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Simultaneous Determination of Olmesartan Medoxomil and Hydrochlorothiazide by Area Under Curve and Dual Wavelength Spectrophotometric Methods

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ABSTRACT-Two simple, accurate and reproducible spectrophotometric methods have been developed and validated for simultaneous estimation of olmesartan medoxomil and hydrochlorothiazide in combined dosage form. Olmesartan medoxomil shows maximum absorbance at 255 nm and hydrochlorothiazide shows maximum absorbance at 270 nm. For area under curve method, the wavelengths ranges between 250 – 260 nm and 265 – 275 nm were selected with reference to absorbance curves plotted between 200 – 400 nm. In dual wavelength method, two wavelengths were selected for each drug in a way so that the difference in absorbance is zero for another drug. Olmesartan medoxomil shows equal absorbance at 242 and 263 nm, where the difference in absorbance was measured for determination of hydrochlorothiazide. Similarly, difference in absorbance at 253 and 284 nm were measured for determination of olmesartan medoxomil. Linearity for detector response was observed in the concentration range of 5 – 40 µg/mL for olmesartan medoxomil and 3 – 24 µg/mL for hydrochlorothiazide for method I, 4 – 32 µg/mL for olmesartan medoxomil and 2.5 – 20 µg/mL for hydrochlorothiazide for method II respectively. Accuracy and precision studies were carried out and results were satisfactory. The proposed methods were validated as per ICH guidelines.

Key words: Olmesartan medoxomil, Hydrochlorothiazide, AUC method, Dual wavelength method, Method validation.

INTRODUCTION

Olmesartan medoxomil (OLM), chemically 2, 3-dihydroxy-2-butenyl 4-(1-hydroxy-1-methylethyl)-2-propyl-1-[p-(o-1H-tetrazol-5-yl phenyl) benzyl] imidazole-5-carboxylate, cyclic 2, 3-carbonate is a prodrug and hydrolysed to olmesartan during absorption from gastrointestinal tract (Fig. 1a). It is a selective AT1 subtype angiotensin II receptor antagonist. Hydrochlorothiazide (HTZ) chemically 6-chloro-3, 4-dihydro-2, 4-1, 2, 4-benzothiadiazine-7-sulphonamide 1, 1-dioxide (Fig. 1b) is a widely used thiazide diuretic [1-3]. Olmesartan and hydrochlorothiazide are available in market as combined dosage form for treatment of hypertension. Extensive literature survey revealed determination of OLM in dosage form by UV-visible spectrophotometry [4,5], HPLC-UV [6], capillary electrophoresis [7]; in biological fluids, HPLC [8] and LC-MS [9,10]. Determination of HTZ in pharmaceutical dosage form and biological fluids include chemiluminescence [11], HPLC [12] and electrochemical study [13]. Determination of OLM and HTZ in combination include UV- spectrophotometry [14-16], RP-HPLC and HPTLC [17].

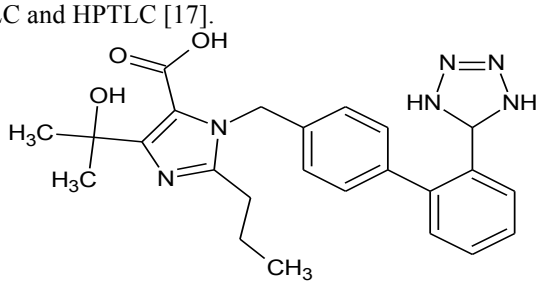

Fig 1a. Chemical structure of Olmesartan Medoxomil

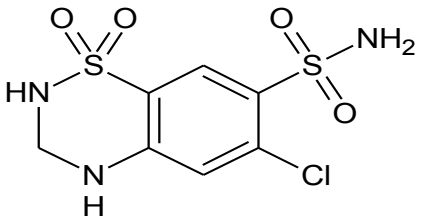

Fig 1b. Chemical structure of Hydrochlorothiazide

However, there is no work reported concerning simultaneous spectrophotometric determination of OLM and HTZ by proposed methods. The aim of present investigation is to develop simple and economical spectrophotometric methods with greater precision, accuracy and sensitivity for simultaneous estimation of OLM and HTZ in pure and tablet dosage forms.

EXPERIMENTAL

Chemicals and Reagents

Pharmaceutical grade OLM and HTZ were supplied by Atoz laboratories (Chennai, India) and certified to contain 99.76% and 100.13% respectively. Tablets, Olmesar-H (Macleods Pharmaceuticals Pvt. Ltd.) and Olmy-H (Zydus Cadila Healthcare Ltd.) both labeled to contain 40 mg OLM and 12.5 mg HTZ were purchased from local pharmacy. Spectroscopy grade methanol was used throughout study.

Equipment

A double beam UV-visible spectrophotometer (Shimadzu, Japan) model UV-170 with quartz cell 1 cm path length,

connected to HP computer version 2.21 was used. Shimadzu balance (AUW-120D) was used for all weighing.

Standard stock solutions

Stock solutions (1 mg/mL) were prepared for OLM and HTZ separately in methanol. From these stock solutions, sub stock solutions (100 µg/mL) were prepared for both drugs. From these sub stocks, eight mixed standards were prepared having OLM and HTZ in the ratio of 3.2:1 (as in combination tablet).

Sample preparation

Twenty tablets were accurately weighed and powdered in a mortar. A quantity of powdered tablet equivalent to 50 mg OLM and HTZ was transferred into 50 mL volumetric flask, 25 mL methanol was added, dissolved and completed to 50 mL with same solvent. After filtering the solution through Whatmann filter paper, suitable aliquots were completed to volume with methanol. The final concentration contains OLM and HTZ in the ratio of 3.2:1.

Method I

Area under curve method

For the selection of analytical wavelength, 10 µg/mL each of OLM and HTZ were prepared by appropriate dilution of standard stock solution. The solutions were scanned in the spectrum mode from 200-400 nm. From the spectra of drugs (Figure 2), area under curve in the range of 250 – 260 nm for OLM and 265 – 275 for HTZ were selected for analysis. The calibration curves were prepared in the range of 5 – 40 µg/mL OLM and 3 – 24 µg/mL HTZ at their respective AUC range. By using calibration curve, the concentration of sample solutions can be determined.

Method II

Dual wavelength method

The spectrum of OLM shows identical absorbance at 242 nm (λ_1) and 263 nm (λ_2) while that of HTZ reveals same absorbance at 253 nm (λ_3) and 284 nm (λ_4), therefore wavelengths at λ_1, λ_2 and λ_3, λ_4 were selected for analysis of OLM and HTZ respectively. The concentrations of two drugs were calculated each from corresponding regression equation.

RESULTS AND DISCUSSION

The main aim of this work was to establish and validate simple, sensitive and accurate spectrophotometric methods as substitutes for HPLC and TLC methods reported for the simultaneous determination of OLM and HTZ in bulk and dosage form with satisfactory precision.

Linearity and sensitivity

The linearity of the methods were evaluated by analysing eight concentrations (5 – 40 µg/mL OLM and 3 – 24 µg/mL HTZ for method I; 4 – 32 µg/mL OLM and 2.5 – 20 µg/mL HTZ for method II respectively) of each drug in triplicate. Table 1 reveals the correlation coefficients along with standard deviation of slope (S_b) and intercept (S_a). The limit of detection (LOD) and quantification (LOQ) were calculated using standard deviation of response and slope of calibration curve.

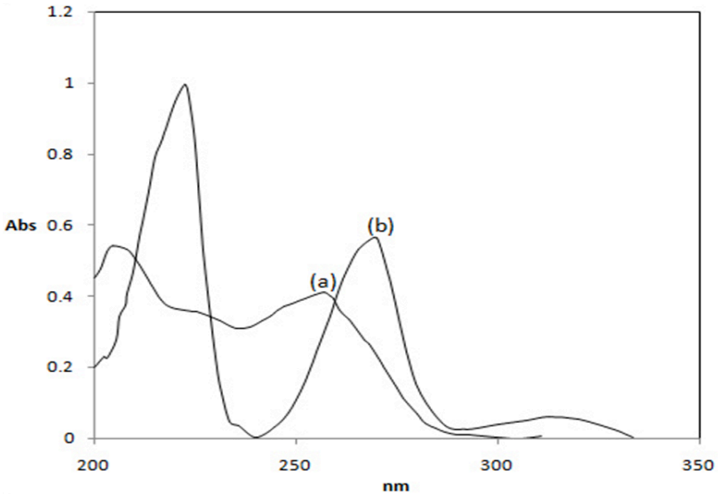

Fig 2. Typical overlain spectra of (a) Olmesartan Medoxomil and (b) Hydrochlorothiazide

Table 1: Validation data for OLM and HTZ

Parameters	*Area under curve*		*Dual wavelength*	
	OLM	*HTZ*	*OLM*	*HTZ*
Linearity (µg/mL)	5-40	3-24	4-32	2.5-20
S_a	0.00015	0.00034	0.00018	0.00042
S_b	0.00023	0.00017	0.00073	0.00056
Correlation coefficient (r^2)	0.9997	0.9990	0.9997	0.9994
LOD (µg/mL)	0.74	0.43	0.53	0.36
LOQ (µg/mL)	2.42	1.86	2.27	1.12
Regression coefficient (r)	0.996	0.999	0.998	0.997

LOD = 3.3×SD/slope, LOQ = 10×SD/slope, S_a = Standard deviation of intercept of regression line, S_b = Standard deviation of slope of regression line

Table 2: Results of recovery study

Drug	*Amount taken (µg/mL)*	*Amount added (µg/mL)*	*Amount recovered ± SD* (µg/mL)*	*% RSD*	*Amount recovered ± SD* (µg/mL)*	*% RSD*
			Method I		*Method II*	
OLM	16	4	20.12 ± 0.014	0.07	20..35 ± 0.046	0.23
		8	23.47 ± 0.057	0.24	24.12 ± 0.032	0.13
		12	28.26 ± 0.031	0.11	28.54 ± 0.076	0.27
HTZ	5	2	6.89 ± 0.011	0.16	6.92 ± 0.032	0.47
		4	8.79 ± 0.042	0.48	8.85 ± 0.046	0.52
		6	10.85 ± 0.019	0.18	10.91 ± 0.015	0.14

Method I: Area under curve method, Method II: Dual wavelength method
*Mean of three determinations

Table 3: Results of intraday and inter day precision

Method	*Precision*	*Amount taken (µg/mL)*		*% Mean**		*% RSD*	
		OLM	*HTZ*	*OLM*	*HTZ*	*OLM*	*HTZ*
I	Intraday	10	3	99.32	98.57	0.057	0.074
	Intraday	15	6	99.56	100.12	0.097	0.113
	Inter day	10	3	101.32	98.45	0.547	1.001
	Inter day	15	6	100.25	98.91	0.452	0.854
II	Intraday	10	3	98.78	97.89	0.094	0.124
	Intraday	15	6	99.24	100.78	0.247	0.197
	Inter day	10	3	101.24	98.78	1.143	0.975
	Inter day	15	6	100.47	99.65	0.875	1.002

Method I: Area under curve method, Method II: Dual wavelength method
*Mean of three determinations

Table 4: Results of tablet analysis

Parameters	*Method I*		*Method II*	
	OLM	*HTZ*	*OLM*	*HTZ*
Label claim (mg per tablet)	40	12.5	40	12.5
Drug content % ± SD*	98.54 ± 0.17	99.63 ± 0.74	98.65 ± 0.67	101.32± 0.28
SEM	0.0760	0.3309	0.2996	0.1252

SEM – Standard error mean
Method I: Area under curve method, Method II: Dual wavelength method
*Mean of five determinations

Precision

Intraday precision (repeatability) was calculated using two concentrations of OLM (10, 15 µg/mL) and HTZ (3, 6 µg/mL) in triplicate using proposed methods. The inter day precision (reproducibility) was repeated three times on three different days for analysis of two different concentration (10:3, 15:6 µg/mL) for both drugs. % RSD (Table 2) for OLM and HTZ for both methods ranged from 0.054 to 1.143 indicating repeatability and reproducibility.

Accuracy

Accuracy of the methods were assured by standard addition technique, which was performed by addition of known amounts of pure OLM and HTZ to known concentrations of tablet powder, and analysed by proposed methods in triplicate. Table 3 indicates good accuracy and shows no interference from tablet excipients.

Assay of tablet formulation

The assay of tablets (Olmesar-H and Olmy-H) for both methods was reported in table 4. The standard deviation of five replicate analysis for each method were found to be < 1.

CONCLUSION

The obtained results from area under curve and dual wavelength methods for simultaneous estimation of olmesartan medoxomil and hydrochlorothiazide indicate that the methods are simple, accurate and precise, hence can be used for routine analysis of commercially available drugs.

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