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Linear support vector regression and partial least squares chemometric models for determination of Hydrochlorothiazide and Benazepril hydrochloride in presence of related impurities: A comparative study

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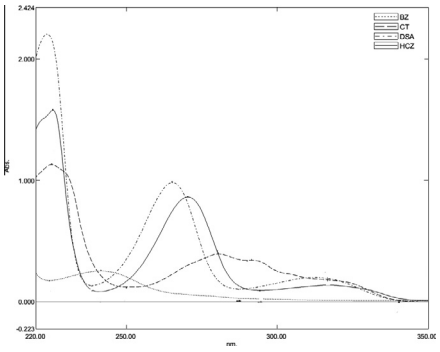
HIGHLIGHTS

- Proper design of experiments for multivariate calibration.
- Analysis of Hydrochlororhiazide and Benazepril in presence of impurities.
- Comparison of PLSR and linear SVR models showing higher ability of SVR.
- Highlights on generalization ability and the spectral linearity.
- Linear SVR for routine analysis against HPLC.

GRAPHICAL ABSTRACT



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ABSTRACT

Partial least squares regression (PLSR) and support vector regression (SVR) are two popular chemometric models that are being subjected to a comparative study in the presented work. The comparison shows their characteristics via applying them to analyze Hydrochlorothiazide (HCZ) and Benazepril hydrochloride (BZ) in presence of HCZ impurities; Chlorothiazide (CT) and Salamide (DSA) as a case study. The analysis results prove to be valid for analysis of the two active ingredients in raw materials and pharmaceutical dosage form through handling UV spectral data in range (220–350 nm). For proper analysis a 4 factor 4 level experimental design was established resulting in a training set consisting of 16 mixtures containing different ratios of interfering species. An independent test set consisting of 8 mixtures was used to validate the prediction ability of the suggested models. The results presented indicate the ability of mentioned multivariate calibration models to analyze HCZ and BZ in presence of HCZ impurities CT and DSA with high selectivity and accuracy of mean percentage recoveries of (101.01 ± 0.80) and (100.01 ± 0.87) for HCZ and BZ respectively using PLSR model and of (99.78 ± 0.80) and (99.85 ± 1.08) for HCZ and BZ respectively using SVR model. The analysis results of the dosage form were statistically compared to the reference HPLC method with no significant differences regarding accuracy and precision. SVR model gives more accurate results compared to PLSR model and show high generalization ability, however, PLSR still keeps the advantage of being fast to optimize and implement.

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Introduction

Hydrochlorothiazide (HCZ), 6-Chloro-3,4-dihydro-2H-l,2,4-benzothiadiazine-7-sulfonamide l,l-dioxide (Fig. 1a), is an antihypertensive diuretic agent used for management of hypertension [1]. Benazepril hydrochloride (BZ), (3S)-1-(Carboxymethyl)-[[(1S)-1-(ethoxycarbonyl)-3-phenylpropyl]-amino]-2,3,4,5-tetrahydro-1H-benzazepin-2-one hydrochloride (Fig. 1b), is an angiotensin-converting enzyme (ACE) inhibitor used in treatment of hypertension and heart failure [2]. Formulation of HCZ with BZ increases the antihypertensive effect. Chlorothiazide (CT), 6-Chloro-2H-1,2,4-benzothiadiazine-7-sulphonamide 1,1-dioxide (Fig. 1c) and Salamide (DSA), 4-amino-6-chlorobenzene-1,3-disulphonamide (Fig. 1d), are considered as specified impurities for HCZ which are synthetic impurities for which a maximum pharmacopoeial limit is defined [3]. Literature review revealed that (HCZ and BZ) have been determined together by different analytical methods, such as spectrophotometry [4-7], reversed phase high performance liquid chromatography (RP-HPLC) [8-11], thin layer chromatography (TLC) [8,9] and chemometric [12,13] methods. Analysis of process-related impurities and of degradation products is very important in the pharmaceutical industry. The possibility of side and toxic effects, and reduced activity of active substances must be reduced to a minimum. For this reason pharmacopoeias and the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) have established very restrictive requirements for levels of impurities in pharmaceutical products. One of the main analytical problems is the large difference between the amounts of active substances and impurities, so a method for their simultaneous identification and quantification must be sufficiently selective [14]. A comprehensive literature review revealed the lack of a suitable method for determination of the studied drugs in their combined pharmaceutical formulations without interference from drug impurities. Accordingly, the presented work, first aims to assay both HCZ and BZ in presence of HCZ impurities; which represent especial challenge when there are small levels of impurities that can act as interferants in UV spectra, where previously published chemometric models [12,13] may not be valid to handle such interference. Second, this work aims to introduce smart solution for separation of this quaternary mixture using cheap and simple instruments like UV spectrophotometer rather than expensive and solvent consuming HPLC and GC techniques especially when number of compounds goes behind their abilities. Hence the chemometric solutions like the one presented here could be of choice. Finally, this paper aims as well to establish a comparison between PLSR and linear SVR chemometric models through analysis of different mixtures of HCZ, BZ, CT and DSA as a case study; highlighting the advantages and disadvantages of each model.

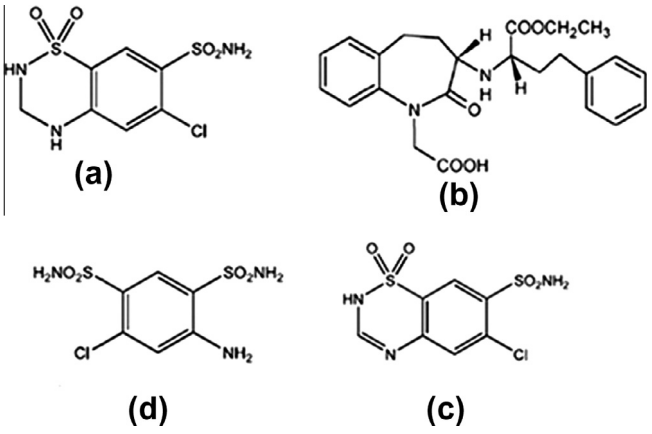

Fig. 1. Chemical structure of (a) hydrochlorothiazide, (b) benazepril hydrochloride, (c) chlorothiazide and (d) salamide.

Experimental

Instruments

A double beam UV–visible spectrophotometer (SHIMADZU, Japan) model UV-1601 PC with quartz cell of 1 cm and UV-PC personal software version 3.7 was used. The spectral band width is 2 nm and wavelength-scanning speed 2800 nm/min.

Materials and laboratory preparation

Authentic samples

Standard HCZ and BZ were kindly supplied by Sigma Pharmaceuticals Industries (El Monofeya, Egypt) with certified purities of 99.6% and 99.7% respectively. Standard CT and DSA were purchased from Sigma Aldrich Chemie (Germany) with certified purities of 99.8% and 99.6% respectively.

Pharmaceutical formulation

Cibadrex® tablets batch no. (Y0006) were manufactured by Novartis Pharma S.A.E (Cairo, Egypt). Each tablet is claimed to contain 20 mg of BZ and 25 mg of HCZ.

Solvents

Methanol HPLC grade (CHROMASOLVE®, Sigma–Aldrich Chemie GmbH, Germany).

Standard solutions

1000 μg ml^{-1} of HCZ, BZ, CT and DSA stock solutions were prepared by accurately weighing 100 mg of pure powder of each into four separate 100-mL volumetric flasks. 50 mL methanol was added into each flask, and the flasks were shaken for complete dissolution, and then volume was made up to the mark with methanol. Dilution of stock solutions was made to obtain 100 μg ml^{-1} of HCZ and BZ and 30 μg ml^{-1} of CT and DSA working solutions. All the preparations were planned based on the percentage of each component in the final mixtures, the market ratio of the main two drugs, the spectral intensity of each and to allow a feasible dilution of the mixed portions up to 10 ml.

Linearity

UV spectra for a series of samples of both drugs ranging from 1–50 μg ml^{-1} were recorded from 220 to 350 nm. HCZ exhibited linearity between 3 and 17 μg ml^{-1} at its λ_{max} at 270.4 nm, while BZ was linear between 3 and 41 μg ml^{-1} at its λ_{max} at 241.6 nm. The superimposed spectra of 10 μg ml^{-1} of HCZ, BZ, CT and DSA are shown in Fig. 2 showing extreme overlap of components.

Experimental design

Calibration and test set

A 4 level 4 factor calibration design was performed using 4 concentrations levels coded as −1, −2, 1 and 2 in which level coded as (−1) represent the central level for each of the 4 components to be analyzed, including the two main drugs and two impurities. The design aims to span the mixture space fairly well; where there are 4 mixtures for each compound at each concentration level resulting in 16 mixtures for the training set [15]. The central level of the design was 12.5 μg ml^{-1} for HCZ and 10 μg ml^{-1} for BZ. The concentration for each level for each compound was based on the