk, pharmaceutical preparations, and body fluids.

The current study aims to evaluate the quaternary synthetic mixture that composed of CAB, CAV, DIA, and FUR in their mixtures via artificial neural networks (ANN). ANN model has the pattern recognition capabilities of the neural networks of the brain and have been used in many pharmaceutical researches [20]. The applications of ANN to quantitative chemical analysis using multivariate instrumental signals with the mathematical aspects involved in the training of neural networks has been reviewed [21]. The principle and theory of the suggested model were discussed in the literature [22-28].

Experimental part

Instruments and software

Shimadzu 1800 UV - Visible Spectrophotometer equipped with 10 mm quartz cells with bundled software version (UV Prob 2.34) was used for recording absorption spectra. The range of the scans was from (200 – 350) nm at data interval of 0.5 nm.

A Simplex Lattice Mixture Design (create by JMP® 11.0.0 SAS Institute Inc.) was used to prepare a set of calibration mixtures for the analysis of the mentioned drugs simultaneously.

Chemicals and reagents

The used raw materials/powders of CAB, CAV, DIA, and FUR were of pharmaceutical grade with purity of 99.99%, which were kindly obtained as a gift from the State Company for Drug Industries and Medical Appliances Samara-Iraq (SDI), while methanol was of analytical grade reagent.

Standard and working solutions

Standard stock solutions (1000 µg/mL) of CAB, CAV, DIA, and FUR were separately prepared by dissolving 0.050 gm of the cited drugs in 50 mL methanol. Serial dilution was done for the preparation of working solutions of each drug.

Data analysis

All obtained data were analysed using MATLAB (version 9.1.0 R2021a, Math Work, Inc).

Results and Discussion

The normalized absorption spectra of CAB, CAR, DIA, and FUR are shown in Figures (2-5) at concertation range (1-20) µg/mL for each component.

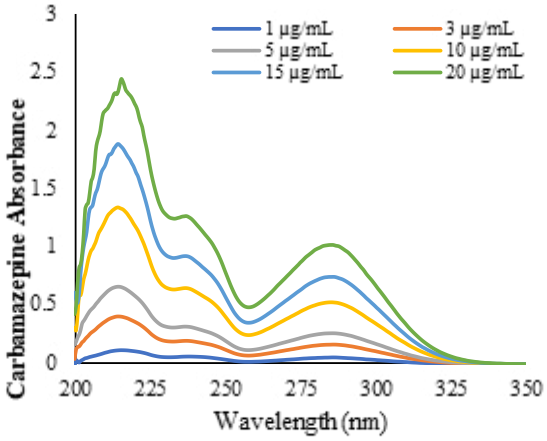

Figure 2: CAB absorbance vs. wavelength

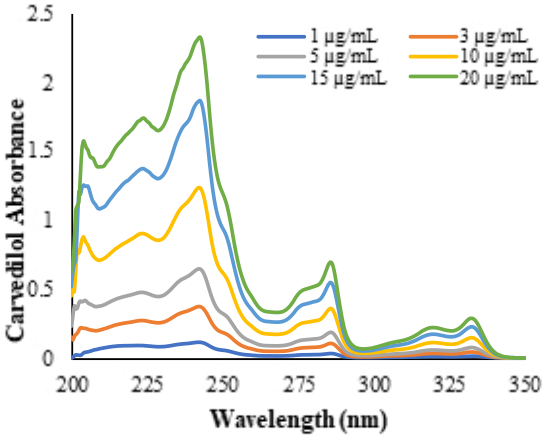

Figure 3: CAV absorbance vs. wavelength

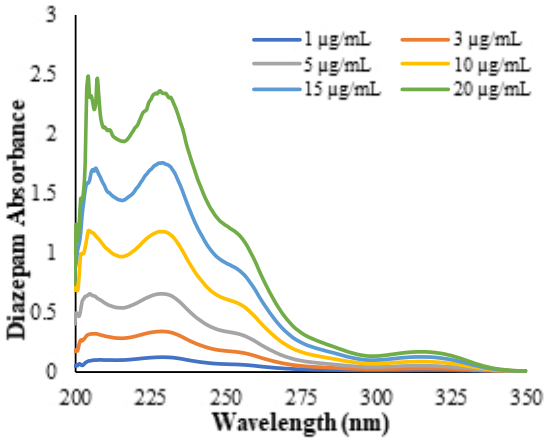

Figure 4: DIA absorbance vs. wavelength

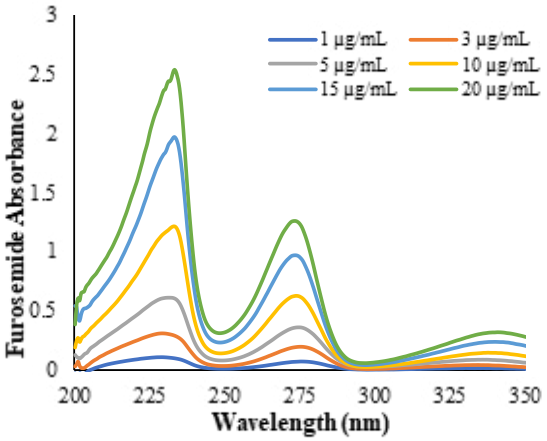

Figure 5: FUR absorbance vs. wavelength

The UV spectra of the examined drugs showed a noteworthy overlap (Figure 6) that humper the application of the traditional spectrophotometric methods for settling their spectra. In this manner, artificial neural network (ANN) model was used for the concurrent investigation of this complex quaternary mixture.

Eighty-four samples were prepared in order to optimize, calibrate, and validate the suggested model. The utilized absorbance information of the scanned samples was in the range (200 – 350) nm, (Figure 7). The wavelengths lower than 205.5 nm, were omitted because of the effect of high noise, for this reason, the data that was obtained out of the specified range would have resulted in a substantial noise level within the calibration matrix, thus influencing the precision.

Artificial Neural Network (ANN) model:

Calibration procedure

Neural network could be considered as an excellent multivariate method in modeling the nonlinear behavior such as multicomponent system in chemical analysis. The aim of multivariate method is to construct a calibration between the concentration of the samples and the absorbance. The first step in model is the design of the calibration network for the quaternary complex mixture.

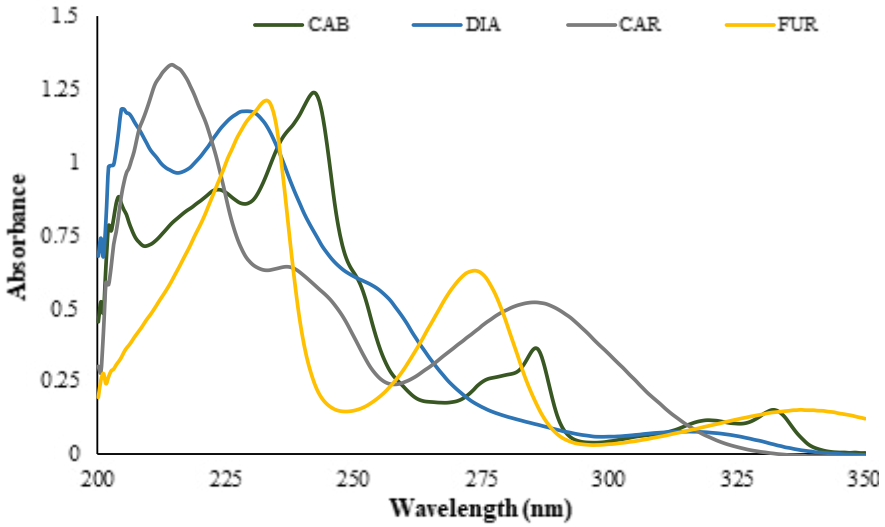

Figure 6: UV absorption spectra of CAB, CAR, DIA, and FUR.

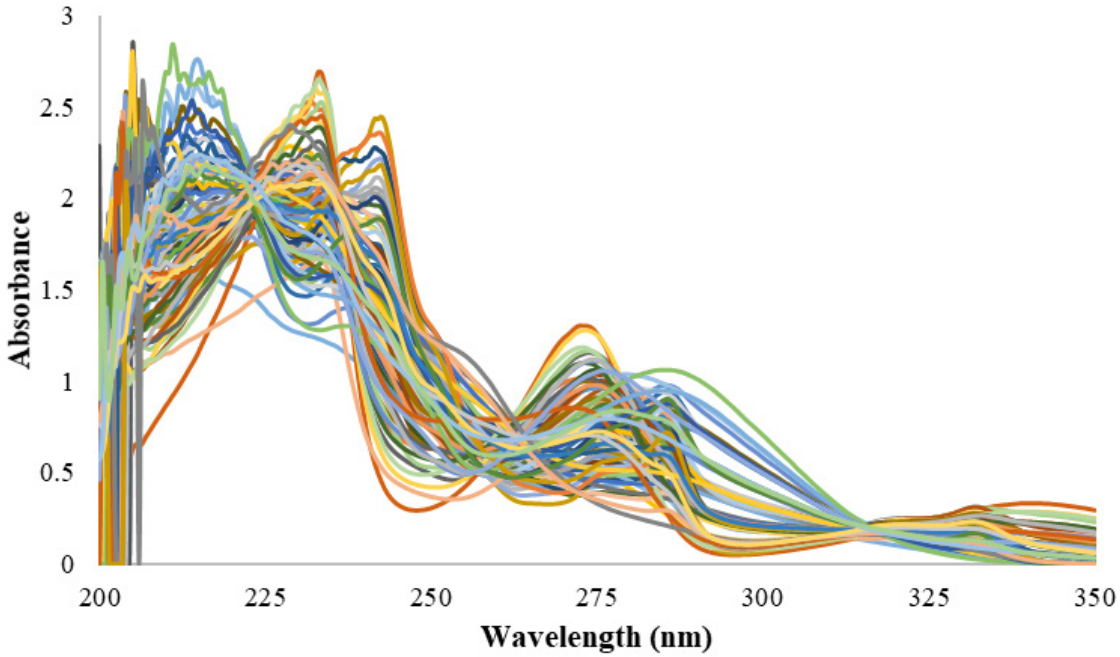

Figure 7: Absorbance spectra of 84 samples of CAB, CAR, DIA, and FUR mixtures in methanol.

The network was configured for 10 neurons in the hidden layer, two input vectors (absorbances and wavelengths) and 4 output vectors (concentration of CAB, CAV, DIA and FUR), the neural network was configured for 290 inputs (absorbance at 205.5 nm – 350 nm). The constructed neural network is illustrated in Figure (8), which demonstrates the training algorithms, the training progress performance.

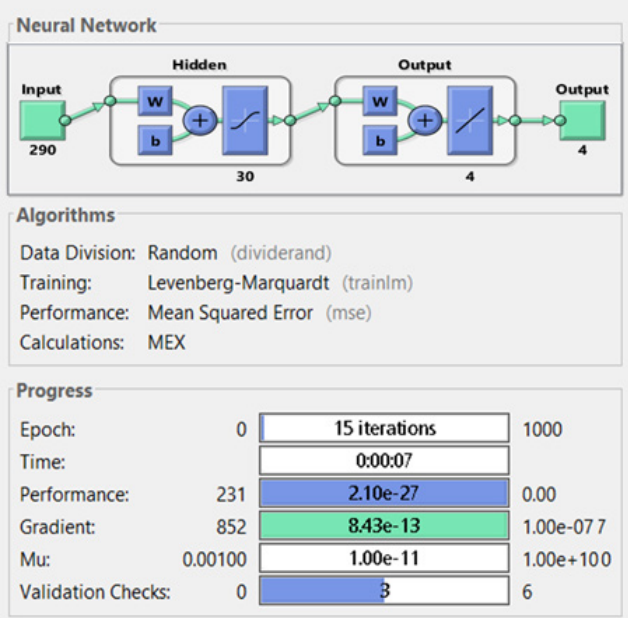

Figure 8: The neural network used for training the experimental results.

While, Figure (9), shows the best validation found at epoch 12.

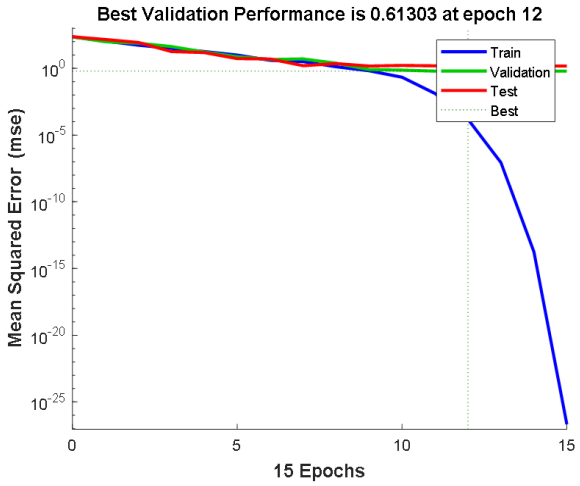

Figure 9: The mean square error versus training epoch.

Results shown in Figure (10) illustrated excellent fitting via statistically R values for training, validation, and testing. One of the important points during calculation mode is to reject and retrain any unsatisfied results.

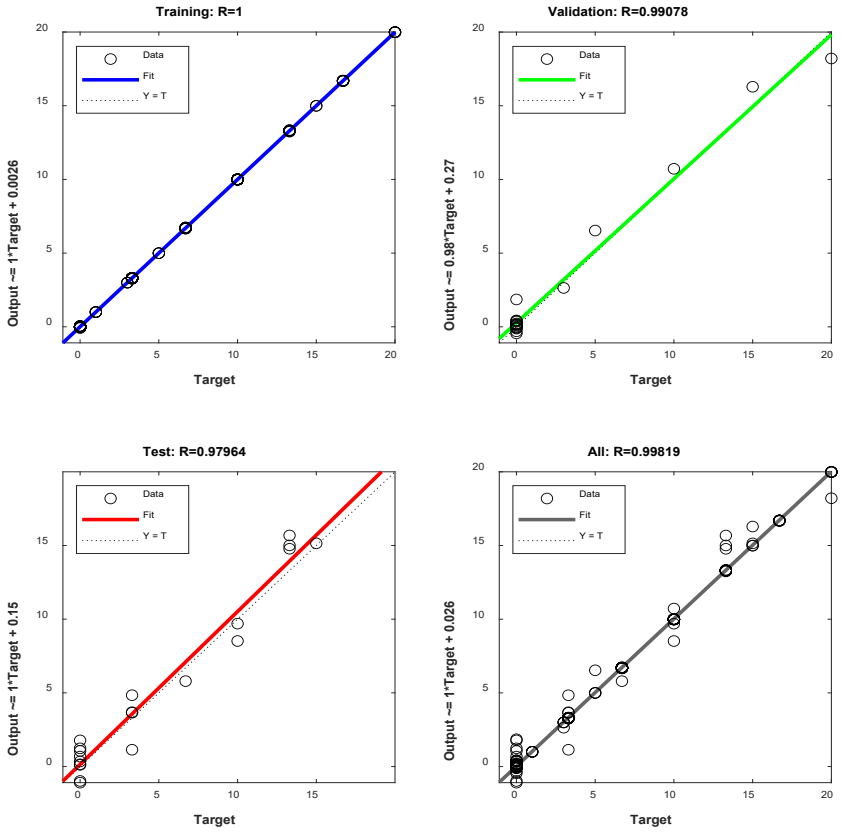

Figure 10: R values for training, validation, testing of the neural network.

Statistically, the MSE and R values for trained, validated, and tested data are shown in Table (1), the total number of trained samples is 108 to get 4 outputs.

For conformation of the ANN model, the data were tested in the model, it showed approximately 100 % fitting after retraining. The architecture of the ANN model was plotted as revealed in the Figures (11-14).

Table 1. MSE and R- values for the training data, validity and test data.

Data	Samples	MSE	R
Train	70%	1.0244E-5	0.9999
Valid	15%	0.6040	0.9882
Test	15%	0.8812	0.9886

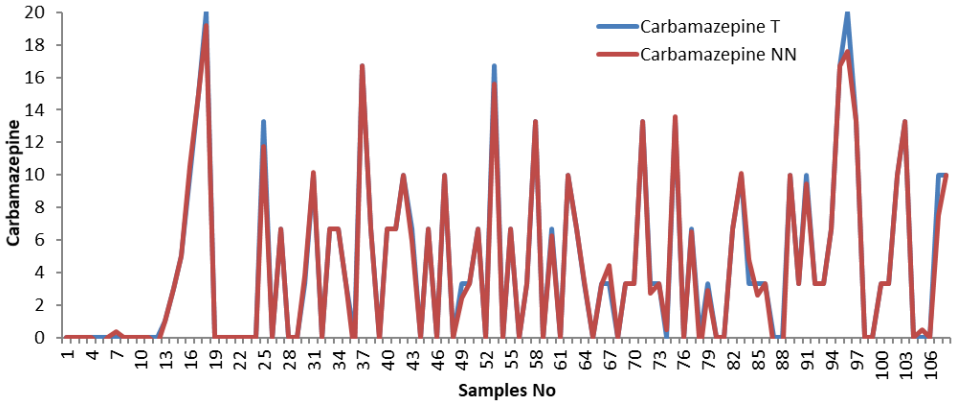

Figure 11: ANN test for Carbamazepine.

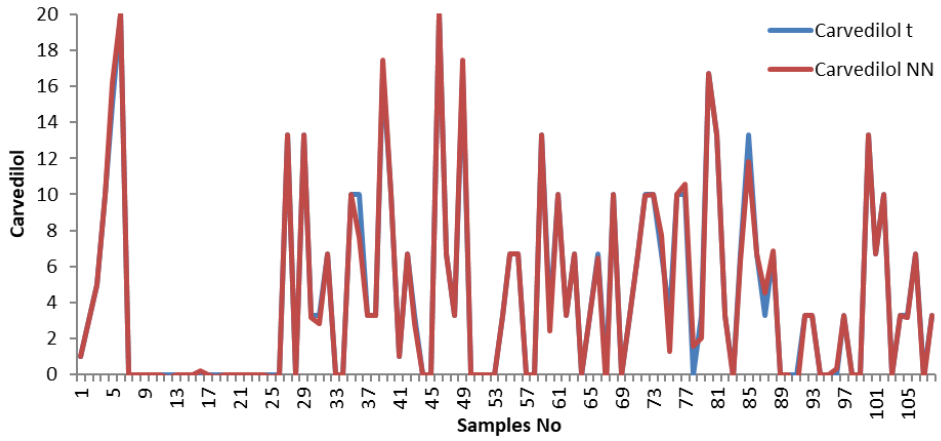

Figure 12: ANN test for Carvedilol.

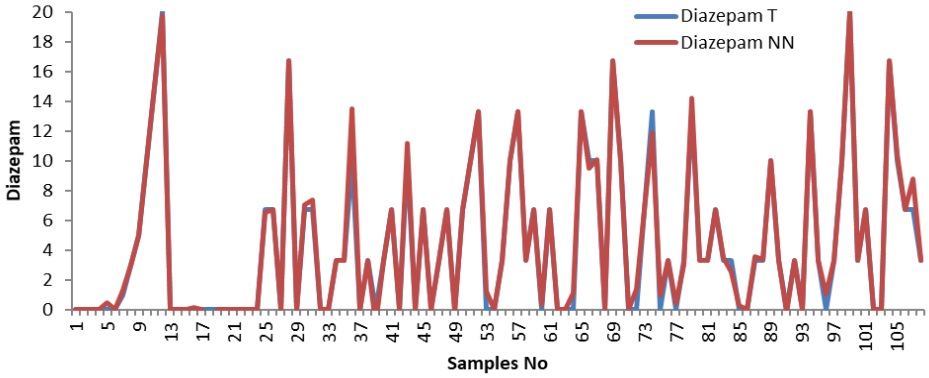

Figure 13: ANN test for Diazepam.

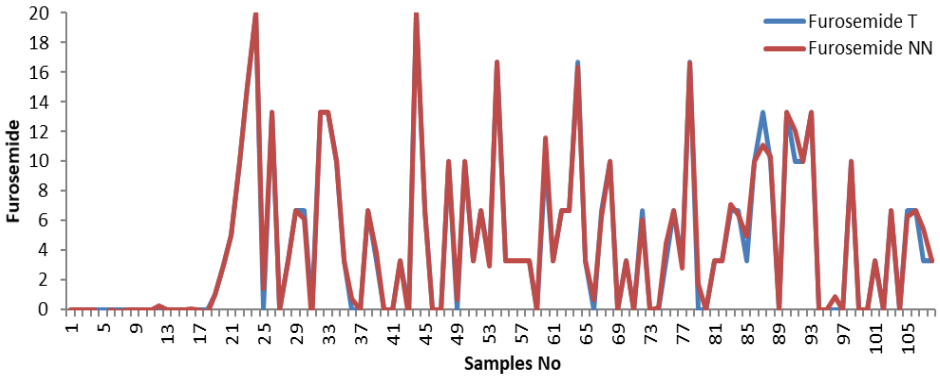

Figure 14: ANN test for Furosemide.

Conclusion

The results of the current study apply evidence to the scientific data regarding the efficiency of the ANN model in simultaneous estimation of quaternary system with high or distinctive overlapped spectra. Adding to that, this method could be suggested for using in quality control without intrusion, with considering it as a smart method for chemometric analysis.

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