Tramadol Hydrochloride Extended-Release Tablets

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Expert Committee	Chemical Medicines Monographs 2
Reason for Revision	Compliance

In accordance with the Rules and Procedures of the 2015-2020 Council of Experts, the Chemical Medicines Monographs 2 Expert Committee has revised the Tramadol Hydrochloride Extended-Release Tablets monograph. The purpose for the revision is to add *Dissolution Test 4* for drug products approved by the FDA.

The liquid chromatographic procedure in *Dissolution Test 4* was validated using a Luna C18 (2) brand of L1 column. The typical retention time for tramadol is about 1.4 minutes.

The Tramadol Hydrochloride Extended-Release Tablets Revision Bulletin supersedes the currently official Tramadol Hydrochloride Extended-Release Tablets monograph. The Revision Bulletin will be incorporated in the *USP 40–NF 35*.

Should you have any questions, please contact Hillary Cai (301–230-3379 or hzc@usp.org).

Tramadol Hydrochloride Extended-Release Tablets

DEFINITION

Tramadol Hydrochloride Extended-Release Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of tramadol hydrochloride ($C_{16}H_{25}NO_2 \cdot HCl$).

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. ULTRAVIOLET ABSORPTION** ⟨**197U**⟩
  Sample solution: Use the *Sample solution* from the *Assay*.
  Analysis: Using separate 1-cm cells, record the UV spectrum of the *Sample solution* and *Standard solution*.
  Acceptance criteria: The UV absorption spectrum of the *Sample solution* exhibits maxima and minima at the same wavelength as that of a similar solution of the *Standard solution*.

ASSAY

- **PROCEDURE**
  Mobile phase: Tetrahydrofuran, trifluoroacetic acid, triethylamine, and water (10: 0.1: 0.1: 90). [NOTE—Maintain at a pH range of 2.2–2.4.]
  Standard stock solution: 1 mg/mL of USP Tramadol Hydrochloride RS prepared by dissolving in 20% of the flask volume of methanol. Sonicate if necessary, and dilute with water to volume.
  Standard solution: 0.13 mg/mL of USP Tramadol Hydrochloride RS in *Mobile phase*, from the *Standard stock solution*
  Sample solution: Nominally 0.13 mg/mL of tramadol hydrochloride in *Mobile phase*. Prepare by dissolving 10 Tablets in 20% of the flask volume of methanol, in a water bath for 60 min, at about 60° with intermittent shaking. Sonicate for 10 min. Add 40% of the flask volume of water, and sonicate for 30 min. If all Tablets are not fully disintegrated, then continue to sonicate until disintegration is completed. Shake the flask vigorously for 10 min using a mechanical shaker, and dilute with water to volume. Centrifuge a portion of the solution, pass through a suitable nylon filter, and collect the filtrate after discarding the first 2 mL. Pipet 5.0 mL of the filtrate into a 200-mL volumetric flask, and dilute with *Mobile phase* to volume.
  Chromatographic system
  (See *Chromatography* ⟨621⟩, *System Suitability*.)
  Mode: LC
  Detector: UV 216 nm
  Column: 4.6-mm × 15-cm; 5-µm packing L11
  Column temperature: 40°
  Flow rate: 1 mL/min
  Injection volume: 10 µL
  System suitability
  Sample: *Standard solution*
  Suitability requirements
  Column efficiency: NLT 2000 theoretical plates
  Tailing factor: NMT 2.0
  Relative standard deviation: NMT 2.0%
  Analysis
  Samples: *Standard solution* and *Sample solution*
  Calculate the percentage of the labeled amount of tramadol hydrochloride ($C_{16}H_{25}NO_2 \cdot HCl$) 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 Tramadol Hydrochloride RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of tramadol hydrochloride in the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

- **DISSOLUTION** ⟨**711**⟩
  Test 1
  Medium: 0.1 N hydrochloric acid; 900 mL
  Apparatus 1: 75 rpm
  Times: 2, 4, 8, 10, and 16 h
  Standard solution: (*L*/900) mg/mL of USP Tramadol Hydrochloride RS in *Medium*, where *L* is the label claim in mg/Tablet
  Sample solution: Withdraw 10 mL of the solution under test, and pass through a suitable filter of 0.45-µm pore size, discarding the first 4 mL of the filtrate. Replace the volume withdrawn with the same volume of *Medium* preheated at 37.0 ± 0.5°.
  Instrumental conditions
  Mode: UV
  Analytical wavelength: 271 nm
  Cell: 5 cm
  Blank: *Medium*
  Analysis
  Samples: *Standard solution* and *Sample solution*
  Calculate the concentration (C_i), in mg/mL, of tramadol hydrochloride ($C_{16}H_{25}NO_2 \cdot HCl$) in the sample withdrawn from the vessel at each time point (*i*):

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

A_U = absorbance of the *Sample solution*
A_S = absorbance of the *Standard solution*
C_S = concentration of USP Tramadol Hydrochloride RS in the *Standard solution* (mg/mL)

Calculate the percentage of the labeled amount of tramadol hydrochloride ($C_{16}H_{25}NO_2 \cdot HCl$) dissolved at each time point (*i*):

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

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

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

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

$$\text{Result}_5 = \{(C_5 \times V) + [(C_4 + C_3 + C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$

C_i = concentration of tramadol hydrochloride in the portion of the sample withdrawn at the specified time point (mg/mL)
V = volume of *Medium*, 900 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 1*.

Table 1

Time Point (*i*)	Time (h)	Amount Dissolved (%)
1	2	NMT 15
2	4	10–40
3	8	50–85
4	10	65–95
5	16	NLT 80

The percentages of the labeled amount of tramadol hydrochloride ($C_{16}H_{25}NO_2 \cdot HCl$) released at the times specified conform to *Dissolution* ⟨711⟩*, Acceptance Table 2*.

Test 2: If the product complies with this test, the labeling indicates that the product meets USP *Dissolution Test 2*.
Medium: 0.1 N hydrochloric acid; 900 mL
Apparatus 1: 75 rpm
Times: 2, 4, 8, 10, and 16 h
Standard stock solution: 5 mg/mL of USP Tramadol Hydrochloride RS in *Medium*. Sonicate if necessary.
Standard solution: Dilute the *Standard stock solution* with *Medium* to obtain a concentration of USP Tramadol Hydrochloride RS (see *Table 2*).

Table 2

Label Claim (mg/Tablet)	Concentration of USP Tramadol Hydrochloride RS (mg/mL)
100	0.075
200	0.100
300	0.200

Sample solution: Pass a portion of the solution under test through a suitable filter.
Instrumental conditions
Mode: UV
Analytical wavelength: 271 nm
Cell
For Tablets labeled to contain 100 mg: 1 cm
For Tablets labeled to contain 200 and 300 mg: 0.5 cm
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of tramadol hydrochloride ($C_{16}H_{25}NO_2 \cdot HCl$) dissolved at each time point (*i*):

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

A_U = absorbance of the *Sample solution*
A_S = absorbance of the *Standard solution*
C_S = concentration of USP Tramadol Hydrochloride RS in the *Standard solution* (mg/mL)
V = volume of *Medium*, 900 mL
L = label claim (mg/Tablet)

Tolerances: See *Table 3*.

Table 3

Time Point (*i*)	Time (h)	Amount Dissolved (%)
1	2	NMT 15
2	4	10–30
3	8	47–72
4	10	60–85
5	16	NLT 80

The percentages of the labeled amount of tramadol hydrochloride ($C_{16}H_{25}NO_2 \cdot HCl$) released at the times specified conform to *Dissolution* ⟨711⟩*, Acceptance Table 2*.

•**Test 3:** If the product complies with this test, the labeling indicates that the product meets USP *Dissolution Test 3*.
Medium: 0.1 N hydrochloric acid; 900 mL
Apparatus 1: 75 rpm
Times: 2, 4, 8, and 16 h
Buffer: Trifluoroacetic acid and water (2:1000)
Mobile phase: Acetonitrile and *Buffer* (30:70)
Standard stock solution: 0.55 mg/mL of USP Tramadol Hydrochloride RS in water
Standard solution: (*L*/900) mg/mL of USP Tramadol Hydrochloride RS in *Medium* from the *Standard stock solution*, where *L* is the label claim of tramadol hydrochloride, in mg/Tablet. Pass the solution through a suitable filter of 0.45-µm pore size. Discard the first 5 mL of filtrate.
Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size. Replace the portion of solution withdrawn with an equal volume of *Medium*. Discard the first 5 mL of filtrate.
Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: LC
Detector: UV 270 nm
Column: 4.6-mm × 25-cm; 5-µm packing L1
Temperatures
Autosampler: 10°
Column: 25°
Flow rate: 1.0 mL/min
Injection volume: 20 µL
System suitability
Sample: *Standard solution*
Suitability requirements
Column efficiency: NLT 2000 theoretical plates
Tailing factor: NMT 2.0
Relative standard deviation: NMT 2.0%
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the concentration (C_i), in mg/mL, of tramadol hydrochloride ($C_{16}H_{25}NO_2 \cdot HCl$) in the sample withdrawn from the vessel at each time point (*i*):

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

r_U = peak response of tramadol from the *Sample solution*
r_S = peak response of tramadol from the *Standard solution*
C_S = concentration of USP Tramadol Hydrochloride RS in the *Standard solution* (mg/mL)

Calculate the percentage of the labeled amount of tramadol hydrochloride ($C_{16}H_{25}NO_2 \cdot HCl$) dissolved at each time point (*i*):

$$Result_1 = C_1 \times V \times (1/L) \times 100$$

$$Result_2 = [(C_2 \times V) + (C_1 \times V_S)] \times (1/L) \times 100$$

$$Result_3 = \{(C_3 \times V) + [(C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$

$$Result_4 = \{(C_4 \times V) + [(C_3 + C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$

C_i = concentration of tramadol hydrochloride in the portion of sample withdrawn at the specified time point (mg/mL)
V = volume of medium, 900 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 (%)	
		100 mg/Tablet and 300 mg/Tablet	200 mg/Tablet
1	2	NMT 40	NMT 35
2	4	45–75	32–62
3	8	NLT 70	NLT 70
4	16	NLT 85	NLT 85

The percentages of the labeled amount of tramadol hydrochloride ($C_{16}H_{25}NO_2 \cdot HCl$) released at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.

● (RB 1-Oct-2015)
●**Test 4:** If the product complies with this test, the labeling indicates that the product meets USP *Dissolution Test 4*.
Medium: 0.1 N hydrochloric acid; 900 mL
Apparatus 1: 75 rpm
Times: 2, 4, 8, 10, and 16 h
Buffer: Dissolve 6.8 g of monobasic potassium phosphate in 1 L of water and adjust with phosphoric acid to a pH of 3.0.
Mobile phase: Acetonitrile and *Buffer* (20:80)
Standard solution: 0.22 mg/mL of USP Tramadol Hydrochloride RS in *Medium*. Sonication may be necessary for complete dissolution.
Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size.
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 270 nm
Column: 4.6-mm × 5-cm; 3-µm packing L1
Flow rate: 1.5 mL/min
Injection volume: 10 µL
Run time: NLT 6 times the retention time of tramadol
System suitability
Sample: *Standard solution*
Suitability requirements
Column efficiency: NLT 1000 theoretical plates
Relative standard deviation: NMT 2%
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the concentration (C_i), in mg/mL, of tramadol hydrochloride ($C_{16}H_{25}NO_2 \cdot HCl$) in the sample withdrawn from the vessel at each time point (*i*):

$$Result_i = (r_U/r_S) \times C_S$$

r_U = peak response of tramadol from the *Sample solution*
r_S = peak response of tramadol from the *Standard solution*
C_S = concentration of USP Tramadol Hydrochloride RS in the *Standard solution* (mg/mL)

Calculate the percentage of the labeled amount of tramadol hydrochloride ($C_{16}H_{25}NO_2 \cdot HCl$) dissolved at each time point (*i*):

$$Result_1 = C_1 \times V \times (1/L) \times 100$$

$$Result_2 = \{[C_2 \times (V - V_S)] + (C_1 \times V_S)\} \times (1/L) \times 100$$

$$Result_3 = (\{C_3 \times [V - (2 \times V_S)]\} + [(C_2 + C_1) \times V_S]) \times (1/L) \times 100$$

$$Result_4 = (\{C_4 \times [V - (3 \times V_S)]\} + [(C_3 + C_2 + C_1) \times V_S]) \times (1/L) \times 100$$

$$Result_5 = (\{C_5 \times [V - (4 \times V_S)]\} + [(C_4 + C_3 + C_2 + C_1) \times V_S]) \times (1/L) \times 100$$

C_i = concentration of tramadol hydrochloride in the portion of sample withdrawn at the specified time point (mg/mL)
V = volume of *Medium*, 900 mL
L = label claim (mg/Tablet)
V_S = volume of the *Sample solution* withdrawn at each time point (mL)

Tolerances: See *Table 5*.

Table 5

Time Point (*i*)	Time (h)	Amount Dissolved (%)
1	2	NMT 35
2	4	35–60
3	8	60–85
4	10	NLT 65
5	16	NLT 75

The percentages of the labeled amount of tramadol hydrochloride ($C_{16}H_{25}NO_2 \cdot HCl$) released at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.● (RB 1-Jun-2016)

- **UNIFORMITY OF DOSAGE UNITS ⟨905⟩:** Meet the requirements

IMPURITIES

Change to read:

- **ORGANIC IMPURITIES**

Mobile phase: Acetonitrile, trifluoroacetic acid, and water (20: 0.1: 80)

Diluent: Methanol and water (1:4)

System suitability stock solution: 0.05 mg/mL each of USP Tramadol Hydrochloride RS and USP Tramadol Related Compound A RS in *Diluent* prepared by dissolving in 20% of the flask volume of methanol. Sonicate if necessary, and dilute with water to volume.

System suitability solution: 2.5 µg/mL each of USP Tramadol Hydrochloride RS and USP Tramadol Related Compound A RS in *Diluent*, from the *System suitability stock solution*

Standard stock solution: 0.05 mg/mL of USP Tramadol Hydrochloride RS in *Diluent* prepared by dissolving in 20% of the flask volume of methanol. Sonicate if necessary, and dilute with water to volume.

Standard solution: 2.5 µg/mL of USP Tramadol Hydrochloride RS in *Diluent*, from the *Standard stock solution*

Sample solution: Nominally 1.2 mg/mL of tramadol hydrochloride in *Diluent*. Finely powder NLT 20 Tablets. Transfer a portion of the powder, equivalent to 300 mg of tramadol hydrochloride, to a 250-mL volumetric flask. Add about 50 mL of methanol and heat in a water bath for 20 min at about 60°, with intermittent shaking to disperse the powder. Sonicate for 10 min. Add 100 mL of water, and sonicate with intermittent shaking for 10 min. Shake the flask vigorously for 10 min using a mechanical shaker. Dilute with water to volume, pass through a suitable nylon filter, and collect the filtrate after discarding the first 4 mL of filtrate.

Chromatographic system

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

Mode: LC

Detector: UV 216 nm

Column: 2.1-mm × 10-cm; 1.7-µm packing L1

Column temperature: 50°

Flow rate: 0.6 mL/min

Injection volume: 3 µL

Run time: 6 min

System suitability

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

Suitability requirements

Resolution: NLT 3.0 between tramadol related compound A and tramadol, *System suitability solution*

Column efficiency: NLT 5000 theoretical plates, *Standard solution*

Capacity factor, *k′*: NLT 1.5, *Standard solution*

Tailing factor: NMT 2.0, *Standard solution*

Relative standard deviation: NMT 6.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in the portion of Tablets taken:

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

r_U = peak response of each individual impurity from the *Sample solution*

r_S = peak response of tramadol from the *Standard solution*

C_S = concentration of USP Tramadol Hydrochloride RS in the *Standard solution* (mg/mL)

C_U = nominal concentration of tramadol hydrochloride in the *Sample solution* (mg/mL)

F = relative response factor (see •*Table 6*)• (RB 1-Jun-2016)

Acceptance criteria: See •*Table 6*.• (RB 1-Jun-2016)

•**Table 6**• (RB 1-Jun-2016)

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Desmethyl tramadol (impurity D)[a]	0.57	1.0	•0.20• (RB 1-Oct-2015)
Tramadol related compound A[b]	0.84	1.0	0.2
Tramadol hydrochloride	1.00	—	—
1,6 Olefin[c]	2.78	3.0	—
1,2 Olefin[d]	3.28	2.2	—
Individual unspecified impurity	—	1.0	•0.20• (RB 1-Oct-2015)
Total impurities	—	—	•0.60• (RB 1-Oct-2015)

[a] 3-{(1*RS*,2*RS*)-2-[(Dimethylamino)methyl]-1-hydroxycyclohexyl}phenol.

[b] *RS,SR*-1-(3-Methoxyphenyl)-2-(dimethylaminomethyl)cyclohexanol •hydrochloride.• (RB 1-Oct-2015)

[c] 1-(3-Methoxyphenyl)-2-(dimethylaminomethyl) cyclohex-6-ene hydrochloride (identified and reported as an individual unspecified impurity if present).

[d] 1-(3-Methoxyphenyl)-2-(dimethylaminomethyl) cyclohex-1-ene hydrochloride (identified and reported as an individual unspecified impurity if present).

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight containers, and store at controlled room temperature.
- **LABELING:** When more than one test for *Dissolution* is given, the labeling states the test for *Dissolution* used only if *Test 1* is not used.

Change to read:

- **USP REFERENCE STANDARDS** ⟨11⟩

USP Tramadol Hydrochloride RS

(±)-*cis*-2-[(Dimethylamino)methyl]-1-(*m*-methoxyphenyl)cyclohexanol hydrochloride.

$C_{16}H_{25}NO_2 \cdot HCl$ 299.84

USP Tramadol Related Compound A RS

RS,SR-1-(3-Methoxyphenyl)-2-(dimethylaminomethyl)cyclohexanol •hydrochloride.• (RB 1-Oct-2015)

$C_{16}H_{25}NO_2 \cdot HCl$ 299.84