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Diphenhydramine Hydrochloride Injection

DEFINITION

Diphenhydramine Hydrochloride Injection is a sterile solution of Diphenhydramine Hydrochloride in Water for Injection. It contains NLT 90.0% and NMT 110.0% of the labeled amount of diphenhydramine hydrochloride ($C_{17}H_{21}NO \cdot HCl$).

IDENTIFICATION

- **A.**

  Sample solution: Dilute a volume of Injection equivalent to 50 mg of diphenhydramine hydrochloride with 0.03 N sulfuric acid to 25 mL.

  Analysis: Proceed as directed in *Identification—Organic Nitrogenous Bases ⟨181⟩*, beginning with “Transfer the liquid to a separator”.

  Acceptance criteria: Meets the requirements

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

ASSAY

- **Procedure**

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

  Solution A: *Buffer*

  Solution B: Acetonitrile

  Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	65	35
4	65	35
7	20	80
9	65	35
13	65	35

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

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

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

Sample solution: Nominally equivalent to 0.07 mg/mL of diphenhydramine hydrochloride in *Diluent* prepared as follows. Transfer 5.0 mL of Injection, equivalent to 250 mg of diphenhydramine hydrochloride, to a 500-mL volumetric flask and dilute with water to volume. Transfer 7.0 mL of this solution to a 50-mL volumetric flask and dilute with *Diluent* to volume.

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*

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

Suitability requirements

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

Relative standard deviation: NMT 2.0%, *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 Injection 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 = nominal concentration of diphenhydramine hydrochloride in the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0%

IMPURITIES

• **ORGANIC IMPURITIES**

Buffer, System suitability solution, and **Chromatographic system:** Proceed as directed in the *Assay* with a run time that is 10 times the retention time of diphenhydramine.

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

Standard solution: 0.002 mg/mL of USP Diphenhydramine Hydrochloride RS in *Mobile phase*

Sample solution: Nominally equivalent to 2 mg/mL of diphenhydramine hydrochloride in water prepared as follows. Transfer a volume of Injection, equivalent to 500 mg of diphenhydramine hydrochloride, to a 250-mL volumetric flask and dilute with water to volume.

System suitability

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

[NOTE—See *Table 2* for the relative retention times. Inject a blank injection between the *System suitability solution* and *Standard solution*.]

Suitability requirements

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

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

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each degradation product in the portion of Injection taken:

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

r_U = peak response of each degradation product 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 = nominal concentration of diphenhydramine hydrochloride in the *Sample solution* (mg/mL)

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

Acceptance criteria: See *Table 2*. Disregard any peaks less than 0.05%.

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Diphenhydramine related compound A	0.9	1.1	0.4
Diphenhydramine	1.0	—	—
Benzhydrol[a]	4.3	1.5	0.4
Benzophenone[b]	8.2	0.8	0.2
Individual unspecified impurity	—	—	0.2
Total impurities	—	—	0.8

[a] Diphenylmethanol.

[b] Diphenylmethanone.

SPECIFIC TESTS

• **pH ⟨791⟩:** 4.0–6.5

• **Bacterial Endotoxins Test ⟨85⟩:** NMT 3.4 USP Endotoxin Units/mg of diphenhydramine hydrochloride

• **Other Requirements:** It meets the requirements in *Injections and Implanted Drug Products ⟨1⟩*.

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in single-dose or multiple-dose containers, preferably of Type I glass, protected from light. Store at controlled 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 INJECTION	Documentary Standards Support	SM52020 Small Molecules 5

Chromatographic Database Information: Chromatographic Database

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