Oxcarbazepine Oral Suspension

Type of Posting  Revision Bulletin
Posting Date     28-Jul-2021
Official Date   29-Jul-2021
Expert Committee Small Molecules 4

In accordance with the Rules and Procedures of the Council of Experts, the Small Molecules 4 Expert Committee has revised the Oxcarbazepine Oral Suspension monograph. The purpose of this revision is to add Dissolution Test 2 to accommodate FDA-approved drug products with different dissolution conditions and/or tolerances than the existing dissolution test(s). A Labeling section has also been added to support the inclusion of Dissolution Test 2.

- **Dissolution Test 2** was validated using the Nucleosil CN brand of column with L10 packing. The typical retention time for oxcarbazepine is about 6.5 min.

The Oxcarbazepine Oral Suspension Revision Bulletin supersedes the currently official monograph.

Should you have any questions, please contact Claire Chisolm, Senior Scientist II (301-230-3215 or cnc@usp.org).
Oxcarbazepine Oral Suspension

**DEFINITION**
Oxcarbazepine Oral Suspension contains NLT 95.0% and NMT 105.0% of the labeled amount of oxcarbazepine ($C_{15}H_{12}N_2O_2$).

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

**ASSAY**

**PROCEDURE**
Protect all solutions from light.

**Buffer:** Dissolve 1.36 g of *sodium acetate trihydrate* and 0.6 g of *glacial acetic acid* in 1 L of *water*. Adjust with *glacial acetic acid* to a pH of 4.4.

**Solution A:** *Acetonitrile*, *tetrahydrofuran*, *tert-butyl methyl ether*, and *Buffer* (130:30:9:830)

**Solution B:** *Acetonitrile*, *tetrahydrofuran*, *tert-butyl methyl ether*, and *Buffer* (670:30:9:290)

**Mobile phase:** See *Table 1*.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Solution A (%)</th>
<th>Solution B (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>93</td>
<td>7</td>
</tr>
<tr>
<td>2</td>
<td>90</td>
<td>10</td>
</tr>
<tr>
<td>10</td>
<td>90</td>
<td>10</td>
</tr>
<tr>
<td>25</td>
<td>10</td>
<td>90</td>
</tr>
<tr>
<td>26</td>
<td>93</td>
<td>7</td>
</tr>
<tr>
<td>35</td>
<td>93</td>
<td>7</td>
</tr>
</tbody>
</table>

**Diluent:** Dissolve 0.1 g of *ascorbic acid* and 1 mL of *acetonitrile* in 1 L of *water*.

**Standard stock solution:** 1 mg/mL of *USP Oxcarbazepine RS* in *acetonitrile*. Sonicate to aid in dissolution.

**Standard solution:** 0.25 mg/mL of *USP Oxcarbazepine RS* from the *Standard stock solution*, prepared as follows. Dilute a suitable volume of the *Standard stock solution* first with *Diluent*, using 70% of the
final volume. Allow the solution to equilibrate to room temperature, and then dilute with acetonitrile to volume.

**System suitability stock solution:** 0.01 mg/mL of USP Oxcarbazepine Related Compound A RS and 0.02 mg/mL of USP Oxcarbazepine Related Compound C RS in acetonitrile

**System suitability solution:** 0.5 µg/mL of USP Oxcarbazepine Related Compound A RS and 1 µg/mL of USP Oxcarbazepine Related Compound C RS from the System suitability stock solution, in Standard solution

**Sample solution:** 0.25 mg/mL of oxcarbazepine from a portion of Oral Suspension, prepared as follows. Dissolve first with Diluent using 8% of the final volume, and then fill to 30% of the final volume with acetonitrile. Sonicate for 15 min. Add Diluent to fill to 36% of the final volume. Shake the flask vigorously. Allow the solution to equilibrate to room temperature, and dilute with Diluent to volume.

**Chromatographic system**
(See *Chromatography* (621), *System Suitability*.)

- **Mode:** LC
- **Detector:** UV 254 nm. For Identification B, use a diode array detector in the range of 210–400 nm.
- **Column:** 3.0-mm × 25-cm; 3-µm packing L1
- **Column temperature:** 50°
- **Flow rate:** 0.6 mL/min
- **Injection volume:** 5 µL

**System suitability**

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

[Note—See Table 2 for the relative retention times.]

**Suitability requirements**

- **Resolution:** NLT 1.3 between oxcarbazepine related compound C and oxcarbazepine related compound A, System suitability solution
- **Relative standard deviation:** NMT 1.0%, Standard solution

**Analysis**

**Samples:** Standard solution and Sample solution

Calculate the percentage of the labeled amount of oxcarbazepine \( \text{C}_{15}H_{12}N_{2}O_{2} \) in the portion of Oral Suspension taken:

\[
\text{Result} = \left( \frac{r_U}{r_S} \right) \times \left( \frac{C_S}{C_U} \right) \times 100
\]

- \( r_U \) = peak response of oxcarbazepine from the Sample solution
- \( r_S \) = peak response of oxcarbazepine from the Standard solution
- \( C_S \) = concentration of USP Oxcarbazepine RS in the Standard solution (mg/mL)
- \( C_U \) = nominal concentration of oxcarbazepine in the Sample solution (mg/mL)

**Acceptance criteria:** 95.0%–105.0%

**PERFORMANCE TESTS**

*Change to read:*

- **Dissolution** (711)

- **Test 1** (RB 29-Jul-2021)

  - **Medium:** 1% sodium dodecyl sulfate in water; 890 mL
  - **Apparatus 2:** 75 rpm
Time: 30 min

Analysis: Shake manually a bottle of Oral Suspension for about 20 s. Using a 10-mL syringe, draw 10.0 mL of the Oral Suspension. Attach a long needle to the syringe. Deliver carefully 10.0 mL of Oral Suspension through the needle to the bottom of the vessel containing preheated Medium. Take about 10 mL of the Medium from the vessel to clean the syringe, and transfer it back to the vessel. Start the paddle rotation immediately after introduction of each sample.

Mobile phase: Methanol, glacial acetic acid, and water (24:1:75)

Standard solution: 0.7 mg/mL of USP Oxcarbazepine RS in Medium

Sample solution: Pass a portion of the solution under test through a suitable filter of 1-µm pore size, discarding the first few milliliters.

Chromatographic system
(See Chromatography (621), System Suitability.)

Mode: LC

Detector: UV 310 nm

Column: 4.6-mm × 25-cm; 10-µm packing L10

Column temperature: 30°

Flow rate: 1.5 mL/min

Injection volume: 10 µL

System suitability
Sample: Standard solution

Suitability requirements
Relative standard deviation: NMT 2.0%

Analysis
Samples: Standard solution and Sample solution

Calculate the percentage of the labeled amount of oxcarbazepine (C_{15}H_{12}N_{2}O_{2}) 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 USP Oxcarbazepine RS in the Standard solution (mg/mL)

\[ L \] = label claim (mg in 10 mL)

\[ V \] = volume of Medium, 900 mL

Tolerances: NLT 80% (Q) of the labeled amount of oxcarbazepine (C_{15}H_{12}N_{2}O_{2}) is dissolved.

Test 2: If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 2.

Medium: 7.5 g/L of sodium dodecyl sulfate in water; 890 mL, deaerated

Apparatus 2: 75 rpm

Time: 15 min

Mobile phase: Methanol, glacial acetic acid, and water (24:1:75)

Standard solution: 0.7 mg/mL of USP Oxcarbazepine RS prepared as follows. Transfer a suitable amount of USP Oxcarbazepine RS to a suitable volumetric flask. Add 20% of the final volume of acetonitrile and sonicate for 10 min with frequent vortexing. Add 50% of the final volume of Medium and sonicate again for 10 min with frequent vortexing. Make sure USP Oxcarbazepine RS is fully dissolved at room temperature. If not fully dissolved, sonicate for an additional 10 min or until
completely dissolved. Dilute with *Medium* to volume and mix well. Pass a portion of the solution through a suitable filter of 1-μm pore size, discarding the first few milliliters. [Note—Immediately keep it at 10° for the *Analysis*. This solution is stable for 24 h at 10°.]

**Sample solution:** Use a separate bottle of Oral Suspension for each vessel. After the dissolution *Medium* has reached the appropriate temperature, remove about 10 mL of heated *Medium* from each vessel and set aside for cannula rinsing after sample introduction. Shake manually a bottle of Oral Suspension for about 20 s. Using a 10-mL syringe, draw 10.0 mL of the Oral Suspension. Wipe the syringe with paper towels to remove excess Oral Suspension that may stick to the outside of the syringe. Attach a suitable cannula to the syringe. Deliver carefully 10.0 mL of Oral Suspension through the cannula to the bottom of the vessel. Start the paddle rotation immediately after introduction of each sample. Rinse the cannula into the vessel with 10 mL of the previously removed *Medium*. Pass a portion of the solution under test through a suitable filter of 1-μm pore size, discarding the first few milliliters. [Note—The plunger of the syringe should be pushed at a consistent rate and sample delivery should be completed in about 15 s.]

**Chromatographic system**

(See *Chromatography* (621), *System Suitability*.)

- **Mode:** LC
- **Detector:** UV 310 nm
- **Column:** 4.6-mm × 25-cm; 10-μm packing L10

**Temperatures**

- **Autosampler:** 10°
- **Column:** 30°

- **Flow rate:** 1.5 mL/min
- **Injection volume:** 10 μL
- **Run time:** NLT 2 times the retention time of oxcarbazepine

**System suitability**

- **Sample:** *Standard solution*

**Suitability requirements**

- **Tailing factor:** NMT 2.5
- **Relative standard deviation:** NMT 2.0%

**Analysis**

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

Calculate the percentage of the labeled amount of oxcarbazepine \((C_{15}H_{12}N_{2}O_{2})\) dissolved:

\[
\text{Result} = \left( \frac{r_U}{r_S} \right) \times \left( \frac{C_S}{L} \right) \times \frac{1}{V} \times 100
\]

- \(r_U\) = peak response of oxcarbazepine from the *Sample solution*
- \(r_S\) = peak response of oxcarbazepine from the *Standard solution*
- \(C_S\) = concentration of USP Oxcarbazepine RS in the *Standard solution* (mg/mL)
- \(L\) = label claim (mg in 10 mL)
- \(V\) = volume of *Medium*, 900 mL

**Tolerances:** NLT 80% (\(Q\)) of the labeled amount of oxcarbazepine \((C_{15}H_{12}N_{2}O_{2})\) is dissolved. ▲ (RB 29-Jul-2021)

- **Deliverable Volume** (698): Meets the requirements

**IMPURITIES**
Protect all solutions from light.

**Solution A, Solution B, Mobile phase, Diluent, System suitability solution, Sample solution, and Chromatographic system:** Proceed as directed in the Assay.

**Standard stock solution:** 0.5 mg/mL of USP Carbamazepine RS in acetonitrile. Sonicate to aid in dissolution.

**Standard solution:** 0.5 µg/mL of USP Carbamazepine RS from the Standard stock solution prepared as follows. Dilute a volume of the Standard stock solution first with Diluent, using 70% of the final volume. Cool to room temperature, and dilute with acetonitrile to volume.

**System suitability**

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

**Suitability requirements**

**Resolution:** NLT 1.3 between oxcarbazepine related compound C and oxcarbazepine related compound A peaks, System suitability solution

**Relative standard deviation:** NMT 5.0%, Standard solution

**Analysis**

**Samples:** Standard solution and Sample solution

Calculate the percentage of each individual impurity in the portion of Oral Suspension taken:

\[
\text{Result} = \left( \frac{r_U}{r_S} \right) \times \left( \frac{C_S}{C_U} \right) \times (1/F) \times 100
\]

- \( r_U \) = peak response of each individual impurity from the Sample solution
- \( r_S \) = peak response of carbamazepine from the Standard solution
- \( C_S \) = concentration of USP Carbamazepine RS in the Standard solution (mg/mL)
- \( C_U \) = nominal concentration of oxcarbazepine in the Sample solution (mg/mL)
- \( F \) = relative response factor (see *Table 2* )

**Acceptance criteria:** See *Table 2*.

### Table 2

<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>Acridine carboxylic acid&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.24</td>
<td>11.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Carbamazepinedione&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.65</td>
<td>0.68</td>
<td>0.2</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>1.0</td>
<td>1.0</td>
<td>—</td>
</tr>
<tr>
<td>Oxcarbazepine related compound C</td>
<td>1.33</td>
<td>12.5</td>
<td>0.1</td>
</tr>
<tr>
<td>Oxcarbazepine related compound A&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.38</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>1.66</td>
<td>1.0</td>
<td>—</td>
</tr>
<tr>
<td>Dibenzazepinodione&lt;sup&gt;d&lt;/sup&gt;</td>
<td>1.97</td>
<td>1.1</td>
<td>0.2</td>
</tr>
<tr>
<td>Acridine&lt;sup&gt;e&lt;/sup&gt;</td>
<td>2.49</td>
<td>11.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Name</td>
<td>Relative Retention Time</td>
<td>Relative Response Factor</td>
<td>Acceptance Criteria, NMT (%)</td>
</tr>
<tr>
<td>----------------------------------------------------------------------</td>
<td>-------------------------</td>
<td>--------------------------</td>
<td>----------------------------</td>
</tr>
<tr>
<td>Dibenzazepinone&lt;sup&gt;f&lt;/sup&gt;</td>
<td>2.62</td>
<td>2.9</td>
<td>0.1</td>
</tr>
<tr>
<td>Any unspecified individual degradation product</td>
<td>—</td>
<td>1.0</td>
<td>0.1</td>
</tr>
<tr>
<td>Total impurities</td>
<td>—</td>
<td>—</td>
<td>0.8</td>
</tr>
</tbody>
</table>

<sup>a</sup> Acridine-9-carboxylic acid.
<sup>b</sup> 10,11-Dioxo-10,11-dihydro-5H-dibenzo[b,f]azepine-5-carboxamide.
<sup>c</sup> For system suitability purposes only.
<sup>d</sup> 5H-Dibenzo[b,f]azepine-10,11-dione.
<sup>e</sup> Acridine.
<sup>f</sup> 10(11H)-Oxo-5H-dibenz[b,f]azepine.

**SPECIFIC TESTS**

- **pH** (791): 2.5–3.7
- **Microbial Enumeration Tests** (61) and **Test for Specified Microorganisms** (62): The total aerobic microbial count is NMT 10<sup>2</sup> cfu/mL. The total yeasts and molds count is NMT 10<sup>1</sup> cfu/mL. It meets the requirements of the test for absence of *Escherichia coli*.

**ADDITIONAL REQUIREMENTS**

- **Packaging and Storage:** Store at controlled room temperature.

Add the following:

- **Labeling:** When more than one Dissolution test is given, the labeling states the Dissolution test used only if Test 1 is not used. ▲ (RB 29-Jul-2021)

- **USP Reference Standards** (11):
  - USP Carbamazepine RS
  - USP Oxcarbazepine RS
  - USP Oxcarbazepine Related Compound A RS
  - USP Oxcarbazepine Related Compound C RS
    - C<sub>16</sub>H<sub>12</sub>N<sub>2</sub>O<sub>3</sub> 280.28
  - Acridin-9(10H)-one.
    - C<sub>13</sub>H<sub>9</sub>NO 195.22