Notice of Intent to Revise
Official: To Be Determined

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

- **A. Spectroscopic Identification Tests ⟨197⟩, *Ultraviolet-Visible Spectroscopy*:** 197U

  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

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

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

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

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 70	NLT 70

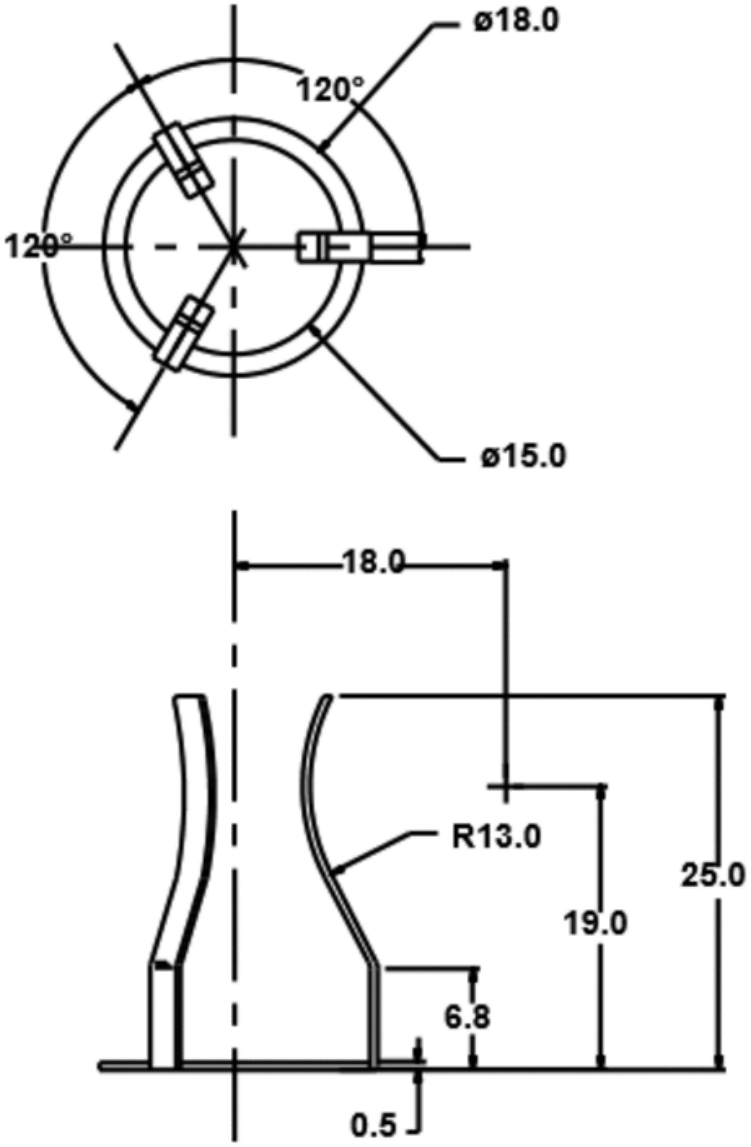
The percentages of the labeled amount of carbamazepine ($C_{15}H_{12}N_2O$) dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.

Test 3: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 3*.

Medium: 5 g/L of sodium dodecyl sulfate in water; 900 mL, deaerated if necessary

Apparatus 1: 100 rpm, with a fixture made of 316 stainless steel to prevent the Tablets from turning during the test (see *Figure 1*).

For Tablets with a release hole, orient the hole facing downward in the basket.



Click image to enlarge

Figure 1. Fixture. All length units are in millimeters.

Times: 3, 6, 12, and 24 h

Standard stock solution: 0.22 mg/mL of USP Carbamazepine RS prepared as follows. Weigh a suitable amount of USP Carbamazepine RS in a suitable volumetric flask. Add methanol to 10% of the flask volume and shake for 10 min to dissolve. Dilute with water to volume.

Standard solution: 0.0088 mg/mL of USP Carbamazepine RS from *Standard stock solution* in *Medium*

Sample solution: At the specified time points, withdraw a suitable volume of the solution under test. Pass through a suitable filter of 0.45-µm pore size, discarding an appropriate volume of filtrate so that a consistent result can be obtained. Dilute with *Medium* to a concentration similar to that of the *Standard solution*.

Instrumental conditions

(See *Ultraviolet-Visible Spectroscopy* ⟨857⟩.)

Mode: UV

Analytical wavelength: 284 nm

Blank: *Medium*

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):

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$

$$\text{Result}_2 = \{[C_2 \times (V - V_S)] + (C_1 \times V_S)\} \times (1/L) \times 100$$

$$\text{Result}_3 = (\{C_3 \times [V - (2 \times V_S)]\} + [(C_2 + C_1) \times V_S]) \times (1/L) \times 100$$

$$\text{Result}_4 = (\{C_4 \times [V - (3 \times V_S)]\} + [(C_3 + C_2 + C_1) \times V_S]) \times (1/L) \times 100$$

C_i = concentration of carbamazepine in the portion of the sample withdrawn at time point i (mg/mL)

V = volume of the *Medium*, 900 mL

L = label claim (mg/Tablet)

V_S = volume of the *Sample solution* withdrawn at each time point from the *Medium* (mL)

Tolerances: See *Table 3*.

Table 3

Time Point (*i*)	Time (h)	Amount Dissolved (%)
1	3	15–40
2	6	42–67
3	12	65–85
4	24	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*.

Test 4: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 4*.

Medium

For Tablets labeled to contain 100 or 200 mg: Water; 900 mL

For Tablets labeled to contain 400 mg: Water; 1800 mL

Apparatus 1: 100 rpm

For Tablets with a release hole, orient the hole facing downward in the basket.

Times: 3, 6, 12, and 24 h

Standard stock solution: 0.22 mg/mL of USP Carbamazepine RS prepared as follows. Transfer a suitable amount of USP Carbamazepine RS to a suitable volumetric flask. Add methanol to 5% of the flask volume. Sonicate to dissolve. Dilute with *Medium* to volume.

Standard solution: 0.011 mg/mL of USP Carbamazepine RS from *Standard stock solution* in *Medium*

Sample stock solution: At the specified time points, withdraw a suitable volume of the solution under test. Pass through a suitable filter of 0.45-µm pore size, discarding an appropriate volume of filtrate so that a consistent result can be obtained. Replace the portion removed from the solution under test with the same volume of *Medium*.

Sample solution

For Tablets labeled to contain 100 mg: Dilute 5 mL of *Sample stock solution* to 50 mL with *Medium*.

For Tablets labeled to contain 200 or 400 mg: Dilute 5 mL of *Sample stock solution* to 100 mL with *Medium*.

Instrumental conditions

(See *Ultraviolet-Visible Spectroscopy* ⟨857⟩.)

Mode: UV

Analytical wavelength: 284 nm

Blank: *Medium*

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):

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$

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

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

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

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 4*.

Table 4

Time Point (*i*)	Time (h)	Amount Dissolved (for Tablets that contain 100 or 200 mg of carbamazepine) (%)	Amount Dissolved (for Tablets that contain 400 mg of carbamazepine) (%)
1	3	10–30	13–33
2	6	40–60	42–62
3	12	65–85	68–88
4	24	NLT 80	NLT 80

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*.

Test 5: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 5*.

Medium

For Tablets labeled to contain 100 or 200 mg: Water; 900 mL, deaerated

For Tablets labeled to contain 400 mg: Water; 1800 mL, deaerated

Apparatus 1: 10-mesh basket, 100 rpm

Use a suitable sinker[1] for Tablets labeled to contain 100 or 200 mg. For Tablets with a release hole, orient the hole facing downward in the basket.

Times: 3, 6, 12, and 24 h

Standard solution

For Tablets labeled to contain 100 mg: 0.11 mg/mL of USP Carbamazepine RS prepared as follows. Transfer a suitable amount of USP Carbamazepine RS to a suitable volumetric flask. Add methanol to 2.5% of the flask volume. Sonicate to dissolve. Dilute with *Medium* to volume.

For Tablets labeled to contain 200 or 400 mg: 0.22 mg/mL of USP Carbamazepine RS prepared as follows. Transfer a suitable amount of USP Carbamazepine RS to a suitable volumetric flask. Add methanol to 5% of the flask volume. Sonicate to dissolve. Dilute with *Medium* to volume.

Sample solution: At the specified time points, withdraw a suitable volume of the solution under test. Pass through a suitable filter of 0.45-µm pore size, discarding an appropriate volume of filtrate so that a consistent result can be obtained.

Instrumental conditions

(See *Ultraviolet-Visible Spectroscopy* ⟨857⟩.)

Mode: UV

Analytical wavelength: 284 nm

Cell

For Tablets labeled to contain 100 mg: 0.2 cm

For Tablets labeled to contain 200 or 400 mg: 0.1 cm

Blank: *Medium*