Status: Currently Official on 14-Feb-2025
Official Date: Official as of 01-Dec-2022
Document Type: USP Monographs
DocId: GUID-350307BB-61B2-4090-8CEA-01374092629F_3_en-US
DOI: https://doi.org/10.31003/USPNF_M11815_03_01
DOI Ref: mp6dl



# Diphenhydramine Hydrochloride Oral Powder

**DEFINITION**

Diphenhydramine Hydrochloride Oral Powder contains NLT 90.0% and NMT 110.0% of the labeled amount of diphenhydramine hydrochloride ($C_{17}H_{21}NO \cdot HCl$).

**IDENTIFICATION**

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

▲▲ (USP 1-Dec-2022)

**Buffer:** 5.52 g/L of monobasic potassium hexafluorophosphate in water▲▲ (USP 1-Dec-2022)

**Solution A:** ▲Add 0.5 mL of phosphoric acid per 1 L of *Buffer*.▲ (USP 1-Dec-2022)

**Solution B:** ▲For each liter, mix 700 mL of acetonitrile with 300 mL of *Buffer*. Add 0.5 mL of phosphoric acid per 1 L of this mixture.▲ (USP 1-Dec-2022)

**Mobile phase:** See *Table 1*.

**Table 1**

| Time (min) | Solution A (%) | Solution B (%) |
|---|---|---|
| 0 | 70 | 30 |
| 0.5 | 70 | 30 |
| 3.4 | 45 | 55 |
| 4.3 | 20 | 80 |
| 4.6 | 20 | 80 |
| 4.7 | 70 | 30 |
| 5.3 | 70 | 30 |

**Diluent:** ▲For each liter, mix 300 mL of acetonitrile, 700 mL of water, and 10 mL of acetic acid, glacial.▲ (USP 1-Dec-2022)

**System suitability solution:** 0.0025 mg/mL each of USP Diphenhydramine Hydrochloride RS, USP Diphenhydramine Related Compound A RS, and USP Benzhydrol RS in *Diluent*. ▲Pass the solution through a polytetrafluoroethylene (PTFE) filter of 0.2-µm pore size.▲ (USP 1-Dec-2022)

**Standard solution:** 0.25 mg/mL of USP Diphenhydramine Hydrochloride RS in *Diluent*. ▲Pass the solution through a PTFE filter of 0.2-µm pore size.▲ (USP 1-Dec-2022)

**Sample solution:** Nominally 0.25 mg/mL of diphenhydramine hydrochloride in *Diluent* prepared as follows. Remove the contents of NLT 5 pouches as completely as possible, and weigh. Transfer a portion of the composite powder, equivalent to 50 mg of diphenhydramine hydrochloride, to a 200-mL volumetric flask. Dilute with *Diluent* to volume. ▲Pass the solution through a PTFE filter of 0.2-µm pore size.▲ (USP 1-Dec-2022)

**Chromatographic system**

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

**Mode:** LC

**Detector:** UV 220 nm. For *Identification B*, use a diode array detector in the range of 210–400 nm.

**Column:** 2.1-mm × 5-cm; 1.7-µm packing L1

**Column temperature:** 40°

**Flow rate:** 0.9 mL/min

**Injection volume:** 2.5 µL

**System suitability**

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

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

**Suitability requirements**

**Resolution:** NLT 2.0 between benzhydrol and diphenhydramine related compound A; NLT 2.0 between diphenhydramine related compound A and diphenhydramine, *System suitability solution*

**Tailing factor:** NMT 2.0, *Standard solution*

**Relative standard deviation:** NMT ▲1.0%,▲ (USP 1-Dec-2022) *Standard solution*

**Analysis**

**Samples:** *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of diphenhydramine hydrochloride ($C_{17}H_{21}NO \cdot HCl$) in the portion of Oral Powder taken:

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

$r_U$ = peak response of diphenhydramine 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)

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

**Acceptance criteria:** 90.0%–110.0%

**PERFORMANCE TESTS**

• **UNIFORMITY OF DOSAGE UNITS ⟨905⟩:** Meets the requirements

**IMPURITIES**

***Change to read:***

• **ORGANIC IMPURITIES**

**Buffer, Solution A, Solution B, Mobile phase, Diluent, System suitability solution,** ▲▲ (USP 1-Dec-2022) and **Chromatographic system:** Proceed as directed in the *Assay*.

**Standard solution:** 0.5 µg/mL each of USP Diphenhydramine Hydrochloride RS and USP Benzophenone RS, ▲1.25 µg/mL▲ (USP 1-Dec-2022) of USP Diphenhydramine Related Compound A RS, and ▲2.5 µg/mL▲ (USP 1-Dec-2022) each of USP Benzhydrol RS and USP Diphenhydramine N-Oxide RS in *Diluent*

▲**Sample solution:** Nominally 250 µg/mL of diphenhydramine hydrochloride in *Diluent* from Oral Powder, prepared as directed in the *Assay*▲ (USP 1-Dec-2022)

**System suitability**

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

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

**Suitability requirements**

**Resolution:** NLT 2.0 between benzhydrol and diphenhydramine related compound A; NLT 2.0 between diphenhydramine related compound A and diphenhydramine, *System suitability solution*

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

**Analysis**

**Samples:** *Standard solution* and *Sample solution*

Calculate the percentage of diphenhydramine related compound A, benzhydrol, benzophenone, or diphenhydramine *N*-oxide in the portion of Oral Powder taken:

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

$r_U$ = peak response of diphenhydramine related compound A, benzhydrol, benzophenone, or diphenhydramine *N*-oxide from the *Sample solution*

$r_S$ = peak response of diphenhydramine related compound A, benzhydrol, benzophenone, or diphenhydramine *N*-oxide from the *Standard solution*

$C_S$ = concentration of USP Diphenhydramine Related Compound A RS, USP Benzhydrol RS, USP Benzophenone RS, or USP Diphenhydramine N-Oxide RS in the *Standard solution* (▲µg/mL▲ (USP 1-Dec-2022))

$C_U$ = nominal concentration of diphenhydramine hydrochloride in the *Sample solution* (▲µg/mL▲ (USP 1-Dec-2022))

Calculate the percentage of any unspecified degradation product in the portion of Oral Powder taken:

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

$r_U$ = peak response of any unspecified degradation product 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* (▲µg/mL▲ (USP 1-Dec-2022))

$C_U$ = nominal concentration of diphenhydramine hydrochloride in the *Sample solution* (▲µg/mL▲ (USP 1-Dec-2022))

**Acceptance criteria:** See *Table 2*.

**Table 2**

| Name | Relative Retention Time | Acceptance Criteria, NMT (%) |
|---|---|---|
| Benzhydrol | 0.8 | 1.0 |
| Diphenhydramine related compound A | 0.9 | 0.5 |
| Diphenhydramine | 1.0 | — |
| Diphenhydramine *N*-oxide | 1.1 | 1.0 |
| Benzophenone | 1.2 | ▲0.4▲ (USP 1-Dec-2022) |
| Any unspecified degradation product | — | 0.2 |
| Total degradation products | — | 3.0 |

## ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in tight, unit-dose containers. Store at controlled room temperature.

***Change to read:***

• **USP Reference Standards** ⟨11⟩

USP Benzhydrol RS

Diphenylmethanol.

$C_{13}H_{12}O$ ▲184.24▲ (USP 1-Dec-2022)

USP Benzophenone RS

▲Benzophenone; also known as▲ (USP 1-Dec-2022) diphenylmethanone.

$C_{13}H_{10}O$ 182.22

USP Diphenhydramine Hydrochloride RS

USP Diphenhydramine Related Compound A RS

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

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

USP Diphenhydramine N-Oxide RS

2-(Benzhydryloxy)-*N*,*N*-dimethylethan-1-amine oxide hydrochloride.

$C_{17}H_{21}NO_2 \cdot HCl$ 307.82

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

| Topic/Question | Contact | Expert Committee |
|---|---|---|
| DIPHENHYDRAMINE HYDROCHLORIDE ORAL POWDER | Documentary Standards Support | SM52020 Small Molecules 5 |

**Chromatographic Database Information:** Chromatographic Database

**Most Recently Appeared In:**
Pharmacopeial Forum: Volume No. 47(3)

**Current DocID: GUID-350307BB-61B2-4090-8CEA-01374092629F_3_en-US**

**DOI: https://doi.org/10.31003/USPNF_M11815_03_01**

**DOI ref: mp6dl**