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# Comparative study between univariate spectrophotometry and multivariate calibration as analytical tools for simultaneous quantitation of Moexipril and Hydrochlorothiazide

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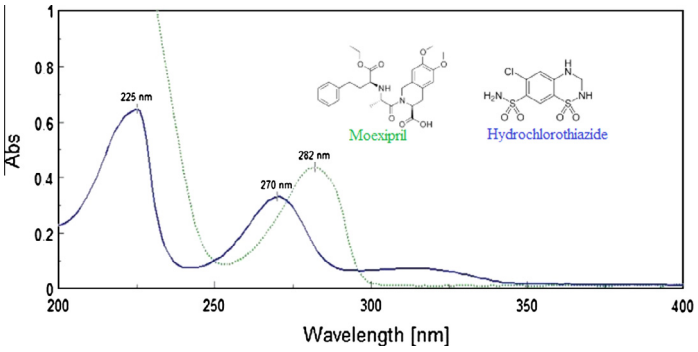
## HIGHLIGHTS

- Comparison between univariate spectrophotometry and multivariate calibration.
- The reported methods need sophisticated and expensive instruments and reagents.
- First chemometric methods done for this combination.
- The good recovery and accuracy makes it applicable in quality control laboratories.

## GRAPHICAL ABSTRACT

Zero order absorption spectra of 30 μg/mL MOX (.....), and 10 μg/mL HCTZ (—) showing severe overlapping.

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## ABSTRACT

Three simple, accurate, reproducible, and selective methods have been developed and subsequently validated for the simultaneous determination of Moexipril (MOX) and Hydrochlorothiazide (HCTZ) in pharmaceutical dosage form. The first method is the new extended ratio subtraction method (EXRSM) coupled to ratio subtraction method (RSM) for determination of both drugs in commercial dosage form. The second and third methods are multivariate calibration which include Principal Component Regression (PCR) and Partial Least Squares (PLSs). A detailed validation of the methods was performed following the ICH guidelines and the standard curves were found to be linear in the range of 10–60 and 2–30 for MOX and HCTZ in EXRSM method, respectively, with well accepted mean correlation coefficient for each analyte. The intra-day and inter-day precision and accuracy results were well within the acceptable limits.



## Introduction

Moexipril (3S)-2-[(2S)-2-[[(1S)-1-(Ethoxycarbonyl)-3-phenyl-propyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-3-

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isoquinolinecarboxylic acid [1] is an antihypertensive drug, which belongs to the group of angiotensin convertase inhibitors. Moexipril hydrochloride is a long-acting nonsulfhydryl angiotensin-converting enzyme (ACE) inhibitor, developed for the treatment of hypertension and congestive heart failure. Moexipril is a pro-drug of moexiprilat, which inhibits ACE in humans and animals. In biological systems it is rapidly de-esterified by esterases, resulting in its active metabolite moexiprilat [2,3].

Hydrochlorothiazide 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide is a diuretic. Diuretics, in particular Hydrochlorothiazide (HCTZ), are often used in association with other drugs in the management of hypertension in patients with ischemic heart disease. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts. Indirectly, the diuretic action of HCTZ reduces plasma volume, with consequent increase in urinary potassium loss, plasma renin activity, aldosterone secretion and decrease in serum potassium [4].

It is reported that MOX was determined by HPLC [5–8], spectrophotometry [9,10], gas chromatography mass spectrometry [11].

Also HCTZ was determined simultaneously with other combinations by HPLC [12–16], or spectrophotometry [17–19].

Primox® plus, a drug used in the Egyptian market, which is a combination of MOX and HCTZ is used for the treatment of hypertension.

This work presents a comparative study between univariate spectrophotometry and multivariate calibration for the simultaneous estimation of MOX and HCTZ in bulk powder and dosage form.

The univariate method used is the extended ratio subtraction method (EXRSM) coupled with ratio subtraction method (RSM) [20,21].

## Experimental

### *Materials and reagents*

- MOX and HCTZ were kindly supplied from National Organization for Drug Control and Research (NODCAR, Cairo, Egypt). The purity of the standards was certified to be higher than 99%. Structures of the compounds are shown in Fig. 1.
- Primox® plus commercial tablets, labeled to contain 15 mg MOX and 25 mg HCTZ batch number GN 520034, GN 520047, GN 520080.
- Methanol: Analytical-grade (El-NASR Pharmaceutical Chemicals Co., Cairo, Egypt).
- Double distilled water was used.

### *Instrument*

A double-beam UV/Visible spectrophotometer model J-760, Jasco, Japan, connected to ACER compatible computer and a LaserJet printer was used. The absorption spectra of the reference and the test solutions were recorded in 1.0 cm quartz cells over the range 200–400 nm at room temperature using Spectramanager software.

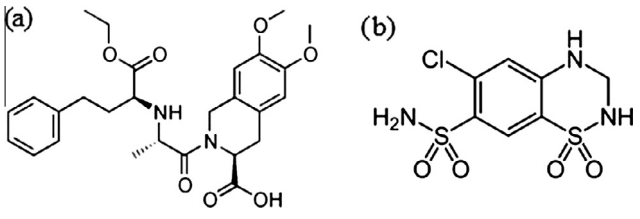


**Fig. 1.** Chemical structures for (a) Moexipril, (b) Hydrochlorothiazide.

For Chemometric methods Matlab 7.0.0.19920 (R14) was used. PCR and PLS were carried out by using PLS toolbox software version 2.1.

### *Procedures*

#### *Preparation of standard solutions and working solutions*

Primary stock solutions of MOX and HCTZ (all at 1.0 mg/mL) were separately prepared by dissolving 100 mg of each standard powder in the least amount of methanol and completed to the volume by distilled water. Primary stock solutions were diluted with distilled water to prepare standard working solutions of MOX and HCTZ (100 μg/mL). All solutions were stored at 4 °C, and equilibrated to room temperature before use.

#### *Spectral characteristics and wavelength selection*

The absorption spectra of 30 μg/mL of MOX and 10 μg/mL of HCTZ were recorded over the spectral wavelength range 200–400 nm using double distilled water as blank.

#### *Linearity and construction of calibration curves for EXRSM method*

Aliquots equivalent to 100–600 μg MOX and 20–300 μg HCTZ were accurately transferred from their standard working solutions into two separate series of 10-mL volumetric flasks then completed to volume with distilled water. The spectra of the prepared standard solutions were scanned from 200 to 400 nm and stored in the computer, then the procedure mentioned under theory of EXRSM was adopted, then the regression equations were computed.

### *Validation*

#### *Accuracy for spectrophotometric methods*

The accuracy of the results was checked by applying the proposed methods for determination of three replicates of different concentrations of the analytes. The concentrations were obtained from the corresponding regression equations.

#### *Precision for spectrophotometric methods*

*Repeatability.* Three concentrations of the analytes were analyzed three times intra-daily using the proposed methods under the same experimental conditions. The relative standard deviations were calculated.

*Reproducibility (intermediate precision).* The previous procedures were repeated inter-daily on three different days for the analysis of the three chosen concentrations. The relative standard deviations were calculated.

*Analysis of MOX and HCTZ in laboratory prepared mixtures (selectivity) by the spectrophotometric methods.* Solutions containing different ratios of the analytes were prepared by transferring accurately measured aliquots from their standard working solutions into a series of 10-mL volumetric flasks and the volume was completed to the mark with distilled water. The final concentration ranges were 10–30 μg/mL for Moexipril and 5–20 μg/mL for HCTZ. Zero order absorption spectra from 200 to 400 nm of these different laboratory prepared mixtures were recorded and the procedures under linearity of both methods were then followed. Concentrations of the analytes in the prepared samples were calculated from the corresponding computed regression equations.

*Experimental design for chemometric methods.* A 5-level, 2-factor calibration design was performed using five concentration levels coded from +2 to −2 for each of the two components to be