Oxcarbazepine Oral Suspension

Type of Posting	Notice of Intent to Revise
Posting Date	25-Jun-2021
Targeted Official Date	To Be Determined, Revision Bulletin
Expert Committee	Small Molecules 4

In accordance with the Rules and Procedures of the Council of Experts and the Pending Monograph Guideline, this is to provide notice that the Small Molecules 4 Expert Committee intends to revise the Oxcarbazepine Oral Suspension monograph.

Based on the supporting data received from a manufacturer awaiting FDA approval, the Expert Committee proposes to add *Dissolution Test 2* to accommodate drug products with different dissolution conditions and tolerances than the existing dissolution test(s). Labeling information has been incorporated to support the inclusion of *Dissolution Test 2*.

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

The proposed revision is contingent on FDA approval of a product that meets the proposed monograph specifications. The proposed revision will be published as a Revision Bulletin and an official date will be assigned to coincide as closely as possible with the FDA approval of the associated product.

See below for additional information about the proposed text.[1]

Should you have any questions, please contact Michael Chang, Principal Scientist (301-230-3217 or mxc@usp.org).

[1] This text is not the official version of a *USP–NF* monograph and may not reflect the full and accurate contents of the currently official monograph. Please refer to the current edition of the *USP–NF* for official text.

USP provides this text to indicate changes that we anticipate will be made official once the product subject to this proposed revision under the Pending Monograph Program receives FDA approval. Once FDA approval is granted for the associated revision request, a Revision Bulletin will be posted that will include the changes indicated herein, as well as any changes indicated in the product's final approval, combined with the text of the monograph as effective on the date of approval. Any revisions made to a monograph under the Pending Monograph Program that are posted without prior publication for comment in the *Pharmacopeial Forum* must also meet the requirements outlined in the USP Guideline on Use of Accelerated Processes for Revisions to the USP–NF.

Notice of Intent to Revise
Official: To Be Determined

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 1

Time (min)	Solution A (%)	Solution B (%)
0	93	7
2	90	10
10	90	10
25	10	90
26	93	7
35	93	7

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 ($C_{15}H_{12}N_2O_2$) in the portion of Oral Suspension taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

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▲ (TBD)

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 ($C_{15}H_{12}N_2O_2$) dissolved:

$$\text{Result} = (r_U/r_S) \times (C_S/L) \times V \times 100$$

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 ($C_{15}H_{12}N_2O_2$) 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 ($C_{15}H_{12}N_2O_2$) dissolved:

$$\text{Result} = (r_U/r_S) \times (C_S) \times (1/L) \times V \times 100$$

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 ($C_{15}H_{12}N_2O_2$) is dissolved. ▲ (TBD)

- **DELIVERABLE VOLUME ⟨698⟩:** Meets the requirements

IMPURITIES

- **ORGANIC 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:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (1/F) \times 100$$

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

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Acridine carboxylic acid[a]	0.24	11.1	0.1
Carbamazepinedione[b]	0.65	0.68	0.2
Oxcarbazepine	1.0	1.0	—
Oxcarbazepine related compound C	1.33	12.5	0.1
Oxcarbazepine related compound A[c]	1.38	—	—
Carbamazepine	1.66	1.0	—
Dibenzazepinodione[d]	1.97	1.1	0.2
Acridine[e]	2.49	11.1	0.1
Dibenzazepinone[f]	2.62	2.9	0.1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Any unspecified individual degradation product	—	1.0	0.1
Total impurities	—	—	0.8

[a] Acridine-9-carboxylic acid.
[b] 10,11-Dioxo-10,11-dihydro-5*H*-dibenzo[*b,f*]azepine-5-carboxamide.
[c] For system suitability purposes only.
[d] 5*H*-Dibenzo[*b,f*]azepine-10,11-dione.
[e] Acridine.
[f] 10(11*H*)-Oxo-5*H*-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 10^2 cfu/mL. The total yeasts and molds count is NMT 10^1 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.▲ (TBD)

- **USP Reference Standards** ⟨11⟩

USP Carbamazepine RS

USP Oxcarbazepine RS

USP Oxcarbazepine Related Compound A RS

N-Formyl-10-oxo-10,11-dihydro-5*H*-dibenzo[*b,f*]azepine-5-carboxamide.

$C_{16}H_{12}N_2O_3$ 280.28

USP Oxcarbazepine Related Compound C RS

Acridin-9(10*H*)-one.

$C_{13}H_9NO$ 195.22

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Not Applicable

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