

RP-HPLC-DAD method for determination of olmesartan medoxomil in bulk and tablets exposed to forced conditions

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A simple, sensitive and precise RP-HPLC-DAD method was developed and validated for the determination of olmesartan medoxomil (AT-II receptor blocker) in the presence of its degradation products. Olmesartan medoxomil and all the degradation products were resolved on a C₁₈ column with the mobile phase composed of methanol, acetonitrile and water (60:15:25, V/V/V, pH 3.5 by orthophosphoric acid) at 260 nm using a photodiode array detector. The method was linear over the concentration range of 1–18 µg mL⁻¹ and precise with RSD < 1 % in intra- and inter-day study. Excellent recoveries of 99.3 ± 0.9 to 100.8 ± 1.2 % proved the accuracy of the method. Developed method was specific, as indicated by chromatographic resolution > 2.0 for each peak and sensitive with LOD 0.03 µg mL⁻¹ and LOQ 0.1 µg mL⁻¹. The method was used to study the drug degradation behavior under forced conditions. Four degradation products (DP-I, II, III, IV) were formed during the degradation study in 0.1 mol L⁻¹ HCl whereas only DP-I, II and III were formed in water, 0.01 mol L⁻¹ NaOH and 3 % H₂O₂. No significant thermal or photolytic degradation was observed in solid drug. The method was applied successfully for the assay of olmesartan medoxomil in the tablet dosage form.

Keywords: olmesartan medoxomil, forced degradation, high performance liquid chromatography, stability

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Stability can be defined as the capacity of a drug substance or drug product to sustain its identity, strength, quality, and purity throughout the retest or expiration period (1). Stability testing of an active substance or finished product provides evidence of the quality of a drug substance or drug product to remain acceptable up to the stated period under storage conditions stated on the label. The International Conference on Harmonization (ICH) guidelines Q1A (R2) require the use of a validated stability-indicating assay method (SIAM) for stability testing of a drug substance or product (2). It also empha-

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sizes the conduct of a forced degradation study on the drug substance to generate information on degradation products that can form under the influence of hydrolytic, oxidative, thermal or photolytic degradation conditions.

Olmesartan medoxomil (OLM) (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxy-4-(1-hydroxy-1-methylethyl)-2-propyl-1-[4-[2-(tetrazol-5-yl)-phenyl]phenyl]methyl imidazo-5-carboxylate (Fig. 1a) is a prodrug and rapidly hydrolyzes in plasma during absorption to form its active metabolite olmesartan (Fig. 1b) (3–5). It is a selective AT1 subtype angiotensin II receptor blocker (6, 7), which was recently approved by the US-FDA (8) to treat patients with hypertension. This reduces blood pressure by causing vasodilation and reducing peripheral resistance (9). OLM is also reported to be effective in animal models of atherosclerosis, liver disorders and diabetic nephropathy (10).

Methods of analyses of olmesartan medoxomil in biological fluids such as human plasma and urine by LC-MS and LC-MS-MS were reported previously (11–13). Use of capillary zone electrophoresis (CZE) for the determination of OLM in pharmaceutical dosage form has also been reported (14). No stability indicating assay of OLM in bulk and solid dosage form could be traced in the literature. However, the method that identified the main degradation products obtained during short-time storage using the hyphenated techniques has been reported (15). This method described the storage of tablets at 40 °C/75 % RH for 6 months and identification of the degradation product by complementary use of the HPLC hyphenated techniques (LC-IR, LC-NMR and LC-MS) without isolation or purification processes.

In the present study, we aimed to develop and validate a stability indicating RP-HPLC-DAD assay method that allowed resolution, detection and quantitation of olmesartan medoxomil in the presence of degradation products obtained during the forced conditions in bulk substance and tablet dosage form.

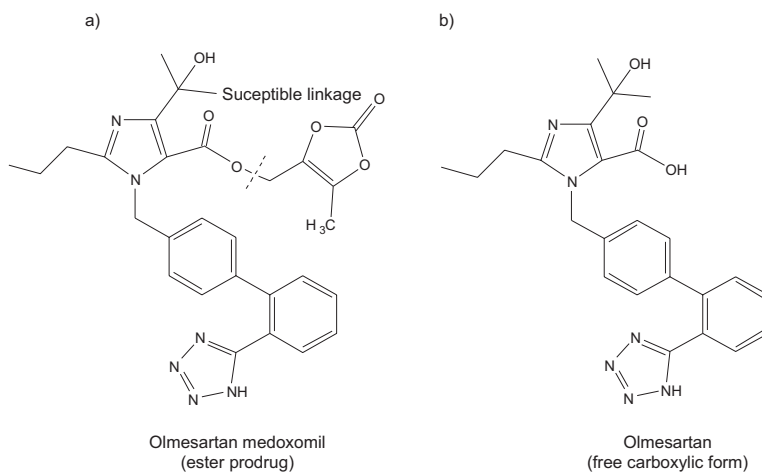


Fig. 1. Chemical structure of olmesartan medoxomil and its free carboxylic acid form olmesartan.

EXPERIMENTAL

Chemicals and reagents

Olmesartan medoxomil was kindly provided as a gift a sample by Torrent Pharmaceutical Ltd. (India) with 99.94 % purity. Tablet dosage form of olmesartan medoxomil (Olmecip, Cipla Ltd. India, 20 mg) was purchased from a local pharmacy. HPLC grade methanol and acetonitrile were purchased from S.D. Fine Chemical, India. Hydrochloric acid, sodium hydroxide pellets, hydrogen peroxide solution, and orthophosphoric acid were also purchased from S.D. Fine Chemical and were of analytical grade. Water for RP-HPLC was prepared by triple distillation in a glass still and filtered through a nylon 0.45 μm membrane filter (Gelman Laboratory, India).

Instruments

The Shimadzu (Japan) LC system (LC-2010c HT) was equipped with a diode array detector (SPD-M20A), auto sampler (SIL-10ADvp) and column oven CTO-10A(C) vp. Chromatographic separations were performed using the Phenomenex (Torrance, USA) C₁₈ column (250 mm \times 4.6 mm id, 5 μm particle size) at 35 $^{\circ}\text{C}$ column oven temperature and analyzed by LC solution software Shimad. For photolytic degradation, the UV cabinet producing short wavelength (254 nm) produced by Acemas Technocracy Pvt. Ltd, India was used. High precision water bath and hot air oven (Narang Scientific Works, India) capable of controlling the temperature within ± 1 and ± 2 $^{\circ}\text{C}$, respectively, were used for the hydrolytic and thermal degradation studies.

Preparation of standard solutions

A stock solution of olmesartan medoxomil was prepared by dissolving the drug in methanol to get a concentration of 1.0 mg mL⁻¹. Fresh stock solution was prepared every day during the experiment. Working solution containing 100 μg mL⁻¹ was prepared from this stock solution as well as seven calibration standards (1–18 μg mL⁻¹) and quality control samples (4, 10 and 14 μg mL⁻¹) by diluting appropriate aliquots of standard solutions.

Preparation of sample solution

Twenty tablets were weighed, transferred to a clean, dry mortar and well ground. Powder equivalent to 50 mg drug was then transferred to a 100-mL volumetric flask containing 50 mL methanol. The flask was attached to a rotary shaker for 10 min to disperse the material completely. The mixture was then sonicated for 20 min and centrifuged at 3,000 rpm for 5 min. An aliquot of supernatant solution was diluted appropriately to give a solution of 500 μg mL⁻¹ and 10 mL of this solution was used for forced degradation studies.

Forced degradation studies

Forced degradation of drug substances and drug products was carried out under acid/neutral/basic hydrolytic, oxidative, thermolytic, and photolytic stress conditions. For hydrolytic and oxidative degradation, drug solutions were prepared with a concentration of 500 $\mu\text{g mL}^{-1}$. After degradation, aliquots were diluted with methanol to achieve a concentration of 10 $\mu\text{g mL}^{-1}$. Methanol (60 %, *V/V*) was used for drug solubilization in acidic, neutral and oxidative media.

Hydrolytic degradation studies were carried out under acid (0.1 mol L^{-1} HCl, pH 1.03), neutral (water, pH 7.12), and basic (0.01 mol L^{-1} NaOH, pH 12.05) conditions at 60 °C as well as at room temperature over 12 to 48 h. Oxidative degradation was carried out in a 3 % H_2O_2 solution at room temperature over 48 h.

Thermal and photo degradation of drug substances and drug products was carried out in the solid state. For thermal degradation, the drug was spread in a borosilicate glass Petri dish and placed in the hot-air oven maintained at 60 °C for 10 days. Also, photolytic studies were carried out by exposing a thin layer of the solid drug in a Petri dish in the UV chamber for 10 days during which time the total light exposure equaled to 1.2×10^6 lx h. After degradation, stock solutions were prepared by dissolving the samples in methanol to achieve a concentration of 1 mg mL^{-1} . From these solutions, aliquots were diluted with methanol to get the final concentration of 10 $\mu\text{g mL}^{-1}$ of OLM. Samples were withdrawn initially, subsequently at prefixed time intervals and stored at 2–8 °C until analysis for all forced conditions.

Method development

Detection wavelength for the HPLC study was selected as 260 nm after recording the UV spectrum from 190 to 400 nm of the drug and representative sample from each forced condition. The maximum area and peak selectivity of OLM was observed at this wavelength. The chromatographic conditions were optimized for resolution of the peak of the drug and degradation products under each forced condition by varying the stationary phase, proportion of methanol/acetonitrile/water in the mobile phase and the flow rate using representative samples from each forced condition. Several trials using various proportions of methanol and water as mobile phase were carried out. However, to attain the selective resolution of OLM and its degradation products, acetonitrile was introduced as the third solvent; apparent pH 3.5 was adjusted by orthophosphoric acid. Subsequently, a mixture of different stress conditions was used to optimize the chromatographic conditions for resolving OLM and all the degradation products in a single run. An appropriate blank was injected before the analysis of all forced samples. Such an optimized method was then used to study the forced degradation behavior of OLM and was also applied in the stability indicating assay of OLM tablets.

Validation of the method

The optimized method was validated in accordance with the ICH guidelines (16). Linearity was determined by analyzing, in triplicate, standard drug solutions of concentrations 1, 2, 4, 6, 10, 14 and 18 $\mu\text{g mL}^{-1}$ using 20 μL of the injection volume. For intra-

-day precision, three quality control drug concentrations (4, 10 and 14 $\mu\text{g mL}^{-1}$) were analyzed seven times on the same day whereas the same drug concentrations were analyzed on three different days for inter-day precision. Accuracy/recovery was evaluated by spiking the mixture of degradation samples with three known drug concentrations and calculating the percent recovery from the differences between the peak areas obtained for concentrated and diluted solutions. Signal-to-noise ratios were employed to estimate limits of detection (3:1) and limits of quantitation (10:1). The specificity of a method is its suitability for analysis of a substance in the presence of potential impurities. Specificity of the method was established through the study of the resolution (R_s) of OLM samples. Overall selectivity was established through determination of drug purity and R_s peak each time. Reproducibility of the method was established through separate studies on a mixture of degradation samples by different persons on the same chromatographic system as well as on different chromatographic systems in different laboratories on different days by another analyst. Various system suitability parameters were also evaluated on a mixture sample on six different days using freshly prepared mobile phase each time.

RESULTS AND DISCUSSION

Method development and optimization

The peak of pure OLM obtained using 50 % methanol and 50 % acetonitrile (V/V) suggested to employ 70 % methanol and 30 % water (V/V), pH 3.5 adjusted with orthophosphoric acid, as the mobile phase. Forced degradation samples were then analyzed using the same mobile phase flowing at a rate of 1.0 mL min^{-1} on a C18 column employing DAD detection. The method resolved the drug and degradation products under neutral, basic and oxidative conditions, but it could not resolve the cluster of peaks observed under acidic conditions. To separate the degradation products formed under acidic conditions, acetonitrile was introduced in the mobile phase and all other variables were kept the same. However, degradation products still remained unresolved under acidic conditions. The alteration in the stationary phase from C18 to C8 and the flow rate of the mobile phase did not furnish promising results either. Many compositions of different mobile phase strength were tried and, finally, mobile phase composed of methanol, acetonitrile and water (60:15:25, V/V/V) pH 3.5 adjusted with orthophosphoric acid, at a flow rate of 1.0 mL min^{-1} on a C18 column, was used. This mobile phase could optimally resolve the OLM and all the degradation products formed under different conditions in the mixture sample in a single run (Fig. 2a). The relative retention time (t_R) of each peak of the degradation product with respect to olmesartan medoxomil is given in Table I.

Validation of the method

Linearity. – Peak area and concentrations were subjected to the least square linear regression analysis to calculate the calibration equations and correlation coefficients. The calibration plot for OLM assay was linear over the calibration range 1–18 $\mu\text{g mL}^{-1}$, and the regression coefficient, slope and intercept were 0.998, 541214 \pm 253.1 and 340.9 \pm 6.2,

respectively. These results demonstrate an excellent correlation between the peak area and analyte concentration.

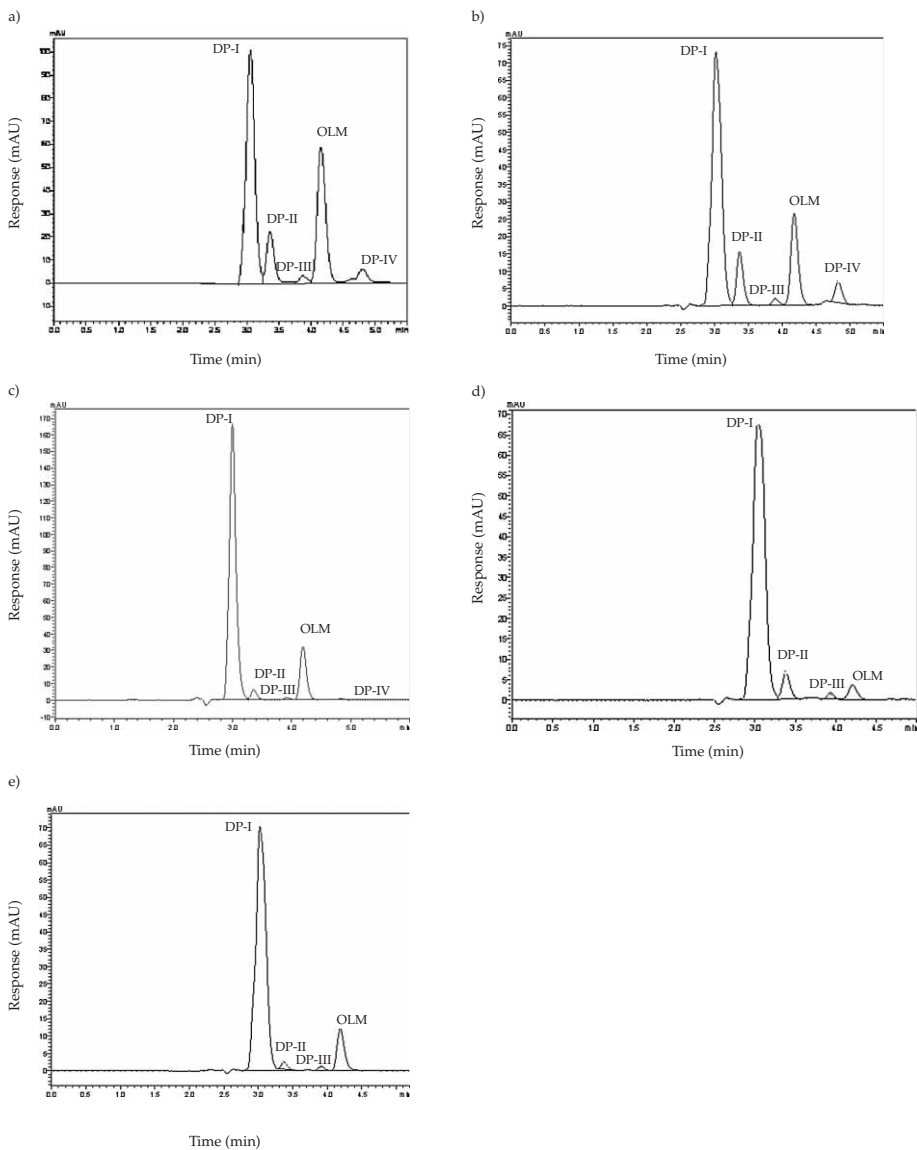


Fig. 2. HPLC chromatograms showing resolution of olmesartan medoxomil and degradation products in: a) mixture of forced degradation samples in a single run, b) 0.1 mol L⁻¹ HCl at 60 °C after 24 h, c) 0.01 mol L⁻¹ NaOH at RT after 4 h, d) water at 60 °C after 48 h, e) 3 % H₂O₂ at RT after 48 h.

Table I. Relative retention time, peak purity data and system suitability parameters of olmesartan medoxomil and its degradation products

Parameter	Peak				
	DP-I	DP-II	DP-III	DP-IV	OLM
Relative retention time (t_R) ^a	0.740	0.809	0.932	1.154	1.000
Peak purity index	0.789	1.000	0.999	0.999	1.000
Purity threshold	0.842	0.998	0.883	0.974	0.999
Asymmetry (As)	1.11	1.28	1.23	1.32	1.06
Tailing factor (T)	1.044	–	–	–	1.058
Chromatographic resolution (R_s)	1.91	1.24	1.99	2.05	1.16
Capacity factor (k')	4.93	5.48	6.47	7.02	8.26
Selectivity (α) ^b	1.11	1.18	1.08	1.17	
Number of theoretical plates (N)	2725.85	3164.63	3195.41	4215.38	2688.93

^a With respect to OLM.

^b With respect to succeeding peak.

Limits of detection and quantification. – LOD was $0.03 \mu\text{g mL}^{-1}$ for OLM at a signal-to-noise ratio of 3:1 and the limit of quantification was determined as $0.1 \mu\text{g mL}^{-1}$ for OLM at a signal-to-noise ratio of 10:1.

Precision. – Intra-day precision was expressed through relative standard deviation of seven repeated assays of samples at three concentration levels. Inter-day precision was determined by analyzing the same set of samples on five different days. RSD in the precision study for the OLM assay was less than 1.0 % and confirmed that the method was highly precise. Results of the precision study for OLM by the proposed RP-HPLC-DAD method are given in Table II.

Recovery. – Standard addition method was used to examine the recovery of the RP-HPLC-DAD method (17). Recovery of OLM from bulk drug samples ranged from 99.3 ± 0.9 to 100.7 ± 1.0 % and that from tablet dosage forms ranged from 99.5 ± 0.8 to 100.8 ± 1.2 % (Table III).

Table II. Precision data of the proposed RP-HPLC-DAD method

Actual conc. ($\mu\text{g mL}^{-1}$)	Measured concentration ($\mu\text{g mL}^{-1}$) ^a	
	Interday	Intraday
4.0	4.0 ± 0.1	3.9 ± 0.4
10.0	9.8 ± 0.3	10.2 ± 0.5
14.0	14.1 ± 0.2	13.8 ± 0.8

^a Mean \pm SD, $n = 7$.

Table III. Recovery for bulk drug substance and drug product

Conc. of drug taken ($\mu\text{g mL}^{-1}$)	Conc. of standard added ($\mu\text{g mL}^{-1}$)	Conc. found ($\mu\text{g mL}^{-1}$)	Recovery (%)
Bulk drug substance			
10.0	5.0	14.9 ± 0.2	99.6 ± 0.8
10.0	10.0	19.9 ± 0.4	99.3 ± 0.9
10.0	15.0	25.1 ± 0.3	100.7 ± 1.0
Drug product			
10.0	5.0	15.0 ± 0.5	100.8 ± 1.2
10.0	10.0	20.0 ± 0.3	100.3 ± 0.6
10.0	15.0	24.9 ± 0.2	99.5 ± 0.8

Mean \pm SD, $n = 3$.

Specificity. – There was no interference due to placebo and sample diluents and degradation products. Resolution between closely eluting degradation products, *i.e.*, between DP-I, DP-II, and between DP-III, OLM, were greater than 2.0, illustrated the chromatographic selectivity of the method.

Stability of stock solution. – During solution stability and mobile phase stability experiments, RSD for the OLM assay was within 1 % for three replicates. Results of the solution stability and mobile phase stability experiments confirmed that standard solutions and solutions in the mobile phase were stable for up to 48 h during the OLM assay.

Forced degradation

During optimization of the hydrolytic degradation process, drug samples were initially placed in 0.1 mol L^{-1} HCl, 0.1 mol L^{-1} NaOH and in water at 60°C . However, after 24 and 48 h, the OLM sample in HCl and water showed 31 and 12 % degradation, respectively, while OLM in 0.1 mol L^{-1} NaOH was completely degraded. Thus, we decided to carry out degradation at room temperature for the 0.1 mol L^{-1} NaOH sample. The compound was completely degraded to DP-I instantly at room temperature. When NaOH concentration was lowered to 0.01 mol L^{-1} , the sample containing OLM was 90 % degraded at room temperature after 4 h.

Degradation pattern under all forced conditions showed the presence of DP-I, which is the major degradation product of OLM formed during every degradation study. As illustrated in Fig. 2b for acidic hydrolysis all the degradation products (DP-I, II, III, IV) were observed in reasonable amounts. The OLM was degraded after 24 h at 60°C in 0.1 mol L^{-1} HCl; here there was more DP-II than in other stress condition samples. For hydrolysis in basic medium, 0.1 mol L^{-1} NaOH, almost all the drug had degraded at room temperature; however, 0.01 mol L^{-1} NaOH at room temperature was appropriate for significant degradation. Three degradation products (DP-I, DP-II and DP-III) were present in these forced samples, DP-I being the major one (Fig. 2c). Degradation in neutral hyd-

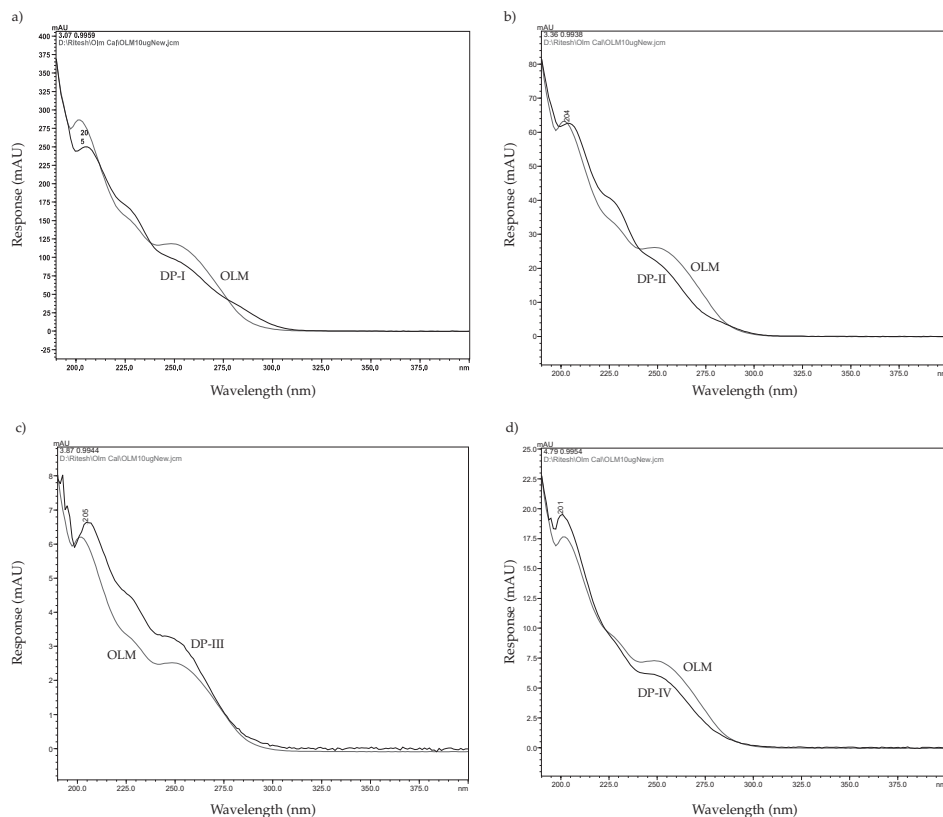


Fig. 3. UV spectra of olmesartan medoxomil (OLM) and degradation products: a) DP-I, b) DP-II, c) DP-III, d) DP-IV.

rolytic medium at 60 °C (Fig. 2d) occurred at a slower rate than under other hydrolytic conditions. Exposure to light and dark did not exhibit any significant difference in the degradation pattern under hydrolytic conditions. Results proved that the degradation of OLM was more pronounced under basic hydrolytic condition than under acidic and neutral conditions.

OLM degradation was 12 % under oxidative conditions (3 % H₂O₂) at room temperature for 48 h. Oxidative degradation produced DP-I, II and III, but DP-I and II were formed in minor amounts (Fig. 2e). No degradation was seen in solid drug kept at 60 °C for 10 days and no degradation was observed upon exposure to light intensity of 1.2×10^6 lx h either. Summary of the data for all forced degradations is given in Table IV.

Peak purity test suggested that the OLM peak as well as the peaks of OLM degradation products were pure for all the forced samples analyzed (Table I). No additional peak was observed after 5 min in chromatograms obtained for the extended runtime of 25 min in a sample study.

Table IV. Summary of forced degradation study results

Stress condition	Time	OLM (%)	Remarks (major degradation product)
Acidic hydrolysis (0.1 mol L ⁻¹ HCl, 60 °C)	24 h	68.7	DP-I and II
Basic hydrolysis (0.01 mol L ⁻¹ NaOH, RT)	4 h	10.3	DP-I
Aqueous hydrolysis (60 °C)	48 h	88.1	DP-I and II
Oxidation (3% H ₂ O ₂ , RT)	48 h	54.3	DP-I
Thermal (60 °C)	10 days	99.4	No degradation product formed
Photo (UV 254 nm)	10 days	99.8	No major degradation product observed

OLM – olmesartan medoxomil; DP – degradation product

The UV spectrum of pure OLM was compared with the spectrum of the drug subjected to the different forced conditions; all the spectra showed slight changes in the absorption pattern. Purity of all degradation products was confirmed by comparing their spectra with the spectrum of OLM (Figs. 3a-d). Comparison of the spectra of two major degradation products, DP-I and II, with the OLM spectrum (Figs. 3a and b) suggested the absence of the ester moiety of OLM in both the DP-I and II, since the absorption maximum characteristic of the 5-methyl-2-oxo-1,3-dioxolen-4-yl-methyl group (ester moiety) in OLM at 260 nm was not visible. Olmesartan medoxomil is an ester prodrug and easily de-esterifies to its active metabolite olmesartan under hydrolytic conditions (4). Analogously to degradation products reported to be formed in losartan tablets stored at 40 °C and 75 % relative humidity (18), the major degradation products are DP-I, likely to be the olmesartan free carboxylic acid form (Fig. 1b) and DP-II, the dimer of its free carboxylic acid form of olmesartan. The goal of determining OLM in the presence of degradation products by the proposed stability indicating RP-HPLC-DAD method was successfully achieved but the method can be also used for routine quality control of tablets.

CONCLUSIONS

The RP-HPLC-DAD method developed for quantitative analysis of olmesartan medoxomil in both bulk drug and pharmaceutical dosage forms is precise, accurate and specific. Satisfactory results were obtained by validation of the method. No attempt was made to quantify the degradation products; quantitation is possible after isolation of degradation products in pure form. This method can be used for the estimation of olmesartan medoxomil in the presence of degradation products obtained under different forced conditions.

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S A Ž E T A K

RP-HPLC-DAD metoda za određivanje olmesartan medoksomila kao čiste supstancije i u tabletama izloženih razgradnji

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U ovom radu razvijena je i validirana jednostavna, osjetljiva i precizna RP-HPLC-DAD metoda za određivanje olmesartan medoksomila (inhibitor AT-II receptora) u prisutnosti njegovih razgradnih produkata. Olmesartan medoksomil i razgradni produkti kromatografirani su na C₁₈ koloni uz mobilnu fazu metanol/ acetonitril/voda (60:15:25 V/V/V; pH 3,5 podešen ortofosfornom kiselinom) pri 260 nm uz detektor s fotodiodnim nizom. Metoda je linearna u koncentracijskom rasponu 1–18 µg mL⁻¹ i precizna s RSD < 1 % tijekom ispitivanja repetabilnosti i intermedijarne ponovljivosti. Povrat od 99,3 ± 0,9 do 100,8 ± 1,2 % dokazuje točnost metode. Razvijena metoda je specifična na što ukazuje kromatografsku rezoluciju veću od 2,0 i osjetljiva (LOD = 0,03 µg mL⁻¹ i LOQ = 0,1 µg mL⁻¹). Metoda je upotrebljena za praćenje razgradnje olmesartan medoksomila u uvjetima potencirane razgradnje. U 0,1 mol L⁻¹ HCl detektirana su četiri razgradna produkta (DP-I, II, III, IV), a u vodi, 0,01 mol L⁻¹ NaOH i 3 % H₂O₂ samo DP-I, II i III. U čvrstom agregatnom stanju nije primjećena značajna termička ni fotolitička razgradnja ljekovite tvari. Metoda je uspješno primijenjena za određivanje olmesartan medoksomila u tabletama.

Keywords: olmesartan medoksomil, razgradnja, tekućinska kromatografija visoke učinkovitosti, stabilnost

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