Journal of the Serbian Chemical Society
JSCS@tmf.bg.ac.yu • www.shd.org.yu/JSCS
J. Serb. Chem. Soc. 73 (1) 87–95 (2008) UDC 543.544:*ibuprofen+*indomethacin+*naproxen:547.288.1
JSCS–3690 *Original scientific paper*

Potentiometric determination of ibuprofen, indomethacin and naproxen using an artificial neural network calibration

A. HAKAN AKTAŞ* and GÜZIDE PEKCAN ERTOKUŞ

Department of Chemistry, Faculty of Science & Art, Süleyman Demirel University, 32260 Isparta, Turkey

(Received 14 July 2006, revised 26 July 2007)

Abstract: In this study, three anti-inflammatory agents, namely ibuprofen, indomethacin and naproxen, were titrated potentiometrically using tetrabutylammonium hydroxide in acetonitrile solvent under a nitrogen atmosphere at 25 °C. MATLAB 7.0 software was applied for data treatment as a multivariate calibration tool in the potentiometric titration procedure. An artificial neural network (ANN) was used as a multivariate calibration tool in the potentiometric titration to model the complex non-linear relationship between ibuprofen, indomethacin and naproxen concentrations and the millivolt (mV) of the solutions measured after the addition of different volumes of the titrant. The optimized network predicted the concentrations of agents in synthetic mixtures. The results showed that the employed ANN can precede the titration data with an average relative error of prediction of less than 2.30 %.

Keywords: anti-inflammatory agents; potentiometric titration; artificial neural network (ANN).

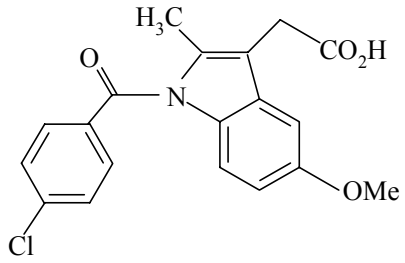
INTRODUCTION

Ibuprofen, indomethacin and naproxen are widely used clinically as non-steroidal anti-inflammatory agents. Their chemical structures are presented in Fig. 1. Several analytical methods have been reported in the literature for the determination of ibuprofen, indomethacin and naproxen in pharmaceutical preparations, including: flow-injection analysis – FTIR,[1] high performance liquid chromatography[2] and a potentiometric titration method for ibuprofen; spectrofluorimetry,[3] titrimetric methods[4,5] and spectrophotometric methods[6,7] for indomethacin; chemiluminescence,[8] capillary electrophoresis,[9,10] spectrofluorometry[11] and high performance liquid chromatography[12,13] for naproxen.

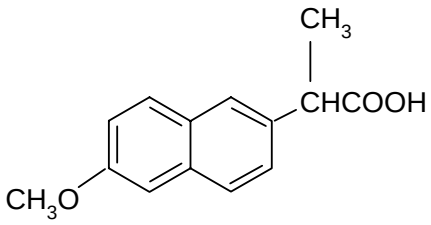
The European Pharmacopoeia describes methods for the routine analysis of these anti-inflammatory agents in pure form or in pharmaceutical formulations. The described volumetric methods, however, have some disadvantages. They are

* Corresponding author. E-mail: ahakan@fef.sdu.edu.tr
doi: 10.2298/JSC0801087A

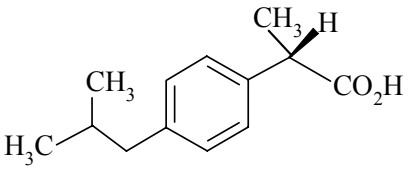
time consuming with poor precision and sensitivity and chemical indicators[14] are used for the end-point determination in the presence of colored or non-soluble excipients in the drug formulations.



Indomethacin



Naproxen



Ibuprofen

Fig. 1. Chemical structure and names of the studied compounds.

Potentiometric titrations are usually accurate but rather time-consuming and not suitable for the determination of very small quantities. A frequently encountered difficulty lies in the end-point determination, which arises from unstable electrode potentials.

Artificial neural networks (ANN) analyses are currently recognized as an effective and advantageous way to handle complex data and solve problems of non-linear calibration, pattern recognition, classification, prediction, and other related fields in analytical chemistry.[15–21] The corresponding non-linear multivariate maps use a non-linear transformation of the input variable to project inputs on to the designated attribute values in the output space. The strength of modeling with layered, feed-forward ANN lies in the flexibility of the distributed soft model defined by the weights of the network. Both linear and non-linear mapping functions can be modeled by suitably configuring the network. Multilayer, feed-forward neural networks trained with a back-propagation learning algorithm have become an increasingly popular technique.[22–24]

The non-linear relationship between mV and analyte concentration can be modeled by an ANN. In this study, a three-layer ANN was used with a back-propagation of error algorithm for modeling the complex relationship between mV and concentration through a multi-component titration. In order to decrease the number of data points, the data were factor analyzed before entering into the ANN. The original data were used as the input of the neural network. The method was applied to the simultaneous determination of ibuprofen, indomethacin and naproxen in their ternary mixtures and satisfactory results were obtained.

There are a number of publications on multivariate analysis, including: PLS and ANN for ibuprofen;[25,26] PLS and ANN for indomethacin[27,28] and PLS for naproxen.[29,30] However, no reports dealing with artificial neural networks of multicomponent analysis for ibuprofen, indomethacin and naproxen together have hitherto appeared.

EXPERIMENTAL

Apparatus

The electrode potentials were measured using a Hanna 9321 Microprocessor pH meter. A glass–silver chloride electrode system was used and the silver–silver chloride electrode was modified by replacing the saturated aqueous KCl solution with a saturated solution of KCl in methanol. All titrations were performed manually, under a nitrogen atmosphere at 25 °C.

Materials

Ibuprofen, indomethacin and naproxen, obtained from Refik Saydam Hygiene Centre (Ankara, Turkey), were chemically pure laboratory working standards having a purity of 99.6, 99.9 and 99.2 %, respectively.

Ibu-600 (Sifar) was labeled as containing 600 mg ibuprofen per tablet. Endol (Deva) was labeled as containing 25 mg indomethacin per capsule. Approwell Fort (Ali Raif) was labeled as containing 550 mg naproxen per tablet.

Potentiometric titration procedure

In a typical titration, a suitable amount of an individual drug agent or a mixture was placed in a 50 ml vessel and 5 ml 2-propanol was added to the solution. The solution was stirred and titrated with 0.0200 M tetrabutylammonium hydroxide solution using a micro-burette. The mV was recorded after each 0.02 ml addition of the titrant. For each solution, at least 70 data points were recorded.

Solutions of the pharmaceutical formulations

Capsule: Ten Endol capsules were weighed, and their average contents were calculated. The contents were pooled and powdered, and the required amount of this powder was accurately weighed and dissolved in 20 ml of acetonitrile as solvent.

Tablets: Ten or twenty Approwell Fort or Ibu-600 tablets were weighed and their averages were calculated. All the tablets were pooled and powdered, and the required amount of this powder was accurately weighed and dissolved in 20 ml of acetonitrile.

Methodology

A feed-forward ANN model with four layers of nodes was constructed as in Fig. 2.

An artificial neuron is the building component of an ANN designed to simulate the function of a biological neuron. The arriving signals, called inputs, multiplied by the connection weighted (adjusted) are first summed (combined) and then passed through a transfer function to the output of that neuron. The activation function is the weighed sum of the neuron's inputs and the most commonly used transfer function is a sigmoid function (Fig. 2).

A logistic function was used as the activation function in the neural network. The training and testing data sets must be normalized into the range 0.1–0.9. The input and the output data sets were normalized using the following equation:

$$X_{\mathrm{N}} = 0.1 + \frac{0.8(X - X_{\min})}{(X_{\max} - X_{\min})} \quad (1)$$

where X_{N} is the normalized value of a variable (the network input or the network output), X is the original value of a variable, and $X_{\max}$ and $X_{\min}$ are the maximum and minimum original

values of the variables, respectively. In order to produce sufficient data for training and testing of the model shown in Fig. 2, 9 different standard solutions were prepared using different concentrations of the agent and each standard solution was subjected to potentiometric titration. Randomly chosen 945 data pairs from these 1260 data pairs were used in the training of the neural network and the rest of the data were used in the testing. The root mean square error values were calculated from the following equation to prove quantitatively the accuracy of the testing results of the neural network models:

$$RMS = \sqrt{0.5N^{-1}\sum_{i=1}^{N}(X_1' - X_1)^2} \quad (2)$$

where N is the number of testing data and X_1' is the target value.

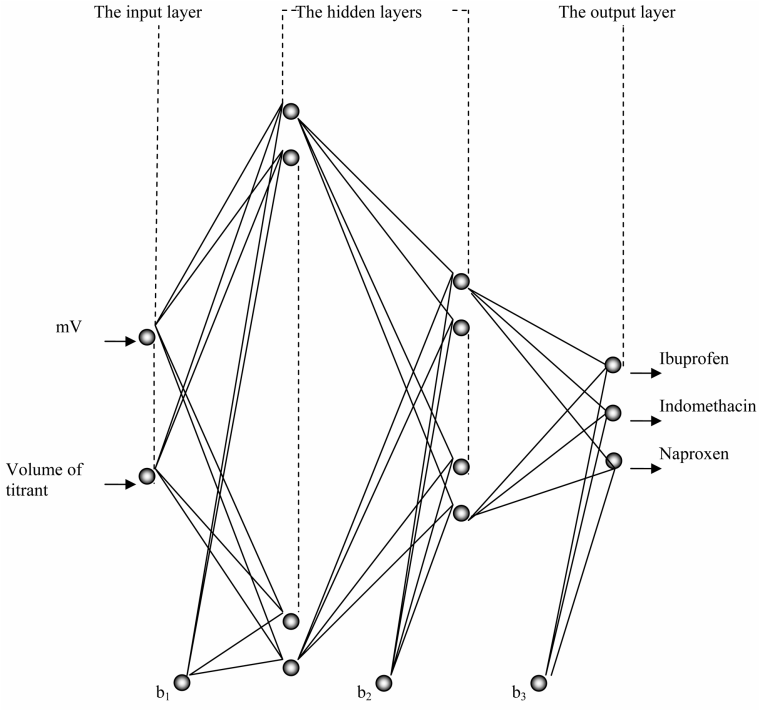


Fig. 2. Network architecture used in the potentiometric titration modeling (b_1 and b_2 are bias units).

MATLAB 7.0 software was used to construct the ANN models which have a sigmoidal logistic function with a back propagation of error algorithm. For this neural network modeling, an input layer, one or two hidden layers and an output layer were used.

RESULTS AND DISCUSSION

Ibuprofen, indomethacin and naproxen were directly titrated potentiometrically in acetonitrile with tetrabutylammonium hydroxide as the titrant. The mV titration curves of these agents and their mixtures are shown in Figs. 3 and 4. It is obvious that the titration curves of these three agents seriously overlap.

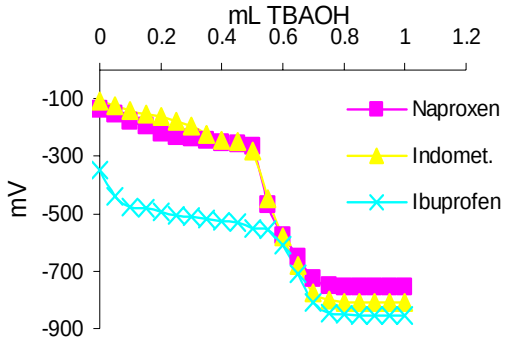


Fig. 3. Potentiometric titration curves for ibuprofen, indomethacin and naproxen titrated with tetrabutylammonium hydroxide in acetonitrile solution.

To obtain the best network performance, the optimal network architecture and parameters must be chosen. Studies of the network structure include the selection of the number of layers and number of nodes in each layer. The number of layers used for this neural network modeling was three, *i.e.*, an input layer, one or two hidden layers and an output layer. As can be seen from Fig. 2, two neurons were used in the input layer, *i.e.*, the mV and volume of the titrant (ml), and those of the hidden layer were optimized for each solution of the agents and mixtures. The titrant volume and mV value of the solution were considered as independent variables of the potentiometric titration method. Therefore, these variables were used as input variables in the network architecture.

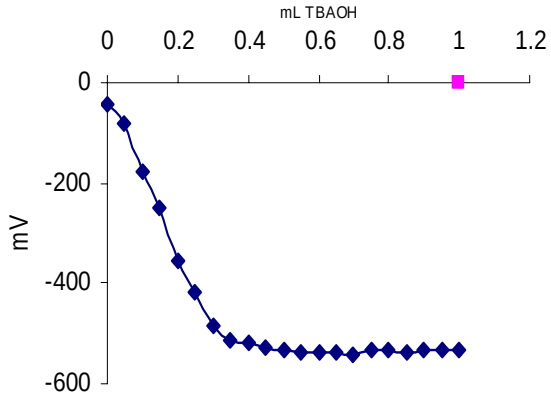


Fig. 4. Titration curves for equimolar ternary mixtures with tetrabutylammonium hydroxide as titrant.

Various neural network models, which have the logistic function, were trained and tested. In this step, the number of the hidden layer units of the network was determined by performance evaluation of the network models, defined in Table I. According to the RMS errors given in Table I, the NN5 2-16-8-3 model which performs best on a testing data set was selected as neural network model to predict the concentrations of the agent.

TABLE I. Comparison of the performances of the neural network models

Model	RMS error					
	Ibuprofen		Indomethacin		Naproxen	
	Training	Testing	Training	Testing	Training	Testing
NN1 2-7-3	0.000949	0.001031	0.001035	0.00332	5.31135×10^{-5}	0.001021
NN2 2-11-3	0.00095	0.00107	0.000998	0.099649	0.00077	0.001027
NN3 2-13-3	0.000904	0.001024	0.000977	0.001474	0.000733	0.001434
NN4 2-16-5-3	0.000795	0.045128	0.000816	0.157202	0.000671	0.04828
NN5 2-16-8-3	0.000624	0.00022	0.000708	0.00017	0.000673	0.00088

Parity plots of the predicted values of the acid concentrations from the NN5 model and those experimentally observed for the training data set are shown in Fig. 5. The correlation between the outputs of the NN5 model and the target values from the actual values for the testing data set are presented in Fig. 6. Predictions with a RMS error of less than 0.001 for all acids indicated that each agent concentration in a given solution was accurately predicted using the NN5 model. In addition, there is a good agreement between experimentally observed results and predicted results from the model structured (see Figs. 5 and 6).

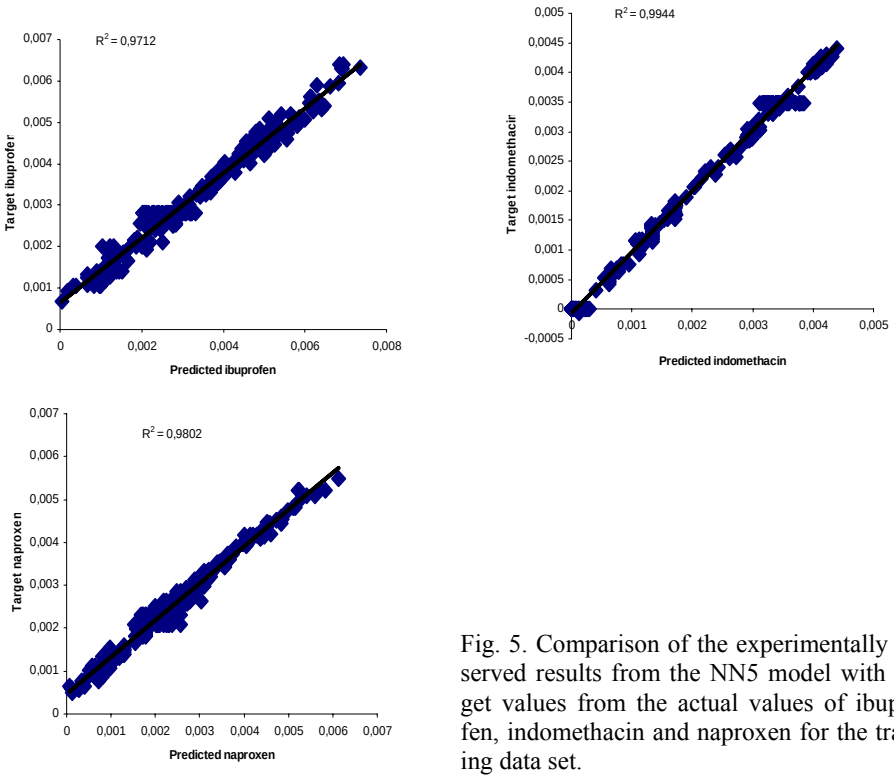


Fig. 5. Comparison of the experimentally observed results from the NN5 model with target values from the actual values of ibuprofen, indomethacin and naproxen for the training data set.

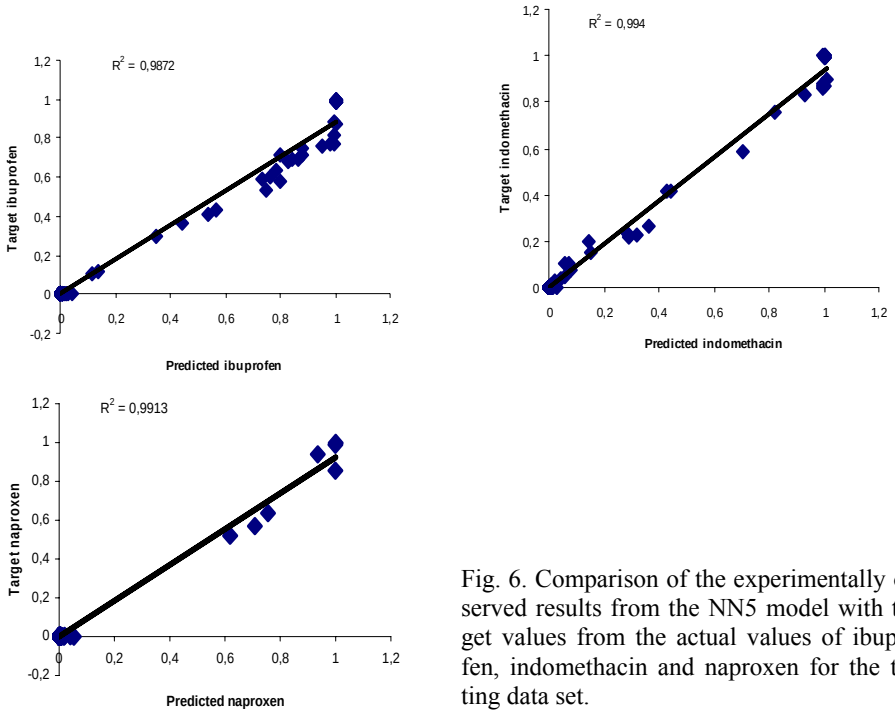


Fig. 6. Comparison of the experimentally observed results from the NN5 model with target values from the actual values of ibuprofen, indomethacin and naproxen for the testing data set.

Furthermore, several additional solutions were prepared and titrated to validate the selected model. Experimental results and estimated results from the model are given in Table II, from which it can be seen that the error in the obtained estimation was at a negligible level. The percent relative standard error of prediction varied between –7.9 and 5.6. The low average relative error of prediction (< 2.30 %) indicates that the employed networks can properly process the titration data and model the complex relationship between the concentration of the agents in the mixture and the mV data at different volumes of the titrant.

TABLE II. Statistical parameters calculated for the prediction set using the optimized neural network models

	Agent mixture composition								
	Ibuprofen			Indomethacin			Naproxen		
	Actual (mM)	Predicted (mM)	RE / %	Actual (mM)	Predicted (mM)	RE / %	Actual (mM)	Predicted (mM)	RE / %
1	0.05	0.0520	4.0	0.10	0.1011	1.1	0.15	0.1484	–1.07
2	0.10	0.0973	–2.7	0.15	0.1508	0.53	0.20	0.2043	2.15
3	0.15	0.149	–0.67	0.20	0.1982	–0.9	0.25	0.2567	2.68
4	0.20	0.2001	0.05	0.10	0.1056	5.6	0.15	0.1501	0.07
5	0.20	0.2005	0.25	0.15	0.1573	4.87	0.10	0.0921	–7.9

CONCLUSION

Agent concentrations in these potentiometric titrations could be estimated by the neural network with an error which might easily be negligible. Neural network modeling was able to process the non-linear relationship between the mV of the solutions at a given volume of titrant, and predict the concentrations of the agents in unknown sample solutions. For all agents, low prediction errors (< 2.30 %) and high correlation coefficients (0.9715, 0.9944 and 0.9802 for ibuprofen, indomethacin and naproxen, respectively) emphasize the high linear relationship between the predicted and actual concentrations.

И З В О Д

ПОТЕНЦИОМЕТРИЈСКО ОДРЕЂИВАЊЕ ИБУПРОФЕНА, ИНДОМЕТАЦИНА И НАПРОКСЕНА ПОМОЋУ МРЕЖЕ ВЕШТАЧКИХ НЕУРОНА

A. HAKAN AKTAŞ и GÜZIDE PEKCAN ERTOKUŞ

Department of Chemistry, Faculty of Science & Art, Süleyman Demirel University, 32260 Isparta, Turkey

Три против-упална чиниоца, ибупрофен, индометацин и напроксен, титрована су у овом раду потенциометријски тетрабутиламонијум-хидроксидом у ацетонитрилу као растварачу, у атмосфери азота на температури од 25 °C. Током процедуре потенциометријске титрације коришћен је за обраду података рачунарски програм MATLAB 7.0, као калибрациони алат са више променљивих. За моделовање комплексних, нелинеарних зависности између концентрације ибупрофена, индометацина и напроксена и миливолта (mV) раствора мерених након додавања различитих запремина титранта, примењена је мрежа вештачких неурона (ANN). Помоћу оптимизоване мреже могу се предвидети концентрације чинилаца у синтентичкој смеши. Резултати показују да се помоћу примењене ANN мреже могу проценити титрациони подаци са просечном релативном грешком процене мањом од 2,30 %.

(Примљено 14. јула 2006, ревидирано 26. јула 2007)

REFERENCES

1. S. Garrigues, M. Gallignani, N. Delaguardia, *Talanta* **40** (1993) 89
2. S. Ravisankar, M. Vasudevan, M. Gandhimathi, B. Suresh, *Talanta* **46** (1998) 1577
3. C. S. P. Sastry, D. S. Mangola, K. E. Rao, *Analyst* **111** (1986) 323
4. *European Pharmacopoeia, 4th Edition*, HM Stationery Office, 2002, pp. 1032–1033, 1359–1360, 1367–1368 and 1617–1618.
5. A. M. Gerakis, M. A. Koupparis, C. E. Efstathiou, *J. Pharm. Biomed. Anal*. **11** (1993) 33
6. C. S. P. Sastry, A. R. M. Rao, *Analysis* **15** (1987) 569
7. P. Nagaraja, R. A. Vasantha, H. S. Yathirajan, *J. Pharm. Biomed. Anal*. **31** (2003) 563
8. A. Campliglio, *Analyst* **123** (1998) 1571
9. M. Fillet, L. Fotsing, J. Bonnard, J. Crommen, *J. Pharm. Biomed. Anal*. **18** (1998) 799
10. A. Guttman, N. Cooke, *J. Chromatogr. A* **685** (1984) 155
11. P. Damiani, M. Bearzotti, M. A. Cabezon, *J. Pharm. Biomed. Anal*. **29** (2002) 229
12. J. H. Satterwhite, F. D. Bourdinat, *J. Chromatogr. Biomed. Appl*. **431** (1988) 444
13. M. Y. Hyun, M. S. Na, C. S. Min, *J. Chromatogr. A* **732** (1996) 209
14. D. A. Skoog, D. M. West, F. J. Haller, *Analytical Chemistry, Sixth Edition*, Saunders College Publishing, 1994, p. 354

15. A. H. Aktaş, S. Yaşar, *Chim. Acta Slov*. **51** (2004) 273
16. O. Çakırer, E. Kılıç, O. Atakol, A. Kenar, *J. Pharm. Biomed. Anal*. **20** (1999) 19
17. G. Gonzales, R. Ventura, A. K. Smith, R. Torre, J. Segura, *J. Chromatogr. A* **719** (1996) 251
18. M. J. Arcos, M. C. Ortiz, B. Villahoz, L. A. Sarabia, *Anal. Chim. Acta* **339** (1997) 63
19. A. H. Aktaş, G. Pekcan, *Asian J. Chem*. **18** (2006) 2025
20. D. B. Strickmann, G. Blaschke, *J. Pharm. Biomed. Anal.* **25** (2001) 974
21. S. Yılmaz, B. Uslu, S. A. Özkan, *Talanta* **54** (2001) 351
22. N. M. El Kousy, *J. Pharm. Biomed. Anal*. **20** (1999) 185
23. R.T. Sane, M. Francis, A.R. Khatri, *J. Planar Chromatogr.-Mod. TLC* **11** (1998) 211
24. Y. Özkan, N. Doğanay, N. Dikmen, A. Işımer, *Farmaco* **55** (2000) 433
25. X. Y. Wang, F. Cui, Y. Yonezowo, H. Sumado, *Chem. Pharm. Bull.* **51** (2003) 772
26. M. M. Sena, C. B. Freitas, L. C. Silva, C. N. Perez, Y. O. Poulo, *Quim. Nova* **30** (2007) 75
27. T. Okumura, M. Nakazono, M. Otsuko, K. Tokayono, *Colloids Surf., B* **49** (2006) 153
28. T. Okumura, M. Otsuko, *Pharm. Res.* **22** (2005) 1350
29. E. Dinç, A. Özdemir, H. Aksoy, Ö. Üstündağ, D. Balenou, *Chem. Pharm. Bull.* **59** (2006) 415
30. M. Kim, H. Chung, Y. Woo, M. Kemper, *Anal. Chim. Acta* **579** (2006) 209.