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A stability indicating LC method for olmesartan medoxomil

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ABSTRACT

A new, sensitive, stability indicating liquid chromatographic method has been developed for the separation, quantitative determination of Olmesartan medoxomil from its three impurities namely imp-1, imp-2, imp-3 and from its degradation products in bulk drug, pharmaceutical dosage form used for the treatment of hypertension in the United States, Japan and European Countries. The developed method is also applicable for the related substances determination. Efficient chromatographic separation was achieved using a C18-CN column (150×4.6) mm with 3.5 µm particles with simple mobile phase combination of buffer and acetonitrile in the ratio of 65:35 (*v/v*). Buffer consist of 20mM (2.76g in 1000 mL water) sodium dihydrogen ortho phosphate monohydrate, pH adjusted to 3.0 using phosphoric acid, delivered in isocratic mode at a flow rate of 1.0 mL $min^{-1}$and quantitation was carried out using ultraviolet detection at a wavelength of 210 nm. In the developed HPLC method the resolution (R_S) between Olmesartan medoxomil and its impurities namely imp-1, imp-2 and imp-3 was found to be greater than 2.0. The drug was subjected to stress conditions of hydrolysis, oxidation, photolysis and thermal degradation. Considerable degradation was found to occur in alkaline medium, acid medium and oxidative stress conditions. Olmesartan medoxomil was completely degraded to imp-1 in the mild alkaline conditions. The stress samples were assayed against a qualified reference standard and the mass balance was found close to 99.5%. The developed reverse phase LC method was validated with respect to linearity, accuracy, precision and robustness.

KEYWORDS

Column liquid chromatography;
Olmesartan medoxomil;
Forced degradation;
Validation;
Stability indicating.

INTRODUCTION

The chemical name of Olmesartan medoxomil is 4-(1-Hydroxy-1-methylethyl)-2-propyl-1-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1H-imidazole-5-carboxylic acid (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl ester (Figure1). Its empirical formula is $C_{29}H_{30}N_6O_6$. Olmesartan medoxomil is a potent and selective angiotensin AT1 receptor blocker[1] which has been approved for the treatment of hypertension in the United States, Japan and European countries. The drug contains a medoxomil ester moiety and is cleaved rapidly by an endogenous esterase to release the active metabolite Olmesartan medoxomil[2].

Only few chromatographic methods have been appeared in the literature. Mustafa Çelebier and

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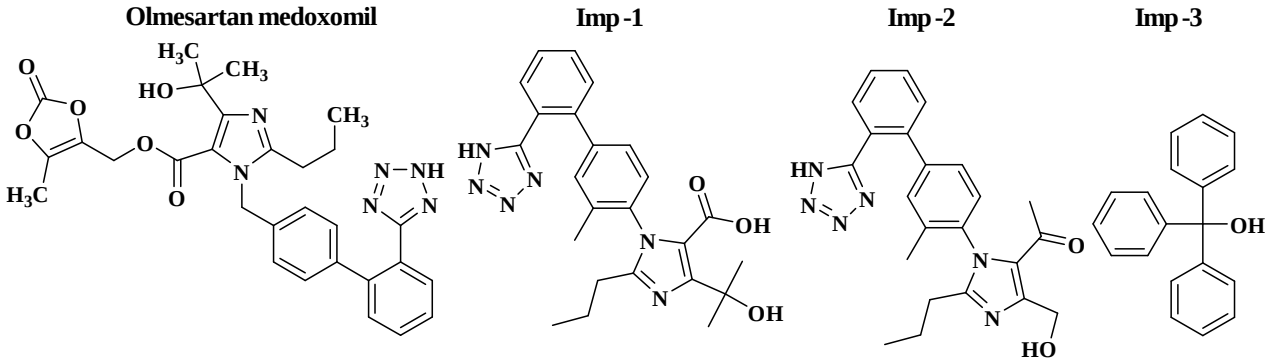

Figure1: Chemical structures and labels of olmesartan medoxomil and its impurities

Sacide Altinöz reported development of a CZE method for the determination of Olmesartan medoxomil in Tablets[3]. Work by Dongyang Liu and etal describes quantitative determination of Olmesartan medoxomil in human plasma and urine by liquid chromatography coupled to tandem mass spectrometry[4]. So far, to our present knowledge there is no stability indicating LC method for the related substance determination and quantitative estimation of Olmesartan medoxomil.

In the present regulatory scenario, it became mandatory to show the stability indicating nature of the drug. As these drugs are life savers, the assessment of its purity is of major concern and which can't be negotiable under any circumstances. An ideal stability indicating chromatographic method should estimate the drug be able to resolve from its potential impurities and degradation products. Hence, an attempt has been made to develop an accurate, rapid, specific, and reproducible method for the determination of Olmesartan medoxomil and all three impurities in bulk drug samples and in pharmaceutical dosage forms in the presence of its degradation products along with method validation as per ICH norms. The stability tests were also performed on both drug substances and drug product as per ICH (TABLE 8).

EXPERIMENTAL

Chemicals

Samples of Olmesartan medoxomil and its related impurities were received from from Dr.Reddy's Laboratories Ltd, Hyderabad, India. Commercially available Olmesartan medoxomil tablets were purchased. HPLC grade acetonitrile, analytical reagent grade sodium dihydrogen ortho phosphate monohydrate and phosphoric acid were purchased from Merck, Darmstadt, Germany. High pure water was prepared by using Millipore Milli-Q plus water purification system.

Equipment

The LC System, used for method development, forced degradation studies and method validation was Waters 2695 binary pump plus auto sampler and a 2996 photo diode array detector. The output signal was monitored and processed using empower software on Pentium computer (Digital equipment Co).

Chromatographic conditions

The chromatographic column used was Zorbax CN (150×4.6) mm with 3.5 µm particles. The mobile phase contains a mixture of buffer and acetonitrile in the ratio of 65:35 (*v/v*), buffer consist of 20mM (2.76g in 1000 mL water) sodium dihydrogen ortho phosphate monohydrate, pH adjusted to 3.0 using phosphoric acid.

The flow rate of the mobile phase was 1.0mLmin^{-1}. The column temperature was maintained at 27°C and the detection was monitored at a wavelength of 210 nm. The injection volume was 10 µL. Acetonitrile: water (8:2 v/v) was used as diluent.

Preparation of solutions

Preparation of standard solutions

A stock solution of Olmesartan medoxomil (5.0 mg

mL^{-1}) was prepared by dissolving appropriate amount in the diluent. Working solutions of 1000 and 100 μg mL^{-1} were prepared from above stock solution for related substances determination and assay determination, respectively. A stock solution of impurity (mixture of Imp-1, Imp-2 and Imp-3) at 1.0 mg mL^{-1} was also prepared in diluent.

Preparation of sample solution

Twenty tablets were weighed and the content transferred into a clean and dry mortar, grinded well. Then equivalent to 100 mg of drug was transferred to 100 mL volumetric flask, 70 mL of diluent added and kept on rotatory shaker for 10 min to disperse the material completely and sonicated for 10 min and diluted to 100 mL (1000 μg mL^{-1}). The resulting solution was centrifuged at 3,000 rpm for 5 min (this solution was filtered and is used for the related substance determination). Supernant solution was taken 10 mL and diluted to 100 mL with diluent (100 μg mL^{-1}). This was filtered using 0.45 μnylon 66-membrane filter (for assay evaluation).

Specificity/Forced degradation studies

Specificity is the ability of the method to measure the analyte response in the presence of its potential impurities[5]. Stress testing of the drug substance can help to identify the likely degradation products, which can in turn help establish the degradation pathways and the intrinsic stability of the molecule and validate the stability indicating power of the analytical procedures used.

The specificity of the developed LC method for Olmesartan medoxomil was determined in the presence of its impurities namely imp-1, imp-2, imp-3 and degradation products. Forced degradation studies were also performed on olmesartan medoxomil to provide an indication of the stability indicating property and specificity of the proposed method[6,7]. The stress conditions employed for degradation study includes light (carried out as per ICH Q1B), heat (60^0C), acid hydrolysis (1N HCl), base hydrolysis (1N NaOH), water hydrolysis and oxidation (6 % H_2O_2). For heat and light studies, study period was 10 days whereas for acid, base, water hydrolysis and oxidation, it was 48 h. Peak purity of stressed samples of olmesartan medoxomil was checked by using 2996 Photo diode array detector of Waters (PDA). The purity angle is within the purity threshold limit obtained in all stressed samples demonstrates the analyte peak homogeneity. All stressed samples of Olmesartan medoxomil [heat (60^0C), acid hydrolysis (1N HCl), base hydrolysis (1N NaOH), water hydrolysis and oxidation (6% H_2O_2)] were studied for extended run time of 60 min (with 90% Acetonitrile in mobile phase) to check the late eluting degradants.

Assay studies were carried out for stress samples against qualified reference standard and the mass balance (% assay+% of impurities +% of degradation products) was calculated. Assay was also calculated for bulk samples and drug product by spiking all impurities (imp-1, imp-2 and imp-3) at the specification level (i.e. 0.15% of analyte concentration which is 1000 μg mL^{-1}).

Method validation

Precision

The precision of the related substance method was checked by injecting six individual preparations of (1000 μg mL^{-1}) olmesartan medoxomil spiked with 0.15% each imp-1, imp-2 and imp-3. The % RSD of area for each imp-1, imp-2 and imp-3 was calculated.

The intermediate precision (ruggedness) of the method was also evaluated using different analyst, different column and a different instrument in the same laboratory.

Assay method precision was evaluated by carrying out six independent assays of test sample of Olmesartan medoxomil against qualified reference standard. The % RSD of six assay values obtained was calculated.

Limit of detection (LOD) and limit of quantification (LOQ)

The LOD and LOQ for imp-1, imp-2 and imp-3 were estimated at a signal-to-noise ratio of 3:1 and 10:1 respectively, by injecting a series of dilute solutions with known concentration[6]. The precision study was also carried out at the LOQ level by injecting six individual preparations of Imp-1, Imp-2 and Imp- 3, calculated the % RSD for the areas of each impurity.

Linearity

Linearity test solutions for assay method were prepared from stock solution at seven concentration levels

from 10 to 200% of assay analyte concentration (10, 25, 50, 75, 100, 150 and 200 μg mL^{-1}). The peak area versus concentration data was performed by least-squares linear regression analysis.

Linearity test solutions for related substance method were prepared by diluting the impurity stock solution to the required concentrations. The solutions were prepared at seven concentration levels. From LOQ to 200% of the permitted maximum level of the impurity (i.e. the LOQ , 0.015%,0.0375%, 0.075%, 0.15%, 0.225% and 0.3% for an analyte concentration of 1000 μg mL^{-1}). The correlation coefficient, slope and Y-intercept of the calibration curve were reported.

Accuracy

The accuracy of the assay method was evaluated in triplicate at three concentration levels, i.e. 50, 100 and 150 μg mL^{-1} in bulk sample and drug product. The percentages of recoveries were calculated.

The bulk sample shows the presence of imp-1 at a level of 0.1% and it shows a total of 0.17% of unknown impurities (limit: not more than 0.15% for single unknown impurity, for total impurities the limit is 0.50%). The study was carried out in triplicate at 0.075%, 0.15% and 0.225% of the analyte concentration(1000μg mL^{-1}). The percentage of recoveries for imp-1 and imp-2 and imp-3 were calculated.

Robustness

To determine the robustness of the developed method, experimental conditions were deliberately changed and the resolution between olmesartan medoxomil, imp-1, imp-2 and imp-3 were evaluated. The flow rate of the mobile phase was 1.0 mL min^{-1}. To study the effect of flow rate on the developed method, 0.2 units of flow changed (i.e. from 1.0 mL min^{-1} to 0.8 mL min^{-1} and 1.2 mL min^{-1}). The effect of pH of solution on the resolution of impurities was studied by varying ± 0.1 pH units (at 2.9 and 3.1 buffer pH). The effect of column temperature on the developed method was studied at 22^0C and 32^0C instead of 27^0C. In the all above varied conditions, the components of the mobile phase were held constant as such. To study the effect of change in mobile phase composition by changing the organic phase ratio, organic content was changed by 10% (from 100% to 90% and 110%) keeping the buffer ratio as constant.

Solution stability and mobile phase stability

The solution stability of olmesartan medoxomil in the assay method was carried out by leaving the test solutions of sample in tightly capped volumetric flask at room temperature for 48 h. The same sample solutions were assayed with 6 h intervals up to the study period with a freshly prepared reference standard solution. The mobile phase stability was also carried out by assaying the freshly prepared sample solutions against freshly prepared reference standard solutions with 6 h intervals up to 48 h. Mobile phase prepared was kept constant during the study period of mobile phase stability. The % RSD of assay of olmesartan medoxomil was calculated for the study period during mobile phase and solution stability experiments.

The solution stability of olmesartan medoxomil and its related impurities were carried out by leaving spiked sample solution in tightly capped volumetric flask at room temperature for 48 h. Impurity content was determined for every 6 h interval up to the study period.

Mobile phase stability was also carried out for 48 h by injecting the freshly prepared sample solutions for every 6 h interval. Impurity content was checked in the test solutions. Mobile phase prepared was kept constant during the study period.

RESULTS AND DISCUSSION

Method development and optimization

The main target of the chromatographic method is to get the separation of closely eluting impurities namely imp-1, imp- 2 and symmetry of olmesartan medoxomil peak. When C18 and C8 (250×4.0) mm with 5 μm particles columns were used with buffer and acetonitrile (70:30,v/v) as a mobile phase the retention time of imp-3 was very high (around 40 min) and the symmetry of olmesartan medoxomil peak is not satisfactory (<1.5). To improve the symmetry buffer concentration increased to 20mM from 5 mM resulted in symmetrical peak (~1.4) for olmesartan. When Zorbax CN (250×4.6) mm with 5 μm particles column was used improvement in symmetry of olmesartan medoxomil peak and the retention time of imp-3 was observed but not satisfactory .(symmetry of olmesartan medoxomil peak is ~1.3 and the retention time of imp-3 is about

30 min). Introduction of Zorbax CN (150×4.6) mm with 3.5µm particles column has given satisfactory results in terms of symmetry of olmesartan medoxomil peak (about 1.0), the retention time of imp-3 (about 17 min) . Satisfactory results were obtained with the mobile phase containing buffer (Phosphate buffer pH 3.0 adjusted with phosphoric acid) and acetonitrile in the ratio of (65:35, *v/v*). The resolution between imp-1 and imp-2 (Rs >2.0) was observed. Variation in buffer pH was also studied, the tailing factor of the olmesartan medoxomil is high (about 1.6), and the resolution between imp-1 and imp-2 was less (Rs< 1.5) when pH of the buffer adjusted 7.2. When pH increased towards acidic side the symmetry of olmesartan medoxomil peak was improved and resolution too. Satisfactory resolution between impurities and symmetry of olmesartan medoxomil peak was observed at pH 3.0 (Figure 2).

The chromatographic separation was achieved on Zorbax CN (150×4.6) mm with 3.5 µm. The mobile phase contains a mixture of buffer and acetonitrile in the ratio of 65:35 (*v/v*) buffer consist of 20mM sodium dihydrogen phosphate monohydrate, pH adjusted to 3.0 using phosphoric acid. The flow rate of the mobile phase was 1.0 mL min^{-1}. The column temperature was maintained at 27°C and the detection was monitored at a wavelength of 210 nm. The injection volume was 10 µL. Acetonitrile and water (8:2 *v/v*) was used as blank; there was no interference of blank with impurities (imp-1, imp-2 and imp-3) and olmesartan medoxomil. The interference of excipients (hydroxypropylcellulose, lactose, microcrystalline cellulose, talc, titanium dioxide, and yellow iron oxide) was also checked by injecting sample solutions of excipients. There was no interference of excipients with impurities (imp-1, imp-2 and imp-3) and olmesartan medoxomil peak. In the optimized conditions olmesartan medoxomil, imp-1, imp-2 and imp- 3 were well separated with a resolution of greater than 2 and the typical retention times of imp-1, imp-2, olmesartan medoxomil and imp-3 were about 2.7, 3.0, 6.6 and 17.7 min respectively. The system suitability results are given (TABLE 1) and the developed LC method was found to be specific for olmesartan medoxomil and its impurities namely imp-1, imp-2 and imp-3 (TABLE 2).

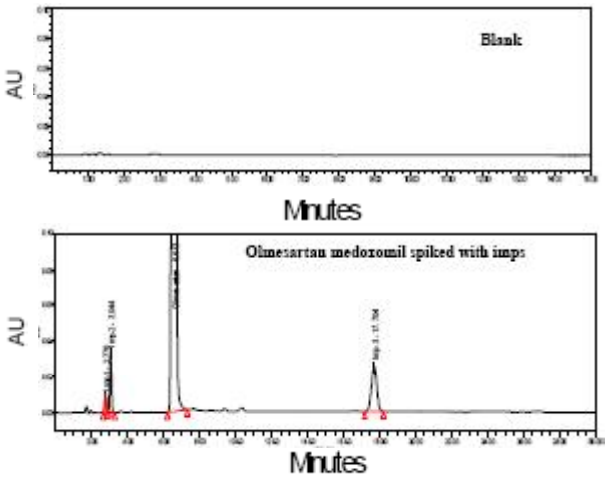

Figure2: Typical chromatogram of olmesartan medoxomil blank Chromatogram, olmesartan medoxomil spiked with impurities

TABLE 1:System suitability report

Compound	USP resolution(R_S)	USP tailing factor
Imp-1	-	1.0
Imp- 2	2.1	1.1
Olmesartan medoxomil	16	0.9
Imp- 3	26	1.0

Analysis was performed for different batches of bulk drug samples (n=3) and for pharmaceutical dosage forms (n=3). Results were given in TABLE 7. Stability study results as per ICH Q1A (R2) for olmesartan medoxomil[5] were given in TABLE 8 and TABLE 9.

Method validation

Precision

The %RSD of assay of olmesartan medoxomil during assay method precision study was 0.1% and the %RSD of area of imp-1, imp-2 and imp-3 in related substance method precision study were within 1.5 %. Confirming the good precision of the method.

TABLE 2: Summary of forced degradation results

Stress condition	Time	% Assay of active substance	Mass balance (%Assay +% impurities+% degradation products)
Acid hydrolysis (1N HCl RT)	24h	94.8%	99.5
Base hydrolysis (1N NaOH RT)	24h	0.0%	99.8
Oxidation (6% H_20_2 RT)	24h	72.8%	99.8
Water hydrolysis (Room Temperature)	24h	97.6%	99.5
Thermal (60°C)	10 days	99.3	99.6
Light (photolytic degradation)	10 days	99.4	99.7

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The %RSD of assay results obtained in intermediate precision study was within 0.5% and the %RSD of area of imp-1, imp-2 and imp-3 were well within 2.1 %, confirming the ruggedness of the method (TABLE 6).

Limit of detection and limit of quantification

The limit of detection of imp-1, imp-2 and imp-3 were 0.002, 0.003 and 0.007% (of analyte concentration, i.e.1000 μg mL^{-1}) respectively for 10 μL injection volume. The limit of quantification of imp-1, imp-2 and imp-3 were 0.006, 0.009 and 0.022% (of analyte concentration, i.e. 1000 μg mL^{-1}) respectively for 10 μL injection volume. The precision at LOQ concentration for imp-1, imp-2 and imp-3 were below 2%.

Linearity

Linear calibration plot for assay method was obtained over the calibration ranges tested, i.e. 10-200 μg $mL^{-1}$and the correlation coefficient obtained was greater than 0.999. The result shows an excellent correlation existed between the peak area and concentration of the analyte. The slope and Y-intercept of the calibration curve were 46832.9 and 10002.6 respectively.

Linear calibration plot for related substance method was obtained over the calibration ranges tested, i.e. LOQ to 0.3% for imp-1, imp-2 and imp-3. The correlation coefficient obtained was greater than 0.999. The result shows an excellent correlation existed between the peak area and concentration of imp-1, imp-2 and imp-3.

Accuracy

The percentage recovery of olmesartan medoxomil in bulk drug samples ranged from 98.5 to 99.6 (TABLE 3) and in pharmaceutical dosage forms ranged from 98.1 to 100.2 % (TABLE 4). The percentage recovery of imp-1, imp-2 and imp-3 in bulk drugs samples ranged from 96.2 to 102.5. HPLC chromatogram of spiked sample at 0.15% level of all five impurities in olmesartan medoxomil bulk drug sample are shown in figure 2.

Robustness

In all the deliberate varied chromatographic conditions (flow rate, pH, column temperature and mobile phase organic content variation), the resolution between closely eluting impurities, namely imp-1 and imp-2 was

TABLE 3: Results of accuracy study for drug substance

Added (μg)(n=3)	Recovered (μg)	% Recovery
50	49.8	99.6
100	99.5	99.5
150	147.8	98.5

n=3, Number of determinations

TABLE 4:Results of accuracy study for drug product

Added (μg)(n=3)	Recovered (μg)	% Recovery
50	49.9	99.8
100	100.2	100.2
150	147.2	98.1

n =3, Number of determinations

TABLE 5: Results of robustness study

S. no.	Parameter	Variation	Resolution(R_s) Between imp-1 and imp-2
1	Temperature (±5^{0}C of set temperature)	(a) At 22°C	2.2
		(b) At 32°C	2.1
2	Flow rate (±20% of the set flow)	(a) At 0.8 mL min^{-1}	2.2
		(b) At 1.2 mL min^{-1}	2.0
3	pH (± 0.1 unit of set pH)	(a) At 2.9	2.1
		(b) At 3.1	2.1

TABLE 7:Batch analysis

Batch no.	Imp-1	Imp-2	Imp-3	Assay by HPLC	Purity by HPLC
Bulk B.No#					
002 01	0.10	ND	ND	99.75%	99.70%
002 02	0.09	ND	ND	99.71%	99.73%
002 03	0.08	ND	ND	99.61%	99.70%
Drug product B.No#					
003 01	0.09	ND	ND	99.61%	99.73%
003 02	0.08	ND	ND	99.52%	99.71%
003 04	0.08	ND	ND	99.56%	99.70%

Where ND = Not Detected

TABLE 6: Results of intermediate precision

S. no.	Parameter	Variation	%RSD for Assay	%RSD for related substances	Resolution between Imp-1 and Imp-2
1	Different system	(a) Waters 2695 alliance system	0.3%	< 1.5%	>2.0
		(b) Agilent 1100 series VWD system	0.4%	< 1.8%	>2.0
2	Different column	(a) B.No: #001 01	0.4%	< 2.0%	>2.0
		(b) B.No:# 001 02	0.4%	< 2.0%	>2.0
3	Different analyst	(a) Analyst-1	0.3%	< 2.0%	>2.0
		(b) Analyst-2	0.4%	< 2.0%	>2.0

greater than 2.0, illustrating the robustness of the method (TABLE 5).

Solution stability and mobile phase stability

The %RSD of assay of olmesartan medoxomil during solution stability and mobile phase stability experiments was within 1%. No significant changes were observed in impurity content during solution stability and mobile phase experiments. The solution stability and mobile phase stability experiments data confirms that sample solutions and mobile phase used during assay and related substance determination were stable up to 48 h.

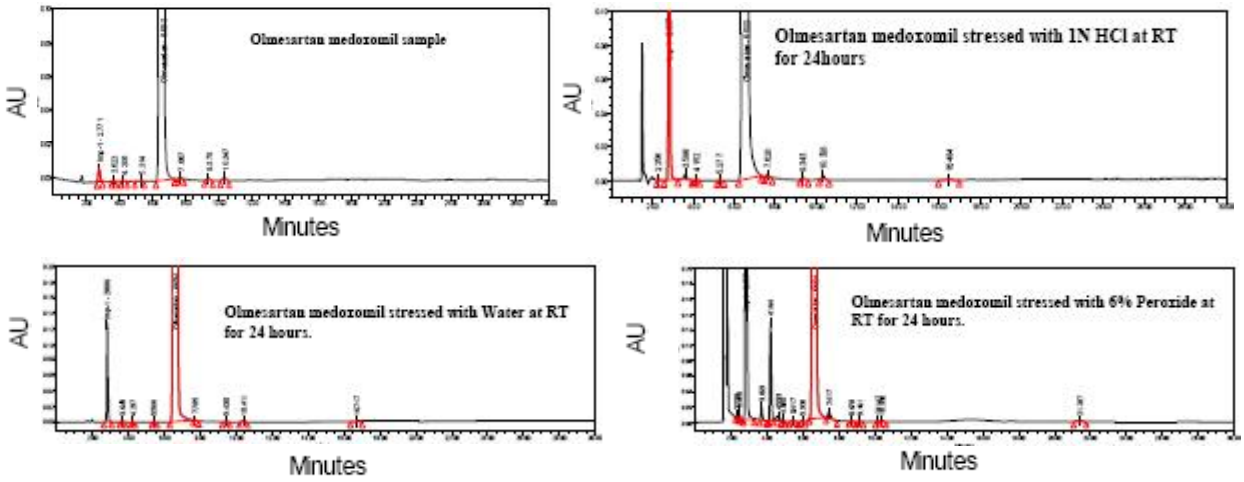

Figure3: Typical chromatogram of Olmesartan medoxomil sample and stressed Olmesartan medoxomil samples

TABLE 8: Accelerated stability data (storage conditions: 40°±2°C / 75 5% RH)

Bulk drug B.no:# 002 01	Temperature 40±2°C and relative humidity 75±5%					
Duration	Related substance by HPLC					
	Imp-1	Imp-2	Imp-3	Purity by HPLC	Assay by HPLC	Remarks
Initial	0.10	ND	ND	99.75%	99.70%	No significant change observed
1st month	0.11	ND	ND	99.73%	99.68%	No significant change observed
2nd Month	0.09	ND	ND	99.72%	99.68%	No significant change observed
3rd Month	0.10	ND	ND	99.80%	99.69%	No significant change observed
Drug product B.No#: 003 01						
Duration	**Imp-1**	**Imp-2**	**Imp-3**	**Purity by HPLC**	**Assay by HPLC**	**Remarks**
Initial	0.09	ND	ND	99.73%	99.61%	No significant change observed
1st month	0.11	ND	ND	99.72%	99.62%	No significant change observed
2nd Month	0.10	ND	ND	99.71%	99.65%	No significant change observed
3rd Month	0.10	ND	ND	99.72%	99.62%	No significant change observed

Where ND = Not Detected

TABLE 9: Long term stability data (storage conditions: 25° ±2°C / 60 ± 5% RH)

Bulk drug B.no#: 002 01	Temperature 25±2°C relative humidity 60± 5%					
Duration	Related substance by HPLC					
	Imp-1	Imp-2	Imp-3	Purity by HPLC	Assay by HPLC	Remarks
Initial	0.10	ND	ND	99.70%	99.75%	No significant change observed
1st Month	0.12	ND	ND	99.71%	99.73%	No significant change observed
2nd Month	0.11	ND	ND	99.72%	99.72%	No significant change observed
3rd Month	0.11	ND	ND	99.69%	99.74%	No significant change observed
Drug Product B.No: 003 01						
Duration	**Imp-1**	**Imp-2**	**Imp-3**	**Purity by HPLC**	**Assay by HPLC**	**Remarks**
Initial	0.09	ND	ND	99.73%	99.61%	No significant change observed
1st Month	0.10	ND	ND	99.75%	99.58%	No significant change observed
2nd Month	0.10	ND	ND	99.72%	99.60%	No significant change observed
3rd Month	0.10	ND	ND	99.71%	99.62%	No significant change observed

Where ND = Not detected

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Results of forced degradation studies

Degradation was not observed in olmesartan medoxomil stressed samples that were subjected to light and heat study. The degradation of drug substance was observed under acid hydrolysis, base hydrolysis, water hydrolysis and oxidative conditions (Figure 3) leads to the formation of imp-1 as a major degradant. Peak purity test results derived from PDA detector, confirmed that the olmesartan medoxomil peak is homogeneous and pure in all the analyzed stress samples. No degradants were observed after 30 min in the extended runtime of 60 min for all the olmesartan medoxomil stressed samples [heat (60^0C), photolysis, acid hydrolysis (1N HCl), base hydrolysis (1N NaOH), water hydrolysis and oxidation (6 % H_2O_2) with 90% acetonitrile in mobile phase.

The mass balance of stressed samples was close to 99.5% (TABLE 2). The assay of olmesartan medoxomil is unaffected in the presence of imp-1, imp-2, imp-3 and its degradation products confirm the stability indicating power of the developed method.

CONCLUSIONS

The isocratic RP-LC method developed for quantitative and related substance determination of olmesartan medoxomil in both bulk drug and pharmaceutical dosage form is precise, accurate and specific. The method was completely validated showing satisfactory data for all the method validation parameters tested. The developed method is stability indicating and can be used for the routine analysis of production samples and also to check the stability of samples of olmesartan medoxomil.

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