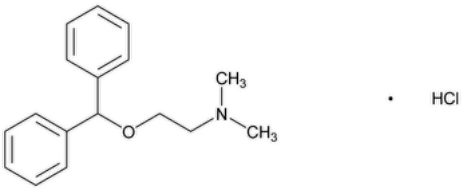
Status: Currently Official on 14-Feb-2025
Official Date: Official as of 01-May-2020
Document Type: USP Monographs
DocId: GUID-67E581CC-E9F4-4595-BD84-EBDB8821DF4E_4_en-US
DOI: https://doi.org/10.31003/USPNF_M27130_04_01
DOI Ref: 79u56

Diphenhydramine Hydrochloride



$C_{17}H_{21}NO \cdot HCl$ 291.82

Ethanamine, 2-(diphenylmethoxy)-*N*,*N*-dimethyl-, hydrochloride;

2-(Diphenylmethoxy)-*N*,*N*-dimethylethylamine hydrochloride CAS RN®: 147-24-0; UNII: TC2D6JAD40.

DEFINITION

Diphenhydramine Hydrochloride contains NLT 98.0% and NMT 102.0% of diphenhydramine hydrochloride ($C_{17}H_{21}NO \cdot HCl$), calculated on the dried basis.

IDENTIFICATION

Change to read:

• **A.** ▲**Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*: 197K**▲ (CN 1-May-2020)

• **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

• **C.** **Identification Tests—General, *Chloride* ⟨191⟩**

ASSAY

• **Procedure**

Buffer: 5.4 g/L of monobasic potassium phosphate. Adjust with phosphoric acid to a pH to 3.0.

Diluent: Acetonitrile and *Buffer* (35:65)

System suitability solution: 0.1 mg/mL each of USP Diphenhydramine Hydrochloride RS and USP Diphenhydramine Related Compound A RS in *Diluent*

Standard solution: 0.07 mg/mL of USP Diphenhydramine Hydrochloride RS in *Diluent*

Sample solution: 0.07 mg/mL of Diphenhydramine Hydrochloride in *Diluent*

Mobile phase: See *Table 1*.

Table 1

Time (min)	Buffer (%)	Acetonitrile (%)
0	65	35
4	65	35
7	20	80
9	65	35
13	65	35

Chromatographic system

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

Mode: LC

Detector: UV 220 nm

Column: 4.6-mm × 25-cm; 5-µm packing L7

Flow rate: 1.2 mL/min

Injection volume: 10 µL

System suitability

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

Suitability requirements

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

Resolution: NLT 1.5 between diphenhydramine related compound A and diphenhydramine, *System suitability solution*

Tailing factor: NMT 1.8, *Standard solution*

Relative standard deviation: NMT 0.85% for six replicate injections, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of diphenhydramine hydrochloride ($C_{17}H_{21}NO \cdot HCl$) in the portion of sample 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 Diphenhydramine Hydrochloride RS in the *Standard solution* (mg/mL)

C_U = concentration of Diphenhydramine Hydrochloride in the *Sample solution* (mg/mL)

Acceptance criteria: 98.0%–102.0% on the dried basis

IMPURITIES

- **RESIDUE ON IGNITION ⟨281⟩:** NMT 0.1%
- **ORGANIC IMPURITIES**

Buffer: 5.4 g/L of monobasic potassium phosphate. Adjust with phosphoric acid to a pH of 3.0.

Mobile phase: Acetonitrile and *Buffer* (35:65)

System suitability solution: 0.1 mg/mL each of USP Diphenhydramine Related Compound A RS, benzhydrol, and USP Diphenhydramine Hydrochloride RS in *Mobile phase*

Standard solution: 0.0035 mg/mL of USP Diphenhydramine Hydrochloride RS in *Mobile phase*

Sample solution: 0.7 mg/mL of Diphenhydramine Hydrochloride in *Mobile phase*

Chromatographic system

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

Mode: LC

Detector: UV 220 nm

Column: 4.6-mm × 25-cm; 5-µm packing L7

Flow rate: 1.2 mL/min

Injection volume: 10 µL

Run time: 7 times the retention time of diphenhydramine

System suitability

[NOTE—See *Table 2* for the relative retention times.]

Sample: *System suitability solution*

Suitability requirements

Resolution: NLT 2.0 between diphenhydramine related compound A and diphenhydramine

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in the portion of Diphenhydramine Hydrochloride taken:

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

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

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

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

C_U = concentration of Diphenhydramine Hydrochloride in the *Sample solution* (mg/mL)

F = relative response factor (see *Table 2*)

Acceptance criteria: See *Table 2*. [NOTE—Disregard peaks that are less than 0.05% of the diphenhydramine peak.]

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Diphenhydramine related compound A[a]	0.9	1.0	0.5
Diphenhydramine	1.0	—	—
4-Methyldiphen hydramine[b]	1.5	1.0	0.3
4-Bromodiphen hydramine[c]	1.8	1.0	0.3
Benzhydrol[d]	2.6	1.4	0.3
Benzophenone[e]	5.1	1.0	0.3
Any other unspecified impurity	—	1.0	0.10
Total impurities	—	—	1.0

[a] 2-(Diphenylmethoxy)-*N*-methylethanamine.

[b] 2-[(*RS*)-(4-Methylphenyl)phenylmethoxy]-*N*,*N*-dimethylethanamine.

[c] 2-[(*RS*)-(4-Bromophenyl)phenylmethoxy]-*N*,*N*-dimethylethanamine.

[d] Diphenylmethanol.

[e] Diphenylmethanone.

SPECIFIC TESTS

- **Acidity or Alkalinity**

  Sample solution: 50 mg/mL of Diphenhydramine Hydrochloride in carbon dioxide-free water

  Analysis: To 10 mL of the *Sample solution*, add 0.15 mL of methyl red TS 2 and 0.25 mL of 0.01 N hydrochloric acid. The solution is pink. Titrate with 0.01 N sodium hydroxide.

  Acceptance criteria: NMT 0.5 mL of 0.01 N sodium hydroxide is required to change the color of the solution to yellow.

- **Loss on Drying** ⟨731⟩

  Sample: Dry a sample at 105° for 3 h.

  Acceptance criteria: NMT 0.5%

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in tight, light-resistant containers. Store at room temperature.
- **USP Reference Standards** ⟨11⟩

  USP Diphenhydramine Hydrochloride RS

  USP Diphenhydramine Related Compound A RS

  2-(Diphenylmethoxy)-*N*-methylethanamine hydrochloride.

  $C_{16}H_{19}NO \cdot HCl$ 277.79

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

Topic/Question	Contact	Expert Committee
DIPHENHYDRAMINE HYDROCHLORIDE	Documentary Standards Support	SM52020 Small Molecules 5

Chromatographic Database Information: Chromatographic Database

Most Recently Appeared In:
Pharmacopeial Forum: Volume No. PF 38(2)

Current DocID: GUID-67E581CC-E9F4-4595-BD84-EBDB8821DF4E_4_en-US

DOI: https://doi.org/10.31003/USPNF_M27130_04_01

DOI ref: 79u56