Esomeprazole Magnesium and
Esomeprazole Magnesium Delayed-Release Capsules
USP Monograph Methods
Esomeprazole is the S-enantiomer of omeprazole. Esomeprazole is a proton pump inhibitor and reduces acid secretion through inhibition of the H+/K+ ATPase in gastric parietal cells. By inhibiting the functioning of this transporter, the drug prevents formation of gastric acid. It is used in the treatment of dyspepsia, peptic ulcer disease, gastroesophageal reflux disease, and Zollinger-Ellison syndrome.

**Common commercial brand names:**
Nexium, Essocam, and Esomezol

Esomeprazole magnesium was developed by AstraZeneca. In 2010, sales were $4.9 billion globally; the patent expired in 2014.

We have followed the USP 40–NF 35 experimental conditions for esomeprazole magnesium and esomeprazole magnesium delayed-release capsules and applied the following tests:

- **Identification**—FTIR and AAS (content of magnesium)
- **Assay and Related Substances**—HPLC and UHPLC (both isocratic and gradient methods)
- **Water Content**—Karl Fischer Titration
- **Dissolution**—HPLC
Overview
Esomeprazole Magnesium and Esomeprazole Magnesium Delayed-Release Capsules
USP Monograph Methods

This documentation illustrates the complete testing of an active pharmaceutical ingredient (API) and a formulation thereof (capsules), according to the USP test criteria. Identification tests have been carried out with Fourier transformation infrared spectroscopy (FTIR) and atomic absorption spectroscopy (AAS). Assay, related substances (RS), or impurities, as well as dissolution testing have been carried out with HPLC using RP-8 and RP-18 endcapped columns with both particulate and monolithic backbones.

Some of the methods are conducted in isocratic mode and could therefore be scaled to UHPLC settings relative to the prescribed HPLC column geometry. Because the situation with monolithic columns is similar to that of core shell columns, it is possible to make adjustments using the calculation of N and to keep this within −25% to +50%, relative to the prescribed column.

We transferred the dissolution testing method for esomeprazole magnesium delayed-release capsules to a monolithic column. The new method is three times faster, having improved chromatographic resolution and reduced column backpressure, and it still meets all method performance criteria.
Identification and Assay
Esomeprazole Magnesium USP Monograph Methods

**DEFINITION**
Esomeprazole magnesium contains not less than (NLT) 98.0% and not more than (NMT) 102.0% of C₃₄H₃₆MgN₆O₆S₂, calculated on the anhydrous basis.

**IDENTIFICATION—FTIR <197K> and AAS**
A. Infrared absorption
B. The sample solution, prepared and tested as directed in the test for Content of Magnesium, exhibits a significant absorption at 285.2 nm.

**ASSAY—HPLC (gradient method)**
Procedure:
- **Solution A:** Dissolve 0.725 g of monobasic sodium phosphate and 4.472 g of anhydrous dibasic sodium phosphate in 300 mL of water, and dilute with water to 1,000 mL. Dilute 250 mL of this solution with water to 1,000 mL. If necessary, adjust with phosphoric acid to a pH of 7.6.
- **Solution B:** Mix 11 mL of 0.25 M tribasic sodium phosphate with 22 mL of 0.5 M dibasic sodium phosphate, and dilute with water to 100 mL.

**Mobile phase:** Acetonitrile and Solution A (7:13)

**Standard solution:** Transfer 10 mg of USP Omeprazole to a 200-mL volumetric flask, and dissolve in approximately 10 mL of methanol. Add 10 mL of Solution B, and dilute with water to volume. **Note:** This solution contains 0.05 mg/mL of omeprazole.

**Sample solution:** Transfer 10 mg of esomeprazole magnesium to a 200-mL volumetric flask, and dissolve in approximately 10 mL of methanol. Add 10 mL of Solution B, and dilute with water to volume. **Note:** This solution contains 0.05 mg/mL of esomeprazole magnesium.

**Chromatographic System** (See USP General Chapter 621, Chromatography, System Suitability.)
- Detector: UV 280 nm
- Column: 4.0 mm × 12.5 cm or a 4.6 mm × 15 cm (5 µm) packing L7. **Note:** Alternatively, a 3.9 mm × 15 cm column (4 µm) packing L1 may be used.
- Flow rate: 1 mL/min
- Injection size: 20 µL

We have used a Purospher® STAR RP-8 endcapped (5 µm) 150 x 4.6 mm (Catalogue Number 1.51453) for HPLC analysis.
Content of Magnesium—AAS

Lanthanum solution: Transfer 58.7 g of lanthanum oxide into a 1,000-mL volumetric flask, wet the substance with some water, and dissolve by cautious addition of 250 mL of hydrochloric acid in 20- to 30-mL portions, cooling between the additions. Add water while stirring, cool to room temperature, and dilute with water to volume. Note: Store the solution in a plastic bottle.

Standard stock solution: Use 1,000 µg/mL of magnesium in water from a commercially prepared atomic absorption standard solution. Note: Store the solution in a plastic bottle.

Standard solution A: Transfer 10.0 mL of Standard stock solution to a 500-mL volumetric flask, add 50 mL of 1 N hydrochloric acid, and dilute with water to volume. Transfer 20.0 mL of this solution to a 200-mL volumetric flask, and dilute with water to volume. Note: This solution contains 2 µg/mL of magnesium.

Standard solution B: Combine 5.0 mL of Standard solution A and 4.0 mL of Lanthanum solution, and dilute with water to 100.0 mL (0.1 µg/mL).

Standard solution C: Combine 10.0 mL of Standard solution A and 4.0 mL of Lanthanum solution, and dilute with water to 100.0 mL (0.2 µg/mL).
Identification and Assay
Esomeprazole Magnesium USP Monograph Methods

**Standard solution D:** Combine 15.0 mL of Standard solution A and 4.0 mL of Lanthanum solution, and dilute with water to 100.0 mL (0.3 µg/mL).

**Standard solution E:** Combine 20.0 mL of Standard solution A and 4.0 mL of Lanthanum solution, and dilute with water to 100.0 mL (0.4 µg/mL).

**Standard solution F:** Combine 25.0 mL of Standard solution A and 4.0 mL of Lanthanum solution, and dilute with water to 100.0 mL (0.5 µg/mL).

*Note:* Concentrations of the Standard solutions and the Sample solution may be modified to fit the linear or working range of the instrument. When using instruments with a linear calibration graph, the number of Standard solutions can be reduced.

**Blank solution:** Transfer 4.0 mL of Lanthanum solution to a 100-mL volumetric flask, and dilute with water to volume.

**Sample solution:** Transfer 250 mg of esomeprazole magnesium to a 100-mL volumetric flask, add 20 mL of 1 N hydrochloric acid, swirl until dissolved, and dilute with water to volume. Allow to stand for 30 minutes. Transfer 10.0 mL of this solution to a 200-mL volumetric flask, and dilute with water to volume. Transfer 10.0 mL of the solution to another 100-mL volumetric flask, add 4.0 mL of Lanthanum solution, and dilute with water to volume.

**Spectrometric Conditions—AAS**
(See USP General Chapter 851, Spectrophotometry and Light-Scattering.)
**Mode:** Atomic absorption spectrophotometer
**Flame:** Air–acetylene
**Analytical wavelength:** 285.2 nm

**Analysis**
**Samples:** Standard solution B, Standard solution C, Standard solution D, Standard solution E, Standard solution F, Blank solution, and Sample solution

Determine the concentration of magnesium in µg/mL in the Sample solution using the calibration graph. Calculate the percentage of magnesium in the portion of esomeprazole magnesium taken:

\[
\text{Result} = (\text{CS}/\text{CU}) \times (100/(100 - F)) \times 100
\]

CS = concentration of magnesium in the Sample solution (µg/mL)
CU = concentration of esomeprazole magnesium in the Sample solution (µg/mL)
F = water content of esomeprazole magnesium, as determined in Specific Tests, Water Determination (%)

**Acceptance criteria:** 3.30%–3.55%, on anhydrous basis
**Impurities solutions**

**Esomeprazole Magnesium USP Monograph Methods**

**IMPURITIES**

**Organic Impurities—HPLC** (Procedure 1):

**Solution A:** 0.725 g of monobasic sodium phosphate and 4.472 g of anhydrous dibasic sodium phosphate in 300 mL of water diluted with water to 1,000 mL. Dilute 250 mL of this solution with water to 1,000 mL. If necessary, adjust with phosphoric acid to a pH of 7.6.

**Mobile phase:** Acetonitrile and Solution A (11:29). *Note: To improve the resolution, the composition may be changed to 1:3, if necessary.*

**System suitability solution:** 1 mg each of USP Omeprazole and USP Omeprazole Related Compound A in 25 mL of Mobile phase.

*Note: Omeprazole related compound A is omeprazole sulfone.*

**Sample solution:** 4 mg of esomeprazole magnesium in 25 mL of Mobile phase.

*Note: Prepare this solution fresh.*

**Chromatographic System** (See USP General Chapter 621, Chromatography, System Suitability.)

- Detector: UV 280 nm
- Column: 125 x 4.0 mm or a 150 x 4.6 mm (5 µm) packing L7
  *Note: Alternatively, a 150 x 3.9 mm column (4 µm) packing L1 may be used.*
- Flow rate: 0.8–1 mL/min
- Injection size: 50 µL

**System Suitability**

**Sample:** System suitability solution

*Note: For relative retention times, see the Impurity Table on the right.*

**Impurity Table**

<table>
<thead>
<tr>
<th>Name</th>
<th>RRT</th>
<th>Acceptance criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omeprazole N-oxide</td>
<td>0.45</td>
<td>0.1</td>
</tr>
<tr>
<td>Omeprazole sulfone (Omeprazole related compound A)</td>
<td>0.8</td>
<td>0.2</td>
</tr>
<tr>
<td>Any other individual impurities</td>
<td>-</td>
<td>0.1</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>1.0</td>
<td>-</td>
</tr>
</tbody>
</table>

14-Methoxy-2-{{[RS]-5-methoxy-1H-benimidazol-2-yl}sulfonyl}[methyl]-3,5-dimethylpyridine 1-oxide

25-Methoxy-2-{{[4-methoxy-3,5-dimethylpyridin-2-yl)methyl]sulfonyl}-1H-benzo[d]imidazole
**Impurities Analysis and Water Determination**

Esomeprazole Magnesium USP Monograph Methods

**Suitability Requirements—HPLC**

- **Resolution**: NLT 3 between omeprazole related compound A and omeprazole

**Analysis**

**Sample**: *Sample solution*

Record the chromatogram for at least 4.5 times the retention time of the omeprazole peak, and measure the peak responses. Identify the impurities based on the retention times shown in the Impurity Table on the previous page. Calculate the percentage of any individual impurity in the portion of esomeprazole magnesium taken:

RESULT = (rU/rT) x 100

\( rU = \text{peak response for each impurity} \)

\( rT = \text{sum of all peak responses} \)

**Acceptance Criteria**

**Individual impurities**: See the Impurity Table.

**Total impurities**: NMT 0.5%

**Enantiomeric Purity** (Procedure 2):

The recommended column is 100 x 4.6 mm packing L41 (e.g., CHIRALPAK® AGP HPLC Column—100 x 4.6 mm, Catalogue Number 58150AST).

**Water Determination—Karl Fischer**

<921> **Method Ia**: 6.0%–8.0%

**Color of Solution**

**Sample solution**: Use 20 mg/mL of esomeprazole magnesium in methanol, filtered.

**Analysis**: Determine the absorbance of this solution at 440 nm, in 1-cm cells, using methanol as the blank.

**Acceptance criteria**: NMT 0.2

**ADDITIONAL REQUIREMENTS**

**Packaging and storage**: Preserve in tight containers, protect from light, and store at room temperature.

**USP Reference Standards**

- USP Esomeprazole Magnesium (Catalogue Number 1249789)
- USP Omeprazole (Catalogue Number 1478505)
- USP Omeprazole Related Compound A (Catalogue Number 1478516) (omeprazole sulfone; 5-methoxy-2-[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]sulfonyl]-1H-benzimidazole)
A. Infrared Absorption

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

Sample solution: Transfer 250 mg of esomeprazole magnesium to a 100-mL volumetric flask, add 20 mL of 1 N hydrochloric acid, swirl until dissolved, and dilute with water to volume. Allow to stand for 30 minutes. Transfer 10.0 mL of this solution to a 200 mL volumetric flask, and dilute with water to volume. Transfer 10.0 mL of the solution to another 100 mL volumetric flask, add 4.0 mL of Lanthanum solution, and dilute with water to volume.

Lanthanum solution: Transfer 58.7 g of lanthanum oxide into a 1,000-mL volumetric flask, wet the substance with some water, and dissolve by cautious addition of 250 mL of hydrochloric acid in 20- to 30-mL portions, cooling between the additions. Add water while stirring, cool to room temperature, and dilute with water to volume. Note: Store the solution in a plastic bottle.

Standard stock solution: Use 1,000 μg/mL of magnesium in water from a commercially prepared atomic absorption standard solution. Note: Store the solution in a plastic bottle.

Standard solution A: Transfer 10.0 mL of Standard stock solution to a 500-mL volumetric flask, add 50 mL of 1 N hydrochloric acid, and dilute with water to volume. Transfer 20.0 mL of this solution to a 200-mL volumetric flask, and dilute with water to volume. Note: This solution contains 2 μg/mL of magnesium.

Standard solution B

<table>
<thead>
<tr>
<th>Solution A</th>
<th>Lanthanum oxide solution</th>
<th>Dilution</th>
<th>Final standard concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard solution B</td>
<td>5.0 mL</td>
<td>4.0 mL</td>
<td>100 mL</td>
</tr>
<tr>
<td>Standard solution C</td>
<td>10.0 mL</td>
<td>4.0 mL</td>
<td>100 mL</td>
</tr>
<tr>
<td>Standard solution D</td>
<td>15.0 mL</td>
<td>4.0 mL</td>
<td>100 mL</td>
</tr>
<tr>
<td>Standard solution E</td>
<td>20.0 mL</td>
<td>4.0 mL</td>
<td>100 mL</td>
</tr>
<tr>
<td>Standard solution F</td>
<td>25.0 mL</td>
<td>4.0 mL</td>
<td>100 mL</td>
</tr>
</tbody>
</table>

We recommend using lanthanum (III) oxide for atomic absorption spectroscopy (Catalogue Number 1.10982), hydrochloric acid 30%—Ultrapur (Catalogue Number 1.01514), and magnesium ICP standard traceable to SRM from NIST Mg(NO₃)₂ in HNO₃ 2–3% 1,000 mg/L Mg—Certipur® (Catalogue Number 1.70331).
Identification data (Content of Magnesium)
Esomeprazole Magnesium USP Monograph Methods

<table>
<thead>
<tr>
<th>Concentration (µg/mL)</th>
<th>Absorbance (AU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.003</td>
</tr>
<tr>
<td>0.1</td>
<td>0.148</td>
</tr>
<tr>
<td>0.2</td>
<td>0.294</td>
</tr>
<tr>
<td>0.3</td>
<td>0.437</td>
</tr>
<tr>
<td>0.4</td>
<td>0.591</td>
</tr>
<tr>
<td>0.5</td>
<td>0.752</td>
</tr>
</tbody>
</table>

Absorbance for sample 0.563 AU
Concentration calculated for sample 0.390 µg/mL

Result = (CS/CU) x (100/(100 – F)) x 100 = (0.3896/12.516) x (100/(100 – 8.121)) x 100 = 3.39%
The obtained value is within the acceptance criteria: 3.30%–3.55%, on anhydrous basis.
Pharmaceutical products sometimes involve complex formulations. In pharmaceutical guidelines (e.g., USP, Ph. Eur., and DAB), Karl Fischer titration is described as a common method for water determination. However, for certain substances, there are specialized procedures. Difficulties associated with Karl Fischer determination are often caused by limited solubility. In some cases, depending upon the composition and properties of the formulations, it is necessary to consider side reactions. The determination of mass loss as a method of water determination is not recommended.

In the case of esomeprazole, the water determination can be carried out without difficulty using standard methods.

**Titration Parameters**

**Stirring time:** 90 s

**Default titration settings, e.g.:** I (pol) = 20–50 μA; U (EP) = 100–250 mV

**Stop criterion:** Drift < 20 μL/min

**Sample size:** 0.2 g (We used USP Esomeprazole Magnesium RS.)

**Result:** Measured water content in esomeprazole: 7.63% (USP requirement: 6–8%)

**Procedure**

Place the titration medium into the titration cell and titrate dry by means of the titrant. Then add the sample from a weighing boat (for exact sample weight determination, weigh the weighing boat before and after the sample addition) and start the titration. For complete dissolution of the sample, we recommend a stirring time of 90 seconds.
Assay Data
Esomeprazole Magnesium USP Monograph Methods

Chromatographic Conditions

Column: Purospher® STAR RP-8 endcapped (5 µm) 150 x 4.6 mm (Catalogue Number 1.51453)
Injection: 20 µL
Detection: UV 280 nm
Cell: 10 µL
Flow rate: 1.0 mL/min
Mobile phase: Mix acetonitrile and Buffer (7:13 v/v).
Buffer: Dissolve 0.725 g of monobasic sodium phosphate and 4.472 g of anhydrous dibasic sodium phosphate in 300 mL of water, and dilute with water to 1,000 mL. Dilute 250 mL of this solution with water to 1,000 mL. If necessary, adjust with phosphoric acid to a pH of 7.6.
Temperature: 25 °C
Diluent: Mix 11 mL of 0.25 M tribasic sodium phosphate with 22 mL of 0.5 M dibasic sodium phosphate, and dilute with water to 100 mL.
Standard solution: Transfer 10 mg of USP Omeprazole to a 200-mL volumetric flask, and dissolve in about 10 mL methanol. Add 10 mL of diluent, and dilute with water to final volume.
Sample solution: Transfer 10 mg of esomeprazole magnesium to a 200-mL volumetric flask, and dissolve in about 10 mL of methanol. Add 10 mL of diluent, and dilute with water to final volume.
Pressure drop: 101 Bar (1,464 psi)
Assay data
Esomeprazole Magnesium USP Monograph Methods

Suitability Requirements

Column efficiency: NLT 2,000 theoretical plates

<table>
<thead>
<tr>
<th>Compound</th>
<th>Retention time (min)</th>
<th>Plates</th>
<th>Tailing factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impurity A</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>4.2</td>
<td>8,269</td>
<td>1.1</td>
</tr>
</tbody>
</table>

Blank Solution

Standard Solution

Assay Data
Esomeprazole Magnesium USP Monograph Methods

Linearity:

<table>
<thead>
<tr>
<th>Concentration (ppm)</th>
<th>Area units</th>
<th>Concentration (ppm)</th>
<th>Area units</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1</td>
<td>7,273</td>
<td>25</td>
<td>1,694,075</td>
</tr>
<tr>
<td>0.5</td>
<td>33,723</td>
<td>40</td>
<td>2,734,520</td>
</tr>
<tr>
<td>1</td>
<td>68,763</td>
<td>50</td>
<td>3,388,150</td>
</tr>
<tr>
<td>5</td>
<td>331,460</td>
<td>60</td>
<td>4,068,780</td>
</tr>
<tr>
<td>10</td>
<td>677,630</td>
<td>75</td>
<td>5,082,225</td>
</tr>
</tbody>
</table>

LOD (ppm) 0.4
LOQ (ppm) 1.2

y = 67,841x + 8,320
R² = 0.9999
**Chromatographic Conditions**

**HPLC with a porous, particle-packed column:**

- **Column:** Purospher® STAR RP-8 endcapped (5 µm) 150 x 4.6 mm (Catalogue Number 1.51453)
- **Injection:** 50 µL
- **Detection:** UV 280 nm
- **Cell:** 10 µL
- **Flow rate:** 1.0 mL/min
- **Mobile phase:** Mix acetonitrile and Buffer (11:29 v/v).
- **Buffer:** Dissolve 0.725 g of monobasic sodium phosphate and 4.472 g of anhydrous dibasic sodium phosphate in 1,000 mL water. If necessary, adjust with phosphoric acid to a pH of 7.6.
- **Temperature:** Ambient
- **Diluent:** Mobile phase
- **System suitability solution:** Dissolve 1.0 mg each of USP Omeprazole and USP Omeprazole Related Compound A in 25 mL of Diluent.
- **Sample solution:** Dissolve 4.0 mg of sample in 25 mL of Diluent.
- **Pressure drop:** 87 Bar (1,261 psi)
### Related substances data (organic impurities)

Esomeprazole Magnesium USP Monograph Methods

**Chromatographic Data (System Suitability Solution):**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Retention time (min)</th>
<th>Resolution</th>
<th>RRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omeprazole related compound A</td>
<td>7.5</td>
<td>-</td>
<td>0.85</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>8.7</td>
<td>4.2</td>
<td>1.00</td>
</tr>
</tbody>
</table>

#### Suitability Requirements

- **Resolution:**
  
  NLT 3 between omeprazole related compound A and omeprazole

- **Relative retention time (RRT):**
  
  0.8 for omeprazole related compound A and 1.0 for omeprazole
Related substances data (organic impurities)
Esomeprazole Magnesium USP Monograph Methods

Chromatographic Conditions
UHPLC with a porous, particle-packed column:

Column: Purospher® STAR RP-8 endcapped (2 µm) 100 x 2.1 mm (Catalogue Number 1.50629)
Injection: 5 µL
Detection: UV 280 nm
Cell: 2.5 µL
Flow rate: 0.3 mL/min
Mobile phase: Acetonitrile and Buffer (27:73 v/v)
Buffer: Dissolve 0.725 g of monobasic sodium phosphate and 4.472 g of anhydrous dibasic sodium phosphate in 1,000 mL of water. If necessary, adjust with phosphoric acid to a pH of 7.6.
Temperature: Ambient
Diluent: Mobile phase
System suitability solution: Dissolve 1.0 mg each of USP Omeprazole and USP Omeprazole Related Compound A in 25 mL of Diluent.
Sample solution: Dissolve 4.0 mg of sample in 25 mL of Diluent.
Pressure drop: 300 Bar (4,350 psi)

Method transfer is possible because of isocratic conditions in the method.

Alternative column chemistry and geometry: 150 x 4.6 mm L7 packing
We used a 100 x 2.1 mm L7 packing column (with a scaling factor of 7.2 in volume). We have modified the Mobile phase composition, flow rate, and injection volume within the allowed ranges. The analytical data meet the system suitability requirements.
Suitability Requirements

- Resolution:
  NLT 3 between omeprazole related compound A and omeprazole

- Relative retention time (RRT):
  0.8 for omeprazole related compound A and 1.0 for omeprazole

Chromatographic Data (System Suitability Solution):

<table>
<thead>
<tr>
<th>Compound</th>
<th>Retention time (min)</th>
<th>Resolution</th>
<th>RRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omeprazole related compound A</td>
<td>3.5</td>
<td>-</td>
<td>0.85</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>4.1</td>
<td>4.2</td>
<td>1.00</td>
</tr>
</tbody>
</table>
Chromatographic Conditions

HPLC with a HighResolution monolithic column and alternative packing:

**Column:** Chromolith® HighResolution RP-18 endcapped 100 x 4.6 mm (Catalogue Number 1.52022)

**Injection:** 20 µL

**Detection:** UV 280 nm

**Cell:** 10 µL

**Flow rate:** 1.0 mL/min

**Mobile phase:** Acetonitrile and Buffer (25:75 v/v)

**Buffer:** Dissolve 0.725 g of monobasic sodium phosphate and 4.472 g of anhydrous dibasic sodium phosphate in 1,000 mL water. If necessary, adjust with phosphoric acid to a pH of 7.6.

**Temperature:** Ambient

**Diluent:** Mobile phase

System suitability solution:

Dissolve 1.0 mg each of USP Omeprazole and USP Omeprazole Related Compound A in 25 mL of Diluent.

Sample solution:

Dissolve 4.0 mg of sample in 25 mL of Diluent.

Pressure drop: 50 Bar (725 psi)

Method transfer is possible because of isocratic conditions in the method.

Alternative column chemistry and geometry: 150 x 3.9 mm (4 µm particle) L1 packing

We used a 150 x 4.6 mm L1 packing column with a monolithic backbone. We have modified the Mobile phase composition and reduced the injection volume within the allowed ranges. The acquired analytical data meet the system suitability requirements.
Suitability Requirements

- **Resolution:**
  NLT 3 between omeprazole related compound A and omeprazole

- **Relative retention time (RRT):**
  0.8 for omeprazole related compound A and 1.0 for omeprazole

### Chromatographic Data (System Suitability Solution):

<table>
<thead>
<tr>
<th>Compound</th>
<th>Retention time (min)</th>
<th>Resolution</th>
<th>RRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omeprazole related compound A</td>
<td>4.6</td>
<td>-</td>
<td>0.82</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>5.6</td>
<td>4.7</td>
<td>1.00</td>
</tr>
</tbody>
</table>
Identification and Assay
Esomeprazole Delayed-Release Capsules USP Monograph Methods

Identification
A. Enantiomeric purity (not performed, as it requires a chiral column [100 x 4.0 mm (5 µm) packing L41] that was not available at the time of testing)

Assay—HPLC

Buffer: Prepare a phosphate buffer with a pH of 7.3 by mixing 10.5 mL of 1.0 M monobasic sodium phosphate buffer and 60 mL of 0.5 M dibasic sodium phosphate buffer, and dilute with water to 1,000 mL.

Diluent: Prepare as directed in Identification Test A.

Mobile phase: Mix 350 mL of acetonitrile and 500 mL of Buffer. Dilute with water to 1,000 mL.

Standard solution: Transfer 10 mg of USP Omeprazole to a 250-mL volumetric flask, and dissolve in about 10 mL of alcohol. Add 40 mL of Diluent, and dilute with water to volume. This solution contains 0.04 mg/mL of USP Omeprazole.

Sample stock solution: Mix the contents of NLT 20 capsules. Transfer a portion of the capsule content, equivalent to 20 mg of esomeprazole, to a 100-mL volumetric flask, add 60 mL of Diluent, and shake for 20 min to dissolve the pellets. Sonicate for a few minutes, if needed, to completely dissolve. Add 20 mL of alcohol and sonicate for a few minutes. Cool and dilute with Diluent to volume. Pass a portion of the solution through a filter of 1 µm pore size.

Sample solution: Dissolve 0.04 mg/mL of esomeprazole from the Sample stock solution in water. Protect from light.

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

Detector: UV 302 nm
Column: 4.6 mm × 15 cm (5 µm) packing L1
Flow rate: 1 mL/min
Injection volume: 20 µL

System Suitability
Sample: Standard solution
Assay and Dissolution Testing
Esomeprazole Delayed-Release Capsules USP Monograph Methods

Suitability Requirements

- Relative standard deviation: NMT 2.0%

Analysis

Samples: Standard solution and Sample solution
Calculate the percentage of the labeled amount of esomeprazole (C_{17}H_{19}N_{3}O_{3}S) in the portion of the capsules taken:

Result = (rU/rS) \times (CS/CU) \times 100

rU = peak response from the Sample solution
rS = peak response from the Standard solution
CS = concentration of USP Omeprazole in the Standard solution (mg/mL)
CU = nominal concentration of esomeprazole in the Sample solution (mg/mL)

Acceptance criteria: 90.0%–110.0%

Dissolution—HPLC <711>

Test 1.

Medium: 0.1 N hydrochloric acid; 300 mL. After 2 h, continue with a pH 6.8 phosphate buffer as follows. To the vessel, add 700 mL of 0.086 M dibasic sodium phosphate, and adjust with 2 N hydrochloric acid or 2 N sodium hydroxide, if necessary, to a pH of 6.8 ± 0.05.

Apparatus 2: 100 rpm

Time: 30 min in a pH 6.8 phosphate buffer

Standard solution: Prepare a solution containing 2 mg/mL of USP Omeprazole in alcohol. Dilute this solution with pH 6.8 phosphate buffer to obtain a solution containing (L/1,000) mg/mL, where L is the label claim, in mg/capsule. Immediately add 2.0 mL of 0.25 M sodium hydroxide to 10.0 mL of this solution, and mix. Note: Do not allow the solution to stand before adding the sodium hydroxide solution.

Sample solution: After 30 min in pH 6.8 phosphate buffer, pass a portion of the solution under test through a suitable filter. Transfer 5.0 mL of the filtrate to a suitable glassware containing 1.0 mL of 0.25 M sodium hydroxide. Mix well. Protect from light.

Buffer, Mobile phase, System suitability, and Chromatographic system: Proceed as directed in the Assay.
Dissolution Testing and Organic Impurities
Esomeprazole Delayed-Release Capsules USP Monograph Methods

Analysis
Samples: Standard solution and Sample solution
Calculate the percentage of esomeprazole (C_{17}H_{19}N_{3}O_{3}S) dissolved:

Result = (rU/rS) \times (CS/L) \times V \times 100

rU = peak response from the Sample solution
rS = peak response from the Standard solution
CS = concentration of the Standard solution (mg/mL)
L = label claim (mg/capsule); V = volume of Medium, 1,000 mL

Tolerances: NLT 75% of the labeled amount of esomeprazole (C_{17}H_{19}N_{3}O_{3}S) is dissolved.

IMPURITIES
Organic Impurities—HPLC
Buffer: Prepare a pH 7.6 phosphate buffer by mixing 5.2 mL of 1.0 M monobasic sodium phosphate buffer and 63 mL of 0.5 M dibasic sodium phosphate buffer and diluting with water to 1,000 mL.

Solution A: Mix 100 mL of acetonitrile and 100 mL of Buffer. Dilute with water to 1,000 mL.

Solution B: Mix 800 mL of acetonitrile and 10 mL of Buffer. Dilute with water to 1,000 mL.

Mobile phase: See table above.

Diluent: Prepare as directed in Identification Test A.

System suitability stock solution: 1 mg/mL each of USP Omeprazole and USP Omeprazole Related Compound A in methanol

System suitability solution: 1 \mu g/mL each of USP Omeprazole and USP Omeprazole Related Compound A, from the System suitability stock solution, in a mixture of Diluent and water (1:4)

Sample solution: Transfer a portion of the powdered pellets (about 80–90 mg), from the capsule content, to a 200-mL volumetric flask, add 20 mL of methanol, and shake for 30 seconds. Add 40 mL of Diluent, shake for 30 seconds by hand, and sonicate for a few minutes. Cool and dilute with water to volume. Pass a portion of the solution through a filter of 0.45 \mu m pore size. Note: The solution is stable for 3 h if stored protected from light.
**Impurity Table**

<table>
<thead>
<tr>
<th>Name</th>
<th>RRT</th>
<th>Acceptance criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omeprazole sulfone</td>
<td>0.93</td>
<td>0.5</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>1.0</td>
<td>-</td>
</tr>
<tr>
<td>Any other individual impurity</td>
<td>-</td>
<td>0.2</td>
</tr>
<tr>
<td>Total impurities</td>
<td>-</td>
<td>2</td>
</tr>
</tbody>
</table>

**Acceptance criteria:** See the Impurity Table.

**ADDITIONAL REQUIREMENTS**

**Packaging and storage:** Preserve in tight containers. Store at room temperature.

**USP Reference Standards**

- USP Omeprazole
- USP Omeprazole Related Compound A (omeprazole sulfone; 5-Methoxy-2-\{[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]sulfonyl\}-1H-benzo[d]imidazole; C_{17}H_{19}N_{3}O_{4}S)

15-Methoxy-2\{[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]sulfonyl\}-1H-benzo[d]imidazole

**Chromatographic System** (See USP General Chapter 621, Chromatography, System Suitability.)

- Detector: UV 302 nm
- Column: 4.6 mm x 10 cm (3 µm) packing L1
- Flow rate: 1 mL/min
- Injection size: 20 µL

**System Suitability**

**Sample:** System suitability solution

*Note: See table for the relative retention times.*

**Suitability Requirements**

- **Resolution:** NLT 2.5 between omeprazole related compound A and omeprazole

**Analysis**

**Sample:** Sample solution

Calculate the percentage of any individual impurity in the portion of the capsules taken:

**Result** = \(r_{U}/r_{T}\) x 100

\(r_{U}\) = peak response for each impurity
\(r_{T}\) = sum of all peak responses
**organic impurities data**

**Esomeprazole Delayed-Release Capsules USP Monograph Methods**

**Chromatographic Conditions**

<table>
<thead>
<tr>
<th></th>
<th>Time (min)</th>
<th>Solution A (%)</th>
<th>Solution B (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>80</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>0</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>31</td>
<td>100</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>45</td>
<td>100</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

**Column:** Purospher® STAR RP-18 endcapped (3 µm) 100 x 4.6 mm (Catalogue Number 1.50469)

**Injection:** 20 µL

**Detection:** UV 302 nm

**Cell:** 10 µL

**Flow rate:** 1.0 mL/min

**Buffer:** Prepare a pH 7.6 phosphate buffer by mixing 5.2 mL of 1.0 M monobasic sodium phosphate buffer and 63 mL of 0.5 M dibasic sodium phosphate buffer, and dilute with water to 1,000 mL.

**Mobile phase**

**Solution A:** Mix 100 mL of acetonitrile and 100 mL of Buffer. Dilute with water to 1,000 mL.

**Solution B:** Mix 800 mL of acetonitrile and 10 mL of Buffer. Dilute with water to 1,000 mL.

**Gradient:** See table.

**Temperature:** 25 °C

**Diluent:** Prepare a pH 11.0 diluent as follows. Dissolve 5.24 g of tribasic sodium phosphate dodecahydrate in water. Add 110 mL of 0.5 M dibasic sodium phosphate solution, and dilute with water to 1,000 mL.

**Standard solution:** Dissolve 1 µg/mL each of USP Omeprazole and USP Omeprazole Related Compound A in methanol.

**Sample solution:** Transfer a portion of the powdered pellets (about 80–90 mg) from the capsule content to a 200 mL volumetric flask, add 20 mL of methanol, and shake for 30 seconds. Add 40 mL of Diluent, shake for 30 seconds by hand, and sonicate for a few minutes. Cool, and dilute with water to volume. Pass a portion of the solution through a filter of 0.45 µm pore size.

**Pressure drop:** 149–95 Bar (2160–1378 psi)
Esomeprazole Delayed-Release Capsules USP Monograph Methods

**Suitability Requirements**

- **Resolution**: NLT 2.5 between omeprazole related compound A and omeprazole
- **Relative retention time (RRT)**: 0.8 for omeprazole related compound A and 1.0 for omeprazole

---

**Chromatographic Data:**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Retention time (min)</th>
<th>RRT</th>
<th>Resolution</th>
<th>Tailing factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impurity A</td>
<td>15.0</td>
<td>0.96</td>
<td>-</td>
<td>1.1</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>15.6</td>
<td>1.00</td>
<td>3.2</td>
<td>1.2</td>
</tr>
</tbody>
</table>

---

**System Suitability Solution (SST)**

**Blank**

---

26 Esomeprazole | November 2017
### Organic Impurities (Sample Analysis)

**Esomeprazole Delayed-Release Capsules USP Monograph Methods**

### Suitability Requirements

- **Resolution**: NLT 2.5 between omeprazole and its related compound A

#### Relative retention time (RRT):

- 0.8 for omeprazole related compound A and 1.0 for omeprazole

### Chromatographic Data:

<table>
<thead>
<tr>
<th>Compound</th>
<th>Retention time (min)</th>
<th>RRT</th>
<th>Resolution</th>
<th>Tailing factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impurity A</td>
<td>15.0</td>
<td>0.96</td>
<td>-</td>
<td>1.1</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>15.6</td>
<td>1.0</td>
<td>3.2</td>
<td>1.2</td>
</tr>
</tbody>
</table>
**Dissolution Testing Data**

**Esomeprazole Delayed-Release Capsules USP Monograph Methods**

**Chromatographic Conditions**

- **Column:** Purospher® STAR RP-18 endcapped (5 µm) 150 x 4.6 mm (Catalogue Number 1.51455)
- **Injection:** 20 µL
- **Detection:** UV 302 nm
- **Cell:** 10 µL
- **Flow rate:** 1.0 mL/min
- **Medium:** 0.1 N hydrochloric acid (HCl); 300 mL. After 2 h, continue with a pH 6.8 phosphate buffer as follows. To the vessel, add 700 mL of 0.086 M dibasic sodium phosphate, and adjust with 2 N HCl or 2 N sodium hydroxide, if necessary, to a pH of 6.8 ± 0.05.
- **Apparatus 2:** 100 rpm (Time: 30 min in a pH 6.8 phosphate buffer)
- **Mobile phase:** Mix 350 mL of acetonitrile and 500 mL of Buffer. Dilute with water to 1,000 mL.
- **Buffer:** Prepare a pH 7.3 phosphate buffer by mixing 10.5 mL of 1.0 M monobasic sodium phosphate buffer and 60 mL of 0.5 M dibasic sodium phosphate buffer, and dilute with water to 1,000 mL. **Temperature:** 25 °C
- **Diluent:** Dissolve 5.24 g of tribasic sodium phosphate dodecahydrate in water. Add 110 mL of 0.5 M dibasic sodium phosphate solution, and dilute with water to 1,000 mL.
- **Standard solution:** Transfer 10 mg of USP Omeprazole to a 250 mL volumetric flask, and dissolve in about 10 mL of alcohol. Add 40 mL of Diluent, and dilute with water to volume.
- **Sample solution:** After 30 min in pH 6.8 phosphate buffer, pass a portion of the test solution through a suitable filter. Transfer 5.0 mL of the filtrate to a suitable glassware containing 1.0 mL of 0.25 M sodium hydroxide. Mix well. Protect from light.
- **Pressure drop:** 149 Bar (2,160 psi)
**Dissolution Testing Data**

Esomeprazole Delayed-Release Capsules USP Monograph Methods

**Peak Purity**

- **UV Analysis**
  - Zero Line
  - Peak
  - Peak Purity
  - mAU
  - nm
  - 0.00
  - 0
  - 200
  - 302
  - 2,000
  - 300
  - 400
  - 500
  - 600
  - 700
  - 800
  - 900
  - 1,000
  - 1,500
  - 2,000
  - 2,500
  - 3,000
  - 3,500
  - 4,000
  - 4,500
  - 5,000
  - 5,500
  - 6,000
  - 6,500
  - 7,000

**Dissolution Testing Data**

- **Esomeprazole Delayed-Release Capsules USP Monograph Methods**
  - Peak Purity
  - UV Analysis
  - mAU
  - nm
Dissolution Testing Data
Esomeprazole Delayed-Release Capsules USP Monograph Methods

Retention time (minutes)

mV

Capsule 1
Capsule 2
Capsule 3
Capsule 4
Capsule 5
Calculate the percentage of esomeprazole dissolved:

\[ \text{Result} = \left( \frac{rU}{rS} \right) \times \frac{CS}{L} \times V \times 100 = 90.1\% \]

- \( rU \) = peak response from the Sample solution
- \( rS \) = peak response from the Standard solution
- \( CS \) = concentration of the Standard solution (mg/mL)
- \( L \) = label claim (mg/capsule)
- \( V \) = volume of Medium, 1,000 mL

**Acceptance criteria:** NLT 75% of the claimed esomeprazole \((C_{17}H_{19}N_{3}O_{3}S)\) is dissolved.
**Chromatographic Conditions**

**Column:** Chromolith® HighResolution RP-18 endcapped 100 x 4.6 mm (Catalogue Number 1.52022)

**Injection:** 5 µL (Note: Linear scaling = 13 µL; but the efficiency is higher than with particle packed column, so we reduced it further.)

**Detection:** UV 302 nm

**Cell:** 10 µL

**Flow rate:** 1.0 mL/min

**Medium:**
0.1 N hydrochloric acid (HCl); 300 mL. After 2 h, continue with a pH 6.8 phosphate buffer as follows. To the vessel, add 700 mL of 0.086 M dibasic sodium phosphate, and adjust with 2 N HCl or 2 N sodium hydroxide, if necessary, to a pH of 6.8 ± 0.05.

**Apparatus 2:**
100 rpm (Time: 30 min in a pH 6.8 phosphate buffer)

**Mobile phase:** Prepare a pH 7.3 phosphate buffer by mixing 10.5 mL of 1.0 M monobasic sodium phosphate buffer and 60 mL of 0.5 M dibasic sodium phosphate buffer, and dilute with water to 1,000 mL. Mix 350 mL of acetonitrile and 500 mL of Buffer. Dilute with water to 1,000 mL.

**Temperature:** 25 °C

**Diluent:** Dissolve 5.24 g of tribasic sodium phosphate dodecahydrate in water. Add 110 mL of 0.5 M dibasic sodium phosphate solution, and dilute with water to 1,000 mL.

**Standard solution:** Transfer 10 mg of USP Omeprazole to a 250 mL volumetric flask, and dissolve it in about 10 mL of alcohol. Add 40 mL of *Diluent*, and dilute with water to volume.

**Sample solution:** After 30 min in pH 6.8 phosphate buffer, pass a portion of the solution under test through a suitable filter. Transfer 5.0 mL of the filtrate to a suitable glassware containing 1.0 mL of 0.25 M sodium hydroxide. Mix well. Protect from light.

**Pressure drop:** 75 Bar (1,080 psi)
Dissolution Testing Data

Esomeprazole Delayed-Release Capsules USP Monograph Methods

Standard Solution

Retention time (minutes)

Intensity (mV)

0.0 1.0 2.0 3.0 4.0 5.0

0 25 50 75 100 125 150 175

Retention time (minutes)

Intensity (mV)

0.0 1.0 2.0 3.0 4.0 5.0

0 50 100 150 200 250

Capsule 5
Capsule 4
Capsule 3
Capsule 2
Capsule 1
**Esomeprazole | November 2017**

![Image](image-url)

## Dissolution Testing Data

**Esomeprazole Delayed-Release Capsules USP Monograph Methods**

<table>
<thead>
<tr>
<th>Sample (area units)</th>
<th>Standard (area units)</th>
<th>Standard solution (mg/ml)</th>
<th>Label claim (mg/capsule)</th>
<th>Media volume (ml)</th>
<th>Dissolution (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>671,494</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>91.6</td>
</tr>
<tr>
<td>656,845</td>
<td>751,234</td>
<td>0.041</td>
<td>40</td>
<td>1,000</td>
<td>89.6</td>
</tr>
<tr>
<td>665,258</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>90.8</td>
</tr>
<tr>
<td>658,643</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>89.9</td>
</tr>
<tr>
<td>655,000</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>89.3</td>
</tr>
</tbody>
</table>

Mean 90.2

Calculate the percentage of esomeprazole dissolved:

**Result** = (rU/rS) × (CS/L) × V × 100 = 90.2%

rU = peak response from the *Sample solution*

rS = peak response from the *Standard solution*

CS = concentration of the *Standard solution* (mg/mL)

L = label claim (mg/capsule)

V = volume of *Medium*, 1,000 mL

**Acceptance criteria:** NLT 75% of the claimed esomeprazole (C₁₇H₁₉N₃O₃S) is dissolved.
**Recommended products**

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

**Content of Magnesium—AAS**
- Lanthanum (III) oxide for atomic absorption spectroscopy (Catalogue Number 1.10982)
- Hydrochloric acid 30%—Ultrapur (Catalogue Number 1.01514)
- Water for chromatography—LiChrosolv® (Catalogue Number 1.15333) or fresh water from the Milli-Q® system

**HPLC Assay and Related Substances (API)**
- Purospher® STAR RP-8 endcapped (5 µm) 150 x 4.6 mm (Catalogue Number 1.51453) for HPLC Assay and RS analysis
- Purospher® STAR RP-8 endcapped (2 µm) 100 x 2.1 mm (Catalogue Number 1.50629) for RS analysis
- Chromolith® High Resolution RP-18 endcapped 100 x 4.6 mm (Catalogue Number 1.52022) for RS analysis
- Sodium dihydrogen phosphate dihydrate for analysis—EMSURE® Reag. Ph. Eur. (Catalogue Number 1.06342)
- Di-sodium hydrogen phosphate dihydrate for analysis—EMSURE® (Catalogue Number 1.06580)
- Tri-sodium phosphate dodecahydrate for analysis—EMSURE® ACS, Reag. Ph. Eur. (Catalogue Number 1.06578)
- Ortho-phosphoric acid 85% for analysis—EMSURE® ACS, ISO, Reag. Ph. Eur. (Catalogue Number 1.00573)
- Acetonitrile (isocratic grade for liquid chromatography)—LiChrosolv® (Catalogue Number 1.14291)
- Water for chromatography—LiChrosolv® (Catalogue Number 1.15333) or fresh water from the Milli-Q® system
Recommended products

Water Determination—Karl Fischer <921> - Ia
- CombiTitrant 5 one-component reagent for volumetric KF titration 1 ml & ca. 5 mg H₂O—Aquastar™ (Catalogue Number 1.88005)
- CombiSolvent methanol-free for volumetric KF titration with one component reagents—Aquastar™ (Catalogue Number 1.88008)

HPLC Assay and Related Substances (Delayed-Release Capsules)
- Purospher® STAR RP-18 endcapped (5 µm) 150 x 4.6 mm (Catalogue Number 1.51455) for assay and dissolution testing
- Chromolith® HighResolution RP-18 endcapped 100 x 4.6 mm (Catalogue Number 1.52022)
- Purospher® STAR RP-18 endcapped (3 µm) 100 x 4.6 mm (Catalogue Number 1.50469) for RS analysis
- Sodium dihydrogen phosphate dihydrate for analysis—EMSURE® Reag. Ph. Eur. (Catalogue Number 1.06342)
- Di-sodium hydrogen phosphate dihydrate for analysis—EMSURE® (Catalogue Number 1.06580)
- Acetonitrile (isocratic grade for liquid chromatography)—LiChrosolv® (Catalogue Number 1.14291)
- Acetonitrile (gradient grade for liquid chromatography)—LiChrosolv® Reag. Ph. Eur. (Catalogue Number 1.00030)
- Water for chromatography—LiChrosolv® (Catalogue Number 1.15333) or fresh water from the Milli-Q® system

Dissolution Testing (Delayed-Release Capsules)
- Hydrochloric acid (fuming 37%) for analysis—EMSURE® ACS, ISO, Reag. Ph. Eur. (Catalogue Number 1.00317)
- Sodium dihydrogen phosphate dihydrate for analysis—EMSURE® Reag. Ph. Eur. (Catalogue Number 1.06342)
- Di-sodium hydrogen phosphate dihydrate for analysis—EMSURE® (Catalogue Number 1.06580)
- Sodium hydroxide solution 50% for analysis—EMSURE® (Catalogue Number 1.58793)
- Water for chromatography—LiChrosolv® (Catalogue Number 1.15333) or fresh water from the Milli-Q® system
- Millex PTFE filter