Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy 125 (2014) 138–146

Contents lists available at ScienceDirect

Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy

journal homepage: www.elsevier.com/locate/saa

Spectrophotometric methods for simultaneous determination of ternary mixture of amlodipine besylate, olmesartan medoxomil and hydrochlorothiazide

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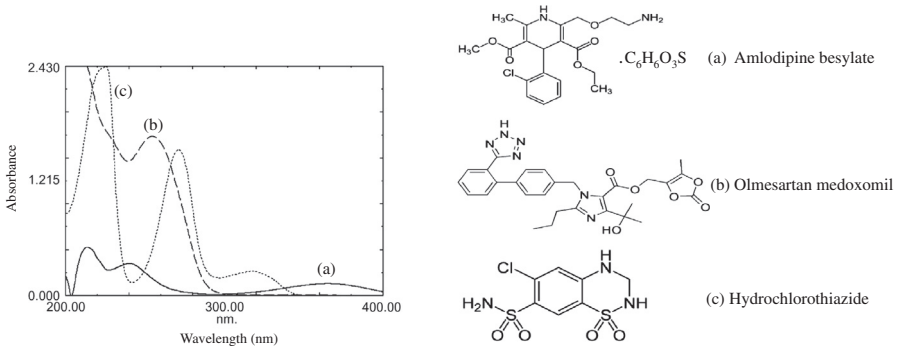
HIGHLIGHTS

- Four simple spectrophotometric methods were successfully applied.
- They are used for simultaneous analysis of complex ternary mixtures.
- They are sensitive and selective and do not require sophisticated techniques.
- They could be easily applied in QC labs lacking liquid chromatographic instruments.
- They are used for analysis of dosage form without prior separation.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 20 September 2013
Received in revised form 28 December 2013
Accepted 19 January 2014
Available online 30 January 2014

Keywords:
Ternary mixture
First derivative ratio spectra
Double divisor
Successive spectrophotometry
Isoabsorptive point
Mean centering

ABSTRACT

Four, accurate, precise, and sensitive spectrophotometric methods are developed for the simultaneous determination of a ternary mixture containing amlodipine besylate (AM), olmesartan medoxomil (OL) and hydrochlorothiazide (HZ), where AM is determined at its λ_{max} 364.6 nm (^{0}D), while (OL) and (HZ) are determined by different methods. Method (A) depends on determining OL and HZ by measuring the second derivative of the ratio spectra (^{2}DD) at 254.4 and 338.6 nm, respectively. Method (B) is first derivative of the double divisor ratio spectra (D-^{1}DD) at 260.4 and 273.0 nm for OL and HZ, respectively. Method (C) based on successive spectrophotometric resolution technique (SSRT). The technique starts with the ratio subtraction method then measuring OL and HZ at their isoabsorptive point at 260.0 nm, while HZ is measured using the amplitude of first derivative at 335.2 nm. Method (D) is mean centering of the ratio spectra (MCR) at 252.0 nm and 220.0 nm for OL and HZ, respectively. The specificity of the developed methods is investigated by analyzing laboratory prepared mixtures containing different ratios of the three drugs and their combined dosage form. The obtained results are statistically compared with those obtained by the official or reported methods, showing no significant difference with respect to accuracy and precision at $p = 0.05$.

Introduction

Amlodipine besylate (AM), (Fig. 1a) is chemically designated as (RS)-3-ethyl 5-methyl 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate] [1]. It is a long acting calcium channel blocker, used for stable angina pectoris and as adjunctive therapy with angiotensin receptor antagonists in management of hypertension to reduce the risk for progression of kidney diseases [2].

Olmesartan medoxomil (OL), (Fig. 1b) is chemically designated as 5-methyl-2-oxo-2H-1,3-dioxol-4-yl)methyl

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http://dx.doi.org/10.1016/j.saa.2014.01.095
1386-1425/

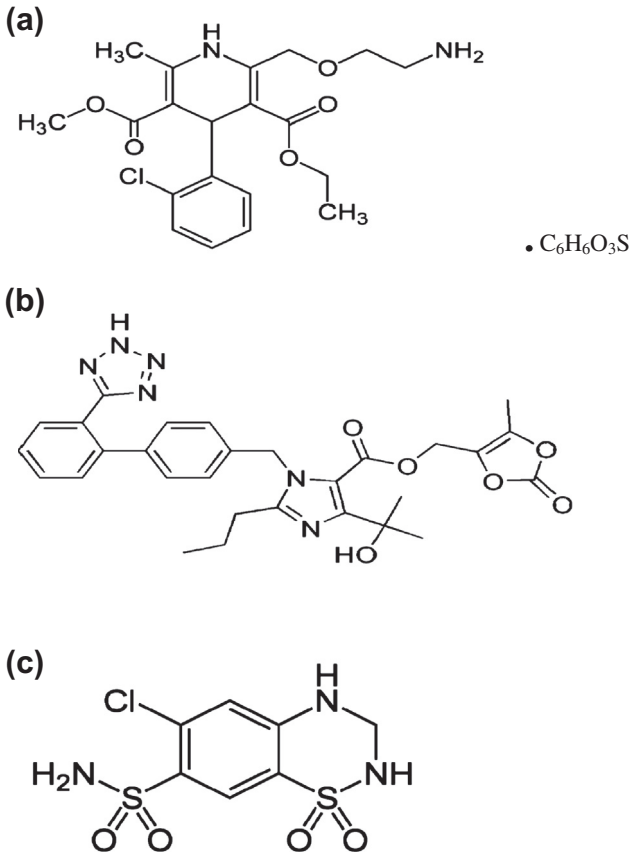

Fig. 1. Chemical structures of (a) amlodipine besylate (AM), (b) olmesartan medoxomil (OL) and (c) hydrochlorothiazide (HZ).

4-(2-hydroxypropan-2-yl)-2-propyl-1-({4-[2-(2H-1,2,3,4-tetrazol-5-yl) phenyl]phenyl}methyl)-1H-imidazole-5-carboxylate [1], It is an ester prodrug that is hydrolysed during absorption from the gastrointestinal tract to the active form olmesartan. OL is an angiotensin II receptor antagonist used in the management of hypertension [3].

Hydrochlorothiazide (HZ), (Fig. 1c) is chemically designated as 6-chloro-1,1-dioxo-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide [1]. It is a thiazide diuretic that lowers blood pressure initially by increasing sodium and water excretion. It counteracts sodium and water retention observed with other agents used in treatment of hypertension, therefore useful in combination therapy with a variety of other antihypertensive agents including angiotensin receptor antagonists and ß-blockers [4].

Olmesartan medoxomil, amlodipine besylate and hydrochlorothiazide are recently introduced in the market as a new three-in-one combined tablet dosage form (Tribenzor®), taken once-daily for the treatment of hypertension.

Amlodipine (AM) and hydrochlorothiazide (HZ) are official drugs, while olmesartan (OL) is unofficial one. Determination of AM is described in British Pharmacopeia [5] and United State Pharmacopeia [6] by reversed phase high performance liquid chromatographic methods. HZ, pure powder is described in British Pharmacopeia [5] by spectrophotometric method. While HZ, dosage form is described in United State Pharmacopeia [7] by high performance liquid chromatographic method.

Literature survey represented that AM, OL and HZ can be determined either alone or in combination with other drugs by several methods including, spectrophotometric methods [8–13], spectrofluorometric methods [13,14], HPTLC [15], mass spectroscopic methods [16], HPLC [17–22], capillary electrophoresis [23] and voltammetric methods [24].

Few methods are available for the simultaneous determination of OL, AM and HZ in combination. These methods include HPLC [25,26], chemometric methods, [27,28], and two spectrophotometric methods [28,29].

The aim of this work is to devolope four, sensitive, accurate, precise, reliable, fast and inexpensive analytical methods for the determination of the three drugs without prior separation.

Experimental

Apparatus

Spectrophotometer: SHIMADZU dual beam UV–visible spectrophotometer (Kyoto/Japan), model UV-1650 PC connected to IBM compatible and a HP1020 laser jet printer. The bundled software, UV-Probe personal spectroscopy software version 2.21 (SHIMADZU) is used. The spectral band is 2 nm and scanning speed is 2800 nm/min with 0.1 nm interval.

Software

Matlab® version 7, release 14.

Pure samples

Amlodipine (AM) was kindly supplied by Al-Hekma Pharmaceutical Company, Cairo, Egypt, its purity was found to be 100.41 ± 0.680 according to the official method [5]. OL was kindly supplied by Apex Pharmaceutical Company Cairo, Egypt, its purity was found to be 100.07 ± 0.815 according to the reported method [30], while HZ was kindly supplied by National Organization for Drug Control and Research (NODCAR), Cairo, Egypt, its purity was found to be 99.96 ± 0.601 according to the official method [5].

Pharmaceutical formulations

Tribenzor® tablets (batch number 249720), manufactured by Daiichi Sankyo, Inc. from Vogue Pharmaceuticals Inc., Calgary, Canada. Each tablet was labeled to contain 13.9 mg Amlodipine besylate (AM), equivalent to 10 mg Amlodipine base 40 mg olmesartan medoxomil (OL) and 25 mg hydrochlorothiazide (HZ).

Reagents

Ethanol of spectroscopy grade was purchased from Sigma–Aldrich, (St. Louis, MO, USA), while water used was of distilled grade.

Standard stock and working solutions

- AM, OL and HZ stock solutions (1 mg/mL of each in ethanol).
- AM, OL and HZ working solutions (100 μg/mL of each in distilled water).

Laboratory prepared mixtures containing different ratios of AM, OL and HZ

Into a series of 10-mL volumetric flasks, aliquots of AM, OL and HZ were transferred from their corresponding standard working solutions (100 μg/mL) of each, and then the volume was completed with distilled water. That prepares mixtures containing different ratios of the three drugs.