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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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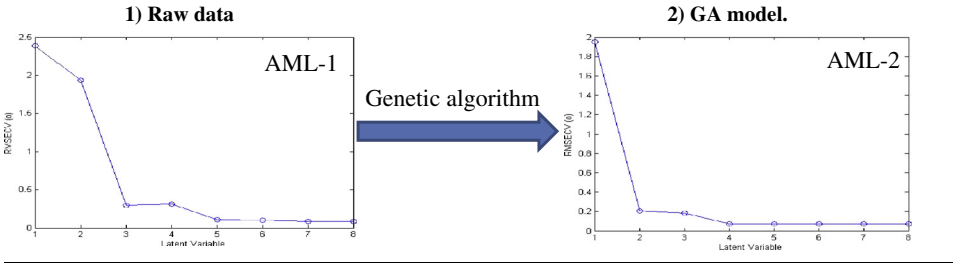
## HIGHLIGHTS

- 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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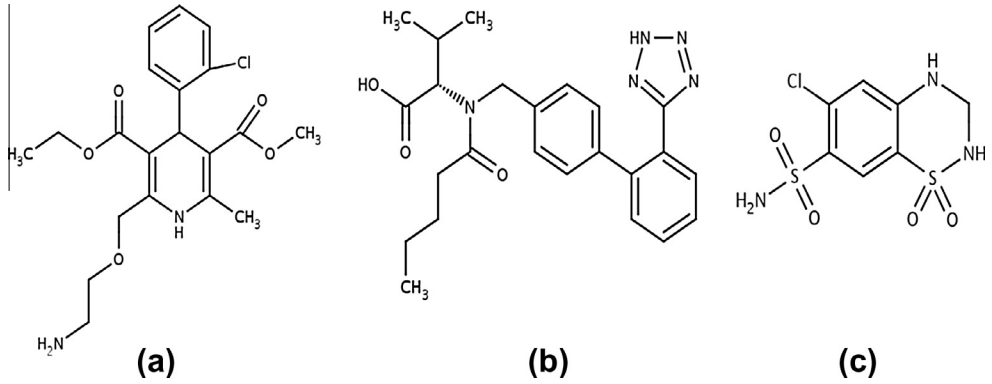


**Fig. 1.** Structural formulae for (a) Amlodipine, (b) Valsartan, and (c) Hydrochlorothiazide.

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.