DEVELOPMENT AND VALIDATION OF STABILITY-INDICATING RP-HPLC METHOD FOR DETERMINATION OF OLMESARTAN MEDOXOMILE IN PHARMACEUTICAL DOSAGE FORM AND IDENTIFICATION, CHARACTERIZATION OF ALKALINE DEGRADATION IMPURITY OF OLMESARTAN MEDOXOMILE DRUG SUBSTANCE AS WELL AS DRUG PRODUCT

Olmesartan medoxomil (OLME) belongs to a group of angiotensin II receptor blockers used as an antihypertensive agent and is currently being used for prevention of hypertension. This paper describes the validation and development of stability indicating RP-HPLC method for the determination of OLME in the presence of its degradation products generated from forced degradation study and characterization of degradation product (impurity). The assay involved gradient elution of OLME and an LC GC BDS C18 column (250 mm x 4.5 mm, 5 μm particle size) was employed for loading the sample. The mobile phase A consisted of 7 ml triethylamine in 1000 ml water (pH adjusted to 3.0 with orthophosphoric acid) and B contained acetonitrile. Quantification was achieved with photodiode array detection at 257 nm. The chromatographic separation was obtained with a retention time of 6.72 min, and the method was linear in the range 50-150 μg/ml. The method was validated according to the ICH guidelines with respect to linearity, precision, accuracy, limit of detection (LOD), limit of quantification (LOQ), specificity and robustness. Impurity found in stressed and stability studies of olmesartan medoxomil in both drug substance and drug product are described. This degradation product is identified as 1-(biphenyl-4-ylmethyl)-1H-imidazole-5-carboxylic acid. An alkaline degradation pathway of Olmesartan Medoxomil, for the formation of this degradation product, has been proposed and the degradation product was characterized.

Keywords: olmesartan medoxomil; alkaline degradation; 1-(biphenyl-4-ylmethyl)-1H-imidazole-5-carboxylic acid impurity; structure elucidation.
spectrophotometric have been reported for the estimation of olmesartan alone or in combination with other drugs [4-10]. The present study compares LC determination of olmesartan by identification and characterizing the impurity of olmesartan medoxomil [11-12].

**Figure 1.** The chemical structure of olmesartan medoxomile and its degradation impurity.

The impurity profile of active pharmaceutical ingredients (APIs) and evaluation of their toxicity effects are necessary steps in developing a safe and effective drug and are essential for medical safety reasons [13].

It is mandatory that any new impurities present in the drug substance and drug product above the threshold limit are identified and characterized. The present manuscript describes the development and validation of stability-indicating RP-HPLC method and identification and characterization of alkaline degradation impurity of olmesartan medoxomile drug substance as well as drug product.

Therefore, the objective of the reported research was to study the degradation of OLME under different International Conference of Harmonization (ICH) recommended stress conditions [14] and to evaluate the degraded products by MS and to establish a stability-indicating RP-HPLC method for accurate quantification of OLME in pharmaceutical dosage forms.

**EXPERIMENTAL**

**Materials and reagents**

Pure samples of olmesartan medoxomil were obtained from Torrent Pharmaceutical Limited as a gift. HPLC grade acetonitrile, AR grade triethylamine and orthophosphoric acid were used. Highly pure water was prepared by double distillation and filtration through a 0.45 µm membrane filter. Hydrochloric acid, sodium hydroxide and hydrogen peroxide of laboratory grade were used.

**High performance liquid chromatography (analytical)**

An Agilent system equipped with a low pressure quaternary gradient pump along with a photo diode array detector and manual rhedynne sample injector has been used for sample. The data was collected and processed using Ezichrom Elite software. An LC GC RP-18.5 µm (250 mm x 4.5 mm) BDS column was employed for the separation of impurity from olmesartan medoxomil. The column eluent was monitored at 257 nm. The sample diluent was a mixture of 7 ml triethylamine in 1000 ml water of pH 3.0 adjusted with orthophosphoric acid and acetonitrile in the ratio of 6:4 (v/v), filtered through a 0.45 µm or finer porosity membrane filter.

**Drug related substances HPLC method**

A simple isocratic reverse-phase HPLC method was optimized for the separation of degradation product where the mobile phases A and B are 7 ml triethylamine in 1000 ml water (pH adjusted to 3.0 with orthophosphoric acid)/acetonitrile, respectively. HPLC method for drug substance: The solvent composition was held at 30% mobile phase A and 70% mobile phase B. The flow rate was 1.4 ml/min. The volume was injected with a Rheodyne manual sampler injector with 20 µL capacity. The chromatographic run time was 10 min. The HPLC method for the drug product (tablet) was the same.

**High performance liquid chromatography (preparative)**

An Agilent preparative HPLC system equipped with a liquid controller pump, photodiode array detector, and manual sample injector fitted with 20 µL loop, was used. The data was collected and processed using Ezichrom Elite software. An LC GC BDS C18 column (250 mm x 4.5mm, 5-Micron) was employed for loading the sample. An analytical method was developed in isocratic mode separately to resolve this degradation product, followed by scaling up the same method for prep-HPLC to collect the required impurity fractions. The mobile phase was of same composition as described in the previous section. The solvent composition was the same as described earlier. The flow rate was set at 1.4 ml/min. Detection was carried out at 257 nm. Approximately 100 µg/ml of sample was prepared using a sample diluent. The sample diluent was a mixture of mobile phase in ratio 6:4.
Mass spectrometry (LC/MS)

Initial LC/MS analysis was performed on a Varian Inc. (USA) 410 Prostar Binary LC with 500 MS IT PDA detectors. The analysis was performed in positive ionization mode with turbo ion spray interface. The parameters for ion source voltage, $IS = 5500$ V, declustering potential, $DP = 70$ V, focusing potential, $FP = 400$ V, entrance potential, $EP = 10$ V were set with nebulizer gas as air at a pressure of 40 psi and curtain gases nitrogen at a pressure of 2 psi in mass spectrometer. Further, to get accurate mass, analysis was performed on a high resolution mass spectrometer using electrospray ionization. The accurate mass obtained from the instrument, theoretical mass and mass error were calculated.

NMR Spectroscopy

The $^1H$ experiment was carried out for unknown impurity at processional frequencies 400.1328 MHz at $25^\circ C$ on a Cona Bruker Avance-300FT NMR spectrometer. $^1H$ chemical shift was recorded on the $\delta$ scale in ppm, relative to tetramethylsilane (TMS) $\delta$ 0.00 in ppm.

Chromatographic condition

The mobile phase A consisted of 7 ml triethylamine in 1000 ml buffer pH 3.0 and mobile phase B consisted of acetonitrile flow in ratio 30:70. A BDS C$_{18}$ column (250mm×4.5 mm, 5-Micron) was found to resolve OLME. The mobile phase was filtered through a 0.45 µm membrane filter and then sonicated for 10 min. The flow rate was set at 1.4 ml/min. The drug showed good absorbance at 257 nm, which was selected as the wavelength for further analysis. All determinations were performed at ambient column temperature. Mobile phases A and B in the ratio of 60:40, v/v, were used as sample diluents.

Preparation of stock solution and standard solution

Accurately weighed 50 mg of olmesartan medoxomil was dissolved in a 50 ml volumetric flask with diluent (stock solution). The stock solution was further diluted by using the mobile phase to get the concentration of 100 µg/ml of olmesartan.

Validation of method

The developed method was validated in terms of linearity, specificity, precision, accuracy, robustness and ruggedness [14].

Preparation of the degradation products

Different stress conditions were used for the forced degradation studies of bulk drug and drug formulations. In this procedure, one sample without drug, i.e., placebo sample and sample with drugs were compared with the force degradation sample. The stress sample was detected at wavelength of 257 nm and the run time was taken the same as for the assay sample.

Acidic condition

For acid hydrolysis, 1 N hydrochloric acid was used for preparation of 100 µg/ml OLME solution. 50 mg of olmesartan API was dissolved in a 50 ml volumetric flask with 10 ml mobile phase and the sample preparation for tablet was equivalent to 40 mg of OLME in 100 ml volumetric flask. Then, 5 ml of 1 N hydrochloric acid was added to the flask and exposed to 30 min at 105 °C under water bath, after which 5 ml of 1 N sodium hydroxide was added for neutralization. The volume was then made up with the mobile phase. For further dilution, 5 ml of each sample was added to a 50 ml volumetric flask (for tablet degradation, 5 ml was added to a 20 ml flask) and the volume was made up with mobile phase.

Alkaline condition

For the base degradation study, 2 N sodium hydroxide was used. 50 mg of olmesartan was added to a 50 ml volumetric flask containing 10 ml of mobile phase. The sample preparation for tablet was equivalent to 40 mg of OLME in a 100 ml volumetric flask containing 10 ml of mobile phase. Then, 10 ml of 2 N sodium hydroxide was added to both stock solutions and they were exposed to 105 °C for 90 min under water bath. To neutralize the solutions, 2 N hydrochloric acid was added to each flask and the volume was made up to the mark with mobile phase. For further dilution, 5 ml of sample stock solution was added to a 50 ml volumetric flask and 5 ml of tablet degradation stock was added to a 20 ml flask, and the volumes were made up with mobile phase to achieve the concentration of 100 µg/ml.

Oxidation condition

For peroxide degradation, 10% hydrogen peroxide was used. 50 mg of olmesartan API was dissolved with 10 ml of mobile phase in a 50 ml volumetric flask with diluent (stock solution). The stock solution was further diluted by using the mobile phase to get the concentration of 100 µg/ml of olmesartan.
Thermal degradation

10 mg of drug was kept in a hot air oven for 48 h at a temperature of 100 °C, then made up with mobile phase. For further dilution, 5 ml of each sample was added to a 50 ml volumetric flask individually, and for tablet degradation, 5 ml was added to a 20 ml flask and made up with mobile phase.

Photo degradation

10 mg of drug was exposed to short wavelength (254 nm) and long wavelength (366 nm) UV light for 48 h, then made up with mobile phase. For further dilution, 5 ml of each sample was added to a 50 ml volumetric flask individually, and for tablet degradation, 5 ml was added to a 20 ml flask and made up with mobile phase.

Detection of impurities by HPLC

Typical HPLC chromatograms of olmesartan medoxomil and its degradation product were observed in drug substance as well as in drug product obtained by using the HPLC method.

Isolation of 1-(biphenyl-4-ylmethyl)-1H-imidazole-5-carboxylic acid impurity by prep HPLC

A simple reverse phase chromatographic system, discussed in the experimental section, was used for isolating the unknown degradation product 1-(biphenyl-4-ylmethyl)-1H-imidazole-5-carboxylic acid. In this chromatographic system, the 1-(biphenyl-4-ylmethyl)-1H-imidazole-5-carboxylic acid impurity eluted at about 2.7 min. Fractions eluting between 2.7 and 4 min were collected, pooled and concentrated by evaporating acetonitrile at room temperature under high vacuum on a Rotavapor. The aqueous layer was evaporated at room temperature. After drying the oily material, HPLC grade methanol was added to form a liquid sample. The purity was checked by HPLC and found to be ~95%, and the sample was characterized by NMR and mass spectrometry experiments.

RESULTS AND DISCUSSION

Optimization of chromatographic conditions

Using a mobile phase consisting of different buffers with methanol and acetonitrile at different buffer-methanol and acetonitrile ratios and at different mobile phase pH values was attempted, but the peak shape and retention time of olmesartan was found to be broad compared to the buffer-acetonitrile composition as mobile phase. After various trials of different buffer and acetonitrile ratios as mobile phase, potassium dihydrogen phosphate was selected as buffer, pH was adjusted to 3.0 with orthophosphoric acid and buffer-acetonitrile ratio was chosen to be 30:70. It showed good resolution of chromatogram with symmetrical peak. The proposed chromatographic conditions were found to be appropriate for the quantitative determination. System suitability tests were carried out as per ICH guidelines and the parameters are summarized in Table 1.

Result of forced degradation experiments

The chromatographic conditions remained the same for the degradation study. Degradation was not observed for olmesartan medoxomil samples under stress conditions like heat, UV and light, except in alkaline, acidic and oxidation conditions. The chromatogram of olmesartan standard solution is shown in Figure 2A. Olmesartan medoxomil was degraded in acidic (Figure 2B), alkaline (Figure 2C) and oxidation (Figure 2D) conditions, forming polar impurities. In the acidic condition 66.82%, in the basic condition 18.05% and in the oxidative condition 32.11% recovery was observed for olmesartan medoxomil. Peak purity results indicate that the olmesartan medoxomil peak was homogeneous in all stress conditions tested. The results of olmesartan exposed to different degradation pathways are shown in Table 2.

Method validation

Linearity

Linearity was studied by preparing standard solutions at different concentration levels. The linearity range for OLME was found to be 50-150 µg/ml (Table 3). The regression equation for OLME was found to be y = 74865x - 48536 with a correlation coefficient $R^2 = 0.999$ (Figure 3).

Specificity

Specificity is the ability to unequivocally assess the analyte in the presence of components that may be expected to be present. Typically, these might include impurities, degradants, matrix, etc. Specificity of an analytical method is its ability to measure accurately and specifically the analyte of interest without

Table 1. System suitability study of OLME and degradation product (impurity)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Retention time, min</th>
<th>RSD of retention time, %</th>
<th>RSD of area, %</th>
<th>Asymmetry</th>
<th>Theoretical plates</th>
</tr>
</thead>
<tbody>
<tr>
<td>OLME</td>
<td>6.72</td>
<td>0.13</td>
<td>0.16</td>
<td>1.43</td>
<td>9289</td>
</tr>
<tr>
<td>1-(biphenyl-4-ylmethyl)-1H-imidazole-5-carboxylic acid</td>
<td>3.30</td>
<td>0.41</td>
<td>0.27</td>
<td>1.36</td>
<td>5453</td>
</tr>
</tbody>
</table>
Figure 2. Chromatograms of OLME A) standard solution (100 μg/mL), B) stressed samples with acid degradation, C) stressed samples with alkaline degradation and D) stressed samples with peroxide degradation.

Table 2. Results of OLME exposed to different degradation pathways

<table>
<thead>
<tr>
<th>Degradation type</th>
<th>% OLME API Recovery</th>
<th>Sample degradation, % OLME recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acid (1 N, 105 °C, 30 min)</td>
<td>66.82</td>
<td>71.49</td>
</tr>
<tr>
<td>Base (2 N, 105 °C, 90 min)</td>
<td>18.05</td>
<td>21.94</td>
</tr>
<tr>
<td>Oxidation (10%, 105 °C, 45 min)</td>
<td>32.11</td>
<td>41.19</td>
</tr>
</tbody>
</table>

Table 3. Result of regression analysis of linearity data of OLME

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean S.D. (N = 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentration range, μg/mL</td>
<td>50-150</td>
</tr>
<tr>
<td>Slope</td>
<td>74865</td>
</tr>
<tr>
<td>Intercept</td>
<td>48563</td>
</tr>
<tr>
<td>Correlation coefficient</td>
<td>0.999</td>
</tr>
</tbody>
</table>

Figure 3. Linearity of olmesartan.
interference from the blank and placebo. Specificity of the peak purity of OLME was assessed by comparing the retention time of standard OLME and the sample and good correlation was obtained. There were no peaks when he placebo and blank were injected and no interferences, hence the method is specific.

**Precision**

Precision was evaluated by carrying out six independent sample preparations of a single lot of formulation. The sample preparation was carried out in same manner as described in sample preparation. Relative standard deviation (% RSD) was found to be less than 2%, which proves that the method is precise (Table 4).

**Accuracy (recovery studies)**

To check the degree of accuracy of the method, recovery studies were performed in triplet by standard addition method at 80, 100 and 120% concentration levels. Known amounts of standard OLME were added to the pre-analyzed samples and were subjected to the proposed HPLC method. The % recovery was found to be within the limits of the acceptance criteria with average recovery of 99.3-100.03% for olmesartan. Results of recovery studies are shown in Table 5.

**Limit of quantification and limit of detection**

LOQ and LOD can be determined based on visual evaluation, signal-to-noise approach, standard deviation of the response and slope (calibration curve method). LOQ and LOD were calculated as $LOQ = 3.3 \times N \times B$ and $LOD = 10 \times N \times B$, where $N$ is the standard deviation of the peak areas of the drugs ($n = 3$), taken as a measure of noise, and $B$ is the slope of the corresponding calibration curve. Limit of detection of OLME was found to be 0.19 µg/ml and the limit of quantification of OLME was determined to be 0.57 µg/ml.

**Robustness of the method**

To evaluate the robustness of the developed RP-HPLC method, small deliberate variations in optimized method parameters were done. The effect of change in flow rate and change in pH retention time, tailing factor and theoretical plates were studied. The method was found to be unaffected by small changes like ±10% in flow rate, ±0.2 change in pH. The results are described in Table 6.

**Ruggedness of the method**

A different analyst carried out precision studies in a similar manner as carried out by the first analyst. The % assay was found to be 98.2-100.3% of OLME. The relative standard deviation (%RSD) was found to be less than 2%, which proves that the method is rugged.

**Identification of alkaline degraded product of olmesartan medoxomil**

Olmesartan medoxomil drug substance and olmesartan medoxomil tablets were subjected to stability tests as per ICH guidelines. The mobile phase composition remained the same as for LC-MS. The retention time for the degradation product was 3.30 min. The LC-MS analysis showed the m/z value for this unknown impurity as 279 [M+H]+ in HPLC method. To further investigate the chemical structure of the unknown impurity, olmesartan medoxomil drug substance sample was kept at 105 °C for 90 min. This sample was subjected to LC-MS/ESI-Q-TOF. The high resolution mass analysis using the Mass Lynx fragmentation tool proposed the following probable elemental compositions/molecular formula: C_{17}H_{14}N_{2}O_{2}. Based on the high resolution mass fragmentation study in comparison to the reported fragmentation pattern of olmesartan medoxomil, the chemical structure of the unknown impurity of m/z 279 was assigned as 1-(biphenyl-4-ylmethyl)-1H-imidazole 5-carboxylic acid impurity. The observed LC-MS Q-TOF fragments of olmesartan medoxomil alkaline degradation impurity m/z 279 are shown in Table 5. 1H-NMR spectra of the
isolated compound of unknown impurity 1-(biphenyl-4-ylmethyl)-1H-imidazole 5-carboxylic acid compared with that of olmesartan medoxomil are described in Table 6. The NMR data indicate the presence of an imidazole 5-carboxylic acid structure. The only significant difference in the 1H-NMR spectra is the chemical shift due to breakage of 4-methyl-1,3-dioxol-2-one ring and tetrazole ring. Based on the above high resolution mass spectral data and NMR data, it is proposed that the unknown impurity is 1-(biphenyl-4-ylmethyl)-1H-imidazole 5-carboxylic acid (Figure 1). We believe that, more precisely, the 4-methyl-1,3-dioxol-2-one ring of olmesartan medoxomil was very prone to degradation in the presence of base. The possible mechanism for the formation this impurity is shown in Figure 4.

Olmesartan medoxomil was found to be susceptible to alkaline stress (in solution form). The summary of results from forced degradation studies of OLME and the percentage of drugs remaining after undergoing stress is given in Table 2. The chemical structure of olmesartan medoxomil was studied and shown that there are one preferred sites of alkaline degradation is 4-methyl-1,3-dioxol-2-one ring, tetrazole ring and 1-hydroxy-1-methyl ethyl leads to the formation of degraded product. The degradant was found to be 1-(biphenyl-4-ylmethyl)-1H-imidazole 5-carboxylic acid impurity. The MS/ESI using selected ion monitoring in the positive ion mode provided a highly selective method for the determination and characterization of olmesartan and its degradation product, respectively. The results of LC-MS and NMR are summarized in Tables 7 and 8, and NMR and LC-MS spectra are shown in Figures 5 and 6.

### Table 7. Mass fragmentation of olmesartan medoxomil and the impurity mass m/z 279.0

<table>
<thead>
<tr>
<th>Name of the compound</th>
<th>Mass observed in LCMS/Q-TOF system</th>
<th>Theoretical mass</th>
<th>Molecular formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-(Biphenyl-4-ylmethyl)-1H-imidazole 5-carboxylic acid</td>
<td>279.0</td>
<td>278.30</td>
<td>C17H14N2O2</td>
</tr>
<tr>
<td>Fragment 1</td>
<td>277</td>
<td>277</td>
<td>C18H18N2O</td>
</tr>
<tr>
<td>Fragment 2</td>
<td>259</td>
<td>262</td>
<td>C17H14N2O</td>
</tr>
<tr>
<td>Fragment 3</td>
<td>234</td>
<td>235</td>
<td>C16H14N2</td>
</tr>
</tbody>
</table>

### Table 8. 1H-NMR assignments for olmesartan medoxomil and 1-(biphenyl-4-ylmethyl)-1H-imidazole 5-carboxylic acid impurity

<table>
<thead>
<tr>
<th>Position</th>
<th>Olmesartan medoxomil 1H ppm</th>
<th>1-(biphenyl-4-ylmethyl)-1H-imidazole 5-carboxylic acid impurity 1H ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td>C6H5</td>
<td>7.311</td>
<td>7.311</td>
</tr>
<tr>
<td>Carboxylic</td>
<td>3.206</td>
<td>3.206</td>
</tr>
<tr>
<td>N of imidazole</td>
<td>3.676</td>
<td>3.676</td>
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<tr>
<td>OH</td>
<td>2.976</td>
<td>2.976</td>
</tr>
<tr>
<td>NH-proton</td>
<td>4.79</td>
<td>-</td>
</tr>
<tr>
<td>CH2</td>
<td>1.99</td>
<td>-</td>
</tr>
<tr>
<td>CH2– Nearest to to -OCO group</td>
<td>1.22</td>
<td>-</td>
</tr>
</tbody>
</table>

Figure 4. The degradation pathway of the impurity.
CONCLUSION

As described in ICH guidelines, the identification and isolation of impurities is a very important task during drug synthesis and storage. It can provide crucial toxicology and safety data of the final drug and dosage forms. We have identified one impurity in aged and stressed samples of olmesartan drug substance and drug product, characterized by analytical
data. The results indicate that the one impurity is the degradation product of olmesartan medoxomil.

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RAZVOJ I VALIDACIJA RP-HPLC METODE ZA ODREĐIVANJE OLMESARTAN MEDOKSOMILA U FARMACEUTSKOJ SUPSTANCI I FARMACEUTSKIM PREPARATIMA I IDENTIFIKACIJA I KARAKTERIZACIJA DEGRADACIIONIH PRODUKATA PRI NJEGOVOM ALKALNOJ DEGRADACIJI

Olmesartan medoksomil (OLME) pripada grupi blokatora angiotenzinskih receptora koji se koristi kao antihipertenzivni agens i za prevenciju hipertenzije. U radu je opisana validacija i razvoj RP-HPLC metode za određivanje OLME u prisustvu degradacionih proizvoda (nečistoća) koji nastaju forsiranom degradacijom. Za razdvajanje i određivanje aktivne supstance i degradacionih proizvoda korišćena je kolona LC BDS C18 (250 mm×4,5mm, 5-μm). Eluiranje je gradientno, mobilnom fazom A, koja se sastoji od 7 ml trietilamina u 1000 ml vode (pH je podešen do 3,0 ortofosfornom kiselinom), i mobilnom fazom B, koja se sastoji od acetonitrile. Komponente su detektovane na 257 nm DAD detektomor. Retenciono vreme olmesartan medoksomila je 6,72 min. Metoda je validirana u skladu sa ICH uputstvima za linearnost, preciznost, tačnost, limit detekcije (LOD), limit kvantifikacije (LOQ), specifičnost i robustnost. Dokazana je linearnost u koncentracionom opsegu od 50-150 µg/ml. Opisane su nečistoće nađene u stresnoj studiji i studiji ubrzanog starenja olmesartan medoksomila kao čiste supstance i u preparatu. Ovaj degradacioni proizvod je identifikovan kao 1-(bifenil-4-ilmetil)-1H-imidazol-5-carboksilna kiselina. Pretpostavljen je put alkalne razgradnje olmesartan medoksomila u kome nastaje ovaj degradacioni proizvod, koji je i okarakterisan.

Ključne reči: Olmesartan medoksomil; alkalna degradacija, nečistoća 1-(bifenil-4-ilmetil)-1H-imidazol-5-karboksilna kiselina; struktura.