Carbamazepine Extended-Release Tablets

Type of Posting	Revision Bulletin
Posting Date	27–Dec–2019
Official Date	01–May–2020
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 Carbamazepine Extended-Release Tablets monograph. The purpose for the revision is to add *Dissolution Test 2* to accommodate FDA-approved drug products with different dissolution conditions and tolerances than the existing dissolution test. Additionally, the existing dissolution test is now named *Dissolution Test 1*, the incorrect reference to "*Q*" within *Dissolution Test 1* is removed, and *Labeling* information has been incorporated to support the inclusion of *Dissolution Test 2*.

The Carbamazepine Extended-Release Tablets 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 R. Joyce, Senior Scientific Liaison (301-998-6792 or hrj@usp.org).

Carbamazepine Extended-Release Tablets

DEFINITION

Carbamazepine Extended-Release Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of carbamazepine ($C_{15}H_{12}N_2O$).

IDENTIFICATION

Change to read:

• **A. ▲SPECTROSCOPIC IDENTIFICATION TESTS** ⟨197⟩**,** *Ultraviolet-Visible Spectroscopy***:** 197U▲ (CN 1-May-2020)
Standard solution: 10 µg/mL of USP Carbamazepine RS in methanol
Sample solution: Finely powder 1 Tablet, and quantitatively transfer the powder, with the aid of methanol, to a 100-mL volumetric flask. Add about 70 mL of methanol, and shake by mechanical means for 60 min. Sonicate for 15 min, and dilute with methanol to volume. Allow to stand for 10–15 min. Dilute a portion of the clear solution with methanol to obtain a solution containing about 10 µg/mL of carbamazepine.
Acceptance criteria: Meet the requirements
• **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**
Mobile phase: Methanol, methylene chloride, and water (450:45:600)
Internal standard solution: 600 µg/mL of phenytoin in methanol
Standard stock solution: 200 µg/mL of USP Carbamazepine RS in methanol
Standard solution: 100 µg/mL of carbamazepine from *Standard stock solution* in *Internal standard solution*
System suitability solution: 50 µg/mL of carbamazepine from *Standard solution* in *Internal standard solution*
Sample stock solution A: Nominally 4 mg/mL of carbamazepine from finely powdered Tablets prepared as follows. Finely powder 10 Tablets. Transfer the powder to an appropriate volumetric flask with the aid of methanol. Add 70% of the flask volume of methanol. Shake by mechanical means for 60 min. Sonicate for 15 min, and dilute with methanol to volume. Allow to stand for 10–15 min, and then filter a portion of the supernatant. Use the clear filtrate.
Sample stock solution B: Nominally 0.2 mg/mL of carbamazepine from *Sample stock solution A* in methanol
Sample solution: Nominally 100 µg/mL of carbamazepine from *Sample stock solution B* in *Internal standard solution*
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 230 nm
Columns
Guard: 4.6-mm × 30-mm; 7-µm packing L7
Analytical: 3.9-mm × 30-cm; packing L1
Flow rate: 2 mL/min
Injection volume: 10 µL
System suitability
Sample: *System suitability solution*
[NOTE—The relative retention times for phenytoin and carbamazepine are about 0.8 and 1.0, respectively.]
Suitability requirements
Resolution: NLT 2.8 between phenytoin and carbamazepine
Relative standard deviation: NMT 2.0%
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of carbamazepine ($C_{15}H_{12}N_2O$) in the portion of Tablets taken:

$$\text{Result} = (R_U/R_S) \times (C_S/C_U) \times 100$$

R_U = peak response ratio of carbamazepine to the internal standard from the *Sample solution*
R_S = peak response ratio of carbamazepine to the internal standard from the *Standard solution*
C_S = concentration of USP Carbamazepine RS in the *Standard solution* (µg/mL)
C_U = nominal concentration of carbamazepine in the *Sample solution* (µg/mL)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

• **DISSOLUTION** ⟨711⟩
▲Test 1▲ (RB 1-May-2020)
Medium
For Tablets labeled to contain 100 mg or 200 mg: Water; 900 mL
For Tablets labeled to contain 400 mg: Water; 1800 mL
Apparatus 1: 100 rpm
Times: 3, 6, 12, and 24 h
Standard solution: USP Carbamazepine RS in *Medium*
Sample solution: Filtered portions of the solution under test, diluted with *Medium* if necessary
Instrumental conditions
Mode: UV
Analytical wavelength: The wavelength of maximum absorbance at about 284 nm
Analysis
Samples: *Standard solution* and *Sample solution*
Determine the percentage of the labeled amount of carbamazepine ($C_{15}H_{12}N_2O$) dissolved at each time using the UV absorption.
Tolerances: See *Table 1*.

Table 1

Time (h)	Amount Dissolved
3	10%–35%
6	35%–65%
12	65%–90%
24	NLT 75%

The percentages ▲▲ (RB 1-May-2020) of the labeled amount of carbamazepine ($C_{15}H_{12}N_2O$) dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.
▲Test 2: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.
Medium
For Tablets labeled to contain 100 or 200 mg: Water; 900 mL
For Tablets labeled to contain 400 mg: Water; 1800 mL

Apparatus 2: 100 rpm, with sinkers
Times: 2, 4, 12, and 24 h
Standard stock solution: 0.55 mg/mL of USP Carbamazepine RS in methanol. Sonication may be used to promote dissolution.
Standard solution: 8.8 µg/mL of USP Carbamazepine RS from *Standard stock solution* in *Medium*
Sample stock solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size. Discard the first 3 mL of the filtrate. Replace the portion removed from the solution under test with the same volume of *Medium*.
Sample solution
For Tablets labeled to contain 100 mg: Transfer 2.0 mL of *Sample stock solution* to a 25-mL volumetric flask and dilute with *Medium* to volume.
For Tablets labeled to contain 200 or 400 mg: Transfer 2.0 mL of *Sample stock solution* to a 50-mL volumetric flask and dilute with *Medium* to volume.
Instrumental conditions
(See *Ultraviolet-Visible Spectroscopy* ⟨857⟩.)
Mode: UV
Analytical wavelength: 284 nm
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the concentration (C_i) of carbamazepine ($C_{15}H_{12}N_2O$) in the sample withdrawn from the vessel at each time point (*i*):

$$\text{Result}_i = (A_U/A_S) \times C_S \times D$$

A_U = absorbance from the *Sample solution* at time point *i*
A_S = absorbance from the *Standard solution*
C_S = concentration of USP Carbamazepine RS in the *Standard solution* (mg/mL)
D = dilution factor for the *Sample solution*

Calculate the percentage of the labeled amount of carbamazepine ($C_{15}H_{12}N_2O$) dissolved at each time point (*i*):

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$
$$\text{Result}_2 = [(C_2 \times V) + (C_1 \times V_S)] \times (1/L) \times 100$$
$$\text{Result}_3 = \{(C_3 \times V) + [(C_1 + C_2) \times V_S]\} \times (1/L) \times 100$$
$$\text{Result}_4 = \{(C_4 \times V) + [(C_1 + C_2 + C_3) \times V_S]\} \times (1/L) \times 100$$

C_i = concentration of carbamazepine in the portion of the sample withdrawn at time point *i* (mg/mL)
V = volume of *Medium*, 900 or 1800 mL
L = label claim (mg/Tablet)
V_S = volume of the *Sample solution* withdrawn at each time point and replaced with *Medium* (mL)

Tolerances: See *Table 2*.

Table 2

Time Point (*i*)	Time (h)	Amount Dissolved (for Tablets that contain 100 mg of carbamazepine) (%)	Amount Dissolved (for Tablets that contain 200 or 400 mg of carbamazepine) (%)
1	2	10–30	10–30
2	4	42–62	35–55
3	12	68–88	68–88
4	24	NLT 75	NLT 75

The percentages of the labeled amount of carbamazepine ($C_{15}H_{12}N_2O$) dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.▲ (RB 1-May-2020)

• **Uniformity of Dosage Units** ⟨905⟩**:** Meet the requirements

IMPURITIES

• **Organic Impurities: Procedure 1**
Mobile phase: Methanol, methylene chloride, and water (450:45:600)
System suitability solution: 60 µg/mL of phenytoin and 20 µg/mL of USP Carbamazepine RS in methanol
Standard solution: 4 µg/mL of USP Carbamazepine RS in methanol
Sample solution: Use *Sample stock solution A* from the *Assay*.
Chromatographic system and **System suitability:** Proceed as directed in the *Assay*.
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of each impurity in the portion of Tablets taken:

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

r_U = peak response of each 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 carbamazepine in the *Sample solution* (mg/mL)

Acceptance criteria
Any individual unspecified degradation product: NMT 0.2%

• **Organic Impurities: Procedure 2**
Mobile phase: Methanol, acetonitrile, and water (35:15:50)
System suitability solution: 12.5 µg/mL of iminostilbene and 5.0 µg/mL of USP Carbamazepine RS in methanol
Standard solution: 4 µg/mL of USP Carbamazepine RS in methanol
Sample solution: Use *Sample stock solution A* from the *Assay*.
Chromatographic system: Proceed as directed in the *Assay*.
System suitability
Sample: *System suitability solution*
[Note—The relative retention times for carbamazepine and iminostilbene are about 0.3 and 1.0, respectively.]
Suitability requirements
Resolution: NLT 10.0 between carbamazepine and iminostilbene
Relative standard deviation: NMT 2.0%
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of each impurity in the portion of Tablets taken:

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

r_U = peak response of each 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 carbamazepine in the *Sample solution* (mg/mL)

Acceptance criteria

Any individual unspecified degradation product: NMT 0.2%

Total impurities: NMT 0.5% for all impurities from *Procedure 1* and *Procedure 2*.

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight containers, and store at controlled room temperature.

Add the following:

▲• **LABELING:** The labeling states the *Dissolution* test used only if *Test 1* is not used.▲ (RB 1-May-2020)

- **USP REFERENCE STANDARDS** ⟨11⟩
  USP Carbamazepine RS