Atomoxetine Capsules

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Expert Committee: Chemical Medicines Monographs 4
Reason for Revision: Compliance

In accordance with the Rules and Procedures of the 2015–2020 Council of Experts, the Chemical Medicines Monographs 4 Expert Committee has revised the Atomoxetine Capsules monograph. The purpose for the revision is to accommodate FDA-approved drug products with slightly different dissolution conditions (no deaeration of the Medium and use of different sinkers).

The Atomoxetine Capsules Revision Bulletin replaces the version that is scheduled to become official on May 1, 2020. Please note that General Notices, 3.10 Applicability of Standards discusses early adoption. For questions regarding compliance, please consult your relevant regulatory authority.

Should you have any questions, please contact Heather Joyce, Senior Scientific Liaison (301-998-6792 or hrj@usp.org).
Atomoxetine Capsules

**DEFINITION**
Atomoxetine Capsules contain NLT 90.0% and NMT 110.0% of the labeled amount of atomoxetine (C₈H₁₇NO).

**IDENTIFICATION**

**Change to read:**

- A. **SPECTROSCOPIC IDENTIFICATION TESTS** (197), **Infrared Spectroscopy:** 197K or 197A *(CN 1-May-2020)*

**Standard:** 6 mg/mL of USP Atomoxetine Hydrochloride RS in methanol. Dry the solution to a dry powder under an air or nitrogen purge for a minimum of 3 h.

**Sample:** Shake the contents of a sufficient number of Capsules, equivalent to about 60 mg of atomoxetine, with 10 mL of methanol. Centrifuge at 4000 rpm for 5 min. Evaporate the solution to a dry powder with the aid of a current of air or stream of nitrogen.

**Acceptance criteria:** The IR spectrum exhibits main bands at (±2) wavenumbers (cm⁻¹) 2955, 2855, 1599–1604, 1492, 1048, 1023, and 1010.

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

**ASSAY**

**PROCEDURE**

**Buffer:** 5.8 g/L of monobasic potassium phosphate in water. To each liter of this solution add 3.0 mL of triethylamine, and adjust with phosphoric acid to a pH of 2.5.

**Mobile phase:** Acetonitrile and Buffer (38:62)

**System suitability solution:** 0.1 mg/mL of atomoxetine (free base) from USP Atomoxetine Hydrochloride RS and 0.02 mg/mL of o-cresol in Mobile phase. Sonicate to aid in dissolution.

**Standard solution:** 0.1 mg/mL of atomoxetine (free base) from USP Atomoxetine Hydrochloride RS in Mobile phase. Sonicate to aid in dissolution.

**Sample stock solution:** From NLT 10 Capsules (including shells) prepared as follows. Add the intact Capsules to a suitable volumetric flask. Add Mobile phase to fill 65% of the final volume. Allow to stand for at least 10 min, then shake for 20 min. Dilute with Mobile phase to volume.

**Sample solution:** Nominally 0.1 mg/mL of atomoxetine, prepared by diluting a suitable volume of Sample stock solution with Mobile phase

**Chromatographic system**

(See Chromatography (621), System Suitability.)

**Mode:** LC

**Detector:** UV 220 nm

**Column:** 4.6-mm × 7.5-cm; 3.5-µm packing L7

**Column temperature:** 35°

**Flow rate:** 1.5 mL/min

**Injection volume:** 10 µL

**Run time:** 1.7 times the retention time of atomoxetine

**System suitability**

**Samples:** System suitability solution and Standard solution

[Note—The relative retention times for atomoxetine and o-cresol are 1.0 and 1.3, respectively.]

**Suitability requirements**

**Resolution:** NLT 3.5 between atomoxetine and o-cresol, System suitability solution

**Tailing factor:** NMT 2.0 for atomoxetine, System suitability solution

**Relative standard deviation:** NMT 1.0% for atomoxetine, Standard solution

**Analysis**

**Samples:** Standard solution and Sample solution

Calculate the percentage of the labeled amount of atomoxetine (C₈H₁₇NO) in the portion of Capsules taken:

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

\(r_u\) = peak response from the Sample solution

\(r_s\) = peak response from the Standard solution

\(C_s\) = concentration of atomoxetine in the Standard solution (mg/mL)

\(C_u\) = nominal concentration of atomoxetine in the Sample solution (mg/mL)

**Acceptance criteria:** 90.0%–110.0%

**PERFORMANCE TESTS**

**Change to read:**

- **Dissolution** (711)

**Medium:** 0.1 N hydrochloric acid; 1000 mL, deaerated, if needed *(RB 1-May-2020)*

**Apparatus 2:** 50 rpm, with suitable *(RB 1-May-2020)* sinker Time: 30 min

**Buffer and Mobile phase:** Prepare as directed in the **Assay**.

**Standard stock solution:** 0.1 mg/mL of atomoxetine (free base) from USP Atomoxetine Hydrochloride RS in Medium. Sonicate to aid in dissolution.

**Standard solution:** Dilute the Standard stock solution with Medium to obtain a final concentration of (L/1000) mg/mL, where L is the Capsule label claim in mg.

**Sample solution:** Pass a portion of the solution under test through a suitable filter.

**Chromatographic system:** Proceed as directed in the **Assay**.

**System suitability**

**Sample:** Standard solution

**Suitability requirements**

**Tailing factor:** NMT 2.0

**Relative standard deviation:** NMT 1.4%

**Analysis**

**Samples:** Standard solution and Sample solution

Calculate the percentage of the labeled amount of atomoxetine (C₈H₁₇NO) dissolved:

\[
\text{Result} = \left( \frac{r_u}{r_s} \right) \times \left( \frac{C_s}{L} \right) \times V \times 100
\]

\(r_u\) = peak response from the Sample solution

\(r_s\) = peak response from the Standard solution

\(C_s\) = concentration of atomoxetine in the Standard solution (mg/mL)

\(L\) = label claim (mg/Capsule)

\(V\) = volume of Medium (mL)

**Tolerances:** NLT 80% (Q) of the labeled amount of atomoxetine (C₈H₁₇NO) is dissolved.

**UNIFORMITY OF DOSAGE UNITS** (905): Meet the requirements

**IMPURITIES**

- **Organic impurities**

**Buffer:** Dissolve 4.9 g of sodium 1-decanesulfonate and 6.9 g of monobasic potassium phosphate in 1 L of water. Adjust with phosphoric acid to a pH of 3.1.

**Mobile phase:** Acetonitrile and Buffer (41:59)

**Sensitivity solution:** 0.1 µg/mL of atomoxetine in Mobile phase

**System suitability solution:** 1 mg/mL of atomoxetine containing atomoxetine N-amide prepared as follows.

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Weigh equal amounts of USP Atomoxetine Hydrochloride RS and urea, and place in a volumetric flask. Add water to fill 10% of the final volume. Sonicate for 3 min. Place the flask in an 85° oven for 40 min. Allow the solution to cool to room temperature. Dilute with Mobile phase to volume. [Note—The oven temperature and time in the oven can be adjusted to give a suitable level of atomoxetine N-amide peak.]

Sample solution: 1 mg/mL of atomoxetine in Mobile phase, from the contents of NLT 5 Capsules prepared as follows.
Transfer the Capsule contents to a suitable volumetric flask. Fill 50% of the final volume with Mobile phase. Swirl, and let stand for 15 min. Dilute with Mobile phase to volume.

Chromatographic system
(See Chromatography (621), System Suitability.)
Mode: LC
Detector: UV 215 nm
Column: 4.6-mm × 15-cm; 3.5-µm packing L7
Column temperature: 30°
Flow rate: 1 mL/min
Injection volume: 10 µL
Run time: 2.3 times the retention time of atomoxetine

System suitability
Samples: Sensitivity solution and System suitability solution
[Note—See Table 1 for the relative retention times.]

Suitability requirements
Resolution: NLT 2.6 between atomoxetine and atomoxetine N-amide, System suitability solution
Relative standard deviation: NMT 5%, Sensitivity solution

Analysis
Sample: Sample solution
Calculate the percentage of each individual impurity in the portion of Capsules taken:

Result = \( \frac{r_u}{r_t} \times 100 \)

\( r_u \) = peak response of each individual impurity from the Sample solution
\( r_t \) = sum of all the peak responses from the Sample solution

Acceptance criteria: See Table 1.

Table 1
<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desmethyl atomoxetine*</td>
<td>0.76</td>
<td>0.3</td>
</tr>
<tr>
<td>Atomoxetine</td>
<td>1.0</td>
<td>—</td>
</tr>
<tr>
<td>Atomoxetine N-amide*</td>
<td>1.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Any individual unspecified degradation product</td>
<td>—</td>
<td>0.2</td>
</tr>
<tr>
<td>Total impurities</td>
<td>—</td>
<td>1.0</td>
</tr>
</tbody>
</table>

* (R)-N-Methyl-3-phenoxy-3-phenylpropan-1-amine.
* (R)-1-Methyl-1-[3-phenyl-3-(o-tolyloxy)propyl]urea.

ADDITIONAL REQUIREMENTS
• Packaging and Storage: Preserve in well-closed containers. Store at controlled room temperature.
• USP Reference Standards (11):
  USP Atomoxetine Hydrochloride RS

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