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Principal component articial neural network calibration models for the simultaneous spectrophotometric estimation of mefenamic acid and paracetamol in tablets

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Abstract: Simultaneous estimation of all drug components in a multicomponent analgesic dosage form with artificial neural networks calibration models using UV spectrophotometry is reported as a simple alternative to using separate models for each component. A novel approach for calibration using a compund spectral dataset derived from three spectra of each component is described. The spectra of mefenamic acid and paracetamol were recorded as several concentrations within their linear range and used to compute a calibration mixture between the wavelengths 220 to 340 nm. Neural networks trained by a Levenberg–Marquardt algorithm were used for building and optimizing the calibration models using MATALAB® Neural Network Toolbox and were compared with the principal component regression model. The calibration models were throughly evaluated at several concentration levels using 104 spectra obtained for 52 synthetic binary mixtures prepared using orthogonal designs. The optimized model showed sufficient robustness even when the calibration sets were constructed from a different set of pure spectra of the components. The simultaneous prediction of both components by a single neural netwook with the suggested calibration approach was successful. The model could accurately estimate the drugs, with satisfactory precision and accuracy, in tablet dosage with no interference from excipients as indicated by the results of a recovery study.

Keywords: artificial neural networks, principal components, UV spectrophotometry, mefenamic acid, paracetamol.

INRODUCTION

Artificial Neural Networks (ANNs) are a data processing system consisting of a large number of simple, highly interconnected processing elements inspired by the biological system and designed to simultate the neurological processing ability of the human brain. Theoretical background information on ANNs can be found elsewhere.[1–5] Applications of ANNs in the field of chemistry and pharmacy have

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been reviewed.[6–13] Computationally, ANN is an approach for handling multivariate and multi-response data and hence suitable for modeling, *i.e.*, for a search for an analytical function that will give a specified *n*-variable output for any *m*-variable input.[11] Unlike standard modeling techniques where a mathematical function must be known in advance, ANN models do not require knowledge of the mathematical function in advance and are called 'soft models', *i.e.*, models which are able to represent the experimental behavior of a system when the exact description is missing or too complex.[14] ANNs adapt to any relation between input and output data on the basis of their supervised training. The flexibility of ANNs and their ability to maintain their performance even in the presence of significant amounts of noise in the input data are highly desirable[2,9] since perfectly linear and noise-free data sets are seldom available in practice, thus making then suitable for multivariate calibration modeling. There are reports on the appilcation of ANNs for mixture analysis,[15–19] although most of them employ separate networks for the estimation of each component and calibration involving synthetic binary mixtures.

The current work evaluates the performance characteristics of principal component artificial neural network (PC–ANN) calibration models trained with a Levenberg–Marquardt algorithm[20] and compares it with principal component regression (PCR) models applied to the analysis of an analgesic combination of mefenamic acid (MNA) 500 mg and paracetamol (PML) 450 mg available in India.

In multivariate calibration, it is desirable to have a sufficiently large calibration dataset which becomes a difficult task especially when the calibration process has to be repeated at periodic intervals. Hence, the present work also demonstrates the use of computed spectral datasets and compares it with the normal practice of using spectra of synthetic mixtures for the calibration models. It is commonly believed that neural network calibration models must exclusively be used only when non-linearity exist in the problem. This work also demonstrates the postulation that neural network models of appropriate configuration could equal the performance of linear models for linear problems, although it is well known that they outperform linear models as non-linearity creeps in.[9] A method for routine pharmaceutical quality control of a tablet dosage form by multivariate calibration based on soft modeling using both artificial neural network calibration models and principal component regression models is presented.

EXPERIMENTAL

Chemicals and reagents

Analytical reagent grade NaOH was used to prepare 0.1 M NaOH solution in distilled water, which then served as a solvent for making the stock solutions and all further dilutions of MNA, PML, their standard combinations and the tablet powder. Class A volumetric glassware, such as pipettes and volumetric flasks, were used for performing the dilutions.

Instruments and software

UV absorption measurements were carried out on a Perkin Elmer Lambda 25 double beam spectrophotometer controlled by UVWINLAB sofware version 2.85.04, using matched 1.0 cm quartz cells. All weights were measured on an electronic balance with 0.01 mg sensitivity. The spec-

tra of all the solutions were recorded against a blank solution containing no analytes, between 200 to 400 nm and seved in ASCII format. Matlab® version 6.1 was employed for building the PC–ANN and PCR calibration models on the same data using custom built functions for the MATLAB in order to provide for a comparative evaluation of their performance. All computations were performed using a desktop computer with a Pentium 4, 1.6 GHz processor and 256 MB RAM.

Preparation of standard solutions

Standard solutions of pure MNA and PML were made at different concentration levels ranging from 5 to 19 mg L^{-1} and 5 to 17 mg L^{-1}, respectively, for the purpose of linearity determination and to design the calibration data matrix from their spectra. The analytical levels of 10 mg L^{-1} and 9 mg L^{-1}, respectively, for MNA and PML were chosen. The absorbance spectra at the analytical level chosen for the two standards, are shown in Fig. 1.

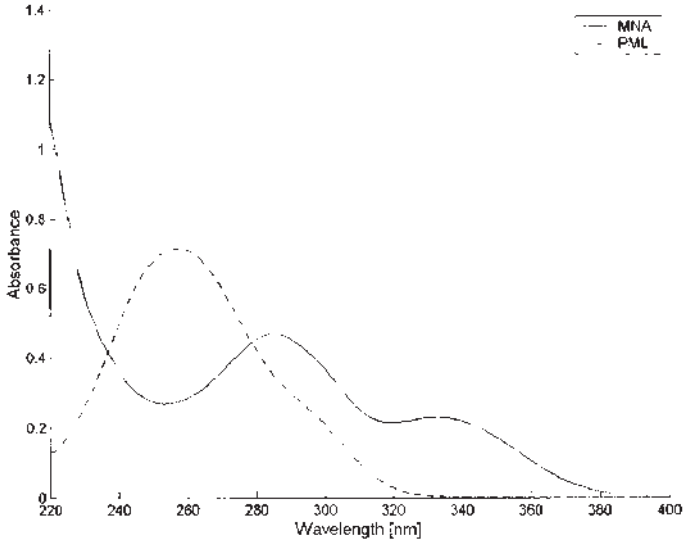

Fig. 1. UV Spectra of mefenamic acid and paracetamol about the analytical level. Overlain spectra of MNA at a concentration of 11.052 mg L^{-1} and PML at a concentration of 9.962 mg L^{-1} in 0.1 M sodium hydroxide.

Calibration data

Since the absorbances were linearly additive in the desired range and no serious baseline problems or interactions were found in trial studies in the desired range of concentration, the process described below was adopted in the design of a calibration data set for training the PC–ANN. Three spectra of each component at three different concentration levels (5.526, 11.052 and 16.578 mg L^{-1} for MNA and 4.981, 9.962 and 16.604 mg L^{-1} for PML) around the chosen analytical level of 10 mg L^{-1} for MNA and 9 mg L^{-1} for PML, were employed in a full factorial design to provide a fair simulation of the calibration data set with some degree of experimental variation. A full factorial design was employed to obtain 49 training pairs (7 concentration levels for each component resulting in $7 \times 7 = 49$ mixtures) from each spectral pair resulting in a total of 441 training pairs (49×9) representing the mixture space evenly with target concentrations that were orthogonal, as illustrated in Fig. 2. A total of 441 thus-obtained training pairs, constituting the complete calibration set, were used to train the PC–ANN model. All the target concentrations in the calibration set were then standardized (to a mean of 0 and standard deviation of 1). The spectral region between 220 and 340 nm at 1 nm intervals was chosen on the basis of visual inspection of the spectra.

Validation data

Randomized validation data sets were used for internal validation and formation of the training of the PC–ANN at the optimum point, to prevent over-fitting and retain the generalized ability of the network. A

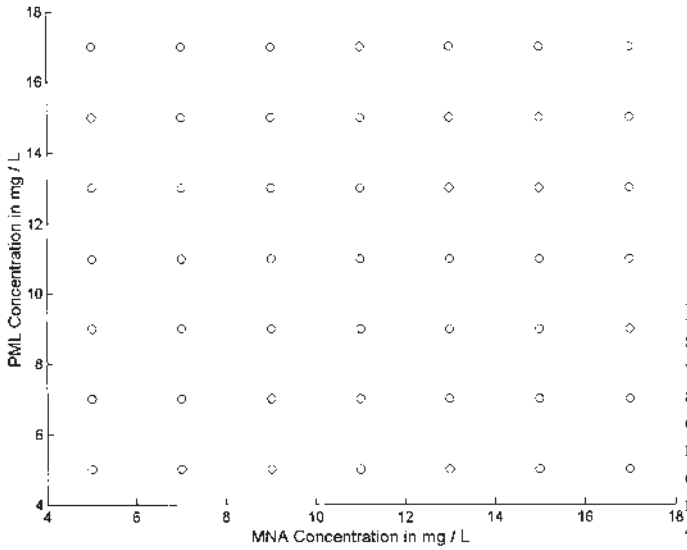

Fig. 2. Calibration dataset design. A full factorial design with each point representing a mixture at the respective concentration of the components. Seven levels of concentrations of each component were used resulting in 49 mixtures.

validation data set of the same size was also designed from three different pairs of spectra of MNA and PML standards, of which at least two pairs were different from those used in the calibration dataset.

Synthetic binary mixtures for model evaluation

Synthetic binary mixtures were prepared on different days from fresh stock solutions of pure MNA and PML, each day by separate weighing, in distilled water. Standard mixtures of the components were prepared with concentrations lying within the known linear absorbance–concentration range by diluting varying proportions of MNA and PML stock solutions; the concentration of MNA varied between 50 to 175 % of the test level concentration, while that of PML vared between 45 to 175 % of its analytical level concentration. The concentrations of the components were selected to span the mixture space fairly evenly, as shown in Fig. 3. Each point on the plot represent a mixture, each of which was assigned to one

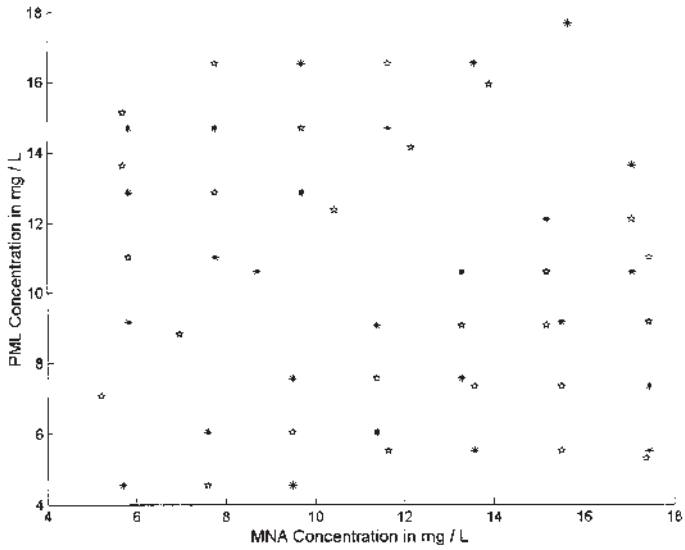

Fig. 3. Synthetic binary mixture design for the testing of the neural networks. Each point represents a mixture at the respective concentration of the components. The mixtures were split in two groups T1 (*) and T2 (☆). The design ensures that the model is thoroughly validated in a well distributed concentration range, especially with regard to the chosen analytical level.

of the two groups, namely, T1 or T2. The mixtures were split into two groups such that the mixtures in each group spanned the concentration range as much as possible. This was done to compare the performance of the models calibrated with the computed calibration datasets *versus* the synthetic binary mixture dataset. When T1 was used for the calibration of the model, T2 was used as the test dataset for evaluation and *vice versa*. All the mixtures were collectively referred as T (T1+T2), the test dataset for evaluating the models calibrated with computed calibration dataset. All the datasets were obtained from the spectra using the same wave length range and interval.

Processing of tablet dosage form

For the analysis of the active components of the analgesic tablet (Meftal Forte, MNA 500 mg and PML 450 mg, Blue Cross Ltd., India, Batch No: HKF 333), twenty tablets were accurately weighed, carefully powdered and mixed. Tablet powder corresponding to the equivalent of 100 mg of MNA was dissolved in distilled water by sonication for 5 min and made up to 100 ml. The solution was centrifuged and 10 mL of the supernatant was diluted to 100 mL to obtain a working dilution. The working dilution was diluted to 100 mL to make the final solution. The final dilutions were made in two replicates from each working dilution, repeating the entire process for a total of 5 weights of the tablet powder. Each dilution was scanned in triplicate, each time with a fresh filling.

For accuracy studies, by recovery, the same tablet powder was used in amounts corresponding to the equivalent of 55 mg of MNA (in order to enable spiking up to the desired levels). The powder was then spiked with a known quantity of pure MNA and PML and dissolved in 0.1 M NaOH by sonication, with the same dilutions was applied as for the tablet powder, as explained above. A total of five powder samples were spiked to different levels in the range of 60 to 150 %, each in two dilution replicates.

PC–ANN Calibration model

Principal component analysis was carried out by employing custom developed functions in MATLAB using the inbuilt Eigen value decomposition function ('eig') to obtain the latent (Eigen) vectors and the corresponding Eigen values. The scores obtained by projecting the standardized absorbance values on to these Eigen vectors were used as inputs. PC–ANNs had an input layer with neurons corresponding to the number of principal components chosen for the employed calibration set, a variable number of neurons in the hidden layer and two neurons in the output layer, corresponding to the two components of interest. The input and output layer nodes had a linear transfer function, whereas the hidden layer nodes had a sigmoid transfer function for the PC–ANN, decided on the basis of earlier studies on neural models.[16,17] The number of principal components was varied from 2 to 5, thus resulting in a corresponding range of inputs for the network. Optimization of the network, to achieve generalization of the model and avoid over-fitting, was done by starting with 2 neurons in the hidden layer and gradually increasing the number until no significant improvement in performance in terms of the relative prediction error (*RPE*) (< 2 % reduction in the mean % *RPE* and also by ANOVA) in the network was achieved for each set of inputs (principal components). The PC–ANNs were trained in five replicates according to the Levenberg–Marquardt[20] algorithm, available in the neural network toolbox of MATLAB through the 'trainlm' function. The training was terminated when the validation performance, as estimated by the mean square error (*MSE*) for a validation dataset, increased continually for more than 10 epochs since the last time it decreased. The mean square error (*MSE*) was calculated according to Eq. (1) and the mean percentage relative prediction error (*% RPE*), computed as given in Eq. (2) for both components was the criterion used in the optimization of the neural network configuration.

$$\textit{Mean Square Error (MSE)} = \frac{1}{m}\sum_{1}^{m}(C_{\text{act}} - C_{\text{pred}})^2 \tag{1}$$

$$\%\ RPE = \frac{100 \times \sqrt{MSE}}{\overline{C}} \tag{2}$$

C_{act} is the desired target, C_{pred} is the output produced by the network for each input vector, $\overline{C}$ is the mean concentration of the comoponent and m is the number of input vectors or samples. Three

different calibration datasets were used for each given configuration and five replicate models obtained each with different initialization of weights by the Nguyen–Widrow[21] method in building the calibration models.

PCR Calibration model

The PCR model also had the same inputs and targets as the PC–ANN model and was built and tested using a custom developed function in MATLAB for multi linear regression. The number of principal components was optimized by evaluating the performance on the test dataset from the synthetic binary mixtures (T) for models calibrated with three different calibration datasets, as for the above neural models.

Evaluation of the models

All trained PC–ANNs with different configurations and the PCR models were evaluated for their modeling capability by testing with the spectral data obtained from the synthetic binary mixtures (Fig. 3). The mean percentage relative prediction error (*% RPE*) representing the combined error for the entire mixture, was used to perform multiple comparisons between all the models developed with three different calibration datasets and chose the optimum configuration for the calibration model. The optimized model of each type was characterized by its performance parameters, such as *% RPE* and other regression parameters, for the actual *versus* the predicted concentrations, such as slope, intercept, residual standard deviation and the square of correlation coefficient (R^2), for each component of the mixture.

Tablet analysis

Spectra recorded from the tablet solutions were analuzed by the chosen optimum PC–ANN and PCR models and the concentrations predicted for each solution were used for the calculation of the tablet content. Similarly MNA and PML concentrations in the solutions prepared for the recovery study were also obtained from the respective spectra and the percentage recovery was calculated to determine the accuracy of the method.

RESULTS AND DISCUSSION

When considered separately, concentrations between 5 to 19 mg L^{-1} for MNA and 5 to 17 mg L^{-1} for PML were studied and found to be linear over the range of 9 concentration levels (absorbances at 285 nm for MNA and 257 nm for PML) with R^2 values of 0.9994 and 1.0, slopes of 0.0408 and 0.0715, intercept of 0.0049 and –0.0016 and residual standard deviation about the regression line being 0.0043 and 0.0018, respectively.

There are many pitfalls in the use of calibration models, perhaps the most serious being the variability in the instrument performance over time. Therefore, it is necessary to reform the calibration model on a regular basis, by running a standard set of samples, possibly on a weekly basis.[22] Like other regression methods, there are constraints concerning the number of samples, which sowetimes may limit the development of an ANN model. The number of adjustable parameters (synaptic weights) is such that the calibration set is rapidly over-fitted if too few training pairs are available, leading to a loss of generalization ability. Therefore, calibration sets of several hundred training pairs may often be necessary to obtain a representative distribution of the concentration across their range. This makes it expensive in terms of time and resources to physically develop calibrations of mixtures in

such large numbers, which is rarely possible in routine laboratory studies, and justifies our attempt to use calibration data set mathematically constructed from the individual spectra of the components. However, this approach cannot be applied in case where significant non-linearity is exhibited. In addition, it also served to demonstrate the eather-studied capability of neural models of linear datasets.

TABLE I. Optimization of PC–ANN calibration model based on % mean *RPE*

PC_S[a]	Hidden Neurons	Mean % *RPE*[b]	Standard Deviation
2	2	2.2738	0.2473
2	3	2.2705	0.2463
2	4	2.2731	0.2475
2	5	2.2862	0.2432
3	2	1.5964	0.1396
3	3	1.7092	0.1448
3	4	1.9127	0.5135
3	5	2.0719	0.3300
4	2	2.5854	0.9591
4	3	2.5912	0.9143
4	4	2.9886	1.0360
4	5	3.0780	1.2718

[a]Principal components chosen for inputs; [b]Average of 15 PC–ANN Models trained over tthree different calibration datasets

The PC–ANN models were evaluated for their performance on the basis of percentage relative prediction error (% *RPE*). The PC–ANN model trained rapidly taking less than one minute and fewer than 300 epochs. Each model of PC–ANN, was trained five times using a test dataset with random initialization of weights and mean % *RPE* and then used to perform ANOVA eith multiple comparisons in MATLAB, whereby the optimum models were determined. Based on these results, shown in Table I, an input of 3 neurons, an output of 2 neurons, both having a linear transfer function, and a hidden layer of 2 neurons, with a sigmoid transfer function, was the optimum configuration for the PC–ANN model. The 3 inputs correspond to the scores on the optimal number of principal components obtained for the standardized calibration data matrix.

The PC–ANN models with the optimal configuration and trained with three different calibration sets and validation sets were evaluated for their prediction characteristics using 104 spectra of 52 synthetic binary mixtures, including replicates. The prediction characteristics of the models were studied by regression of the actual *versus* the predicted concentrations of each component of the binary synthetic mixture (T), which are presented in Table II for MNA and Table III for PML.

TABLE II. Mefenamic acid prediction characteristics using various calibration models

Model	Calib Dataset[a]	Test Dataset[b]	% *RPE*	Slope	Interect	Res. SDc	R^2
PC–ANN	C1	T	1.572	0.992	0.139	0.175	0.998
	C2	T	1.604	0.992	0.158	0.173	0.998
	C3	T	1.536	0.991	0.127	0.176	0.998
	T1	T2	1.124	1.013	– 0.190	0.126	0.999
	T2	T1	1.660	0.992	0.152	0.181	0.998
PCR	C1	T	1.556	0.992	0.139	0.172	0.998
	C2	T	1.584	0.992	0.156	0.170	0.998
	C3	T	1.515	0.991	0.126	0.173	0.998
	T1	T2	1.254	1.018	– 0.247	0.140	0.999
	T2	T1	1.640	0.991	0.167	0.177	0.998

[a]Calibration dataset, C1, C2, C3 are calibration datasets used for the calibration of the models. [b]T1 and T2 are binary synthetic mixtures as illustrated in Fig. 3. T = (T1+T2). When T1 is used for calibration, T2 is used for evaluation and *vice versa*. [c]Residual standard deviation of the predictions by the model. The % *RPE* between PC–ANN and PCR models were not significantly different (*P*-value = 0.9301); the residual standard deviations were also not significantly different across the models (*P*-value = 0.9873), as found by ANOVA

TABLE III. Paracetamol prediction characteristics using various calibration models

Model	Calib Dataset[a]	Test Dataset[b]	% *RPE*	Slope	Intercept	Res.SD[c]	R^2
PC–ANN	C1	T	1.519	0.999	0.077	0.142	0.998
	C2	T	1.958	1.009	0.016	0.171	0.997
	C3	T	1.405	0.999	0.027	0.146	0.999
	T1	T2	2.048	0.989	0.024	0.192	0.997
	T2	T1	1.499	0.997	0.085	0.149	0.998
PCR	C1	T	1.507	0.999	0.080	0.141	0.998
	C2	T	1.953	1.009	0.018	0.171	0.997
	C3	T	1.400	0.999	0.030	0.145	0.999
	T1	T2	1.949	0.996	– 0.033	0.188	0.997
	T2	T1	1.438	0.992	0.131	0.142	0.999

[a]Calibration dataset, C1, C2, C3 are calibration datasets used for the calibration of the models. [b]T1 and T2 are binary synthetic mixtures as illustrated in Fig. 3. T = (T1 + T2). When T1 is used for calibration, T2 is used for evaluation and *vice versa*. [c]Residual standard deviation of the difference (*P*-value = 0.8457); the residual standard deviations were also not significanlty different across the models (*P*-value = 0.8505), as found by ANOVA

Spectra obtained from 30 tablet solutions (including replicates) prepared from 5 different weighings as described in the Experimental section were analzyed by the optimum calibration models and the average content was calculated. The results are summarized in Tables IV and V for MNA and PML, respectively, for ease of comparison. There was no significant difference in the content predicted across the models as found by ANOVA. The accuracy of the method for the analysis of tablets was further investigated using recovery studies, as described in the Experimental section. The mean percentage recoveries of both MNA and PML and their relative standard deviation closely agreed (no significant difference was found by ANOVA) between the PC–ANN and the PCR models, as indicated in Tables VI, VII.

TABLE IV. Mefenamic acid content prediction in tablet samples using vaiour calibration models

	PC–ANN			PCR		
	C1	C2	C3	C1	C2	C3
Sample 1/mg	504.11	505.81	502.75	504.15	505.80	502.73
Sample 2/mg	501.37	502.60	500.16	501.36	502.53	500.08
Sample 3/mg	500.33	500.75	499.36	500.28	500.63	499.24
Sample 4/mg	502.97	502.93	502.15	502.84	502.72	501.94
Sample 5/mg	496.90	497.01	496.03	496.77	496.79	495.82
Mean Tablet content/mg	501.14	501.82	500.09	501.08	501.69	499.96
Standard Deviation	2.777	3.242	2.660	2.821	3.307	2.705
Relative Std Deviation	0.554	0.646	0.532	0.563	0.659	0.541
Amount on the label/mg	500.00	500.00	500.00	500.00	500.00	500.00
% Of the reported content	100.23	100.36	100.02	100.22	100.34	99.99

C1, C2 and C3 are the calibration datasets. MNA content prediction by PC–ANN and PCR models calibrated with the respective datasets are shown. The tablet content prediction by the PC–ANN and PCR models across the calibration datasets were not significantly different (P-value = 0.9206), as found by ANOVA

TABLE V. Paracetamol content prediction in table samples using various calibration models

	PC–ANN			PCR		
	C1	C2	C3	C1	C2	C3
Sample 1/mg	432.01	435.76	429.90	432.36	436.20	430.06
Sample 2/mg	436.64	439.15	434.56	436.94	439.55	434.68
Sample 3/mg	438.24	438.68	436.21	438.51	439.04	436.31
Sample 4/mg	439.21	438.43	437.18	439.44	438.76	437.25
Sample 5/mg	442.32	441.91	440.29	442.52	442.20	440.34

TABLE V. Continued

	PC–ANN			PCR		
	C1	C2	C3	C1	C2	C3
Mean Tablet content/mg	437.68	438.79	435.63	437.96	439.15	435.73
Standard Deviation	3.790	2.188	3.821	3.730	2.141	3.781
Relative Std Deviation	0.866	0.499	0.877	0.852	0.488	0.868
Amount on the label/mg	450.000	450.000	450.000	450.000	450.000	450.000
% Of the reported content	97.26	97.51	96.81	97.32	97.59	96.83

C1, C2 and C3 are the calibration datasets. PML content prediction by PC–ANN and PCR models calibrated with the respective datasets are shown. The tablet content prediction by the PC–ANN and PCR models across the calibration datasets were not significantly different (P-value = 0.8448), as found by ANOVA

TABLE VI. Mefenamic acid recovery studies using the calibration models

Spiked Sample	PC–ANN			PCR		
	Actual/mg	Found/mg	% Recovery	Actual/mg	Found/mg	% Recovery
1	70.44	73.04	103.68	70.44	73.13	103.82
2	80.05	82.43	102.97	80.05	82.50	103.07
3	106.33	107.39	100.99	106.33	107.35	100.96
4	132.06	132.92	100.65	132.05	132.78	100.55
5	155.88	155.42	99.70	155.87	155.37	99.68
Mean			101.60			101.62
RSD			1.637			1.725

No significant difference in the recovery percentage of MNA was found by ANOVA (P-value = 0.9871)

TABLE VII. Paracetamol recovery studies using the calibration models

Spiked Sample	PC–ANN			PCR		
	Actual/mg	Found/mg	% Recovery	Actual/mg	Found/mg	% Recovery
1	62.37	62.45	100.12	62.40	62.50	100.16
2	71.33	71.83	100.70	71.36	71.91	100.77
3	95.69	94.89	99.16	95.72	94.93	99.17
4	119.57	118.35	98.98	119.60	118.29	98.91
5	141.79	139.49	98.38	141.82	139.40	98.29
Mean			99.47			99.46
RSD			0.935			0.999

No significant difference in the recovery percentage of PML was found by ANOVA (P-value = 0.9898)

The use of linear transfer functions in the output layer in the neural network calibration models resulted in faster training with no significant difference from the PCR performance. The ANN model performed well in estimating both the components simultaneously when tested with spectra recorded on different days and exhibited ruggedness even when different sets of constructed calibration data were used in the model development. The tablet dosage could be analysed without any interference from the excipients. Since it took less than 1 minute for training, the PC–ANN model can be quickly calibrated whenever the spectrophotometer performance characteristics alter using only three pairs of spectra of the individual components, which is a considerable advantage.

Our elaborate study confirmed the observations of Gemperline *et al.*[23] from a study with simulated data, who stated that 'Artificial neural networks having the appropriate architecture can be used to develop linear calibration models that perform as well as linear calibration models developed by PCR or PLS' and Despagne *et al*.[9] remarks that 'ANNs outperform linear methods for the strongly non-linear data set, which is not surprising, but their performance on slightly non-linear and linear data is comparable to the performance of lilnear methods such as PLS or PCR'. The results thus indicate that it may be redundant to train and optimize individual neural network models for each component in the mixture, which can be achieved by a single ANN.

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ИЗВОД

PCA–ANN КАЛИБРАЦИОНИ МОДЕЛ ЗА ИСТОВРЕМЕНО ОДРЕЂИВАЊЕ МЕФЕНАМИНСКЕ КИСЕЛИНЕ И ПАРАЦЕТАМОЛА У ТАБЛЕТАМА

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У раду је приказано истовремено одређивање свих лековитих компоненти у мултикомпонентном дозираном облику помоћу PCA–ANN (Principal Component Artificial Neural Network) калибрационог модела, уз коришћење UV спектрометрије, као алтернативе моделима који се примењују за одређивање појединачних компоненти. Описан је нови приступ калибрацији коришћењем спектара изведених из три спектра сваке појединачне компоненте. Снимљени спектри мефенаминске киселине и парацетамола, на неколико концентрационих нивоа унутар опсега линеарности су употребљени за израчунавање калибрационе смесе у опсегу таласних дужина 220 – 340 nm. ANN базиране на Levenberg–Marquardt-овом алгоритму примењене су за постављање и оптимизацију калибрационих модела коришћењем MATLAB® Neural Network Toolbox и упоређене са PCR (principal component regression) моделом. Калибрациони модели су у потпуности евалуирани на неколико концентрационих нивоа, коришћењем 104 спектра, добијена за 52 синтетичке бинарне смесе, припремљене уз коришћење ортогоналног

дизајна. Оптимизовани модел има задовољавајућу робустност чак и када су калибрациони сетови конструисани за различите сетове спектара чистих компоненти. Применом ANN са предложеним приступом калибрацији, успешно су истовремено одређене обе компоненте. Овим моделом се могу одређивати лековите компоненте са задовољавајућом прецизношћу и тачношћу у таблетираним дозираним облициам без интерференција ексципијената што је и потврђено резултатима добијеним одређивањем процената приноса.

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