Department of Analytical Chemistry, Faculty of Pharmacy, Hacettepe University, Sihhiye/Ankara, Turkey

Determination of olmesartan medoxomil in tablets by UV-Vis spectrophotometry

M. Celebier, S. Altinoz

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Prof. Dr. Sacide Altinoz, Department of Analytical Chemistry, Faculty of Pharmacy, Hacettepe University, 06100 Sihhiye/Ankara, Turkey
saltinoz@hacettepe.edu.tr

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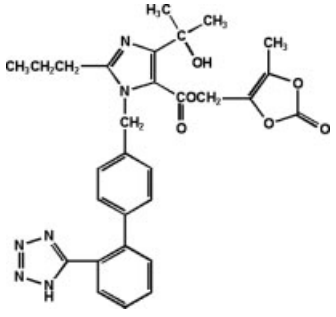
A simple, rapid and reliable UV spectrophotometric method was developed for the determination of olmesartan medoxomil in pharmaceutical dosage forms. The solutions of standard, tablet and synthetic tablet were prepared in acetonitrile and in NaOH-Water. 258 nm and 250 nm were chosen for acetonitrile and for NaOH-Water solutions respectively. The developed method was validated with respect to stability, linearity, sensitivity, specificity, precision, accuracy, robustness and ruggedness. The linearity range of the method was 1.0–70.0 $\mu g \cdot mL^{-1}$ for acetonitrile solutions and 1.0–75.0 $\mu g \cdot mL^{-1}$ for NaOH-Water solutions. The developed and validated method was applied for the determination of olmesartan medoxomil in pharmaceutical dosage forms.

1. Introduction

Olmesartan medoxomil (OLM) is a prodrug, which, after ingestion, liberates the only active metabolite, olmesartan. Olmesartan is a competitive and selective AII type 1 receptor antagonist. The hydrolysis of olmesartan medoxomil occurs readily by the action of esterases which are present abundantly in the gastrointestinal tract, liver and plasma. The active metabolite, olmesartan, is not further metabolized (Koike et al. 2003; Mire et al. 2005; Unger et al. 2004). OLM is chemically described as 2,3-dihydroxy-2-butenyl-4-(1-hydroxy-1-methylethyl)-2-propyl-1-[*p*-(*o*-1*H*-tetrazol-5-ylphenyl)benzyl]imidazole-5-carboxylate, cyclic-2,3-carbonate.



Olmesartan medoxomil

In the literature, there hasn't been any method described for the determination of OLM in pharmaceutical dosage forms. Therefore it is a necessity to develop a method for the determination of OLM in pharmaceutical dosage forms.

The main propose of this study was to develop a simple, rapid, accurate, precise, linear, sensitive, robust and rugged spectrophotometric method for the determination of OLM in pharmaceutical dosage forms. Thus, a completely validated UV spectrophotometric method was developed and proposed for the determination of OLM in pharmaceutical dosage forms. Two different kinds of solvent, acetonitrile (ACN) and NaOH-Water solution, were used to perform analysis.

2. Investigations, results and discussion

Different kinds of solvents were tried to find the optimum conditions to perform the method. Since OLM is sparingly soluble in water at room temperature, organic solvents such as methanol (MeOH) and acetonitrile (ACN) were used to dissolve OLM. When MeOH was used, OLM could not preserve its stability at room temperature although prevented from daylight (Fig. 1).

The stability problem was eliminated when another organic solvent, acetonitrile, was chosen. OLM was solved in ACN and measurements were performed at 258 nm. The UV absorption of standard, tablet and synthetic tablet solutions of OLM was identical at 258 nm when recorded from 200 nm to 400 nm in ACN.

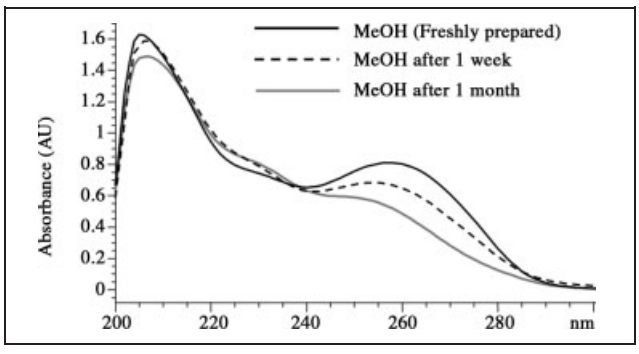


Fig. 1: Unstable behavior of OLM solved in MeOH

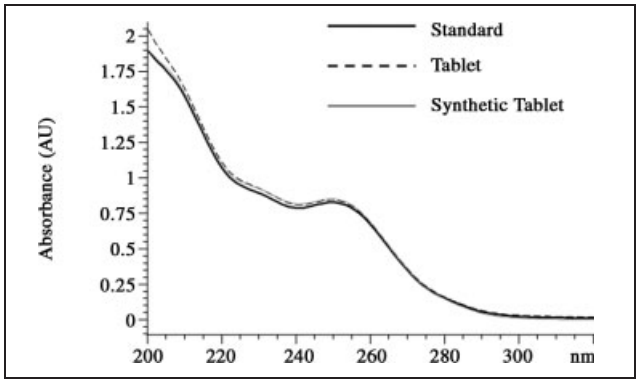


Fig. 2: Spectrum of standard, tablet and synthetic tablet solutions of OLM in NaOH-Water (20 $\mu g \cdot mL^{-1}$)

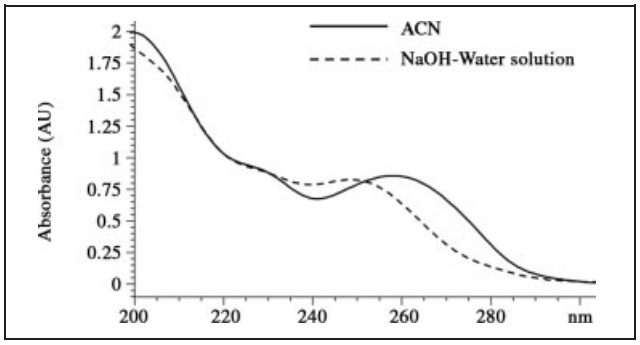


Fig. 3: Spectrum of OLM (20 $\mu g \cdot mL^{-1}$) in ACN and in NaOH-Water

Despite sparingly soluble in water, OLM could be easily solved in a NaOH-Water solution. For this reason, the second chosen solvent was 0.02 N NaOH-Water solution. After OLM was solved, a yellowish solution occured.

The UV absorption of standard, tablet and synthetic tablet solutions were identical at 250 nm when recorded from 200 nm to 400 nm after solved in 0.02 N NaOH and diluted with deionised water (Fig. 2). The UV Spectrum of 20 ppm OLM in ACN and in NaOH-Water solution were compared at Fig. 3.

For the developed method, quantitative analysis was performed at 258 nm for ACN solutions, 250 nm for NaOH-water solutions.

The method was validated with respect to stability, linearity, sensitivity, specificity, precision, accuracy, robustness and ruggedness (ICH 1995; Green 1996; Braggio et al. 1996; Fabre and Altria 2001; Vander Heyden et al. 2001; Taverniers et al. 2004; Ermer and Ploss 2005).

Table 1: Data of the calibration curve for OLM using the proposed method (n = 6)

Solvent Regression equation	ACN * y = 0.0424x + 0.0141	NaOH-Water * y = 0.0416x + 0.0145
r	0.9996	0.9998
S_1	0.0004	0.0006
S_2	0.0061	0.0037
Linearity range ($\mu g \cdot mL^{-1}$)	1.00–70.00	1.00–75.00
LOQ ($\mu g \cdot mL^{-1}$)	0.47	0.16
LOD ($\mu g \cdot mL^{-1}$)	0.24	0.08

* y = aX + b where X is the concentration of OLM ($\mu g \cdot mL^{-1}$); y is the absorbance for UV spectrophotometric method; (a is the slope and b is the intercept)
r: Coefficient of correlation
S1: Standard error of intercept at regression line
S2: Standard error of slope at regression line
LOQ: Limit of quantitation
LOD: Limit of detection

The standard stock solutions of OLM were stored under two different conditions; +4 °C and ambient temperature. These solutions were for 1 month and prevented from daylight. During this period, UV spectra of solutions were taken periodically. They were compared with freshly prepared solutions and not any difference was found between them. This indicated that OLM was stable under the above mentioned conditions for at least one month.

In quantitative analysis, the calibration curves for OLM in ACN and in NaOH-Water solution were constructed and found to be linear over the range of 1.00 to 70.00 $\mu g \cdot mL^{-1}$ and 1.00 to 75.00 $\mu g \cdot mL^{-1}$ respectively. The regression equations, standard errors of slopes and intercepts, correlation coefficients and linearity ranges are given in Table 1.

The limit of detection (LOD) (k = 3.3) and limit of quantition (LOQ) (k = 10) of the method were established according to the ICH definitions ($C_1 = k\ S_0/s$ where C_1 is LOD or LOQ S_0 is the standard error of blank determination, s is the slope of standard curve and k is the constant related to the confidence interval). The standard errors of absorbance measurements for blank solution in the developed method were 0.002 and 0.001 respectively. The LOD and LOQ values are given in Table 1.

The precision of the analysis was determined by calculating the relative standard deviation (RSD %). The precision around the mean value should not exceed 1.5%.

Three different concentrations of OLM (10, 30 and 50 $\mu g \cdot ml^{-1}$) in the linear range were prepared and analyzed in one day (intra-day) and six consecutive day (inter-day). For OLM, the RSD % values varied from 0.52 to 1.44 for ACN solution and from 0.28 to 1.85 for NaOH-Water solution (Table 2).

Table 2: Precision and accuracy for the analysis of OLM (n = 6)

		Intra-day			Inter-day		
Solvent	Added ($\mu g \cdot mL^{-1}$)	Found $\bar{x}$ ($\mu g \cdot mL^{-1}$)	Precision RSD %	Accuracy Bias %	Found $\bar{x}$ ($\mu g \cdot mL^{-1}$)	Precision RSD %	Accuracy Bias %
ACN	10	10.06 ± 0.02	0.52	−0.63	10.18 ± 0.09	0.92	−1.87
	30	29.98 ± 0.22	0.55	0.06	29.84 ± 0.24	0.81	0.51
	50	49.61 ± 0.22	0.56	0.76	50.32 ± 0.72	1.44	−0.66
NaOH-Water	10	9.95 ± 0.02	0.45	0.44	9.95 ± 0.08	1.85	0.42
	30	29.91 ± 0.14	1.23	0.31	30.12 ± 0.14	1.15	−0.41
	50	49.77 ± 0.02	0.28	0.60	49.70 ± 0.11	0.26	0.58

% Bias = [(found – added)/added] × 100
$\bar{x}$: Mean ± SE
SE: standard error, RSD: Relative standard deviation

Table 3: Recovery data of OLM obtained from the standard addition technique (n = 6)

Solvent	Added ($\mu g \cdot mL^{-1}$)	$\bar{x} \pm SE$	RSD %	Recovery %
ACN	5	5.10 ± 0.01	0.5	101.91
	10	9.81 ± 0.03	0.7	98.13
	20	19.96 ± 0.04	0.5	99.82
NaOH-Water	5	4.99 ± 0.04	2.1	99.98
	10	9.97 ± 0.08	1.9	99.73
	20	19.77 ± 0.07	0.9	98.86

$\bar{x}$: Mean ± SE
SE: Standard error
RSD: Relative standard deviation

The accuracy of a method is determined by calculating recovery % and the percent difference (bias %) between the measured mean concentrations and the corresponding nominal concentrations. Intra and inter day bias % values are given in Table 2.

Calculating the percentage relative error between the measured and added concentrations of OLM showed that the developed method was highly accurate.

In order to evaluate the effect of the presence of excipients on the proposed method, the standard addition technique was applied (Nemutlu et al. 2005). For this reason, known amounts of OLM standard solutions were added at three different concentrations (5, 10 and 20 $\mu g \cdot ml^{-1}$) and six samples were prepared for each recovery level. The results obtained are shown in Table 3, from which it is clear that the recoveries were satisfactory.

Another recovery study was performed with synthetic tablet solutions. The recovery results were 101.03% ± 0.03 for ACN and 100.09% ± 0.04 for NaOH-water solutions of OLM ($\bar{x} \pm SE$ where $\bar{x}$ is mean, SE: Standard error).

In addition to this, the spectra obtained from standard, tablet and synthetic tablet solutions containing an equivalent concentration of OLM were identical (Fig. 2).

These data show that there was no interaction of excipients in the analysis of OLM in tablet dosage forms.

In addition to this, standard addition technique was applied to the same preparations which were analysed by the calibration curve method. The regression equations of standard addition curves of the method for tablet analysis were found to be $y = 0.0432x + 0.8587$ for ACN and $y = 0.0405x + 0.8181$ for NaOH-Water (x is the concentration of OLM ($\mu g \cdot mL^{-1}$)).

Since the slopes of the standard and standard addition curves were identical, it was concluded that there was no spectral interaction in the analysis of OLM in tablet dosage forms with the developed method.

Table 4: Robustness and ruggedness data (n = 6) (OLM 30 $\mu g \cdot mL^{-1}$)

Solvent	Conditions	$\bar{x} \pm SE$	RSD %
ACN	Standard	29.93 ± 0.05	0.5
	259 nm Wavelength	29.90 ± 0.05	0.5
	257 nm Wavelength	29.88 ± 0.05	0.5
	Different device	29.64 ± 0.21	1.8
	$p = 0.537 > p = 0.05$		
NaOH-Water	Standard	30.21 ± 0.16	1.3
	251 nm Wavelength	30.01 ± 0.15	1.3
	249 nm Wavelength	30.30 ± 0.16	1.3
	Different device	30.53 ± 0.12	1.0
	$p = 0.086 > p = 0.05$		

$\bar{x}$: Mean ± SE
SE: standard error
RSD: Relative standard deviation

On the basis of these results, the proposed method could be considered as selective.

The robustness of the method was tested by making deliberate small changes in selected wavelengths. For ruggedness, OLM analyses were performed in a different laboratory (interdisciplinary laboratory) with a different device (Agilent 8453 UV Spectrophotometer).

Obtained results were close to those obtained under standard conditions. In addition to this, when a statistical comparison was done by Friedman Analysis, there was no difference between the results (Table 4). Therefore the method is rugged and robust under small changes in experimental conditions.

The developed method was successfully applied to the determination of OLM in a pharmaceutical tablet formulation (Olmetec® Tablet). OLM in six different tablet solutions derived from three dosage forms (10, 20 and 40 mg) was analyzed by calibration curve and standard addition techniques. These techniques were performed at 258 or 250 nm according to the used solvent (ACN or NaOH-Water). For the calibration curve technique, the tablet solutions of OLM, prepared as six independent series, were analyzed three times for three dosage forms.

For the standard addition technique, tablet analysis was performed six times by the addition of known amounts of OLM standard solutions to the tablet solutions (Olmetec® Tablet 10, 20 and 40 mg) to give the final concentration. After the measurement of absorbances, the concentration of tablet solutions were found through the regression equation.

The results and statistical data are given in Table 5. Performance of the developed method was statistically compared by the Wilcoxon test and no differences were found statistically.

Table 5: Tablet analysis (OLM 30 $\mu g \cdot mL^{-1}$)

Solvent	Technique	Olmetec® 10 mg		Olmetec® 20 mg		Olmetec® 40 mg	
		$\bar{x} \pm SE$	RSD %	$\bar{x} \pm SE$	RSD %	$\bar{x} \pm SE$	RSD %
ACN	Calibration curve	9.70 ± 0.09	1.7	20.18 ± 0.13	1.5	40.65 ± 0.40	2.4
	Standard addition	9.70 ± 0.14	3.6	20.36 ± 0.17	2.1	40.44 ± 0.69	4.1
		$p = 0.753 > p = 0.05$		$p = 0.345 > p = 0.05$		$p = 0.753 > p = 0.05$	
NaOH-Water	Calibration curve	9.81 ± 0.10	2.5	20.14 ± 0.18	2.2	39.40 ± 0.27	0.7
	Standard addition	9.67 ± 0,08	2.1	19.88 ± 0.03	0.3	39.48 ± 0.07	0.5
		$p = 0.463 > p = 0.05$		$p = 0.225 > p = 0.05$		$p = 0.917 > p = 0.05$	

$\bar{x}$: Mean ± SE
SE: standard error
RSD: Relative standard deviation

The developed method is found to be simple, accurate, precise, rugged and robust. Moreover, it is fast and inexpensive. They can be directly and easily applied to the analysis of the pharmaceutical dosage forms of OLM (Olmetec® Tablet).

3. Experimental

3.1. Apparatus

The spectrophotometric measurements were carried out using an Aglient 8453 model UV-VIS spectrophotometer with a diode array detector (DAD) (190–1100 nm). UV spectra of reference and sample solutions were recorded in 1 cm quartz cells.

3.2. Chemicals and reagents

OLM was kindly supplied by Daiichi Sankyo. Pharmaceutical preparations of OLM (Olmetec® Tablets) were obtained from Pfizer. Methanol, acetonitrile and NaOH were purchased from Merck.

3.3. Standard solutions

Stock solutions of OLM were prepared at a concentration of 1000 $\mu g \cdot mL^{-1}$ in ACN and 0.02 N NaOH. 50.00 mg OLM was accurately weighed and transferred to a 50 mL volumetric flask and 30 mL of solvent (ACN or 0.02 N NaOH) was added. It was treated in an ultrasonic bath for 15 min at 25 °C and then the volume was completed with solvent. These solutions were kept at +4 °C maximum for 1 month and the stock solutions were stable during this period. Working standard solutions were prepared daily in 10 mL volumetric flasks from diluting the stock solution with ACN for method 1 and with deionised water for method 2.

3.4. Tablet solutions and procedure

Ten tablets of OLM (Olmetec® 10, 20 and 40 mg) were accurately weighed and powdered. Equivalent amount to one tablet was weighed and transferred to a 50 mL volumetric flask and 30 mL solvent (ACN or 0.02 N NaOH) was added. It was treated in an ultrasonic bath for 15 min at 25 °C and then completed to volume with solvent. After shaking, a part of the flask content was centrifuged at 3500 rpm for 15 min. Appropriate solutions were prepared by taking suitable aliquots of the clear supernatant and diluting them with ACN for ACN solutions and deionised water for 0.02 N NaOH solutions to give the final concentration (20 $\mu g \cdot mL^{-1}$). UV spectra were recorded against ACN or deionised water which are used as blank solutions. From a calibration curve the amount of one tablet was calculated.

3.5 Synthetic tablet solutions and procedure

For preparing the synthetic tablets, common inactive ingredients (microcrystalline cellulose, lactose monohydrate, talc, magnesium stearate, titanium dioxide) and standard OLM (20 mg) equivalent to one tablet were weighed and transfered to a 50 mL volumetric flask and the above mentioned procedure was applied.

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