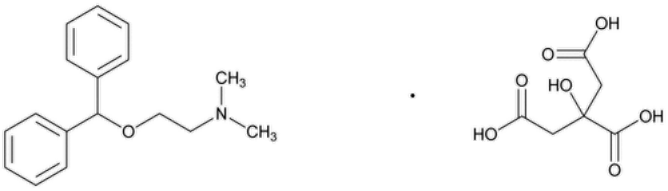
Status: Currently Official on 14-Feb-2025
Official Date: Official as of 01-May-2020
Document Type: USP Monographs
DocId: GUID-D6FC9CF1-7B7A-4B77-87CF-80A9EE8B5598_4_en-US
DOI: https://doi.org/10.31003/USPNF_M27120_04_01
DOI Ref: ogc5h

Diphenhydramine Citrate



$C_{17}H_{21}NO \cdot C_6H_8O_7$ 447.48

Ethanamine, 2-(diphenylmethoxy)-*N*,*N*-dimethyl-, 2-hydroxy-1,2,3-propanetricarboxylate (1:1);
2-(Diphenylmethoxy)-*N*,*N*-dimethylethylamine citrate (1:1) CAS RN®: 88637-37-0; UNII: 4OD433S209.

DEFINITION
Diphenhydramine Citrate contains NLT 98.0% and NMT 102.0% of diphenhydramine citrate ($C_{17}H_{21}NO \cdot C_6H_8O_7$), 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, *Citrate* ⟨191⟩

ASSAY

• **Procedure**

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

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

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

System suitability solution: 0.15 mg/mL of USP Diphenhydramine Citrate RS and 0.1 mg/mL of USP Diphenhydramine Related Compound A RS in *Diluent*

Standard solution: 0.12 mg/mL of USP Diphenhydramine Citrate RS in *Diluent*

Sample solution: 0.12 mg/mL of Diphenhydramine Citrate in *Diluent*

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 citrate ($C_{17}H_{21}NO \cdot C_6H_8O_7$) in the portion of Diphenhydramine Citrate taken:

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

r_U = peak response for diphenhydramine from the *Sample solution*

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

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

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

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

IMPURITIES

- **RESIDUE ON IGNITION ⟨281⟩**

Sample: 8 g

Analysis: To the *Sample* add 5 mL of sulfuric acid, and char. After the substance is thoroughly charred, add 4 mL of nitric acid and a few drops of sulfuric acid, heat gently until fumes are no longer evolved, and ignite at 800 ± 25° until the carbon is consumed. Place in a muffle furnace at 550 ± 50° for about 1 h. Continue the ignition until constant weight is attained.

Acceptance criteria: NMT 0.1% remains.

- **ORGANIC IMPURITIES**

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

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

System suitability solution: 0.15 mg/mL each of USP Diphenhydramine Related Compound A RS, benzhydrol, and USP Diphenhydramine Citrate RS in *Mobile phase*

Standard solution: 0.005 mg/mL of USP Diphenhydramine Citrate RS in *Mobile phase*

Sensitivity solution: 0.5 µg/mL of USP Diphenhydramine Citrate RS in *Mobile phase* from the *Standard solution*

Sample solution: 1.1 mg/mL of Diphenhydramine Citrate 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: 8 times the retention time of diphenhydramine

System suitability

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

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

Suitability requirements

Resolution: NLT 2.0 between diphenhydramine related compound A and diphenhydramine

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

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in the portion of Diphenhydramine Citrate 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 Citrate RS in the *Standard solution* (mg/mL)

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

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

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

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Citric acid[a]	0.3	—	—
Diphenhydramine related compound A[b]	0.9	1.6	0.5
Diphenhydramine	1.0	—	—
4-Methyldiphenhydramine[c]	1.4	1.4	0.3
4-Bromodiphenhydramine[d]	1.8	1.4	0.3
Benzhydrol[e]	3.8	2.4	0.3
Benzophenone[f]	7.7	1.4	0.3
Any other unspecified impurity	—	1.0	0.10
Total impurities	—	—	1.0

[a] Salt counter ion is included in the table for identification purposes only.

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

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

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

[e] Diphenylmethanol.

[f] Diphenylmethanone.

SPECIFIC TESTS

• **Loss on Drying ⟨731⟩**

Sample: Dry at 105° for 3 h.

Acceptance criteria: NMT 0.5%

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in tight, light-resistant containers.

• **USP Reference Standards ⟨11⟩**

USP Diphenhydramine Citrate 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 CITRATE	Documentary Standards Support	SM52020 Small Molecules 5

Chromatographic Database Information: Chromatographic Database

Most Recently Appeared In:
Pharmacopeial Forum: Volume No. PF 38(4)
Current DocID: GUID-D6FC9CF1-7B7A-4B77-87CF-80A9EE8B5598_4_en-US
DOI: https://doi.org/10.31003/USPNF_M27120_04_01
DOI ref: ogc5h