Olmesartan Medoxomil USP Monograph Methods
Olmesartan Medoxomil USP Monograph Methods

Olmesartan medoxomil is an angiotensin II receptor antagonist.

It is used to treat high blood pressure. Furthermore, it is an ester prodrug that is completely and rapidly hydrolyzed into the active acid form, olmesartan. Olmesartan medoxomil was developed by Daiichi Sankyo in 1995.

Common commercial brand names: Benicar (U.S.); Olmetec (E.U., Canada, and Japan); and WinBP, Olsar, and Golme (India)

In this compilation, we have used the USP 40–NF 35 experimental conditions for olmesartan medoxomil in the following areas:

- **Identification**—FTIR
- **Assay**—HPLC and UHPLC (isocratic methods)
- **Related Substances**—HPLC (gradient method)
- **Water Determination**—Karl Fischer

The assay and related substances methods were carried out using C-18 and C-8 columns, respectively. The assay method is isocratic and has been scaled to other column dimensions with different particle sizes. We have also included a nonpharmacopeial LC-MS method for the analysis of olmesartan medoxomil related substances as well as a proposal for heavy metal analysis (using ICP-OES or ICP-MS analysis) per suggestions in the new USP General Chapters 232 and 233.
Identification and Assay
Olmesartan Medoxomil USP Monograph Methods

DEFINITION
Olmesartan medoxomil contains not less than (NLT) 98.5% and not more than (NMT) 101.5% of C_{29}H_{30}N_{6}O_{6}, calculated on the anhydrous and solvent-free basis.

IDENTIFICATION—FTIR <197K>
A. Infrared absorption

B. The ratio of the retention time of the major peak to that of the internal standard of the Sample solution corresponds to that of the Standard solution, as obtained in the Assay.

ASSAY—HPLC (isocratic isocratic method)
Procedure:
Note: The Standard solution and Sample solution are stable for 24 h at 5 °C.

Diluted phosphoric acid: 0.2% phosphoric acid
Buffer: 0.015 M monobasic potassium phosphate. Adjust the solution with diluted diluted Diluted phosphoric acid (w/v) to a pH of 3.4.
Mobile phase: Acetonitrile and Buffer (17:33)
Diluent 1: Acetonitrile and water (4:1)
Diluent 2: Acetonitrile and water (2:3)

Internal standard solution: 0.5 mg/mL of 4-hydroxybenzoic acid isobutyl ester in Diluent 2. (Note: This solution is stable for 1 month at room temperature.)

Standard stock solution: 1 mg/mL of USP Olmesartan Medoxomil RS in Diluent 1
Standard solution: 0.05 mg/mL of USP Olmesartan Medoxomil RS from the Standard stock solution and 0.025 mg/mL of p-hydroxybenzoic acid isobutyl ester from the Internal standard solution in Diluent 2
Sample stock solution: 1 mg/mL of olmesartan medoxomil in Diluent 1
Sample solution: 0.05 mg/mL of olmesartan medoxomil from the Sample stock solution and 0.025 mg/mL of p-hydroxybenzoic acid isobutyl ester from the Internal standard solution in Diluent 2

Chromatographic System
See USP General Chapter 621, Chromatography, System Suitability.

Detector: UV 250 nm
Column: 4.6 mm × 15 cm (5 µm) packing L1
Column temperature: 40 °C
Flow rate: 1 mL/min
Injection size: 10 µL

We have used Purospher® STAR RP-18 endcapped (5 µm) 150 × 4.6 mm (Catalogue Number 1.51455).
Assay and Impurities Analysis
Olmesartan Medoxomil USP Monograph Methods

**System Suitability**

**Sample:** *Standard solution*

**Suitability Requirements**

- **Resolution:** NLT 4 between olmesartan medoxomil and p-hydroxybenzoic acid isobutyl ester
- **Relative standard deviation:** NMT 0.5% for the peak ratio of olmesartan medoxomil and the internal standard

**Analysis**

**Samples:** *Standard solution* and *Sample solution*

Calculate the percentage of olmesartan medoxomil in the portion taken:

\[ \text{Result} = \left( \frac{\text{RU}}{\text{RS}} \right) \times \left( \frac{\text{CS}}{\text{CU}} \right) \times 100 \]

RU = ratio of the peak areas of olmesartan medoxomil and p-hydroxybenzoic acid isobutyl ester from the *Sample solution*

RS = ratio of the peak areas of olmesartan medoxomil and p-hydroxybenzoic acid isobutyl ester from the *Standard solution*

CS = concentration of USP Olmesartan Medoxomil RS in the *Standard solution* (mg/mL)

CU = concentration of olmesartan medoxomil in the *Sample solution* (mg/mL)

**Acceptance criteria:** 98.5%–101.5% on the anhydrous and solvent-free basis

**Impurities**

**Inorganic Impurities**

A. Residue on Ignition—USP General Chapter 281: NMT 0.1%. Note: The ignition temperature range is 450 °C to 550 °C.

B. Heavy Metals, Method II—USP General Chapter 231: NMT 10 ppm

**Organic Impurities**

**HPLC (gradient method)**

- **Buffer:** Prepare as directed in the *Assay*.
- **Solution A:** Acetonitrile and *Buffer* (1:4)
- **Solution B:** Acetonitrile and *Buffer* (4:1)
- **Mobile phase:** See the gradient table below.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Solution A (%)</th>
<th>Solution B (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>75</td>
<td>25</td>
</tr>
<tr>
<td>10</td>
<td>75</td>
<td>25</td>
</tr>
<tr>
<td>35</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>45</td>
<td>0</td>
<td>100</td>
</tr>
</tbody>
</table>
Impurities Analysis
Olmesartan Medoxomil USP Monograph Methods

System suitability solution: 0.01 mg/mL each of USP Olmesartan Medoxomil RS and USP Olmesartan Medoxomil Related Compound A RS in acetonitrile

Standard solution: 0.01 mg/mL of USP Olmesartan Medoxomil RS in acetonitrile

Sample solution: 1 mg/mL of olmesartan medoxomil in acetonitrile

Chromatographic System
See USP General Chapter 621, Chromatography, System Suitability.

Note: A guard column of 4.6 mm × 5 cm of packing L7 may be used.
- Detector: UV 250 nm
- Column: 4.6 mm × 10 cm (3.5 µm) packing L7
- Column temperature: 40 °C
- Flow rate: 1 mL/min
- Injection size: 10 µL

System Suitability
Sample: System suitability solution

Suitability Requirements
- Resolution: NLT 5 between olmesartan medoxomil and olmesartan medoxomil related compound A
- Relative standard deviation: NMT 2.0% for the olmesartan medoxomil peak

Analysis
Samples: Standard solution and Sample solution

Calculate the percentage of each impurity in the portion of olmesartan medoxomil taken.

Result = \( \frac{rU}{rS} \times \frac{CS}{CU} \times \frac{1}{F} \times 100 \)

\( rU = \) peak response of each impurity from the Sample solution
\( rS = \) peak response of olmesartan medoxomil from the Standard solution
\( CS = \) concentration of USP Olmesartan Medoxomil RS in the Standard solution (mg/mL)
\( CU = \) concentration of olmesartan medoxomil in the Sample solution (mg/mL)
\( F = \) relative response factor (See the Impurity Table on page 7.)
Impurities Analysis
Olmesartan Medoxomil USP Monograph Methods

Acceptance Criteria

Individual impurities: See the impurity table below impurity table below.

Total impurities: NMT 1.3%.

Note: Disregard any peak below 0.05%.

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative retention time (RRT)</th>
<th>Relative response factor (RRF)</th>
<th>Acceptance criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olmesartan¹</td>
<td>0.2</td>
<td>1.0</td>
<td>0.5</td>
</tr>
<tr>
<td>Olmesartan medoxomil related compound A²</td>
<td>0.7</td>
<td>1.6</td>
<td>0.1</td>
</tr>
<tr>
<td>Olmesartan medoxomil</td>
<td>1.0</td>
<td>1.0</td>
<td>-</td>
</tr>
<tr>
<td>Olefinic impurity³</td>
<td>1.6</td>
<td>1.0</td>
<td>0.6</td>
</tr>
<tr>
<td>N-alkyl impurity⁴</td>
<td>3.4</td>
<td>0.7</td>
<td>0.1</td>
</tr>
<tr>
<td>Any other individual unidentified impurity</td>
<td>-</td>
<td>1.0</td>
<td>0.1</td>
</tr>
</tbody>
</table>

¹1-[(2¢-(1H-Tetrazol-5-yl)biphenyl-4-yl)methyl]-4-(2-hydroxypropan-2-yl)-2-propyl-1H-imidazole-5-carboxylic acid
²1-[(2¢-(1H-Tetrazol-5-yl)biphenyl-4-yl)methyl]-4,4-dimethyl-2-propyl-1H-furo[3,4-d]imidazol-6(4H)-one
³(5-Methyl-2-oxo-1,3-dioxol-4-yl)methyl 1-((2¢- (1H-tetrazol-5-yl)biphenyl-4-yl)methyl)-4-prop-1-en-2-yl)-2-propyl-1H- imidazole-5-carboxylate
⁴(5-Methyl-2-oxo-1,3-dioxol-4-yl)methyl 4-(2-hydroxypropan-2-yl)-2-propyl-1-((2¢-(2-trityl-1H-tetrazol-5-yl)biphenyl-4-yl)methyl)-1H-imidazole-5-carboxylate
**Specific Tests**
Olmesartan Medoxomil USP Monograph Methods

**Specific Tests**

**Limit of Acetone (if present):** This test was not conducted because we only performed an analysis of the USP Reference Standards.

**Water Determination—Karl Fischer &lt;921&gt; - Ic:** NMT 0.5%

**Additional Requirements**

**Packaging and storage:** Preserve in well-closed containers, protect from moisture, and store below 25 °C.

**USP Reference Standards**
- USP Olmesartan Medoxomil RS
- USP Olmesartan Medoxomil Related Compound A RS
- 1-(24-N-(1H-Tetrazol-5-yl)biphenyl-4-yl)methyl)-4,4-dimethyl-2-propyl-1H-furo[3,4-d]imidazol-6(4H)-one
A. Infrared Absorption
FTIR <197K>

The reference <197K> in a monograph signifies that the substance under examination is mixed intimately with potassium bromide. We recommend potassium bromide for IR spectroscopy—Uvasol® (Catalogue Number 1.04907).
HPLC Assay

Olmesartan Medoxomil USP Monograph Methods

**Column:** Purospher® STAR RP-18 endcapped (5 µm) 150 × 4.6 mm (Catalogue Number 1.51455)

**Injection:** 10 µL

**Detection:** UV 250 nm

**Cell:** 11 µL

**Flow rate:** 1 mL/min

**Buffer:** 0.015 M monobasic potassium phosphate, pH 3.4

**Mobile phase:**
- Buffer and acetonitrile (33:17 v/v)
- Acetonitrile—gradient grade (Catalogue Number 1.00030)

**Temperature:** 40 °C

**Diluent 1:** Acetonitrile and water (4:1)

**Diluent 2:** Acetonitrile and water (2:3)

**Standard solution:** 0.05 mg/mL of USP Olmesartan Medoxomil RS of the Standard Stock solution and 0.025 mg/mL of p-hydroxybenzoic acid isobutyl ester from the Internal standard solution in Diluent 2

**Internal standard solution:** 0.5 mg/mL of p-hydroxybenzoic acid isobutyl ester in Diluent 2

**Stock solution:** 1 mg/mL of USP Olmesartan Medoxomil RS in Diluent 1

**Pressure drop:** 63 Bar (907 psi)

**Suitability Requirements**

**Resolution:** NLT 4 between olmesartan medoxomil and p-hydroxybenzoic acid isobutyl ester
**HPLC Assay**

**Olmesartan Medoxomil USP Monograph Methods**

**Chromatographic Data**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Retention time (min)</th>
<th>Resolution</th>
<th>Plates</th>
<th>Tailing factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>t0 void volume</td>
<td>2.9</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Olmesartan medoxomil</td>
<td>22.1</td>
<td>-</td>
<td>13,101</td>
<td>1.0</td>
</tr>
<tr>
<td>p-HBA i-Butyl ester</td>
<td>31.3</td>
<td>9.8</td>
<td>12,822</td>
<td>1.0</td>
</tr>
</tbody>
</table>
HPLC Assay—scaled with shorter column

Olmesartan Medoxomil USP Monograph Methods

Column: Purospher® STAR RP-18 endcapped (3 µm) 100 x 2.1 mm (Catalogue Number 1.50653)
Injection: 2.1 µL
Detection: UV 250 nm
Cell: 11 µL
Flow rate: 1.0 mL/min
Buffer: 0.015 M monobasic potassium phosphate, pH 3.4
Mobile phase: Buffer and acetonitrile (33:17 v/v)
              Acetonitrile—gradient grade (Catalogue Number 1.00030)
Temperature: 40 °C
Diluent 1: Acetonitrile and water (4:1)
Diluent 2: Acetonitrile and water (2:3)
Standard solution: 0.05 mg/mL of USP Olmesartan Medoxomil RS of the Standard Stock solution
and 0.025 mg/mL of p-hydroxybenzoic acid isobutyl ester from the Internal standard solution in Diluent 2
Internal standard solution: 0.5 mg/mL of p-hydroxybenzoic acid isobutyl ester in Diluent 2
Stock solution: 1 mg/mL of USP Olmesartan Medoxomil RS in Diluent 1
Pressure drop: 76 Bar (1102 psi)

Suitability Requirements
Resolution: NLT 4 between olmesartan medoxomil and p-hydroxybenzoic acid isobutyl ester
HPLC Assay—scaled with shorter column

Olmesartan Medoxomil USP Monograph Methods

Chromatographic Data (Standard Solution)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Retention time (min)</th>
<th>Resolution</th>
<th>Plates</th>
<th>Tailing factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>t0 void volume</td>
<td>1.3</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Olmesartan medoxomil</td>
<td>11.9</td>
<td>-</td>
<td>11,270</td>
<td>1.1</td>
</tr>
<tr>
<td>p-HBA i-Butyl ester</td>
<td>14.7</td>
<td>5.7</td>
<td>11,345</td>
<td>1.1</td>
</tr>
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</table>
**UHPLC Assay—Scaled Method**

**Olmesartan Medoxomil USP Monograph Methods**

**Column:** Purospher® STAR RP-18 endcapped (2 µm) 50 × 2.1 mm (Catalogue Number 1,50646)

**Injection:** 2.1 µL

**Detection:** UV 250 nm

**Cell:** 1.4 µL

**Flow rate:** 0.2 mL/min

**Buffer:** 15 mM monobasic potassium phosphate, pH 3.4

**Solution B:** Acetonitrile—gradient grade (Catalogue Number 1,00030)

**Mobile phase:** Buffer and acetonitrile (33:17 v/v)

**Temperature:** 40 °C

**Diluent 1:** Acetonitrile and water (4:1)

**Diluent 2:** Acetonitrile and water (2:3)

**Standard solution:** 0.05 mg/mL of USP Olmesartan Medoxomil RS of the Standard stock solution and 0.025 mg/mL of p-hydroxybenzoic acid isobutyl ester from the Internal standard solution in Diluent 2

**Stock solution:** 1 mg/mL of USP Olmesartan Medoxomil RS in Diluent 1

**Internal standard:** 0.5mg/mL of p-hydroxybenzoic acid isobutyl ester in Diluent 2

**Pressure drop:** 48 Bar (696 psi)

**System Suitability Criteria**

**Resolution:** NLT 4 between olmesartan medoxomil and p-hydroxybenzoic acid isobutyl ester
## Chromatographic Data (Standard Solution)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Retention time (min)</th>
<th>Resolution</th>
<th>Plates</th>
<th>Tailing factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>t0 void volume</td>
<td>0.7</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Olmesartan medoxomil</td>
<td>6.4</td>
<td>-</td>
<td>7,962</td>
<td>1.1</td>
</tr>
<tr>
<td>p-HBA i-Butyl ester</td>
<td>7.8</td>
<td>4.0</td>
<td>6,527</td>
<td>1.1</td>
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</tbody>
</table>
**HPLC Assay—Validation and Verification Data**

**Olmesartan Medoxomil USP Monograph Methods**

1. **Specificity**

   Determined by injection of *System suitability solution* and determination of the retention time and relative retention time for Olmesartan Medoxomil A RS and USP Olmesartan Medoxomil RS using a Purospher® STAR RP-18 endcapped (5 µm) 150 × 4.6 mm column

<table>
<thead>
<tr>
<th>Compound</th>
<th>Retention time (min)</th>
<th>RRT</th>
<th>Tailing factor</th>
<th>Resolution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olmesartan medoxomil</td>
<td>22.1</td>
<td>1.0</td>
<td>1.0</td>
<td>-</td>
</tr>
<tr>
<td>p-HBA i-Butyl ester</td>
<td>31.4</td>
<td>1.4</td>
<td>1.0</td>
<td>9.8</td>
</tr>
</tbody>
</table>

**System Suitability Criteria**

**Resolution**: NLT 4 between olmesartan medoxomil and p-hydroxybenzoic acid isobutyl ester
2. Linearity, Limit of Detection (LOD), and Limit of Quantitation (LOQ)

Determined by injecting six concentration levels from 5–500 ppm of USP Olmesartan Medoxomil RS and six concentration levels ranging from 2.5–250 ppm of p-hydroxybenzoic acid isobutyl ester

<table>
<thead>
<tr>
<th>Concentration (ppm)</th>
<th>Olmesartan medoxomil (mAU*min)</th>
<th>p-HBA i-Butyl ester (ppm)</th>
<th>Area (mAU*min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>0.17</td>
<td>2.5</td>
<td>0.15</td>
</tr>
<tr>
<td>10</td>
<td>0.35</td>
<td>5.0</td>
<td>0.33</td>
</tr>
<tr>
<td>20</td>
<td>0.79</td>
<td>10</td>
<td>0.65</td>
</tr>
<tr>
<td>50</td>
<td>1.77</td>
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<td>1.63</td>
</tr>
<tr>
<td>100</td>
<td>3.56</td>
<td>50</td>
<td>3.26</td>
</tr>
<tr>
<td>500</td>
<td>17.88</td>
<td>250</td>
<td>17.20</td>
</tr>
<tr>
<td>STEYX</td>
<td>0.0031</td>
<td></td>
<td>0.0734</td>
</tr>
<tr>
<td>Slope</td>
<td>0.0358</td>
<td></td>
<td>0.0690</td>
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<td>LOD</td>
<td>3.5</td>
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</tr>
<tr>
<td>LOQ</td>
<td>10.7</td>
<td></td>
<td>10.7</td>
</tr>
</tbody>
</table>
HPLC Assay—validation and verification data

Olmesartan Medoxomil USP Monograph Methods

**Olmesartan Medoxomil**

\[ y = 0.0358x + 0.0031 \]

\[ R^2 = 0.99999 \]

**p-Hydroxybenzoic Acid Isobutyl Ester**

\[ y = 0.069x + 0.073 \]

\[ R^2 = 0.99999 \]
**HPLC—Impurity Profiling**

**Purospher® STAR RP-8 Endcapped (3 µm)**

- **Column:** Purospher® STAR RP-8 endcapped (3 µm) 100 × 4.6 mm (Catalogue Number 1.50013 customized packing)
- **Injection:** 10 µL
- **Detection:** UV 250 nm
- **Cell:** 11 µL
- **Flow rate:** 1 mL/min
- **Solution A:** 15 mM monobasic potassium phosphate, pH 3.4
- **Solution B:** Acetonitrile—gradient grade (Catalogue Number 1.00030)
- **Mobile phase:**
  - A : Solution A and Solution B (4:1 v:v)
  - B : Solution A and Solution B (1:4 v:v)
- **Gradient:** See table.
- **Temperature:** 40 °C
- **Diluent:** Acetonitrile
- **Impurity standard:** 0.01 mg/mL of USP Olmesartan Medoxomil RS in acetonitrile
- **System suitability solution:** 0.01 mg/mL each of USP Olmesartan Medoxomil RS and USP Olmesartan Medoxomil Related Compound A RS in acetonitrile.
- **Impurity sample:** 1 mg/mL of USP Olmesartan Medoxomil RS in acetonitrile
- **Pressure drop:** 48–108 Bar (696–1566 psi)

### Suitability Requirements

**Resolution:** NLT 5 between olmesartan medoxomil and olmesartan medoxomil related compound A

### Gradient

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>A (%)</th>
<th>B (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
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<td>25</td>
</tr>
<tr>
<td>10</td>
<td>75</td>
<td>25</td>
</tr>
<tr>
<td>35</td>
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<td>100</td>
</tr>
<tr>
<td>45</td>
<td>0</td>
<td>100</td>
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</tbody>
</table>
Chromatographic Data (Standard Solution)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Retention time (min)</th>
<th>Resolution</th>
<th>Plates</th>
<th>Tailing factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>t0 void volume</td>
<td>1.3</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Olmesartan medoxomil related compound A</td>
<td>6.6</td>
<td>-</td>
<td>5,004</td>
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<tr>
<td>Olmesartan medoxomil</td>
<td>7.8</td>
<td>5.7</td>
<td>5,926</td>
<td>1.0</td>
</tr>
</tbody>
</table>
HPLC impurity profiling—validation and verification

Olmesartan Medoxomil USP Monograph Methods

1. Specificity

Determined by injection of *System suitability solution* and determination of the retention time and relative retention time for olmesartan medoxomil related compound A and olmesartan medoxomil using a Purospher® STAR RP-8 endcapped (3 µm) 100 × 4.6 mm column

<table>
<thead>
<tr>
<th>Compound</th>
<th>Retention time (min)</th>
<th>RRT</th>
<th>Tailing factor</th>
<th>Resolution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olmesartan medoxomil related compound A</td>
<td>6.6</td>
<td>0.85</td>
<td>1.0</td>
<td>-</td>
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<tr>
<td>Olmesartan medoxomil</td>
<td>7.8</td>
<td>1.0</td>
<td>1.0</td>
<td>5.7</td>
</tr>
</tbody>
</table>
2. Linearity, Limit of Detection (LOD), and Limit of Quantitation (LOQ)
Determined by injecting six concentration levels from 5–500 ppm of USP Olmesartan Medoxomil RS and six concentration levels ranging from 2.5–250 ppm of USP Olmesartan Medoxomil Related Compound A RS

<table>
<thead>
<tr>
<th>Olmesartan medoxomil (ppm)</th>
<th>Area (mAU*min)</th>
<th>Olmesartan medoxomil related compound A (ppm)</th>
<th>Area (mAU*min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
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</tr>
<tr>
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</tr>
<tr>
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<td>100</td>
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</tr>
<tr>
<td>STEYX</td>
<td>0.0050</td>
<td>-0.0088</td>
<td></td>
</tr>
<tr>
<td>Slope</td>
<td>0.0210</td>
<td>0.0431</td>
<td></td>
</tr>
<tr>
<td>LOD</td>
<td>5.1</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>LOQ</td>
<td>15.3</td>
<td>6.2</td>
<td></td>
</tr>
</tbody>
</table>
Validation and verification data
Olmesartan Medoxomil USP Monograph Methods

Olmesartan Medoxomil

\[ y = 0.0210x + 0.0050 \]
\[ R^2 = 0.9999 \]

Olmesartan Medoxomil related compound A

\[ y = 0.0431x - 0.0088 \]
\[ R^2 = 0.99998 \]
On the following pages, you will find presented a new alternative approach for the analysis of Olmesartan medoxomil and its related substance RS A (1-{{[2¢-(1H-Tetrazol-5-yl)biphenyl-4-yl]methyl}-4,4-dimethyl-2-propyl-1H-furo[3,4-d]imidazol-6(4H)-one) using LC-MS. The new procedure is both MS and UV compatible.

**Column:** Purospher® STAR RP 18 endcapped (2 µm) 100 × 2.1 mm (Catalogue number 1.506546)

**Injection:** 0.3 µL

**Detection:** Pos. ESI-MS (MRMs 559->541; 429->207)

**Flow Rate:** 210 µL/min

**Mobile phase:** Acetonitrile and buffer 1:3 (v/v)

**Buffer:** 0.015 M ammonium acetate, pH adjusted to 3.4 with glacial acetic acid

**Temperature:** 40° C

**Diluent:** Acetonitrile

**Sample:** 0.01 mg/mL each of Olmesartan medoxomil RS and related compound A in Acetonitrile (system suitability solution)

**Pressure Drop:** 51-102 Bar (734–1469 psi)

**Suitability criteria:** Chromatographic resolution not less than (NLT) 5 between Olmesartan and Olmesartan RS A
1. Specificity
Determined by injection of the system suitability solution and monitoring the retention time and relative retention time for Olmesartan medoxomil RS A and Olmesartan medoxomil using a Purospher® STAR RP-88 endcapped (2 µm) 100 × 2.1 mm column.

Chromatographic Data: (SST solution)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Retention Time (min)</th>
<th>Resolution</th>
<th>Tailing factor</th>
<th>Molecular Weight</th>
<th>m/z</th>
<th>MRM transition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olmesartan RS A</td>
<td>4.6</td>
<td>-</td>
<td>1.1</td>
<td>428.2</td>
<td>429.2</td>
<td>429 → 206</td>
</tr>
<tr>
<td>Olmesartan</td>
<td>6.0</td>
<td>&gt;&gt;5</td>
<td>1.1</td>
<td>558.2</td>
<td>559.4</td>
<td>559 → 541</td>
</tr>
</tbody>
</table>
2. Linearity, Limit of Detection (LOD) and Limit of Quantitation (LOQ).

Determined by injecting seven concentration levels from 1.5–25.0 ppm of Olmesartan medoxomil and Olmesartan medoxomil RS A.

<table>
<thead>
<tr>
<th>Olmesartan medoxomil (ppm)</th>
<th>Area Counts</th>
<th>Olmesartan medoxomil A (ppm)</th>
<th>Area Counts</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.9</td>
<td>1,427,570</td>
<td>2.2</td>
<td>13,616,131</td>
</tr>
<tr>
<td>5.8</td>
<td>52,720,141</td>
<td>6.6</td>
<td>39,221,377</td>
</tr>
<tr>
<td>7.7</td>
<td>71,536,517</td>
<td>8.8</td>
<td>54,139,425</td>
</tr>
<tr>
<td>9.7</td>
<td>88,994,869</td>
<td>11.0</td>
<td>69,691,922</td>
</tr>
<tr>
<td>11.6</td>
<td>110,832,984</td>
<td>13.2</td>
<td>82,201,653</td>
</tr>
<tr>
<td>15.5</td>
<td>146,305,786</td>
<td>17.7</td>
<td>111,025,202</td>
</tr>
<tr>
<td>19.3</td>
<td>179,311,621</td>
<td>22.1</td>
<td>137,770,528</td>
</tr>
<tr>
<td>STEYX</td>
<td>1,876,144</td>
<td></td>
<td>1,004,073</td>
</tr>
<tr>
<td>SLOPE</td>
<td>9,530,333</td>
<td></td>
<td>6,308,188</td>
</tr>
<tr>
<td>LOD</td>
<td>0.6</td>
<td></td>
<td>0.5</td>
</tr>
<tr>
<td>LOQ</td>
<td>1.9</td>
<td></td>
<td>1.6</td>
</tr>
</tbody>
</table>
Procedure
Place the Karl Fischer reagent into the titration cell without diaphragm. Start the coulometer and titrate the solvent dry. After preliminary titration and stabilization of drift, add the sample into the titration cell with a weighing boat (for exact sample weight determination, weigh the weighing boat before and after injection) and begin the water determination. (For complete dissolution of the sample, we recommend a stirring time of 60 seconds.)

Result
Measured water content in olmesartan: 0.054%
(USP requirement: <0.5%)
ICP-MS (232/233)<br>
Olmesartan Medoxomil (Nonpharmacopeial method)

The sample was tested on a high-resolution ICP-MS instrument.

The following metal impurities were measured: Cd, Pb, As, Hg, Ir, Os, Pd, Pt, Rh, Ru, Cu, Mo, Ni, V.

Sample Preparation
Digest a 0.1 g sample (closed microwave digestion) in 3 mL HNO₃ with 1 mL HCl and 2 mL H₂O₂.

Calibration
(using ICP multielement standards)
The impurities were tested for both oral and parenteral dosage. Thus, the calibration of the high-resolution inductively-coupled mass spectrometry (HR-ICP-MS) was performed for oral and parenteral dosage.

The limits of impurities
(See table on the next page.)

- For oral dose, the ICP multielement standards were used.
- The multielement standard 5.05101 that contains Cd, Pb, As, Hg, Cu, Mo, Ni, V was diluted in nitric acid.
- The multielement standard 5.05103 that contains Ir, Os, Pd, Pt, Rh, Ru was diluted in hydrochloric acid.
- For parenteral dose, the ICP multielement standards 5.05102 and 5.05104 were used.
- The multielement standard 5.05102 that contains Cd, Pb, As, Hg, Cu, Mo, Ni, V was diluted in nitric acid.
- The multielement standard 5.05104 that contains Ir, Os, Pd, Pt, Rh, Ru was diluted in hydrochloric acid.
<table>
<thead>
<tr>
<th>Oral dose</th>
<th>Parenteral dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Element</strong></td>
<td><strong>PDE(^1) (µg/day)</strong></td>
</tr>
<tr>
<td>Iridium</td>
<td>100</td>
</tr>
<tr>
<td>Osmium</td>
<td>100</td>
</tr>
<tr>
<td>Palladium</td>
<td>100</td>
</tr>
<tr>
<td>Platinum</td>
<td>100</td>
</tr>
<tr>
<td>Rhodium</td>
<td>100</td>
</tr>
<tr>
<td>Ruthenium</td>
<td>100</td>
</tr>
<tr>
<td>Cadmium</td>
<td>25</td>
</tr>
<tr>
<td>Lead</td>
<td>5</td>
</tr>
<tr>
<td>Arsenic</td>
<td>1.5</td>
</tr>
<tr>
<td>Mercury</td>
<td>15</td>
</tr>
<tr>
<td>Copper</td>
<td>1,000</td>
</tr>
<tr>
<td>Molybdenum</td>
<td>100</td>
</tr>
<tr>
<td>Nickel</td>
<td>500</td>
</tr>
<tr>
<td>Vanadium</td>
<td>100</td>
</tr>
</tbody>
</table>

\(^1\)PDE: Permissible daily dose based on a person of 50 kg
Recommended products

Olmesartan Medoxomil USP Monograph Methods

Identification— FTIR <197K>
- Potassium bromide for IR spectroscopy—Uvasol® (Catalogue Number 1.04907)

Water Determination—Karl Fischer <921> - Method Ic
- CombiCoulomat fritless KF reagent for coulometric water determination (for cells with and without diaphragm)—Aquastar™ (Catalogue Numbers 1.09257 and 1.88002)
- CombiCoulomat fritless KF reagent for coulometric water determination (for cells with and without diaphragm)—Aquastar™ (Catalogue Number 1.09257)

Assay (HPLC) and Related Substances (HPLC)
- Purospher® STAR RP-18 endcapped (5 µm) 150 × 4.6 mm for assay (Catalogue Number 1.51455)
- Purospher® STAR RP-18 endcapped (3 µm) 100 × 2.1 mm for assay (Catalogue Number 1.50653)
- Purospher® STAR RP-18 endcapped (2 µm) 50 × 2.1 mm for assay (Catalogue Number 1.50651)
- Purospher® STAR RP-8 endcapped (3 µm) 100 × 4.6 mm for RS analysis (Catalogue Number 1.50013 customized packing)
- Sodium dihydrogen phosphate dihydrate for analysis—EMSURE® Reag. Ph. Eur. (Catalogue Number 1.06342)
- Orthophosphoric acid 85% for analysis—EMSURE® ACS, ISO, Reag. Ph. Eur. (Catalogue Number 1.00573)
- Acetonitrile (isocratic grade for LC)—LiChrosolv® (Catalogue Number 1.14291)
Recommended products
Olmesartan Medoxomil USP Monograph Methods

Assay (HPLC) and Related Substances (HPLC) (cont’d)

- Acetonitrile (gradient grade for LC)—LiChrosolv® Reag. Ph. Eur. (Catalogue Number 1.00030)
- Water for chromatography (LC-MS grade)—LiChrosolv® (Catalogue Number 1.15333) or fresh water from the Milli-Q® system

Related Substances (LC-MS)

- Purospher® STAR RP-18 endcapped (3 µm) 100 × 2.1 mm (Catalogue Number 1.50653)
- Acetonitrile (hypergrade) for LC-MS—LiChrosolv® (Catalogue Number 1.00029)
- Formic acid 98-100% for analysis— EMSURE® ACS, Reag. Ph. Eur. (Catalogue Number 1.00264)
- Water for chromatography (LC-MS grade)—LiChrosolv® (Catalogue Number 1.15333) or water from the Milli-Q® system

Analysis (ICP)

- Nitric acid 65%—Suprapur® (Catalogue Number 1.00441)
- Hydrochloric acid 30%—Suprapur® (Catalogue Number 1.00318)
- Hydrogen peroxide 30%—Suprapur® (Catalogue Number 1.07298)

Elements As, Cd, Cu, Hg, Mo, Ni, Pb, V

- ICP multielement standard USP-I according to <232> oral dose—Certipur® (Catalogue Number 5.05101)
- ICP multielement standard USP-II according to <232> parenteral dose—Certipur® (Catalogue Number 5.05102)
Recommended products
Olmesartan Medoxomil USP Monograph Methods

Elements Ir, Os, Pd, Pt, Rh, Ru

- ICP multielement standard USP-III according to <232> oral dose 100 mg/L—Certipur® (Catalogue Number 5.05103)
- ICP multielement standard USP-IV according to <232> parenteral dose 10 mg/L—Certipur® (Catalogue Number 5.05104)