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Evaluation of multivariate calibration models with different pre-processing and processing algorithms for a novel resolution and quantitation of spectrally overlapped quaternary mixture in syrup

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ABSTRACT

A novel approach for the resolution and quantitation of severely overlapped quaternary mixture of carbinoxamine maleate (CAR), pholcodine (PHL), ephedrine hydrochloride (EPH) and sunset yellow (SUN) in syrup was demonstrated utilizing different spectrophotometric assisted multivariate calibration methods. The applied methods have used different processing and pre-processing algorithms. The proposed methods were partial least squares (PLS), concentration residuals augmented classical least squares (CRACLS), and a novel method; continuous wavelet transforms coupled with partial least squares (CWT-PLS). These methods were applied to a training set in the concentration ranges of 40–100 μg/mL, 40–160 μg/mL, 100–500 μg/mL and 8–24 μg/mL for the four components, respectively. The utilized methods have not required any preliminary separation step or chemical pretreatment. The validity of the methods was evaluated by an external validation set. The selectivity of the developed methods was demonstrated by analyzing the drugs in their combined pharmaceutical formulation without any interference from additives. The obtained results were statistically compared with the official and reported methods where no significant difference was observed regarding both accuracy and precision.

1. Introduction

Carbinoxamine maleate (CAR), 2-[(4-Chlorophenyl)(2-pyridinyl)methoxy]-N,N-dimethylethanamine (2Z)-2-butenedioate is an antihistamine with anticholinergic and sedative properties. It is used for the relief of allergic conditions such as rhinitis and is a common ingredient of compound preparations for symptomatic treatment of coughs and common cold [1]. Pholcodine (PHL), 7,8-Didehydro-4,5α-epoxy-17-methyl-3-[2-(morpholin-4-yl) ethoxy] morphinan-6α-ol is a centrally acting cough suppressant. It helps in the suppression of unproductive coughs and also has a mild sedative effect, but has little or no analgesic effect [1]. Ephedrine HCl (EPH), (1R,2S) -2-methylamino-1-phenyl-1-propanol hydrochloride is a sympathomimetic amine commonly used as decongestant and bronchodilator. It works by reducing swelling, constricting blood vessels in the nasal passages and widening the lung airways, allowing easier breathing [1]. Sunset yellow (SUN) also known as orange yellow, disodium 6-hydroxy-5-[(4-sulfophenyl) azo]-2-naphthalenesulfonate is a petroleum-derived orange azo dye used in food, cosmetics, and drugs [2–5]. For example, it is used in candy, desserts, snacks, sauces, and preserved fruits [6]. The molecular structure of each of the studied compounds is shown in Fig. 1.

The combination of CAR, PHL and EPH is indicated for the relief of non-productive cough and upper respiratory symptoms associated with allergy and common cold.

Literature survey has revealed that CAR, PHL and EPH could be determined either alone or in combination with other drugs by several methods. Numerous analytical methods were developed for the assay of CAR as spectrophotometric methods [7,8], HPLC [9,10] capillary electrophoresis [11], gas chromatography [12] and LC-MS [13]. Regarding the analysis of PHL, beside the pharmacopoeial method [14], several methods were introduced as HPLC [15,16], capillary electrophoresis [17], gas chromatography [18] and LC-MS [19]. With respect to EPH; beside the pharmacopoeial method [14] it was determined by spectrophotometric methods [20,21], HPLC [22,23], capillary electrophoresis [24], gas chromatography [25] and LC-MS [26]. Lastly, SUN was determined by spectrophotometric methods [27–29], differential pulse polarography [30,31] and HPLC [32,33].

To the best of our knowledge only one HPLC method was reported for the analysis of the combination of CAR, PHL and EPH [34]. In addition, no method was found in the literature for the determination of the quaternary mixture of CAR, PHL, EPH and SUN. Thus, we were motivated to develop novel methods for the determination of this quaternary combination.

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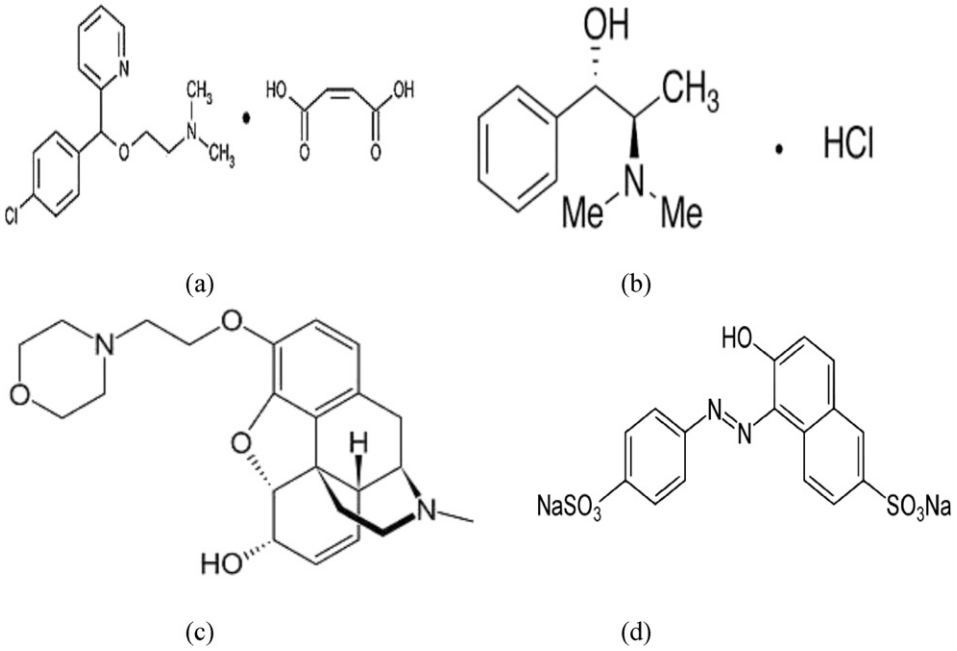

Fig. 1. The chemical structures of (a) CAR, (b) EPH, (c) PHL and (d) SUN.

The quality control labs receive many samples that should be analyzed daily, spectrophotometry is considered a very rapid and accurate technique and of lower cost than liquid chromatography-diode array detector system (LC-DAD), gas chromatography–mass spectrometry (GC-MS) and liquid chromatography-mass spectrometry (LC-MS), etc. These techniques are considered time and solvent consuming which makes spectrophotometry advantageous in quality control of pharmaceuticals.

In this context, the main aim of our proposed work was to develop and validate chemometric methods namely; PLS, CWT coupled with PLS and CRACLS for resolving and quantification of CAR, PHL, EPH and SUN in pharmaceutical formulation. The proposed study emphasized on exploiting the advantages of the use of CWT as a pre-processing step for the PLS method over the ordinary PLS aiming that this novel, hybrid approach will offer new possibilities and alternative ways for the resolution of mixtures of the active compounds having overlapping UV spectra.

1.1. Theoretical background of the applied methods

1.1.1. Partial least squares (PLS)

PLS is considered the conventional chemometric method. The algorithm of PLS is well established and reported [35–37].

1.1.2. Theory of the continuous wavelet transforms (CWT)

Wavelet transform (WT) is one of the techniques that was recently developed and used for processing signals. It is defined as mathematical functions that cut up data into different frequency components, and then study each component with a resolution matched to its scale [38,39]. The most general principle of the wavelet construction is to use both dilations and translations. Commonly used wavelets form a complete orthonormal system of functions with a finite support. Therefore, by changing a scale they can distinct the local characteristics of a signal at various scales, and by translations they cover the whole region in which it is investigated. CWT method is an important signal processing technique for the overlapping peak resolution and for the significant peak identification. This method is successfully applied to the spectrophotometric multicomponent analysis of relevant compounds in samples. Given a mother wavelet [40,41] $\Psi(\lambda)$ by scaling (or dilatation) and shifting (or translation) of $\Psi(\lambda)$ a set of functions denoted by $\Psi_{a,b}$ (λ) is obtained as indicated below:

$$\Psi a,b(\lambda)=\frac{1}{\sqrt{|a|}}\Psi\left(\frac{\lambda-b}{a}\right) \quad , \quad a\neq 0 \quad , \quad a,b\in R$$

where a denotes the scale parameter which is a variable used to control the scaling, b represents the translation parameter controlling the translation and R is the domain of real numbers. A mother wavelet Ψ (λ) generates the set of functions $\Psi a,b$ (λ) by scaling (or dilatation) and shifting (or translation).

1.1.3. Concentration augmented classical least squares (CRACLS)

Unlike classical least squares (CLS), CRACLS is an alternative new method that estimates absorptivity (ˆ S) by a process of repetitive approximation as shown in the following steps [42]:

Step 1 $\hat{S}$ is calculated: $\hat{S}=(C'C)^{-1}C'A$
Step 2 $\hat{S}$ is used to predict C': $C'=A\hat{S}'(\hat{S}\hat{S}')^{-1}$
Step 3 Error in C': $E=C'-C$
Step 4 One vector of E is augmented to the original C (E is considered as a new component).
Step 5 Step (1) is repeated using the augmented C until no further improvement in prediction is achieved.

2. Experimental

2.1. Apparatus and software

Shimadzu – UV 1800 double beam UV–Visible spectrophotometer (Japan) with matched 1 cm quartz cells at 200–600 nm range was used for all absorbance measurements. Spectra were automatically obtained by Shimadzu UV-Probe 2.32 system software. All computations were performed by Matlab® Version 7.9 and PLS toolbox 2.0 was used.

2.2. Chemicals and solvents

2.2.1. Pure samples

CAR, PHL and EPH were kindly supplied by Amoun Pharmaceutical Co. (El-Obour city, Cairo, Egypt). Their purities were found to be