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Different approaches in Partial Least Squares and Artificial Neural Network models applied for the analysis of a ternary mixture of Amlodipine, Valsartan and Hydrochlorothiazide

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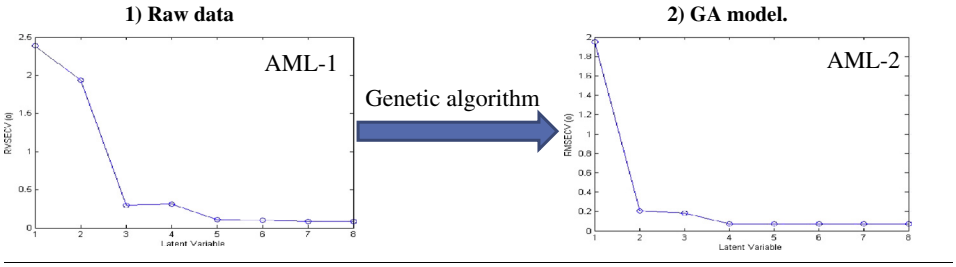
HIGHLIGHTS

- Advanced chemometric methods developed for this ternary mixture.
- Traditional (PLS) and advanced (ANN) chemometric models.
- Difference between GA and PCA as preceding step to chemometric models.
- GA can improve the prediction with less LVs or neurons.

GRAPHICAL ABSTRACT



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ABSTRACT

Different chemometric models were applied for the quantitative analysis of Amlodipine (AML), Valsartan (VAL) and Hydrochlorothiazide (HCT) in ternary mixture, namely, Partial Least Squares (PLS) as traditional chemometric model and Artificial Neural Networks (ANN) as advanced model. PLS and ANN were applied with and without variable selection procedure (Genetic Algorithm GA) and data compression procedure (Principal Component Analysis PCA). The chemometric methods applied are PLS-1, GA-PLS, ANN, GA-ANN and PCA-ANN. The methods were used for the quantitative analysis of the drugs in raw materials and pharmaceutical dosage form via handling the UV spectral data. A 3-factor 5-level experimental design was established resulting in 25 mixtures containing different ratios of the drugs. Fifteen mixtures were used as a calibration set and the other ten mixtures were used as validation set to validate the prediction ability of the suggested methods. The validity of the proposed methods was assessed using the standard addition technique.

Introduction

Amlodipine (AML), 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridine carboxylic acid 3-ethyl 5-methyl ester) [1] (Fig. 1a) is a dihydropyridine derivative acts as a calcium channel blocker. It is used in the management of hypertension, stable angina and variant angina [2].

Valsartan (VAL), N-[p-(o-1H-Tetrazol-5-ylphenyl)benzyl]-N-valeryl-L-valine [1] (Fig. 1b), is an antagonist of the angiotensin-II AT_1-receptor. It is used for treatment of hypertension, heart failure, and post-myocardial infarction [3].

Hydrochlorothiazide (HCT), 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulphonamide-1,1-dioxide [1] (Fig. 1c), is a benzothiadiazines diuretic widely used in antihypertensive pharmaceutical formulations [4].

Literature survey revealed that AML and HCT are official in British Pharmacopoeia [5], while VAL, HCT and their mixture are official in United States Pharmacopoeia [6]. There are many reported methods for the determination of AML, VAL or HCT in different dosage forms [7–14], but only few chromatographic methods were reported for the simultaneous estimation of AML, VAL and HCT in their ternary mixture [15–19]. Also, spectrophotometric

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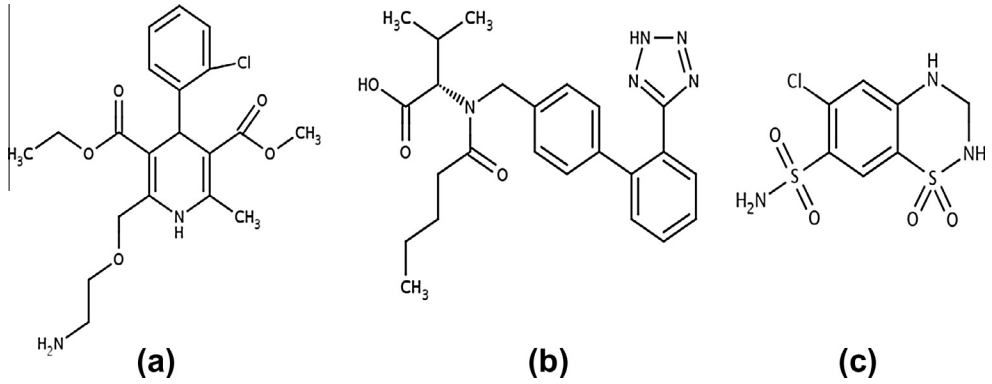

Fig. 1. Structural formulae for (a) Amlodipine, (b) Valsartan, and (c) Hydrochlorothiazide.

and traditional chemometric methods were applied on this mixture [20–22].

The rationales of this work were to:

a. Develop simple and accurate methods for the simultaneous determination of AML, VAL and HCT in their tablets.
b. Show the effect of variable selection (GA) and data compression (PCA) methods on enhancing the prediction power of different chemometric models.

Neural networks

Artificial Neural Network (ANN) is a type of artificial intelligence method that resembles biological nervous system in having the ability to find the relationship between inputs and outputs. A network is made up of a number of interconnected nodes (called neurons) arranged into three basic layers (input, hidden and output) that are interconnected by connections called weights. The type of ANN used in this manuscript is feed-forward network trained with the back propagation of errors learning algorithm. The input nodes in this representation perform no computation but are used to distribute inputs into the network. It is called feed-forward ANN as information passes one way through the network from the input layer, through the hidden layer and finally to the output layer. The outputs (predicted concentrations) are compared with targets (actual concentrations), and the difference between them is called error [23]. ANN parameters to be optimized:

- The transfer functions: There are two transfer functions used in ANN; one between input and output of a node in the hidden layer and the other is applied in output layer. The use of these functions depends on relationship between the inputs and outputs. Tansig-purelin transfer functions are commonly used for non-linear systems [24] while purelin-purelin functions are used for linear ones [25].
- Hidden neurons number (HNN): It is related to the converging performance of the output error function during the learning process.
- Number of neurons: Unfortunately, there are no fixed rules as to how many neurons should be included in the hidden layer. If there are too few nodes in the hidden layer the network may have difficulty generalizing to problems it has never encountered before. On the other hand, if there are too many nodes in the hidden layer, the network may take an unacceptably long time to learn anything of any value.
- Lc, Lcd and Lci: The learning coefficient (Lc) controls the degree at which connection weights are modified during the learning process. The learning coefficient decrease (Lcd) and learning coefficient increase (Lci) control the variation of Lc value. It varies as a function of performance of the ANN.

Experimental

Materials and reagents

- *Amlodipine*; kindly supplied by Al-Hekma pharmaceutical Company, Egypt, its purity was certified to be 99.9 ± 0.7.
- *Valsartan*; kindly supplied by Novartis pharmaceutical Company, Egypt, its purity was certified to be 99.7 ± 0.2.
- *Hydrochlorothiazide*; kindly supplied by Al-Hekma pharmaceutical Company, Egypt, its purity was certified to be 99.8 ± 0.4.
- EXFORGE HCT® tablet dosage forms; labeled to contain 5(AML)/160(VAL)/12.5(HCT) mg batch number 5002125, 5/160/25 mg batch number 5002141 and 10/320/25 mg batch number 5002159, manufactured by Novartis Pharmaceuticals Corporation, USA. They were procured from U.S.A. market.
- *Methanol*; El-NASR Pharmaceutical Chemicals Co., Egypt.

Instruments

SHIMADZU dual beam UV–visible spectrophotometer (Kyoto/Japan), model UV-1650 PC connected to IBM compatible and a HP1020 laserjet printer. The bundled software, UV-Probe personal spectroscopy software version 2.21 (SHIMADZU) was used. The spectral band was 2 nm and scanning speed is 2800 nm/min with 0.1 nm interval.

Software

All chemometric methods were implemented in Matlab® 7.0.0.19920 (R14). PLS, GA-PLS, ANN, GA-ANN and PCA-ANN were carried out by using PLS toolbox software version 2.1 in conjunction with Neural Network toolbox. The *t*-test and *F*-test were performed using Microsoft® Excel. All calculations were performed using a Dual CPU, 1.47 GHz, 2.00 GB of RAM under Microsoft Windows Vista™.

Procedures

Standard solutions

(a) Standard stock solutions of AML, VAL and HCT 1 mg/mL in methanol.
(b) Standard working solutions for AML and VAL 80 μg/mL and for HCT 62.5 μg/mL were prepared from stock solutions by appropriate dilutions with methanol.

Spectral characteristics of AML, VAL and HCT

The zero-order (D_0) absorption spectra of AML, VAL and HCT (20 μg/mL for each) solutions were recorded against methanol as a blank over a range of 200–400 nm.

Experimental design for chemometric methods

A 5-level, 3-factor design was performed using 5 concentration levels for each of the 3 compounds to be analyzed. The design spans the mixture space fairly well; where there are 5 mixtures for each compound at each concentration level, resulting in 25 mixtures [26]. The central level of the design is 6, 32 and 9.375 μg/mL for AML, VAL and HCT, respectively. The concentration for each level for each compound is based on the calibration range of each drug, the ratio of AML, VAL and HCT in the market pharmaceutical product was involved. Table 1 represents the concentration design matrix. The regions from 200 to 230 nm were rejected. Fifteen mixtures of this design were used as a calibration set and the other 10 mixtures were used as a validation set to test the predictive ability of the developed multivariate models.

Analysis of AML, VAL and HCT in EXFORGE HCT® tablets by the proposed methods

Five tablets of each Exforge HCT® formulation were accurately weighed and finely powdered. An amount of the powder equivalent to 8 mg VAL was weighed and dissolved in methanol by shaking in ultrasonic bath for about 30 min. The solutions were filtered into separate 100-mL measuring flasks, and the volume was completed with methanol. Five mL aliquots were transferred into 10-mL measuring flasks and suitable aliquots of AML were transferred from their standard working solutions for spiking the solutions to reach concentrations within linearity range and then volumes were completed with methanol. The spectra of these solutions were scanned from 200 to 400 nm, stored in the computer and analyzed by the proposed methods.

Table 1
The 5-level, 3-factor experimental design shown as concentrations of the mixture components in μg/mL.

Mix. No.	AML	VAL	HCT
1.	6	32	9.375
2. [a]	10	28	15.625
3.	6	24	3.125
4.	10	32	6.25
5.	2	24	15.625
6.	4	36	15.625
7.	2	40	6.25
8.	8	40	12.5
9.	4	40	9.375
10.	10	36	9.375
11.	6	28	6.25
12.	8	32	15.625
13.	4	28	12.5
14.	10	40	3.125
15.	6	40	15.625
16.	8	24	9.375
17.	10	24	12.5
18.	8	36	6.25
19.	2	36	3.125
20.	8	28	3.125
21.	2	32	12.5
22.	6	36	12.5
23.	4	24	6.25
24.	2	28	9.375
25.	4	32	3.125

[a] The shaded rows represent the validation set

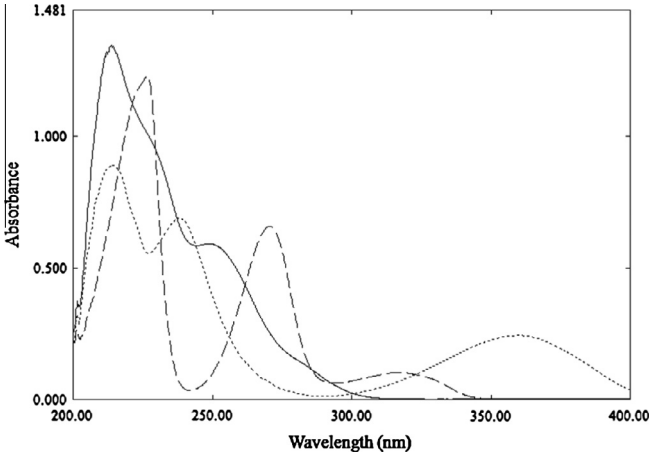

Fig. 2. Zero order absorption spectrum of 20 μg/mL AML (. . .), 20 μg/mL VAL (–) and 20 μg/mL HCT (– – –) using methanol as blank.

Results and discussion

The absorption spectra of the three compounds, AML, VAL and HCT show highly overlapped spectral band in the region 200–300 nm as shown in Fig. 2. Only AML can be determined by zero order spectrophotometry.

The goal of this study was to develop accurate and simple chemometric methods for simultaneous determination of AML, VAL and HCT in their pharmaceutical preparations and to present the effect of data compression and variable selection procedures on enhancing the predictive power of PLS and ANN models.

The first step in model building, involves constructing the calibration matrix for the ternary mixture. In this study the model was optimized with the aid of the 5-level 3-factor design [26] resulting in 25 sample mixtures. Table 1 shows the composition of the 25 sample mixtures. These 25 sample mixtures were split to 15 training mixtures (for building the models) and 10 validation mixtures (for measuring predictive power of the models).

The quality of multicomponent analysis is dependent on the wavelength range and spectral mode used [27]. The wavelengths used were in range 231–400 nm for AML, 231–320 nm for VAL and 231–360 nm for HCT. Wavelengths less than 231 nm were rejected due to the noisy content. Wavelengths more than 320 nm for VAL and 360 nm for HCT were not used because corresponding compounds do not absorb in these regions.

Variable selection: Genetic Algorithm (GA)

Molecular spectroscopy has been greatly improved by the use of variety of multivariate statistical methods [28,29]. Methods such as Partial Least Squares (PLS) or principal component regression (PCR), allow to take into account the whole spectrum without performing variable selection [30]. It has been recognized that an efficient variable selection can be beneficial to improve the

predictive ability of the model and to reduce its complexity [31]. Several techniques devoted to variable selection in PLS models applied to spectral data have been presented [32,33]. It has already been shown that Genetic Algorithms (GAs) can be successfully used as a variable selection technique [34,35]. The architecture of a GA can be divided into five components: Initiation, Evaluation, Exploitation, Exploration and Mutation. An important issue of successful GA performance is the adjustment of GA parameters [36].

The fitness values were used as response variables. Mutation rate was 0.005 in all cases as when it increased above this value, no convergence occurred between average fitness and best fitness values and model stop. The adjusted GA parameters are shown in Table 2.

The GA was run on 170, 90 and 130 variables for AML, VAL and HCT, respectively, using a PLS with maximum number of factors allowed is the optimal number of components determined by cross-validation on the model containing all the variables, and the selected variables were used for running of PLS model and as input data for ANN. GA reduced absorbance matrix to about 36–46% of the original matrix (62, 42 and 54 wavelengths for AML, VAL and HCT, respectively).

Partial Least Squares (PLS-1)

The purpose of PLS method is to build a calibration model between the concentration of the analytes under study (AML, VAL and HCT in our case) and the latent variables of the data matrix [37]. Two different approaches can be used in Partial Least Squares called PLS-1 and PLS-2. PLS-2 uses the whole information about the concentration of all components to form latent variables (LVs), while PLS-1 uses only the information about the concentration of one component to create the LVs used by the model [38].

Including extra LVs in the model increases the possibility of the known problem of overfitting. On the other hand, if the number of LVs was too small meaningful data that could be necessary for the calibration might be discarded. Therefore optimization of number of the LVs is a critical issue in PLS method. Leave one out (LOO) cross validation [39] and the bootstrap [40] can be applied to predict the optimum number of PLS components.

PLS-1 method was run on the calibration data of absorption spectra. To select the number of factors in the PLS-1 algorithm, a cross validation (CV) method leaving out one sample at a time [41] was applied using calibration set of 15 calibration spectra. RMSECV (Root Mean Squares Error of Cross-Validation) indicates both of the precision and accuracy of predictions. It was recalculated upon addition of each new factor to the PLS-1. The method developed by Haaland and Thomas [28] was used for selecting the optimum number of factors, which involves selecting that model including the smallest number of factors that results in an insignificant difference between the corresponding RMSECV and the minimum RMSECV Fig. 3.

Table 2
Parameters of the Genetic Algorithms.

Parameter	Value
Population size	20
Maximum generations	50
Mutation rate	0.005
The number of variables in a window (window width)	2
Per cent of population the same at Convergence	100, except VAL (50)
% Wavelengths used at initiation	50
Crossover type	Single
Maximum number of latent variables	3, except AML (2)
Cross validation	Random
Number of subsets to divide	
Data into for cross validation	4
Number of iterations for cross validation at each generation	2

ANN

The large number of nodes in input layer of the network (wavelength readings) increases the CPU time for ANN modeling, the absorbance matrix was reduced either by Genetic Algorithm (variable selection procedure) to about 36–46% of the original matrix or Principal Component Analysis (PCA) (variable compression procedure) to three principal components. Thus three ANNs (ANN, GA-ANN and PC-ANN) were applied in our work. The output layer is the concentration matrix of one component. The hidden layer consists of just single layer which has been considered sufficient to solve similar or more complex problems. Moreover, more hidden layers may cause overfitting [25].

The values of the optimized ANN parameters for each drug are shown in Table 3. From the most important parameters that should be optimized carefully, transfer function pair. Choosing of transfer function depends on the nature of data you work on. In our case, purelin–purelin transfer function was implemented in our models due to linear correlation between absorbance and concentration.

After optimization of architectures and parameters of the ANNs, the training step was done. ANN was trained by different training functions and there was no difference in performance (no decrease in Mean Square Error MSE). Levenberg–Marquardt back propagation (TRAINLM) [42] was thus preferred as it is time saving. To avoid overfitting of our model, the validation set was encountered in training step and ANN stops when MSE of calibration set decreased and that of validation set increased. Analysis from raw data, Genetic Algorithm model and Principal Component Analysis was implemented to test for improvement of predictions.

The proposed chemometric methods were run on the calibration data using optimal parameters. The concentrations of the three drugs in the calibration set (15 mixtures) were calculated. By plotting predicted concentrations of each component versus actual concentrations, a straight line was obtained (Table 1, Supplementary Material). In order to validate the proposed methods, the validation set (10 mixtures) was analyzed with the proposed methods (Table 4).

The proposed PLS-1, GA-PLS, ANN, GA-ANN and PCA-ANN methods were successfully applied for the determination of AML, VAL and HCT in Exforge HCT® tablets, Table 5. The validity of the proposed methods was further assessed by applying the standard addition technique (Table 2, Supplementary Material).

The results obtained for the analysis of AML, VAL and HCT in Exforge HCT® tablets by the suggested methods were statistically compared with those obtained by applying the reported HPLC method [16] and no significant difference between the results was obtained as shown in Table 6.

GA reduced the optimal number of latent variables of PLS-1 model for AML from three into two factors. Also, recoveries and RMSEP (Root Mean Square Error of Prediction) were decreased indicating a better resolution power of GA-PLS model than PLS-1 model (Table 4).

GA allowed the use of less number of neurons (shorter training time) for AML than those used in the network utilized the raw data. While PCA-ANN did not show any improvement than ANN, even the results were worse (Table 4). These results indicate that variable selection models (GA) are more suitable than data compression procedure (PCA), when preceding ANN, for the analysis of this ternary mixture. This result may be attributed to the fact that GA introduces the most relevant wavelengths to the drug concentration.

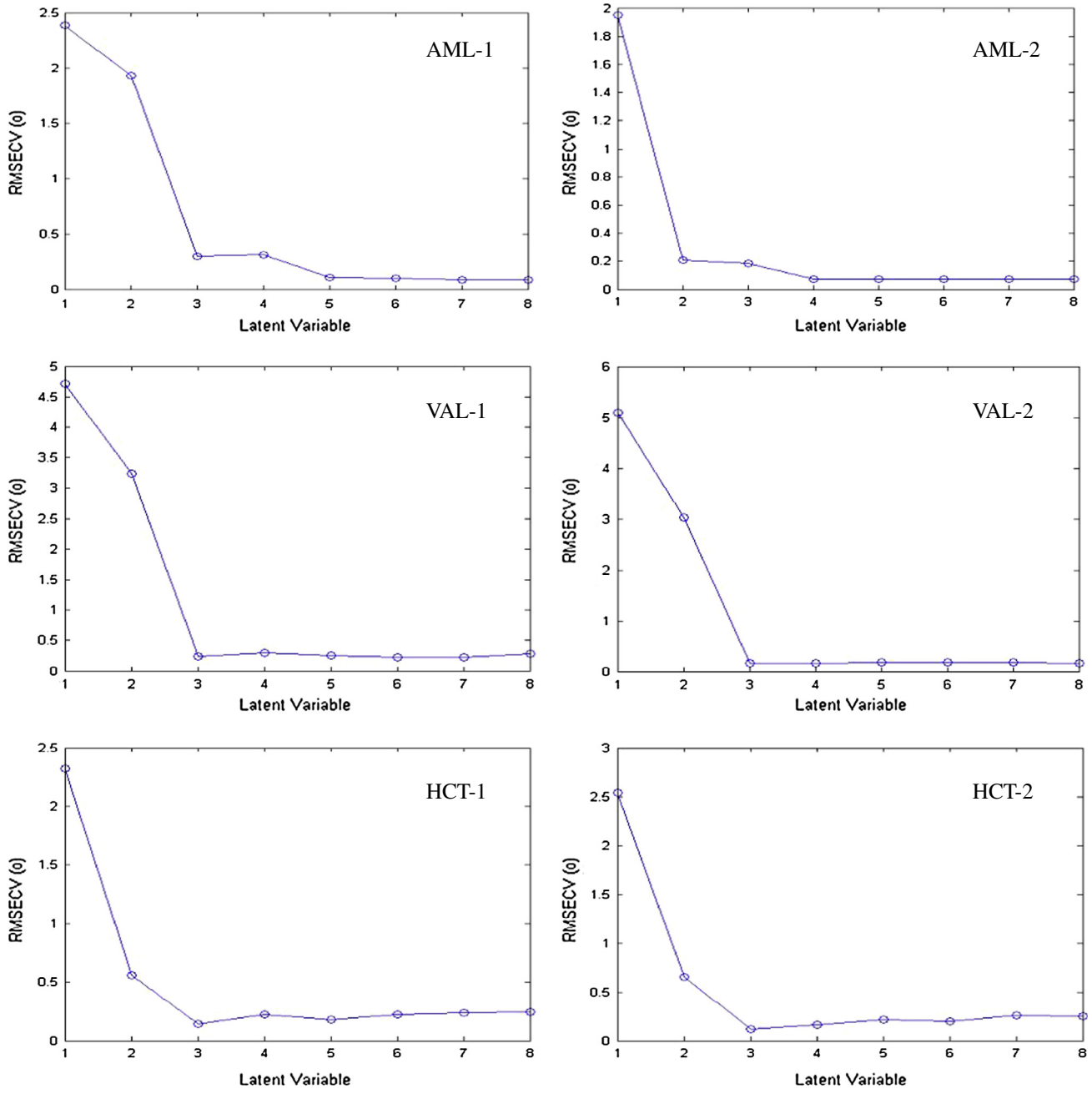

Fig. 3. The optimum number of LV for AML, VAL and HCT concentration prediction from (1) raw data and from (2) GA model.

Table 3
Optimized parameters of ANNs.

Method	ANN			GA-ANN			PCA-ANN		
Drug	AML	VAL	HCT	AML	VAL	HCT	AML	VAL	HCT
Architecture	170-10-1	90-10-1	130-1-1	62-7-1	42-10-1	54-1-1	3-3-1	3-3-1	3-3-1
Hidden neurons number	10	10	1	7	10	1	3	3	3
Transfer functions	Purelin–Purelin								
Learning coefficient	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001
Learning coefficient decrease	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001
Learning coefficient increase	100	100	100	100	100	100	100	100	100

Table 4
Determination of AML, VAL and HCT in validation set by the proposed chemometric methods.

Concentration (μg/mL)			PLS-1			GA-PLS			ANN			GA-ANN			PCA-ANN		
			Recovery %[a]														
AML	VAL	HCT	AML	VAL	HCT	AML	VAL	HCT	AML	VAL	HCT	AML	VAL	HCT	AML	VAL	HCT
10	28	15.625	99.8	100.6	99.4	99.2	99.9	99.3	100.2	99.3	98.8	100.3	99.3	99.4	99.0	101.1	97.7
10	32	6.25	98.8	100.3	100.4	99.0	100.0	101.5	98.7	99.7	100.1	98.6	99.8	100.1	98.8	100.4	102.9
4	36	15.625	99.8	99.7	99.2	99.2	99.5	99.4	99.7	98.7	99.4	100.0	99.3	99.3	101.6	99.7	99.8
8	40	12.5	98.6	100.6	101.0	99.3	100.6	100.9	99.3	99.5	100.7	99.8	100.0	100.9	98.6	101.2	101.2
10	36	9.375	98.9	99.0	101.4	98.9	99.4	100.4	98.9	99.3	100.8	99.0	99.3	101.1	97.3	99.6	101.4
8	32	15.625	99.2	98.8	100.9	99.2	99.1	101.0	99.3	99.2	100.0	99.9	99.3	100.0	98.6	98.5	100.9
10	40	3.125	98.9	99.6	100.9	99.4	99.0	101.0	99.2	99.7	101.1	99.6	99.6	100.7	99.0	98.6	101.0
8	24	9.375	102.4	98.6	99.2	102.0	99.9	100.0	99.6	99.8	98.8	99.5	99.8	99.2	102.4	98.6	99.4
8	36	6.25	98.6	98.7	100.9	99.8	99.3	100.0	101.0	100.4	100.4	100.4	100.3	100.3	99.4	98.5	102.1
8	28	3.125	99.6	99.0	100.9	100.3	99.1	100.4	100.7	99.4	100.9	100.7	99.3	100.2	98.0	97.9	100.5
	Mean		99.5	99.5	100.4	99.6	99.6	100.4	99.7	99.5	100.1	99.8	99.6	100.1	99.3	99.4	100.7
	RSD%		1.1	0.8	0.8	0.9	0.5	0.7	0.8	0.4	0.8	0.6	0.4	0.7	1.6	1.2	1.5
	RMSEP[b]		0.10	0.29	0.09	0.08	0.22	0.08	0.07	0.23	0.08	0.06	0.17	0.07	0.14	0.41	0.16

[a] Average of three determinations.
[b] Root Mean Square Error of Prediction.

Table 5
Determination of AML, VAL and HCT in Exforge HCT® tablets by the proposed ANN and GA-ANN methods.

Product	Drug	PLS-1[a]	GA-PLS[a]	ANN[a]	GA-ANN[a]	PCA-ANN[a]
Exforge HCT® 5/160/12.5	AML	99.9 ± 0.8	100.1 ± 0.4	99.7 ± 1.0	99.9 ± 0.7	100.2 ± 1.1
	VAL	100.1 ± 0.9	100.1 ± 0.6	100.1 ± 0.6	100.1 ± 0.7	99.6 ± 0.9
	HCT	99.7 ± 0.9	100.0 ± 0.8	100.8 ± 0.6	100.2 ± 0.6	100.0 ± 0.6
Exforge HCT® 5/160/25	AML	100.0 ± 0.8	99.6 ± 1.0	99.7 ± 1.2	99.8 ± 0.8	99.7 ± 0.8
	VAL	100.0 ± 1.0	100.2 ± 0.8	100.5 ± 0.9	100.1 ± 0.8	100.0 ± 0.9
	HCT	99.7 ± 0.8	99.6 ± 0.6	100.3 ± 1.0	99.8 ± 0.7	99.6 ± 1.0
Exforge HCT® 5/160/25	AML	100.7 ± 1.1	100.7 ± 1.1	100.6 ± 1.1	100.3 ± 1.0	100.5 ± 1.1
	VAL	99.5 ± 1.2	99.7 ± 1.1	99.7 ± 0.8	99.7 ± 1.0	99.7 ± 1.3
	HCT	99.8 ± 0.9	99.6 ± 1.3	99.9 ± 0.8	99.9 ± 1.0	99.9 ± 1.8

[a] Average of three determinations.

Table 6
Statistical comparison for the results obtained by the proposed methods and the reported method [16] for the analysis of AML, VAL and HCT in Exforge HCT® tablets.

Value		Mean	RSD%	*n*	Variance	Student's *t* test[a] (2.12)	*F* value[a] (3.44)
PLS-1	AML	100.2	0.9	9	0.790	0.032	1.472
	VAL	99.9	1.0	9	0.904	0.899	1.697
	HCT	99.8	0.7	9	0.533	0.822	1.109
GA-PLS	AML	100.1	0.9	9	0.855	0.164	1.593
	VAL	100.0	0.8	9	0.601	0.700	1.128
	HCT	99.7	0.8	9	0.680	0.803	1.416
ANN	AML	100.0	1.0	9	1.031	0.457	1.920
	VAL	100.1	0.7	9	0.558	0.401	1.047
	HCT	100.3	0.8	9	0.657	0.866	1.369
GA-ANN	AML	100.0	0.8	9	0.594	0.618	1.107
	VAL	100.0	0.8	9	0.586	0.693	1.099
	HCT	99.9	0.7	9	0.511	0.257	1.064
PCA-ANN	AML	100.1	0.9	9	0.856	0.198	1.596
	VAL	99.8	0.9	9	0.885	1.177	1.661
	HCT	99.8	1.1	9	1.224	0.543	2.547
Reported Method[b]	AML	100.2	0.7	9	0.537	–	–
	VAL	100.2	0.7	9	0.533		
	HCT	100.0	0.7	9	0.480		

[a] The values in the parenthesis are the corresponding theoretical values of *t* and *F* at $P = 0.05$.
[b] HPLC method using Luna C_{18} column, a mobile phase consisting of methanol – phosphate buffer (30 mM, pH 5.5) (62:38 by volume) at a flow rate of 1 mL/min and UV detection at 234 nm.

ANN gave better recoveries & RMSEP than PLS-1 (Table 4), which may be due to the fact that ANN is a type of artificial intelligence and that in ANN there is no chance for overfitting that may occur in PLS calibrations.

The proposed chemometric methods show higher sensitivity over the sequential spectrophotometric method [22] and better mean recovery and RMSEP than the traditional methods applied in our previous work [20] being advanced methods using artificial

intelligence and preceded by variable selection or data compression procedures.

Conclusion

Five chemometric methods (PLS-1, GA-PLS, ANN, GA-ANN and PCA-ANN) have been presented as powerful chemometric methods to resolve the ternary mixture of AML, VAL and HCT in their powder and pharmaceutical dosage forms. The effect of GA and PCA as preceding step for chemometrics was studied. The results in this paper suggested that the proposed methods can be classified among accurate and sensitive methods. These merits show the possibility to use the proposed methods in quality control analysis of AML, VAL and HCT in laboratories lacking liquid chromatographic instruments.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.saa.2013.11.045.

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