Status: Currently Official on 17-Feb-2025
Official Date: Official as of 01-May-2017
Document Type: USP Monographs
DocId: GUID-A38A48A7-8C1C-4DD4-B0EF-77855DCD7421_1_en-US
DOI: https://doi.org/10.31003/USPNF_M607_01_01
DOI Ref: 2wa7d

Tramadol Hydrochloride and Acetaminophen Tablets

DEFINITION

Tramadol Hydrochloride and Acetaminophen Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of tramadol hydrochloride ($C_{16}H_{25}NO_2 \cdot HCl$) and acetaminophen ($C_8H_9NO_2$).

IDENTIFICATION

• **A.** The retention times of the *Tramadol sample solution* and the *Acetaminophen sample solution* correspond to those of the *Standard solution*, as obtained in the *Assay*.

ASSAY

• **Procedure**

Mobile phase: Tetrahydrofuran, triethylamine, water, and trifluoroacetic acid (8:0.1:92:0.1). The apparent pH of the final solvent mixture should be between 2.2 and 2.4.

Diluent: Methanol and water (1:9)

Standard solution: 0.065 mg/mL of USP Acetaminophen RS and 0.075 mg/mL of USP Tramadol Hydrochloride RS in *Diluent*. Sonication may be used to aid dissolution.

Sample stock solution: Weigh NLT 20 Tablets, and determine the average Tablet weight. Grind the Tablets into a fine powder, and transfer an amount equivalent to one Tablet to a 50-mL volumetric flask. Add 30 mL of *Diluent* with continuous shaking to disperse the powder. Sonicate for 15 min with intermittent shaking, and shake the flask on a mechanical shaker for 30 min. Dilute with *Diluent* to volume, and mix well. Centrifuge the suspension, and use the supernatant for subsequent dilutions.

Tramadol sample solution: Nominally 75 µg/mL of tramadol hydrochloride in *Diluent* from the *Sample stock solution*

Acetaminophen sample solution: Nominally 65 µg/mL of acetaminophen in *Diluent* from the *Sample stock solution*

Chromatographic system

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

Mode: LC

Detector: UV 216 nm for tramadol hydrochloride and UV 249 nm for acetaminophen

Column: 4.6-mm × 15-cm; 5-µm packing L11

Column temperature: 50°

Flow rate: 1 mL/min

Injection volume: 20 µL

Run time: 4 times the retention time of acetaminophen

System suitability

Sample: *Standard solution*

Suitability requirements

Resolution: NLT 10.0 between acetaminophen and tramadol

Tailing factor: NMT 2.0 for each analyte

Relative standard deviation: NMT 2.0% for each analyte

Analysis

Samples: *Standard solution*, *Tramadol sample solution*, and *Acetaminophen 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 of tramadol from the *Tramadol 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 *Tramadol sample solution* (mg/mL)

Calculate the percentage of the labeled amount of acetaminophen ($C_8H_9NO_2$) in the portion of Tablets taken:

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

r_U = peak response of acetaminophen from the *Acetaminophen sample solution*

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

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

C_U = nominal concentration of acetaminophen in the *Acetaminophen sample solution* (mg/mL)

Acceptance criteria

Tramadol hydrochloride: 90.0%–110.0% of the labeled amount of tramadol hydrochloride ($C_{16}H_{25}NO_2 \cdot HCl$)

Acetaminophen: 90.0%–110.0% of the labeled amount of acetaminophen ($C_8H_9NO_2$)

PERFORMANCE TESTS

• **Dissolution** ⟨711⟩

Test 1

Medium: 0.1 N hydrochloric acid; 900 mL

Apparatus 2: 50 rpm

Time: 30 min

Buffer solution: 6.8 mg/mL of monobasic potassium phosphate in water. Adjust with phosphoric acid to a pH of 2.50.

Mobile phase: Acetonitrile and *Buffer solution* (1:4)

Standard solution: 0.36 mg/mL of USP Acetaminophen RS and 0.04 mg/mL of USP Tramadol Hydrochloride RS in *Medium*

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 272 nm

Column: 4.6-mm × 15-cm; 5-µm packing L7

Column temperature: 25°

Flow rate: 1 mL/min

Injection volume: 25 µL

Run time: 2 times the retention time of tramadol

System suitability

Sample: *Standard solution*

[Note—The relative retention times for acetaminophen and tramadol are about 0.5 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 5.0 between the acetaminophen and tramadol peaks

Relative standard deviation: NMT 2.0% for both the acetaminophen and tramadol peaks

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of acetaminophen ($C_8H_9NO_2$) and tramadol hydrochloride ($C_{16}H_{25}NO_2 \cdot HCl$) dissolved:

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

r_U = peak response of acetaminophen or tramadol from the *Sample solution*

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

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

V = volume of *Medium*, 900 mL

L = label claim for acetaminophen or tramadol hydrochloride (mg/Tablet)

Tolerances: NLT 80% (*Q*) of the labeled amount of acetaminophen ($C_8H_9NO_2$) and tramadol hydrochloride ($C_{16}H_{25}NO_2 \cdot HCl$) is dissolved.

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

Medium: 0.1 N hydrochloric acid; 900 mL

Apparatus 2: 50 rpm

Time: 20 min

Buffer solution, Mobile phase, Standard solution, Sample solution, Chromatographic system, System suitability, and **Analysis:** Proceed as directed in *Dissolution Test 1*.

Tolerances: NLT 80% (*Q*) of the labeled amount of acetaminophen ($C_8H_9NO_2$) and tramadol hydrochloride ($C_{16}H_{25}NO_2 \cdot HCl$) is dissolved.

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

IMPURITIES

- **4-Aminophenol in Acetaminophen-Containing Drug Products ⟨227⟩:** Meet the requirements
- **Organic Impurities**

Mobile phase, Diluent, and **Sample stock solution:** Proceed as directed in the *Assay*.

Standard solution: 0.75 µg/mL each of USP Tramadol Hydrochloride RS and USP Tramadol Related Compound A RS in *Diluent*

Sample solution: Pass a suitable volume of *Sample stock solution* through a nylon membrane filter of 0.45-µm pore size. Use the filtrate after discarding the first 4 mL of filtrate.

Chromatographic system

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

Mode: LC

Detector: 216 nm

Column: 4.6-mm × 15-cm; 5-µm packing L11

Column temperature: 50°

Flow rate: 1 mL/min

Injection volume: 30 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Resolution: NLT 2.0 between tramadol related compound A and tramadol hydrochloride

Relative standard deviation: NMT 6.0% for tramadol hydrochloride

Analysis

Samples: *Diluent*, *Standard solution*, and *Sample solution*. Disregard the peaks due to the *Diluent*.

Calculate the percentage of each degradation product 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 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* (µg/mL)

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

Acceptance criteria: See *Table 1*.

Table 1

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
O-Desmethyl-tramadol[a]	0.60	0.2
Tramadol related compound A	0.80	0.2
Tramadol	1.0	—

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Acetaminophen	0.38	—
Any individual, unspecified degradation product	—	0.2
Total degradation products	—	0.8

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

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in tight containers. Store at controlled room temperature.
- **Labeling:** When more than one *Dissolution* test is given, the labeling states the *Dissolution* test used only if *Test 1* is not used.
- **USP Reference Standards** ⟨11⟩

USP Acetaminophen RS

USP 4-Aminophenol RS

4-Amino-1-hydroxybenzene.

C_6H_7NO 109.13

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.

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
TRAMADOL HYDROCHLORIDE AND ACETAMINOPHEN TABLETS	Documentary Standards Support	SM22020 Small Molecules 2
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM22020 Small Molecules 2

Chromatographic Database Information: Chromatographic Database

Most Recently Appeared In:
Pharmacopeial Forum: Volume No. PF 42(1)

Current DocID: GUID-A38A48A7-8C1C-4DD4-B0EF-77855DCD7421_1_en-US

DOI: https://doi.org/10.31003/USPNF_M607_01_01

DOI ref: 2wa7d