*Asian Journal of Chemistry* Vol. 17, No. 1 (2005), 117–124

# Simultaneous Spectrophotometric Determination of Mefenamic Acid and Paracetamol in Pharmaceutical Preparation by Using Artifical Neural Network

M.R. SOHRABI, P. ABDOLMALEKI†, M. DAVALLO*, F. TADAYYON and F. HAGHOLLAHI
*Department of Chemistry, Islamic Azad University (North Branch)*
*P.O. Box 19136, Tehran, Iran*
*E-mail: m_davallo@yahoo.com*

The present paper describes the spectrophotometric method for determination of mixture of paracetamol (PAR) and mefenamic acid (MEF) by using artificial neural network (ANN). The spectrum of PAR and MEF showed strong overlapping. Therefore, to reduce the overlapping, absorption data were extracted from the spectrum of the mixture of PAR and MEF and the concentration sets were used as input and output for ANN, respectively. A three layer feed-forward neural network with back-propagation algorithm was then constructed. To obtain the best topology for ANN, several parameters were optimized. Thus, in each step, root mean square error (RMSE) for both PAR and MEF was calculated. Finally, in the latter step, real sample based on conventional standard method (USP) was analyzed. The results obtained showed some differences between the standard method and the proposed method (ANN).

**Key Words: Spectrophotometry, Mefenamic Acid, Paracetamol, Artificial Neural Network.**

## INTRODUCTION

Paracetamol (PAR) and mefenamic acid (MEF) are effective and analgesic agents used worldwide for the relief of mild to moderate pain associated with headache, backache and rheumatoid arthritis. PAR is used for the reduction of fever of bacterial or viral origin. Combination of MEF with PAR is frequently prescribed as an analgesic and anti-inflammatory agent in rheumatoid arthritis.

Various methods including spectrophotometry[1–5], HPLC[6–8], ratio derivative spectrophotometry[9–11] and chemometrics methods[12–15] have been used for the determination of MEF and PAR in pharmaceutical preparations containing MEF and PAR mixture.

Artificial neural network (ANN) is a computer algorithm which is able to learn important relationship from a set of data and it is therefore able to apply this knowledge to evaluate the new cases as an expert system, in contrast to the

†Department of Biophysics, Tarbiat Modarres University, Tehran, Iran.

conventional algorithmic and rule-based approaches, which the programmer needs to know either a mathematical description of the input or a set of rules describing how to handle the input in order to achieve an output. ANN is an important class of pattern recognizers that can have many useful chemometric applications[16–21]. It is reported[22] that ANN has a great potential to be used in the modelling of the complex non-linear systems. ANN are computational simulations of biological parallel signal processing. The basic elements of ANN are processing elements (Pes) and weighted connections. The collection of processing elements defined as a layer includes the inputs, one or more hidden layers, and an output layer. Each processing element receives values from all its input connections, performs a mathematical operation and produces a single output value (Fig. 1). The connection weights then store the information in the form of weight matrices. The value of the connection weights is determined by the neural network learning

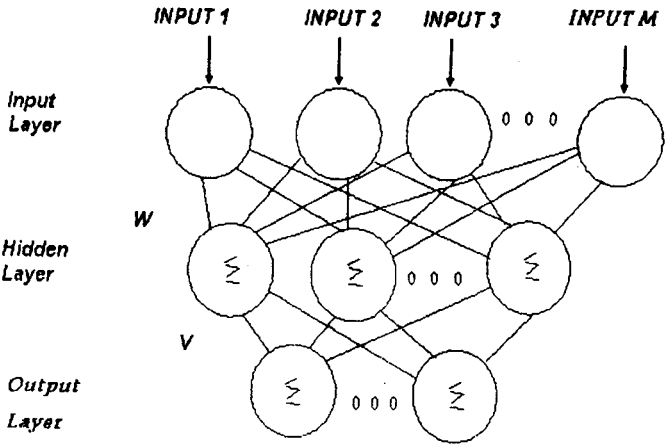


Fig. 1. Schematic diagram showing the topology of a three layered neural network.

procedure. Learning, therefore, is the most appealing quality of the ANN that could be either supervised, where sample input-output pairs are presented or unsupervised, where the network organizes itself. The most successful algorithm in chemical applications so far has been the back-propagation learning method in which the partial derivative of an error criterion with respect to the weights is adjusted as the negative gradient to minimize the error function[22–25]. In this study, an artificial neutral network (ANN) for processing the spectral data to reduce overlapping between the PAR and the MEF was used. These spectral data were then used as the original input patterns for the optimization process of ANN and the training parameters were used to obtain the minimum error of the model.

## EXPERIMENTAL

A double beam spectrophotometer UV-I CON 922 was used for absorbance measurements The network was constructed on a personal computer (Pentium III,

600 MHz, IBM compatible machine). The software used to construct the artificial neural network was written locally in MATLAB programming language[26].

**Materials:** MEF and PAR were provided by Darupakhsh Razy and Kimi Daru Company (Iran).

**Standard solutions:** Solutions of (25 mg/25 mL) of MEF and (25 mg/25 mL) of PAR were prepared in 0.1 M NaOH : methanol (1 : 9), respectively.

**Procedure.** The calibration sets (mixed standard solutions) were used for construction of ANN model and the independent test set was used to evaluate the quality of the model based on root mean square error (RMSE). The RMSE of prediction set is given by:

$$RMSE = \left\{ \frac{\sum_{i=1}^{n} (y_i - \hat{y}i)^2}{n} \right\}^{1/2} \quad (1)$$

where $y_i$ is the found concentration of drug, $\hat{y}_i$ is the actual concentration of drug and n is the total number of synthetic mixture.

The neural network which was employed had three layers. The first layer consisted of sixteen input elements, each of which corresponded to data extracted from the absorption spectra, the second layer was the hidden layer node and finally the third layer was the output layer. Therefore, parameters such as topology and learning rate were optimized and in each step RMSE was calculated.

**Real sample analysis:** In order to test the performance of the ANN in the real application, solutions of MEF and PAR tablets were separately analyzed with the established neural network. The solutions were also analyzed by the conventional standard method (USP).

## RESULTS AND DISCUSSION

The absorption data of standard solutions of PAR and MEF (used as calibration sets) at wavelengths between 190 and 400 nm were recorded which showed strong overlapping (Fig. 2). The calibration sets obtained are shown in Table-1. To reduce overlapping for the spectrum of PAR and MEF, absorptions at wavelength between 203 and 244 nm in the intervals of 1 nm were extracted and the extracted data and the concentration sets were used as input and output for ANN, respectively. In each step the sum square error (SSE) was used as an index of efficiency of the ANN during the training process. The neural network which was employed had three layers. The first layer consisted of sixteen input elements, each of which corresponded to data extracted from the absorption spectra and the second layer was the hidden layer nodes and finally the third layer was the output layer. In order to obtain the best topology for artificial neural network the number of nodes in the hidden layer and the learning rates for PAR and MEF were optimized. Figs. 3 and 4 show the plot of SSE *vs.* learning rate and plot of SSE *vs.* number of nodes in the hidden layer for PAR, respectively. From Figs. 3 and 4 it can be observed that the best optimized learning rate and the number of nodes in the hidden layer are 15 and 0.8, respectively. Similarly, Figs. 5 and 6 show the plot of SSE vs. learning rate and plot of SSE vs. number of nodes in the hidden

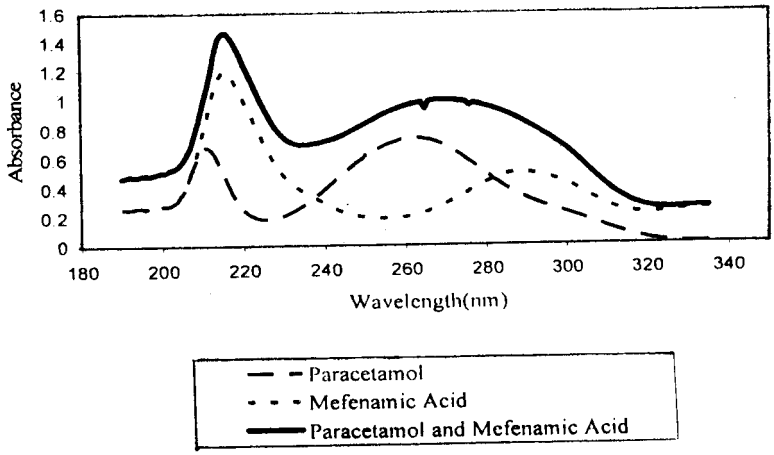


Fig. 2. Absorption spectra obtained for (a) paracetamol, (b) mefenamic acid and (c) mixture of paracetamol and mefenamic acid

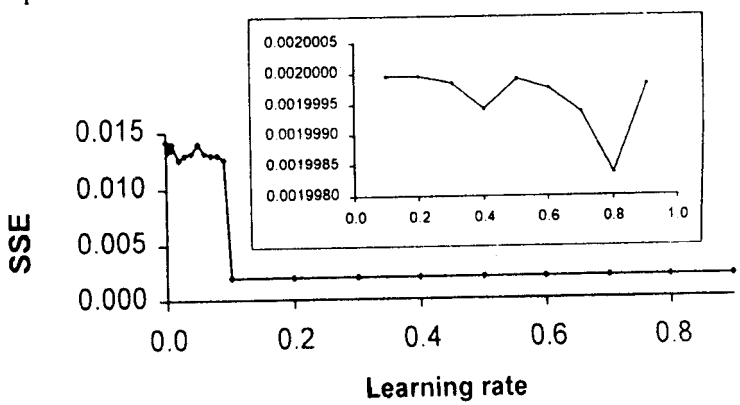


Fig. 3. The relationship between the sum square error (SSE) and the learning rate (LR) which defines the best learning rate used for ANN in the determination of paracetamol

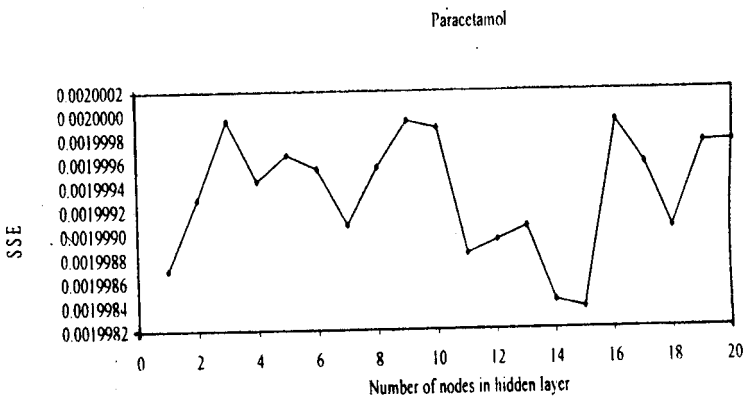


Fig. 4. Effect of the variation of the number of neurons in the hidden layer on the performance of ANN, used for paracetamol determination

layer for MEF, respectively, Again, from Figs. 5 and 6 it can be observed that the best optimized learning rate and the number of nodes in the hidden layer are 0.5 and 15 respectively.

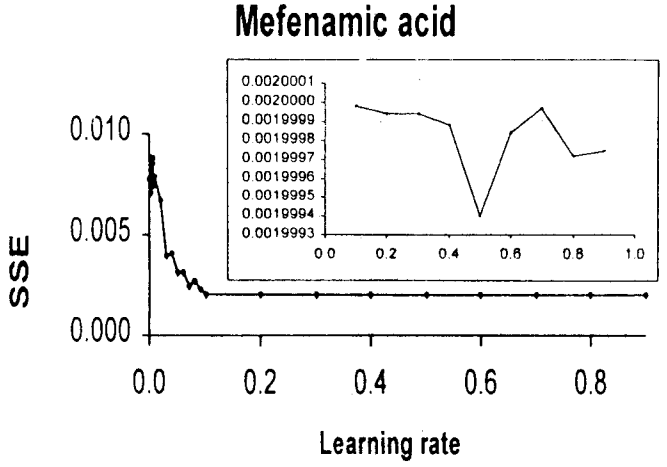


Fig. 5. The relationship between the sum square error (SSE) and the learning rate (LR) which defines the best learning rate used for mefenamic acid determination

TABLE-1
CONCENTRATION OF THE CALIBRATION SETS (mg/mL)

| Sample | Paracetamol | Mefenamic acid |
|---|---|---|
| 1 | 0.00 | 0.00 |
| 2 | 0.00 | 0.03 |
| 3 | 0.00 | 0.06 |
| 4 | 0.00 | 0.09 |
| 5 | 0.03 | 0.00 |
| 6 | 0.06 | 0.00 |
| 7 | 0.09 | 0.00 |
| 8 | 0.03 | 0.00 |
| 9 | 0.03 | 0.06 |
| 10 | 0.03 | 0.09 |
| 11 | 0.06 | 0.03 |
| 12 | 0.06 | 0.06 |
| 13 | 0.06 | 0.09 |
| 14 | 0.09 | 0.03 |
| 15 | 0.09 | 0.06 |
| 16 | 0.09 | 0.09 |

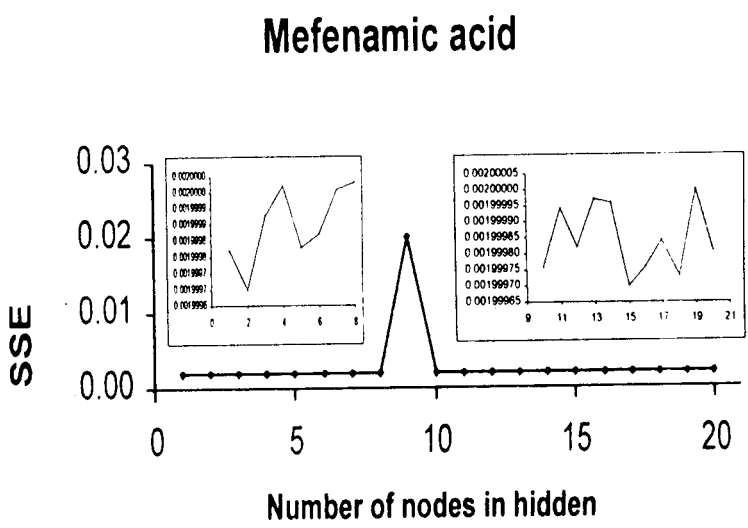


Fig. 6. Effect of the variation of the number of neurons in the hidden layer on the performance of ANN, used for mefenamic acid determination

Thus, the RMSE for both drugs were calculated from eqn. (1) and the results obtained are shown in Table-2 which shows the RMSE calculated for both paracetamol and mefenamic acid using test sets for prediction of concentrations are 0.04866 and 0.0342, respectively. Finally, the sample solutions were also analyzed by conventional standard method and the results obtained (Table-3) were compared with those of the proposed method. However, the results obtained show some differences between the standard method (USP) and the proposed method (ANN).

TABLE-2
TEST SET FOR PREDICTION OF CONCENTRATIONS
(mg/mL)

| Paracetamol | | Mefenamic acid | |
|---|---|---|---|
| Found | Target | Found | Target |
| 0.06 | 0.09 | 0.05 | 0.09 |
| 0.05 | 0.09 | 0.04 | 0.06 |
| 0.03 | 0.06 | 0.05 | 0.09 |
| 0.03 | 0.09 | 0.06 | 0.09 |
| 0.02 | 0.09 | 0.06 | 0.09 |
| RMS = 0.04866 | | RMS = 0.0342 | |

TABLE-3
COMPARISON OF RMSE OBTAINED BY PROPOSED METHOD (ANN) AND CONVENTIONAL STANDARD METHOD (USP) FOR PARACETAMOL AND MEFENAMIC ACID SOLUTIONS

| | Paracetamol | Mefenamic acid |
|---|---|---|
| Standard method (USP) | 0.3830 | 0.2120 |
| Proposed method (ANN) | 0.0566 | 0.0358 |

## Conclusions

The optimization process of ANN and the training parameters were used to obtain the minimum error of the model. The results obtained during the optimization process for the best learning rate and the best number of nodes in the hidden layer for PAR are 0.8 and 15, respectively. Similarly, the results obtained for the best learning rate and the best number of nodes in the hidden layer for MEF are 0.5 and 15, respectively, using artificial neural networks (ANNs). As a result, the RMSE calculated for both paracetamol and mefenamic acid are 0.04866 and 0.0342, respectively. The sample solutions were also analyzed by conventional standard method and the results obtained were compared with the proposed method. Thus, the results obtained show relatively little differences between the standard method (USP) and the proposed method (ANN). To overcome overlapping of spectrophotometric determination of mixture of PAR and MEF for spectrophotometric analysis, it required a separation method. Hence, artificial neural network is shown to be an interesting tool in chemometrics method to overcome such problem.

## REFERENCES

1. M.I. Toral, P. Richter, E. Araya and S. Fuentes, *Anal. Lett.*, **29**, 2679 (1996).
2. C. Yücesoy, K. Tülek and Fabad, *J. Pharm. Sci.*, **25**, 91 (2000).
3. P. Parimoo, C.V.N. Prasad and R. Vineeth, *J. Pharm. Biomed. Anal.*, **14**, 389 (1996).
4. L.R. Paschoal and W.A. Ferreira, *J. Farmaco*, **55**, 687 (2000).
5. V. Rodena, M.S. García, C. Sánchez-Pedreño and M.I. Albero, *Talanta*, **52**, 517 (2000).
6. C.M. Lai, R.G. Stoll, Z.M. Look and A. Yacobi, *J. Pharm. Sci.*, **68**, 1243 (1979).
7. H. Richardson and B.A. Bidingmeyer, *J. Pharm. Sci.*, **73**, 1480 (1984); A. Yacobi, Z.M. Look and C.M. Lai, *J. Pharm. Sci.*, **67**, 1668 (1978).
8. E. Dinc, C. Yücesoy, and F. Onur, *J. Pharm. Biomed. Anal.*, **28**, 1091 (2002).
9. E. Dinc, Ö. Üstündağ, F. Yurtsever and F. Onur, *J. Pharm. Biomed. Anal.*, **28**, 591 (2002).
10. E. Nevin, *J. Pharm. Biomed. Anal.*, **20**, 429 (1999).
11. H.C. Goicoechea and A.C. Olivieri, *J. Pharm. Biomed. Anal.*, **20**, 681 (1999).
12. ML. Luis, J.M.G. Fraga, F. Jiménez, A.I. Jiménez and J.J. Arias, *Talanta*, **53**, 761 (2001).
13. M. Blanco, J. Coello, H. Iturriaga, S. Maspoch and N. Villegas, *Analyst*, **124**, 911 (1999).
14. M.C. Ferraro, P.M. Castellano and T.S. Kaufman, *J. Pharm. Biomed. Anal.*, **26**, 443 (2001).
15. A. Safavi, G. Absalan and S. Maesum, *Anal. Chim. Acta*, **432**, 229 (2000).
16. G. Absalan, A. Safavi and S. Maesum, *Talanta*, **55**, 1227 (2001).
17. N. Yongnian, L. Chao and K. Serge, *Anal. Chim. Acta*, **419**, 185 (2000).

18. M. Blanco, J. Coello, H. Iturriaga, S. Maspoch and M. Porcel, *Anal. Chim. Acta*, **398**, 83 (1999).
19. B. Rezaei, A A. Ensafi and F. Shandizi, *Microchem. J.*, **70**, 35 (2001).
20. L. Cliffor,(Ed.), Neural Network: Theoretical Foundation and Analysis, IEEE Press, New York, pp. 3–24 (1992).
21. D.E. Rumelhar, in: J.L. McClelland (Ed.), Parallel Distributed Processing: Explorations in the Microstructures of Cognition, Vol. 1, MIT Press, Cambridge, pp. 675–695 (1986).
22. B.P. Bergeron, R.S. Shiffman and R.L. Rouse, *Comput. Biol. Med.*, **24**, 157 (1994).
23. P.D. Wasserman, Neural Computing: Theory and Practice, Van Nostrand Reinhold, New York, pp. 1–16 (1989).
24. A. Bos, M. Bos and W.E. Linden, "Artifical Neural Networks as a Tool for Soft-Modelling in Quantitative Analytical Chemistry: the Prediction of the Water Content of Cheese, *Anal. Chim. Acta*, **256**, 133 (1992).
25. MATLAB User's Guide, The MathWorks Inc. (1998).

(*Received*: 21 January 2004; *Accepted*: 6 July 2004) AJC-3502