Citalopram Hydrobromide

C₂₀H₂₁FN₂O · HBr  405.30
5-Isobenzofurancarbonitrile, 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-monohydrobromide; 1-[3-(Dimethylamino)propyl]-1-(p-fluorophenyl)-5-phthalan-carbonitrile monohydrobromide [59729-32-7].

DEFINITION
Citalopram Hydrobromide contains NLT 98.0% and NMT 102.0% of citalopram hydrobromide (C₂₀H₂₁FN₂O · HBr), calculated on the anhydrous basis.

IDENTIFICATION
A. INFRARED ABSORPTION (197K)
B. The retention time of the major peak of the Sample solution corresponds to that of the Standard solution, as obtained in the Assay.
C. IDENTIFICATION TESTS—GENERAL, Bromide (191)
Sample solution: 10 mg/mL of Citalopram Hydrobromide in water
Acceptance criteria: Meets the requirement of the silver nitrate precipitate test.

ASSAY

Change to read:

PROCEDURE
Buffer: Dissolve 1 g of sodium acetate in 800 mL of water, and add 6 mL of triethylamine. Adjust with acet-ric acid to a pH of 4.6, and dilute with water to 1 L.
Mobile phase: Acetonitrile and Buffer (20:80). The apparent pH is 5.0 ± 0.1. Make adjustments, if necessary.
Diluent: Methanol and water (50:50)
Standard solution: 0.625 mg/mL of USP Citalopram Hydrobromide RS in Diluent
Sample solution: 0.625 mg/mL of Citalopram Hydrobromide in Diluent
Chromatographic system
(See Chromatography (621), System Suitability.)
Mode: LC
Detector: UV 239 nm
Column: 4.6-mm × 15-cm; 5-µm packing L7
Column temperature: 50°C
Flow rate: 1 mL/min
Injection volume: 20 µL
Run time: *1.3 times the retention time of citalopram

System suitability
Sample: Standard solution
Suitability requirements
Column efficiency: NLT 3000 theoretical plates
Tailing factor: 0.8–1.5 for citalopram, System suitability solution
Relative standard deviation: NMT 2.0% for citalopram

Analysis
Samples: Diluent, Standard solution, and Sample solution
Verify that there are no interfering peaks, using the Diluent. Calculate the percentage of citalopram hydrobromide (C₂₀H₂₁FN₂O · HBr) in the portion of Citalopram Hydrobromide taken:

\[
\text{Result} = \left( \frac{r_u}{r_s} \right) \times \left( \frac{C_u}{C_s} \right) \times \left( \frac{M_1}{M_2} \right) \times \left( \frac{1}{f} \right) \times 100
\]

\[
r_u = \text{peak response of each impurity from the Sample solution}
\]

\[
r_s = \text{peak response of citalopram from the Standard solution}
\]

\[
C_s = \text{concentration of USP Citalopram Hydrobromide RS in the Standard solution (mg/mL)}
\]

IMPURITIES

A. RESIDUE ON IGNITION (281)
Analysis: Moisten the sample with 2 mL of nitric acid and 5 drops of sulfuric acid.
Acceptance criteria: NMT 0.1%

B. HEAVY METALS, Method II (231): NMT 20 ppm

Change to read:

A. ORGANIC IMPURITIES, Procedure 1

[Note—On the basis of the synthetic route used, perform either Procedure 1 or Procedure 2. However, if the chloro and bromo analogs are potential related compounds in the synthetic route used, Procedure 2 is recommended.]

Buffer, Mobile phase, Diluent, and Sample solution: Proceed as directed in the Assay.
System suitability solution: 1 µg/mL each of USP Citalopram Hydrobromide RS and USP Citalopram Related Compound D RS in Diluent

Acceptance criteria:

- System suitability solution:
  - Resolution: NLT 1.8 between citalopram related compound D and citalopram
  - Tailing factor: 0.8–1.5 for citalopram
  - Relative standard deviation: NMT 5% for citalopram

Signal-to-noise ratio: NLT 3

Analysis
Samples: Diluent, Standard solution, and Sample solution
Verify that there are no interfering peaks, using the Diluent. Calculate the percentage of each impurity in the portion of Citalopram Hydrobromide taken:

\[
\text{Result} = \left( \frac{r_u}{r_s} \right) \times \left( \frac{C_u}{C_s} \right) \times \left( \frac{M_1}{M_2} \right) \times (1/f) \times 100
\]

\[
r_u = \text{peak response of each impurity from the Sample solution}
\]

\[
r_s = \text{peak response of citalopram from the Standard solution}
\]

\[
C_u = \text{concentration of USP Citalopram Hydrobromide RS in the Standard solution (mg/mL)}
\]

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C_U = concentration of Citalopram Hydrobromide in the Sample solution (mg/mL)
M_C = molecular weight of citalopram, 324.39
M_S = molecular weight of citalopram hydrobromide, 405.30
F = relative response factor (see Table 1)

Acceptance criteria: See Table 1.

Table 1

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Relative Response Factor (F)</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram ketone</td>
<td>0.13</td>
<td>0.34</td>
<td>0.1</td>
</tr>
<tr>
<td>Citalopram related compound A</td>
<td>0.18</td>
<td>0.77</td>
<td>0.1</td>
</tr>
<tr>
<td>Citalopram open ring</td>
<td>0.26</td>
<td>0.99</td>
<td>0.1</td>
</tr>
<tr>
<td>Citalopram related compound B</td>
<td>0.40</td>
<td>0.98</td>
<td>0.1</td>
</tr>
<tr>
<td>Citalopram related compound C</td>
<td>0.67</td>
<td>0.69</td>
<td>0.1</td>
</tr>
<tr>
<td>Citalopram related compound D</td>
<td>0.90</td>
<td>1.04</td>
<td>0.1</td>
</tr>
<tr>
<td>Citalopram</td>
<td>1.0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Citalopram related compound E</td>
<td>1.29</td>
<td>0.91</td>
<td>0.1</td>
</tr>
<tr>
<td>Individual unknown impurity</td>
<td>—</td>
<td>1.0</td>
<td>0.1</td>
</tr>
<tr>
<td>Total impurities</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

*The relative response factors provided are for each impurity relative to citalopram (free base).
*4-[(Dimethylamino)-1-{1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-yl]butan-1-one.
*4-[4-[(Dimethylamino)-1-(4-fluorophenyl)-1-hydroxybutyl]-3-(hydroxymethyl)benzonitile.
*1-[(3-Dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrole.
*1-[(3-Dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile-N-oxide.

Change to read:

**ORGANIC IMPURITIES, PROCEDURE 2**

Buffer: To each L of 2.7 g/L of monobasic potassium phosphate in water prepared, add 1 mL of N,N-dimethyloctylamine, and adjust with phosphoric acid to a pH of 3.0.

Solution A: Methanol, tetrahydrofuran, and Buffer (24:6:70)
Solution B: Acetonitrile and Buffer (80:20)

Mobile phase: See Table 2.

<table>
<thead>
<tr>
<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>
</tr>
<tr>
<td>18</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>40</td>
<td>10</td>
<td>90</td>
</tr>
<tr>
<td>45</td>
<td>10</td>
<td>90</td>
</tr>
<tr>
<td>46</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>55</td>
<td>100</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 3

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Relative Response Factor*</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram related compound A</td>
<td>0.40</td>
<td>0.73</td>
<td>0.15</td>
</tr>
<tr>
<td>Citalopram related compound C</td>
<td>0.88</td>
<td>1.7</td>
<td>0.15</td>
</tr>
<tr>
<td>Citalopram</td>
<td>1.0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Citalopram related compound D</td>
<td>1.09</td>
<td>0.93</td>
<td>0.15</td>
</tr>
</tbody>
</table>

*The relative response factors provided are for each impurity relative to Citalopram Hydrobromide.
*This peak is due to the counterion. It is not an impurity and should not be included in the Total impurities.
### Table 3 (Continued)

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Relative Response Factor*</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram related compound G</td>
<td>2.20</td>
<td>1.2</td>
<td>0.15</td>
</tr>
<tr>
<td>Citalopram related compound H</td>
<td>2.30</td>
<td>1.1</td>
<td>0.15</td>
</tr>
<tr>
<td>Individual unspecified impurity</td>
<td></td>
<td></td>
<td>0.1</td>
</tr>
<tr>
<td>Total impurities</td>
<td></td>
<td></td>
<td>0.75</td>
</tr>
</tbody>
</table>

*The relative response factors provided are for each impurity relative to Citalopram hydrobromide.

### SPECIFIC TESTS

- **Optical Rotation, Specfic Rotation (781S)**
  - Sample solution: 25 mg/mL of Citalopram Hydrobromide in methanol
  - Acceptance criteria: −0.2° to +0.2° at 20°

- **pH (791)**
  - Sample solution: 5 mg/mL of Citalopram Hydrobromide in water
  - Acceptance criteria: 5.5–6.5

- **Water Determination, Method I (921)**
  - Sample: 250 mg of Citalopram Hydrobromide
  - Acceptance criteria: NMT 0.5%

- **Completeness of Solution**
  - Blank: 96% alcohol
  - Sample solution: 25 mg/mL of Citalopram Hydrobromide in 96% alcohol
  - Analytical wavelength: 410 nm
  - Acceptance criteria: Absorbance is NMT 0.040 in a 1-cm quartz cell

### ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in well-closed containers, and store at controlled room temperature.

- **Labeling:** If a procedure for Organic Impurities other than Procedure 1 is used, then the labeling states with which Organic Impurities procedure the article complies.

### Change to read:

- **USP Reference Standards (11)**
  - USP Citalopram Hydrobromide RS
  - USP Citalopram Related Compound A RS
  - USP Citalopram Related Compound C RS
  - USP Citalopram Related Compound D RS

- **PH (791)**
  - Sample solution: 5 mg/mL of Citalopram Hydrobromide in water
  - Acceptance criteria: 5.5–6.5

- **Water Determination, Method I (921)**
  - Sample: 250 mg of Citalopram Hydrobromide
  - Acceptance criteria: NMT 0.5%

- **Completeness of Solution**
  - Blank: 96% alcohol
  - Sample solution: 25 mg/mL of Citalopram Hydrobromide in 96% alcohol
  - Analytical wavelength: 410 nm
  - Acceptance criteria: Absorbance is NMT 0.040 in a 1-cm quartz cell

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