

## Carbamazepine Tablets

<b>Type of Posting</b>	Notice of Intent to Revise
<b>Posting Date</b>	26-Feb-2021
<b>Targeted Official Date</b>	TBD
<b>Expert Committee</b>	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 Carbamazepine Tablets monograph.

Based on the supporting data received from a manufacturer awaiting FDA approval, the Expert Committee proposes to add *Dissolution Test 4* to accommodate drug products with different dissolution conditions and tolerances than the existing dissolution tests.

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.<sup>1</sup>

Should you have any questions, please contact Yanyin Yang, Scientific Liaison (301-692-3623 or [yanyin.yang@usp.org](mailto:yanyin.yang@usp.org)).

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<sup>1</sup> 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](#).

# Carbamazepine Tablets

## DEFINITION

Carbamazepine Tablets contain NLT 92.0% and NMT 108.0% of the labeled amount of carbamazepine (C<sub>15</sub>H<sub>12</sub>N<sub>2</sub>O).

## IDENTIFICATION

- **A. SPECTROSCOPIC IDENTIFICATION TESTS** (197), *Infrared Spectroscopy*: 197M

**Sample solution:** Nominally 250 mg of carbamazepine from powdered Tablets in 15 mL of [acetone](#)

**Analysis:** Boil the *Sample solution* for 5 min in a suitable beaker. Filter while hot, using two 5-mL portions of hot [acetone](#) to effect transfer. Evaporate the filtrate with the aid of nitrogen to 5 mL, and cool in an ice bath until crystals are formed. Filter the crystals, wash with 3 mL of cold [acetone](#), and dry under vacuum at 70° for 30 min. Use the crystals.

**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](#), [tetrahydrofuran](#), and [water](#) (12:3:85). Add 0.22 mL of [formic acid](#) and then 0.5 mL of [triethylamine](#) to each L.

**Diluent:** [Methanol](#) and [water](#) (50:50)

**System suitability stock solution:** 0.1 mg/mL of [USP Carbamazepine RS](#) and 0.5 mg/mL of [USP Carbamazepine Related Compound A RS](#) in [methanol](#). Sonication may be used to aid in dissolution.

**System suitability solution:** 0.01 mg/mL of [USP Carbamazepine RS](#) and 0.05 mg/mL of [USP Carbamazepine Related Compound A RS](#) from *System suitability stock solution* in *Diluent*

**Standard stock solution:** 2 mg/mL of [USP Carbamazepine RS](#) in [methanol](#). Sonication may be used to aid in dissolution.

**Standard solution:** 0.2 mg/mL of [USP Carbamazepine RS](#) from *Standard stock solution* in *Diluent*

**Sample stock solution:** Nominally 2 mg/mL of carbamazepine from NLT 20 Tablets prepared as follows. Finely powder the Tablets, and transfer a portion of the powder to a suitable volumetric flask. Add 80% of the final flask volume of [methanol](#), sonicate for 15 min, and allow to cool to room temperature. Dilute with [methanol](#) to volume. Pass through a suitable filter and discard the first few mL of filtrate.

**Sample solution:** Nominally 0.2 mg/mL of carbamazepine from *Sample stock solution* in *Diluent*

### Chromatographic system

(See [Chromatography \(621\), System Suitability](#).)

**Mode:** LC

**Detector:** UV 230 nm

**Column:** 4.0- or 4.6-mm × 25-cm; 7-µm packing [L10](#)

**Flow rate:** 1.5 mL/min

**Injection volume:** 20 µL

**Run time:** NLT 1.6 times the retention time of carbamazepine

### System suitability

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

[NOTE—See [Table 3](#) for the relative retention times.]

### Suitability requirements

**Resolution:** NLT 1.7 between carbamazepine related compound A and carbamazepine, *System suitability solution*

**Relative standard deviation:** NMT 2.0%, *Standard solution*

### 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 from the *Sample solution*

$r_S$  = peak response 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:** 92.0%–108.0%

## PERFORMANCE TESTS

### Change to read:

#### • [DISSOLUTION \(711\)](#)

##### For products labeled as 100-mg chewable Tablets

**Test 1:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 1*.

**Medium:** [Water](#) containing 1% [sodium dodecyl sulfate](#); 900 mL

**Apparatus 2:** 75 rpm

**Time:** 60 min

**Standard solution:** [USP Carbamazepine RS](#) in *Medium*. [NOTE—A volume of [methanol](#) NMT 1% of the final total volume of the *Standard solution* may be used to dissolve the carbamazepine.]

**Sample solution:** Filtered portion of the solution under test, diluted with *Medium* if necessary

##### Instrumental conditions

**Mode:** UV

**Analytical wavelength:** Maximum absorbance at about 288 nm

##### Analysis

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

Calculate the percentage of the labeled amount of carbamazepine ( $C_{15}H_{12}N_2O$ ) dissolved:

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

$A_U$  = absorbance of the *Sample solution*

$A_S$  = absorbance of the *Standard solution*

$C_S$  = concentration of [USP Carbamazepine RS](#) in the *Standard solution* (mg/mL)

$V$  = volume of the *Medium*, 900 mL

$L$  = label claim (mg/Tablet)

**Tolerances:** NLT 75% ( $Q$ ) of the labeled amount of carbamazepine ( $C_{15}H_{12}N_2O$ ) is dissolved. Use [Dissolution \(711\)](#), [Acceptance Table 1](#) with the following exceptions: at  $S_2$ , no unit is less than  $Q - 5\%$ ; at  $S_3$ , no unit is less than  $Q - 10\%$ ; and NMT 2 of the 24 units are less than  $Q - 5\%$ .

##### For products labeled as 200-mg Tablets

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

**Medium, Apparatus 2, Standard solution, Sample solution, and Instrumental conditions:** Proceed as directed in *Test 1*.

**Times:** 15 and 60 min

##### 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 ( $i$ ):

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

$A_U$  = absorbance of the *Sample solution*

$A_S$  = absorbance of the *Standard solution*

$C_S$  = concentration of [USP Carbamazepine RS](#) in the *Standard solution* (mg/mL)

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

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

$$\text{Result}_2 = [(C_2 \times V_2) + (C_1 \times V_S)] \times (1/L) \times 100$$

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

$V$  = volume of the *Medium*, 900 mL

$L$  = label claim (mg/Tablet)

$V_2$  = volume of the *Medium* at time point 2 (mL)

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

**Tolerances:** See [Table 1](#).

**Table 1**

Time Point ( $i$ )	Time (min)	Amount Dissolved (%)
1	15	45–75
2	60	NLT 75

Use [Dissolution \(711\)](#), [Acceptance Table 2](#) with the following exceptions. At 15 min: at  $L_2$ , no unit is more than 5% outside the stated range; at  $L_3$ , no unit is more than 10% outside the stated range; and NMT 2 of the 24 units are more than 5% outside the stated range. At 60 min: at  $L_2$ , no unit is less than  $Q - 5\%$ ; at  $L_3$ , no unit is less than  $Q - 10\%$ ; and NMT 2 of the 24 units are less than  $Q - 5\%$ .

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

**Medium, Apparatus 2, Standard solution, Sample solution, and Instrumental conditions:** Proceed as indicated in *Test 1*.

**Times:** 15 and 60 min

**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 ( $i$ ):

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

$A_U$  = absorbance of the *Sample solution*

$A_S$  = absorbance of the *Standard solution*

$C_S$  = concentration of [USP Carbamazepine RS](#) in the *Standard solution* (mg/mL)

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

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

$$\text{Result}_2 = [(C_2 \times V_2) + (C_1 \times V_S)] \times (1/L) \times 100$$

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

$V$  = volume of the *Medium*, 900 mL

$L$  = label claim (mg/Tablet)

$V_2$  = volume of the *Medium* at time point 2 (mL)

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

**Tolerances:** See [Table 2](#).

**Table 2**

Time Point ( $i$ )	Time (min)	Amount Dissolved (%)
1	15	60–85
2	60	NLT 75

Use [Dissolution <711>](#), [Acceptance Table 2](#) with the following exceptions. At 15 min: at  $L_2$ , no unit is more than 5% outside the stated range; at  $L_3$ , no unit is more than 10% outside the stated range; and NMT 2 of the 24 units are more than 5% outside the stated range. At 60 min: at  $L_2$ , no unit is less than  $Q - 5\%$ ; at  $L_3$ , no unit is less than  $Q - 10\%$ ; and NMT 2 of the 24 units are less than  $Q - 5\%$ .

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

**Medium:** [Water](#) containing 1% [sodium dodecyl sulfate](#); 900 mL

**Apparatus 2:** 75 rpm

**Time:** 45 min

**Standard stock solution:** 0.9 mg/mL of [USP Carbamazepine RS](#) in [methanol](#). Sonicate to dissolve as needed.

**Standard solution:** 9 µg/mL of [USP Carbamazepine RS](#) from *Standard stock solution* in *Medium*

**Sample solution:** Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size and discard the first 3 mL of the filtrate. Dilute with *Medium* to a concentration similar to that of the *Standard solution*.

#### Instrumental conditions

(See [Ultraviolet-Visible Spectroscopy <857>](#).)

**Mode:** UV

**Analytical wavelength:** 288 nm

**Cell length:** 1 cm

**Blank:** *Medium*

#### Analysis

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

Calculate the percentage of the labeled amount of carbamazepine ( $C_{15}H_{12}N_2O$ ) dissolved:

$$\text{Result} = (A_U/A_S) \times C_S \times D \times V \times (1/L) \times 100$$

$A_U$  = absorbance of the *Sample solution*

$A_S$  = absorbance of the *Standard solution*

$C_S$  = concentration of [USP Carbamazepine RS](#) in the *Standard solution* (mg/mL)

$D$  = dilution factor

$V$  = volume of the *Medium*, 900 mL

$L$  = label claim (mg/Tablet)

**Tolerances:** NLT 80% (Q) of the labeled amount of carbamazepine ( $C_{15}H_{12}N_2O$ ) is dissolved. ▲ (TBD)

- [UNIFORMITY OF DOSAGE UNITS \(905\)](#): Meet the requirements

## IMPURITIES

### • ORGANIC IMPURITIES

**Mobile phase, Diluent, and System suitability solution:** Proceed as directed in the Assay.

**Standard stock solution:** 0.02 mg/mL each of [USP Carbamazepine RS](#), [USP Carbamazepine Related Compound B RS](#), and [USP 9-Methylacridine RS](#) in [methanol](#). Sonication may be used to aid in dissolution.

**Standard solution:** 0.001 mg/mL each of [USP Carbamazepine RS](#), [USP Carbamazepine Related Compound B RS](#), and [USP 9-Methylacridine RS](#) from *Standard stock solution* in *Diluent*

**Sample solution:** Nominally 1 mg/mL of carbamazepine from NLT 20 Tablets prepared as follows. Finely powder the Tablets, and transfer a portion of the powder to a suitable volumetric flask. Add about 50% of the final flask volume of *Diluent*, sonicate for 15 min, and allow to cool to room temperature. Dilute with *Diluent* to volume. Pass through a suitable filter and discard the first few mL of filtrate.

**Chromatographic system:** Proceed as directed in the Assay except use a *Run time* of NLT 3.5 times the retention time of carbamazepine.

### System suitability

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

[NOTE—See [Table 3](#) for the relative retention times.]

### Suitability requirements

**Resolution:** NLT 1.7 between carbamazepine related compound A and carbamazepine, *System suitability solution*

**Relative standard deviation:** NMT 10.0% each for carbamazepine, carbamazepine related compound B, and 9-methylacridine, *Standard solution*

### Analysis

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

Calculate the percentage of carbamazepine related compound B and 9-methylacridine in the portion of Tablets taken:

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

$r_U$  = peak response of carbamazepine related compound B or 9-methylacridine from the *Sample solution*

$r_S$  = peak response of carbamazepine related compound B or 9-methylacridine from the *Standard solution*

$C_S$  = concentration of [USP Carbamazepine Related Compound B RS](#) or [USP 9-Methylacridine RS](#) in the *Standard solution* (mg/mL)

$C_U$  = nominal concentration of carbamazepine in the *Sample solution* (mg/mL)

Calculate the percentage of other degradation products in the portion of Tablets taken:

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

$r_U$  = peak response of any individual unspecified degradation product 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:** See [Table 3](#). Disregard peaks below 0.05%.

**Table 3**

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
9-Methylacridine	0.54	0.2
Carbamazepine related compound A <sup>a</sup>	0.87	—
Carbamazepine	1.0	—
Carbamazepine related compound B	3.1	0.2
Any individual unspecified degradation product	—	0.2
Total degradation products	—	0.30

<sup>a</sup> This is a process impurity that is controlled in the drug substance. It is not to be reported or included in the total degradation products.

### ADDITIONAL REQUIREMENTS

● **PACKAGING AND STORAGE:** Preserve in tight containers, preferably of glass. Protect from light and moisture. Store at controlled room temperature.

● **LABELING:** The labeling indicates the *Dissolution* test with which the product complies.

● **USP REFERENCE STANDARDS (11)**

[USP Carbamazepine RS](#)

[USP Carbamazepine Related Compound A RS](#)

10,11-Dihydrocarbamazepine.

$C_{15}H_{14}N_2O$  238.28

[USP Carbamazepine Related Compound B RS](#)

5H-Dibenz[*b,f*]azepine.

$C_{14}H_{11}N$  193.24

[USP 9-Methylacridine RS](#)

9-Methylacridine.

$C_{14}H_{11}N$  193.24

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### Page Information:

Not Applicable

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