Benztropine Mesylate

Type of Posting	Revision Bulletin
Posting Date	29-Jan-2021
Official Date	1-May-2021
Expert Committee	Small Molecules 4

In accordance with the Rules and Procedures of the Council of Experts, the Small Molecules 4 Expert Committee has revised the Benztropine Mesylate monograph. The purpose for the revision is to replace the incorrect references to USP Benzphetamine Related Compound A RS with references to USP Benztropine Related Compound A RS in the *Assay*, *Organic Impurities*, and *USP Reference Standards* sections of the monograph.

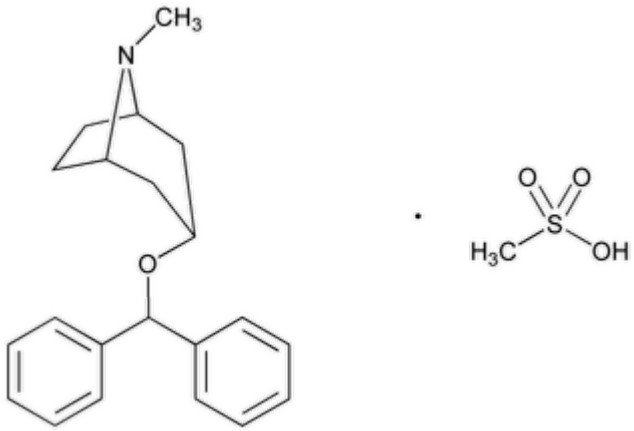
The Benztropine Mesylate Revision Bulletin supersedes the version to become official on May 1, 2021.

Should you have any questions, please contact Heather Joyce, Senior Scientific Liaison (301-998-6792 or hrj@usp.org).

Revision Bulletin
Official: May 1, 2021

Benztropine Mesylate

Change to read:



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$C_{21}H_{25}NO \cdot CH_4O_3S$ ▲403.54▲ (USP 1-May-2021)

8-Azabicyclo[3.2.1]octane, 3-(diphenylmethoxy)-*N*-methyl-, *endo*-, methanesulfonate;
3α-(Diphenylmethoxy)-1α*H*,5α*H*-tropane methanesulfonate;
▲(1*R*,3*r*,5*S*)-3-(Benzhydryloxy)-8-methyl-8-azabicyclo[3.2.1]octane methanesulfonate▲ (USP 1-May-2021)
[132-17-2].

DEFINITION

Change to read:

Benztropine Mesylate contains NLT 98.0% and NMT ▲102.0%▲ (USP 1-May-2021) of benztropine mesylate ($C_{21}H_{25}NO \cdot CH_4O_3S$), calculated on the dried basis.

IDENTIFICATION

Change to read:

● **A. Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*:** 197K ▲or 197A▲ (USP 1-May-2021)

Add the following:

▲● **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.▲ (USP 1-May-2021)

ASSAY

Change to read:

● **Procedure**

▲**Solution A:** 2.7 g/L of monobasic potassium phosphate in water. Adjust with phosphoric acid to a pH of 3.2.

Solution B: Acetonitrile

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	75	25
6	75	25
10	30	70
10.1	75	25
17	75	25

Diluent: Acetonitrile and water (30:70)

System suitability solution: 500 µg/mL of USP Benztropine Mesylate RS and 5 µg/mL of ▲USP Benztropine Related Compound A RS▲ (RB 1-May-2021) in *Diluent*

Standard solution: 500 µg/mL of USP Benztropine Mesylate RS in *Diluent*

Sample solution: 500 µg/mL of Benztropine Mesylate in *Diluent*

Chromatographic system

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

Mode: LC

Detector: UV 220 nm

Column: 2.1-mm × 15-cm; 1.7-µm packing L43. [NOTE—A guard column with similar packing may be used.]

Flow rate: 0.3 mL/min

Injection volume: 2 µL

System suitability

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

[NOTE—The relative retention times for benztropine related compound A and benztropine are 0.9 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 1.3 between benztropine related compound A and benztropine, *System suitability solution*

Tailing factor: NMT 3.0, *Standard solution*

Relative standard deviation: NMT 0.73%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of benztropine mesylate ($C_{21}H_{25}NO \cdot CH_4O_3S$) in the portion of Benztropine Mesylate 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 Benztropine Mesylate RS in the *Standard solution* (µg/mL)

C_U = concentration of Benztropine Mesylate in the *Sample solution* (µg/mL)▲ (USP 1-May-2021)

Acceptance criteria: 98.0%–▲102.0%▲ (USP 1-May-2021) on the dried basis

IMPURITIES

● **Residue on Ignition** ⟨281⟩**:** NMT 0.1%

Add the following:

▲● **Organic Impurities**

Solution A, Solution B, Diluent, System suitability solution, Sample solution, and **Chromatographic system:** Proceed as directed in the *Assay*.

Mobile phase: See *Table 2*.

Table 2

Time (min)	Solution A (%)	Solution B (%)
0	75	25
6	75	25
25	45	55
26	30	70
27	30	70
27.1	75	25
36	75	25

Sensitivity solution: 0.25 µg/mL of USP Benztropine Mesylate RS in *Diluent*

Standard solution: 0.5 µg/mL of USP Benztropine Mesylate RS and 1 µg/mL each of ▲USP Benztropine Related Compound A RS,▲ (RB 1-May-2021)USP Benzhydrol RS, and USP Benzophenone RS in *Diluent*

System suitability

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

[Note—See *Table 3* for the relative retention times.]

Suitability requirements

Resolution: NLT 1.3 between benztropine related compound A and benztropine, *System suitability solution*

Relative standard deviation: NMT 5.0% for benztropine, *Standard solution*

Signal-to-noise ratio: NLT 10, *Sensitivity solution*

Analysis

Samples: *Sample solution* and *Standard solution*

Calculate the percentage of benztropine related compound A, benzhydrol, or benzophenone in the portion of Benztropine Mesylate taken:

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

r_U = peak response of benztropine related compound A, benzhydrol, or benzophenone from the *Sample solution*

r_S = peak response of the corresponding Reference Standard from the *Standard solution*

C_S = concentration of the corresponding Reference Standard in the *Standard solution* (µg/mL)

C_U = concentration of Benztropine Mesylate in the *Sample solution* (µg/mL)

Calculate the percentage of diphenylmethane or any individual unspecified impurity in the portion of Benztropine Mesylate taken:

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

r_U = peak response of diphenylmethane or any individual unspecified impurity from the *Sample solution*

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

C_S = concentration of USP Benztropine Mesylate RS in the *Standard solution* (µg/mL)

C_U = concentration of Benztropine Mesylate in the *Sample solution* (µg/mL)

F = relative response factor (see *Table 3*)

Acceptance criteria: See *Table 3*. The reporting threshold is 0.05%.

Table 3

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Benztropine related compound A	0.9	—	0.10
Benztropine	1.0	—	—
Benzhydrol	1.6	—	0.10
Benzophenone	2.4	—	0.10
Diphenylmethane	3.2	2.2	0.10
Any individual unspecified impurity	—	1.0	0.10
Total impurities	—	—	0.50▲ (USP 1-May-2021)

SPECIFIC TESTS

Delete the following:

▲● **Melting Range or Temperature** ⟨741⟩**:** 141°–148°▲ (USP 1-May-2021)

Change to read:

● **Loss on Drying** ⟨731⟩

Analysis: Dry ▲▲ (USP 1-May-2021) at 105° for 2 h.

Acceptance criteria: NMT 5.0%

ADDITIONAL REQUIREMENTS

● **Packaging and Storage:** Preserve in tight containers.

Change to read:

● **USP Reference Standards** ⟨11⟩

▲ USP Benzhydrol RS

Diphenylmethanol.

$C_{13}H_{12}O$ 184.24

USP Benzophenone RS

Benzophenone; also known as Diphenylmethanone.

$C_{13}H_{10}O$ 182.22▲ (USP 1-May-2021)

USP Benztropine Mesylate RS

▲▲ USP Benztropine Related Compound A RS▲ (RB 1-May-2021)

(1*R*,3*r*,5*S*)-3-(Benzhydryloxy)-8-azabicyclo[3.2.1]octane hydrochloride.

$C_{20}H_{23}NO \cdot HCl$ 329.87▲ (USP 1-May-2021)

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