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Novel spectrophotometric methods for simultaneous determination of Amlodipine, Valsartan and Hydrochlorothiazide in their ternary mixture

Hayam M. Lotfy [a], Maha A. Hegazy [a], Shereen Mowaka [b,c], Ekram Hany Mohamed [b,*]

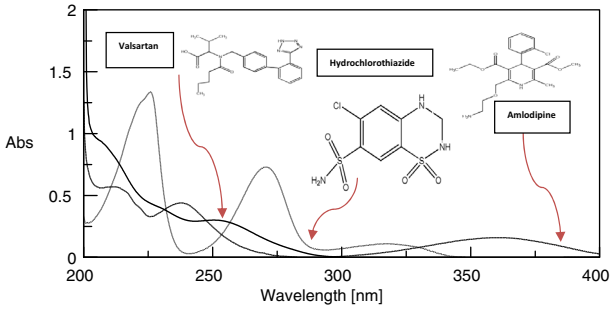
[a] Analytical Chemistry Department, Faculty of Pharmacy, Cairo University, Kasr El-Aini Street, 11562 Cairo, Egypt
[b] Analytical Chemistry Department, Faculty of Pharmacy, British University in Egypt, 11837 El-Sherouk City, Egypt
[c] Analytical Chemistry Department, Faculty of Pharmacy, Helwan University, Ein Helwan, 11795 Cairo, Egypt

HIGHLIGHTS

- Successive and progressive spectrophotometric resolution for multicomponent mixtures.
- Simultaneous quantification of VAL, HCT and AML in bulk and dosage forms.
- Smart and novel methods were applied and validated as per ICH guidelines.
- AS and AM methods were recently applied for the determination of ternary mixture.

GRAPHICAL ABSTRACT

Zero order absorption spectra of 10 μg/mL AML (———), 7.5 μg/mL VAL (– – –), and 10 μg/mL HCT (···) using methanol as blank.



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ABSTRACT

This work represents a comparative study of two smart spectrophotometric techniques namely; successive resolution and progressive resolution for the simultaneous determination of ternary mixtures of Amlodipine (AML), Hydrochlorothiazide (HCT) and Valsartan (VAL) without prior separation steps. These techniques consist of several consecutive steps utilizing zero and/or ratio and/or derivative spectra. By applying successive spectrum subtraction coupled with constant multiplication method, the proposed drugs were obtained in their zero order absorption spectra and determined at their maxima 237.6 nm, 270.5 nm and 250 nm for AML, HCT and VAL, respectively; while by applying successive derivative subtraction they were obtained in their first derivative spectra and determined at $P_{230.8–246}$, $P_{261.4–278.2}$, $P_{233.7–246.8}$ for AML, HCT and VAL respectively. While in the progressive resolution, the concentrations of the components were determined progressively from the same zero order absorption spectrum using absorbance subtraction coupled with absorptivity factor methods or from the same ratio spectrum using only one divisor via amplitude modulation method can be used for the determination of ternary mixtures using only one divisor where the concentrations of the components are determined progressively. The proposed methods were checked using laboratory-prepared mixtures and were successfully applied for the analysis of pharmaceutical formulation containing the cited drugs. Moreover comparative study between spectrum addition technique as a novel enrichment technique and a well established one namely spiking technique was adopted for the analysis of pharmaceutical formulations containing low concentration of AML. The methods were validated as per ICH guidelines where accuracy, precision

* Corresponding author. Tel.: +20 1120702314.
E-mail address: ekramhany84@yahoo.com (E.H. Mohamed).

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and specificity were found to be within their acceptable limits. The results obtained from the proposed methods were statistically compared with the reported one where no significant difference was observed.

Introduction

Improved medication compliance for patients by reducing the pill burden was recently achieved through drug combination.

The majority of hypertensive patients need at least two drugs to control the blood pressure, so it was a need to co-formulate different antihypertensive drugs. Exforge HCT is an example of fixed drug combination. It is composed of three drugs AML, VAL and HCT.

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 with calcium antagonist activity. It is used for management of hypertension, chronic stable angina pectoris, and prinzmetal's variant angina [2]. Various analytical methods have been recently reported for the assay of AML single or in combination with other antihypertensive agents in pharmaceutical formulations and different biological fluids. They include UV spectroscopic [3,4], spectroflourimetric methods [5,6], and chromatographic methods including TLC [7], LC [8,9] and electrophoresis [10].

Valsartan (VAL), N-(1-oxopentyl)-N-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-L-valine[11](Fig. 1b), is a potent and specific competitive antagonist of the angiotensin-II AT1-receptor. It is used for treatment of hypertension, heart failure, and post-myocardial infarction [12]. Recently different analytical methods were reported for the assay of VAL single or in combination with other drugs including UV spectroscopic [13] and chromatographic methods; including LC [14,15].

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 either as single formulation or in combination with other drugs [16]. Recently various analytical methods have been reported for the assay of HCT single or in combination with other drugs either in dosage form or different biological fluids including UV spectroscopic [17,18], chromatographic methods like; UPLC [19], LC [20] and HPTLC [21].

Amlodipine (AML) was simultaneously determined in presence of VAL using UV spectroscopic [22] and chromatographic methods [22,23]. Also it was determined in presence of HCT using UV spectroscopic [24] and capillary zone electrophoresis [25].

VAL and HCT were also determined simultaneously using UV spectroscopic [26], chromatographic methods including, TLC [26] and LC [27].

Different analytical methods were reported for estimation of the triple mixture including UV spectroscopic [28–30], chemometric [30,31] and chromatographic methods [32,33].

A novel enrichment technique namely spectrum addition technique was introduced to overcome the challenges on the analysis of one or more component present in low concentration or low absorptivity at proposed wavelength in the mixtures to facilitate the determination of one or more component(s), there is a need to increase its concentration to eliminate the deviation from Beer's law which occurs in case of low contribution [34]. Moreover, this novel enrichment technique could be considered superior to spiking technique since application of spectrum addition eliminates all types of error giving high degree of accuracy of the analytical signals and it could be done for applying resolution technique in order to eliminate one or more spectrum. The sum of the stored spectra could be performed with the help of UVPC software which was previously applied in the analysis of ternary mixtures using double divisor method [35,36].

The aim of this work was to establish novel, simple, sensitive and accurate analytical methods for simultaneous determination of AML, VAL and HCT in their bulk powder and pharmaceutical dosage forms with satisfactory precision and accuracy.

Theoretical background

Spectrum addition technique

Spectrum addition technique is a novel sample enrichment technique [37] and it could be adopted in either binary or ternary mixtures where the spectrum of one of the components is extended and its spectrum shows low absorbance at the extended part which hinders its analysis by the methods utilizing the constant at the extended region using either zero order absorption spectrum or derivative spectrum due to inaccurate determination of the constant value. The spectrum addition technique is not only restricted to an extended component only or just for obtaining the constant of the extended drug. It could be generally applied with

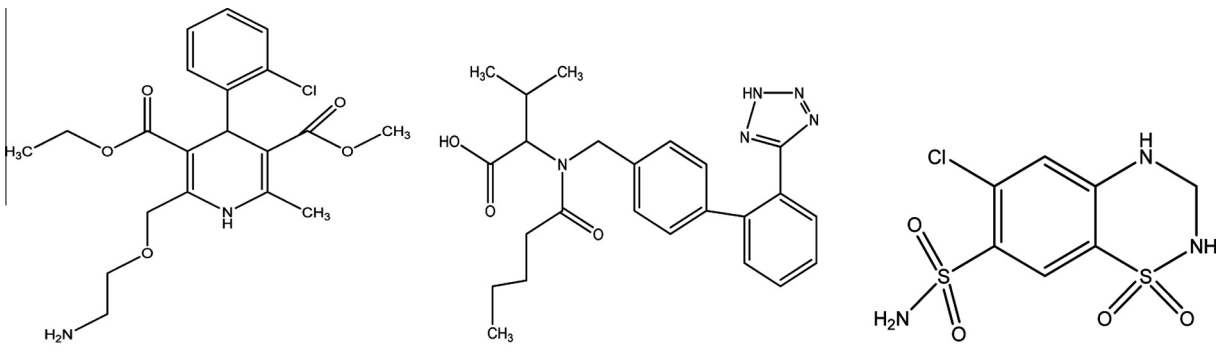

Fig. 1. Structural formulae for (a) Amlodipine, (b) Valsartan, and (c) Hydrochlorothiazide.