Trazodone Hydrochloride Tablets

Type of Posting	Revision Bulletin
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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 Trazodone Hydrochloride Tablets monograph. The purpose for the revision is to add *Dissolution Test 2* to accommodate drug products that were approved with different dissolution conditions. A *Labeling* section also has been added.

- *Dissolution Test 2* was validated using the Inertsil ODS-3V brand of L1 column. The typical retention time for trazodone is about 3.8 min.

The Trazodone Hydrochloride Tablets Revision Bulletin supersedes the currently official monograph. The Revision Bulletin will be incorporated in the *USP 42–NF 37*.

Should you have any questions, please contact Sridevi Ramachandran, Ph.D., Associate Scientific Liaison (sdr@usp.org).

Trazodone Hydrochloride Tablets

DEFINITION

Trazodone Hydrochloride Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of trazodone hydrochloride ($C_{19}H_{22}ClN_5O \cdot HCl$).

IDENTIFICATION

Delete the following:

▲• **A. THIN-LAYER CHROMATOGRAPHIC IDENTIFICATION TEST** ⟨201⟩

Standard solution: 20 mg/mL of USP Trazodone Hydrochloride RS in methanol

Sample solution: Nominally 20 mg/mL of trazodone hydrochloride in methanol from a suitable number of Tablets (equivalent to NLT 150 mg) prepared as follows. Place the Tablets in a tube. Add the required amount of methanol, and sonicate until the Tablets have disintegrated. Shake the tube, by hand, for a few seconds to mix, and then filter.

Application volume: 1 µL

Developing solvent system: Cyclohexane, alcohol, toluene, and diethylamine (80:30:20:20)

Analysis

Samples: *Standard solution* and *Sample solution*

Proceed as directed in the chapter, except locate the spots on the plate by examination under long-wavelength UV light.▲ 1S (USP41)

Add the following:

▲• **A.** The UV spectrum of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.▲ 1S (USP41)

• **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

Change to read:

• **PROCEDURE**

Buffer: 1.15 g/L of monobasic ammonium phosphate, adjusted with sodium hydroxide to a pH of 6.0

Mobile phase: Methanol and *Buffer* (75:25)

Standard solution: 0.1 mg/mL of USP Trazodone Hydrochloride RS in 0.01 N hydrochloric acid ▲TS▲ 1S (USP41)

Sample solution: Nominally 0.1 mg/mL of trazodone hydrochloride from NLT 20 finely powdered Tablets. Transfer a suitable quantity of the powder to a suitable volumetric flask. Dissolve in 0.01 N hydrochloric acid ▲TS▲ 1S (USP41) and dilute with 0.01 N hydrochloric acid ▲TS▲ 1S (USP41) to volume. Sonicate for about 30 min, and pass through a ▲suitable▲ 1S (USP41) filter of 0.45-µm pore size.

Chromatographic system

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

Mode: LC

Detector: UV 246 nm. ▲For *Identification A*, use a diode array detector in the range of 200–400 nm.▲ 1S (USP41)

Column: 5-mm × 10-cm; 4-µm packing L1

Flow rate: 1.5 mL/min

Injection volume: 20 µL

▲**Run time:** NLT 4.5 times the retention time of trazodone▲ 1S (USP41)

System suitability

Sample: *Standard solution*

Suitability requirements

Column efficiency: NLT 900 theoretical plates

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of trazodone hydrochloride ($C_{19}H_{22}ClN_5O \cdot HCl$) in the portion of Tablets taken:

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

r_U = peak response of trazodone from the *Sample solution*

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

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

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

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

• **DISSOLUTION** ⟨711⟩

▲**Test 1**▲ (RB 1-Apr-2018)

Medium: 0.01 N hydrochloric acid ▲TS▲ 1S (USP41); 900 mL

Apparatus 2: 50 rpm

Time: 60 min

▲**Buffer,**▲ 1S (USP41) **Mobile phase, Standard solution, Chromatographic system,** and **System suitability:** Proceed as directed in the *Assay*.

Sample solution: Pass ▲a portion of▲ 1S (USP41) the solution ▲under test▲ 1S (USP41) through a ▲suitable▲ 1S (USP41) filter of 0.45-µm pore size.

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of trazodone hydrochloride ($C_{19}H_{22}ClN_5O \cdot HCl$) dissolved:

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

r_U = peak response of trazodone from the *Sample solution*

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

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

V = volume of *Medium*, 900 mL

L = label claim (mg/Tablet)

Tolerances: NLT 80% (Q) of the labeled amount of trazodone hydrochloride ($C_{19}H_{22}ClN_5O \cdot HCl$) is dissolved.

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

Medium: 0.01 N hydrochloric acid TS; 900 mL

Apparatus 2: 50 rpm

Time: 30 min

Buffer: To each liter of water add 5 mL of triethylamine, and adjust with phosphoric acid to a pH of 3.0.

Mobile phase: Acetonitrile and *Buffer* (25:75)

Standard solution: (L/900) mg/mL of USP Trazodone Hydrochloride RS in *Medium*. Sonicate if necessary.

Sample solution: Pass the solution through a suitable filter of 0.45-µm pore size. Discard the first 5 mL of the filtrate.
Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: LC
Detector: UV 246 nm
Column: 4.6-mm × 15-cm; 5-µm packing L1
Column temperature: 45°
Flow rate: 1.5 mL/min
Injection volume: 10 µL
Run time: NLT 1.6 times the retention time of trazodone
System suitability
Sample: *Standard solution*
Suitability requirements
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 trazodone hydrochloride ($C_{19}H_{22}ClN_5O \cdot HCl$) dissolved:

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

r_U = peak response of trazodone from the *Sample solution*
r_S = peak response of trazodone from the *Standard solution*
C_S = concentration of USP Trazodone Hydrochloride RS in the *Standard solution* (mg/mL)
V = volume of *Medium*, 900 mL
L = label claim (mg/Tablet)

Tolerances: NLT 80% (*Q*) of the labeled amount of trazodone hydrochloride ($C_{19}H_{22}ClN_5O \cdot HCl$) is dissolved. ▲ (RB 1-Apr-2018)

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

IMPURITIES

Change to read:

• **Organic Impurities**
Solution A: 6.75 g/L of monobasic potassium phosphate. Add 1.0 mL of triethylamine for each liter of the solution, and mix.
Solution B: Acetonitrile
Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	90	10
5	90	10
30	60	40
35	60	40
60	42	58
63	30	70
78	30	70
78.1	90	10
90	90	10

Diluent: Methanol, water, and hydrochloric acid (650:350:3)
System suitability solution: 0.7 µg/mL of USP Trazodone Hydrochloride RS and 1.5 µg/mL of USP Trazodone Related Compound C RS in *Diluent*
Standard solution: 0.7 µg/mL of USP Trazodone Hydrochloride RS in *Diluent*
Sample solution: Nominally 500 µg/mL of trazodone from finely powdered Tablets (NLT 20) prepared as follows. Transfer a portion of powdered Tablets (NLT 50 mg) to a suitable volumetric flask. Add about 80% of the flask volume of *Diluent*, and sonicate for 10 min. Dilute with *Diluent* to volume. Pass a portion of the solution through a suitable membrane filter of 0.45-µm pore size.
Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: LC
Detector: UV 254 nm
Column: 4.0-mm × 15-cm; 3-µm packing L1
Flow rate: 0.7 mL/min
Injection volume: 10 µL
System suitability
Samples: *System suitability solution* and *Standard solution*
[NOTE—See *Table 2* for the relative retention times.]
Suitability requirements
Resolution: NLT 2.5 between the trazodone related compound C and trazodone peaks, *System suitability solution*
Tailing factor: NMT 2.0, *Standard solution*
Relative standard deviation: NMT 5.0%, ▲ ▲ 1S (USP41) *Standard solution*
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of each ▲degradation product▲ 1S (USP41) 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 ▲degradation product▲ 1S (USP41) from the *Sample solution*
r_S = peak response of trazodone from the *Standard solution*
C_S = concentration of USP Trazodone Hydrochloride RS in the *Standard solution* (µg/mL)
C_U = nominal concentration of trazodone in the *Sample solution* (µg/mL)

Acceptance criteria: See *Table 2*.

Table 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Triazolopyridinone[a, b]	0.1	—
Chlorophenylpiperazine[a, c]	0.6	—
Hydroxypropyl chlorophenylpiperazine[a, d]	0.7	—
Isotrazodone[a, e]	0.8	—
Trazodone related compound C[a]	0.97	—
Trazodone hydrochloride	1.0	—
Trazodone dimer[a, f]	1.5	—
Trazodone related compound F[a, g]	1.6	—
Bispiperazine analog[a, h]	1.8	—
Bis(3-chlorophenyl)piperazine[a, i]	2.2	—

Table 2 *(continued)*

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Any individual unspecified degradation product	—	1.0
Total ▲degradation products▲ 1S (USP41)	—	2.0

[a] Process impurity included for identification only. ▲Process impurities are controlled in the drug substance, and are not to be reported or included in the total impurities for the drug product.▲ 1S (USP41)
[b] [1,2,4]Triazolo[4,3-*a*]pyridin-3(2*H*)-one.
[c] 1-(3-Chlorophenyl)piperazine.
[d] 3-[4-(3-Chlorophenyl)piperazin-1-yl]propan-1-ol.
[e] 1-{3-[4-(3-Chlorophenyl)piperazin-1-yl]propyl}-[1,2,4]triazolo[4,3-*a*]pyridin-1-ium-3-olate.
[f] 1,1-Bis{2-chloro-[4-(3-{1,2,4-triazolo[4,3-*a*]pyridin-3-(2*H*)-on-2-yl}propyl)piperazine-1-yl]phenyl}ethane trihydrochloride.
[g] 1-(3-Chlorophenyl)-4-(3-chloropropyl)piperazine.
[h] 1,3-Bis(4-(3-chlorophenyl)piperazin-1-yl)propane.
[i] 1,4-Bis(3-chlorophenyl)piperazine.

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight, light-resistant containers. 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.▲ (RB 1-Apr-2018)

- **USP REFERENCE STANDARDS** ⟨11⟩
  USP Trazodone Hydrochloride RS
  USP Trazodone Related Compound C RS
  2-{3-[4-(4-Chlorophenyl)piperazin-1-yl]propyl}-[1,2,4]triazolo[4,3-*a*]pyridin-3(2*H*)-one hydrochloride.
  $C_{19}H_{22}ClN_5O \cdot HCl$ 408.32