Diphenhydramine Hydrochloride Oral Solution

Type of Posting	Revision Bulletin
Posting Date	25–Mar–2016
Official Date	01–May–2016
Expert Committee	Chemical Medicines Monographs 6
Reason for Revision	Compliance

In accordance with the Rules and Procedures of the 2015-2020 Council of Experts, the Chemical Medicines Monographs 6 Expert Committee has revised the Diphenhydramine Hydrochloride Oral Solution monograph. The purpose for the revision is to postpone the *Organic Impurities* section of this monograph, because of comments received regarding the inclusion of limits for unspecified impurities, which is scheduled to become official on May 01, 2016.

The Diphenhydramine Hydrochloride Oral Solution Revision Bulletin supersedes the currently official Diphenhydramine Hydrochloride Oral Solution monograph. The Revision Bulletin will be incorporated in *USP 40–NF 35.*

Should you have any questions, please contact Clydewyn M. Anthony, Ph.D (301–816–8139 or cma@usp.org.)

Diphenhydramine Hydrochloride Oral Solution

DEFINITION

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

IDENTIFICATION

Delete the following:

▲• **A. IDENTIFICATION—ORGANIC NITROGENOUS BASES** ⟨181⟩
Sample: Oral Solution equivalent to 50 mg of diphenhydramine hydrochloride
Analysis: Place the *Sample* in a separator, add 0.5 mL of 2 N sulfuric acid, and extract with three 15-mL portions of ether, discarding the extracts. Add 5 mL of water. In a second separator, dissolve 50 mg of USP Diphenhydramine Hydrochloride RS in 25 mL of water. Treat each solution as follows. Add 2 mL of 1 N sodium hydroxide, and extract with 75 mL of *n*-heptane. Wash the *n*-heptane extract with 10 mL of water, evaporate the extract to dryness, and dissolve the residue in 4 mL of carbon disulfide. Pass through a dry filter to clarify the solution, if necessary, and proceed as directed in the Chapter beginning with "Determine the absorption spectra of the filtered solutions".
Acceptance criteria: Meets the requirements▲*USP39*

Add the following:

▲• **A.** The UV spectrum of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay.*▲*USP39*
• **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

Change to read:

• **PROCEDURE**
▲**Solution A:** 11.24 g/L of sodium perchlorate monohydrate in water. Add 1 mL of trifluoroacetic acid to each L of solution prepared.
Solution B: Acetonitrile and trifluoroacetic acid (1000:1)
Solution C: *Solution A* and *Solution B* (82:18)
Solution D: *Solution A* and *Solution B* (50:50)
Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution C (%)	Solution D (%)
0	100	0
14.0	0	100
20.0	0	100
20.1	100	0
25.0	100	0

Diluent: Acetonitrile and water (18:82)
Standard stock solution: 1.0 mg/mL of USP Diphenhydramine Hydrochloride RS in *Diluent*
Standard solution: 0.25 mg/mL of USP Diphenhydramine Hydrochloride RS from the *Standard stock solution*
System suitability stock solution: 0.0125 mg/mL of USP Diphenhydramine Related Compound A RS prepared as follows. Transfer an appropriate amount of the Reference Standard to a volumetric flask. Add 5% of the flask volume of acetonitrile and dilute with *Diluent* to volume. Dilute this solution (1 in 10) with *Diluent*.
System suitability solution: 0.25 mg/mL of USP Diphenhydramine Hydrochloride RS and 0.00025 mg/mL of USP Diphenhydramine Related Compound A RS in *Diluent* from the *Standard stock solution* and *System suitability stock solution*, respectively
Sample solution: Nominally 0.25 mg/mL of diphenhydramine hydrochloride from a suitable volume of Oral Solution in *Diluent*. Pass a portion of the resulting solution through a suitable filter of 0.45-µm pore size, discarding the first few mL of filtrate. Use the filtrate.
Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: LC
Detector: UV 220 nm. For *Identification A,* use a diode-array detector in the range of 200–400 nm.
Column: 4.6-mm × 15-cm; 5-µm packing L1
Column temperature: 35°
Flow rate: 1.2 mL/min
Injection volume: 10 µL
System suitability
Samples: *Standard solution* and *System suitability solution*
[NOTE—See *Table 2* for the relative retention times.]
Suitability requirements
Resolution: NLT 1.5 between diphenhydramine and diphenhydramine related compound A, *System suitability solution*
Tailing factor: 0.5–2.0, *Standard 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 Oral Solution 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%▲*USP39*

OTHER COMPONENTS

• **ALCOHOL DETERMINATION** ⟨611⟩ (if present)**:** 90.0%–110.0% of the labeled amount of ethanol (C_2H_5OH)

IMPURITIES

Change to read:

▲• **ORGANIC IMPURITIES**
Mobile phase, Diluent, and **Sample solution:** Proceed as directed in the *Assay*.
Standard stock solution: 0.25 mg/mL of USP Diphenhydramine Hydrochloride RS in *Diluent*

Impurity stock solution: 0.25 mg/mL each of USP Diphenhydramine Related Compound A RS, USP Diphenhydramine Related Compound B RS, USP Diphenhydramine *N*-Oxide RS, USP Benzhydrol RS, and USP Benzophenone RS in *Diluent*

Standard solution: 0.0025 mg/mL each of USP Diphenhydramine Hydrochloride RS, USP Diphenhydramine Related Compound A RS, USP Diphenhydramine Related Compound B RS, USP Diphenhydramine *N*-Oxide RS, USP Benzhydrol RS, and USP Benzophenone RS in *Diluent* from the *Standard stock solution* and *Impurity stock solution*, respectively

System suitability stock solution: 0.0125 mg/mL each of USP Diphenhydramine Related Compound A RS and USP Diphenhydramine Related Compound B RS prepared as follows. Transfer an appropriate amount of each Reference Standard to a volumetric flask. Add 5% of the flask volume of acetonitrile and dilute with *Diluent* to volume. Dilute this solution (1 in 10) with *Diluent*.

System suitability solution: 0.00025 mg/mL each of USP Diphenhydramine Hydrochloride RS, USP Diphenhydramine Related Compound A RS, and USP Diphenhydramine Related Compound B RS in *Diluent* from the *Standard stock solution* and *System suitability stock solution*, respectively

Chromatographic system: Proceed as directed in the *Assay* except for the *Detector* parameters.

Detector: UV 272 nm. Switch to 220 nm at 8.5 min and 254 nm at 16.0 min.

System suitability

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

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

Suitability requirements

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

Relative standard deviation: NMT 6.0% for each component, *Standard solution*

Analysis

Samples: *Sample solution* and *Standard solution*

Calculate the percentage of each specified degradation product in the portion of Oral Solution taken:

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

r_U = peak response of each specified degradation product from the *Sample solution*

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

C_S = concentration of the appropriate USP Reference Standard in the *Standard solution* (mg/mL)

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

Calculate the percentage of each unspecified degradation product in the portion of Oral Solution taken:

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

r_U = peak response of each 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* (mg/mL)

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

Acceptance criteria: See *Table 2*. Disregard any impurity peak less than 0.1%.

Table 2

Name		Relative Retention Time	Acceptance Criteria, NMT (%)
Sodium benzoate[a]		0.50	—
Diphenhydramine		1.00	—
Diphenhydramine *N*-oxide		1.07	3.0
Benzhydrol		1.12	2.0
Benzophenone		1.45	0.4
Unspecified degradation products	Diphenhydramine related compound B[b]	0.93	0.2 each
	Diphenhydramine related compound A	0.96	
	Any individual unspecified degradation product	—	
Total impurities		—	3.0

[a] Included in the table for identification only.

[b] Monitor for this degradation product in liquid formulations that contain glycerin.

●(Postponed indefinitely)● (RB 1-May-2016)▲*USP39*

PERFORMANCE TESTS

Add the following:

▲● **DELIVERABLE VOLUME** ⟨**698**⟩**:** Meets the requirements▲*USP39*

SPECIFIC TESTS

Add the following:

▲● **pH** ⟨**791**⟩**:** 3.5–5.5▲*USP39*

Add the following:

▲● **MICROBIAL ENUMERATION TESTS** ⟨**61**⟩ and **TESTS FOR SPECIFIED MICROORGANISMS** ⟨**62**⟩**:** It meets the requirements of the test for the absence of *Escherichia coli*. The total aerobic microbial count does not exceed 10^2 cfu/mL. The total yeasts and molds count does not exceed 10^1 cfu/mL.▲*USP39*

ADDITIONAL REQUIREMENTS

Change to read:

• **PACKAGING AND STORAGE:** ▲Store at controlled room temperature.▲*USP39*

Change to read:

- **USP REFERENCE STANDARDS** ⟨**11**⟩

▲USP Benzhydrol RS
Diphenylmethanol.
$C_{13}H_{12}O$ 184.23 •(Postponed indefinitely)• (RB 1-May-2016)

USP Benzophenone RS
Diphenylmethanone.
$C_{13}H_{10}O$ 182.22 •(Postponed indefinitely)• (RB 1-May-2016)
▲*USP39*

USP Diphenhydramine Hydrochloride RS

▲USP Diphenhydramine *N*-Oxide RS
2-(Benzhydryloxy)-*N*,*N*-dimethylethan-1-amine oxide hydrochloride.
$C_{17}H_{21}NO_2 \cdot HCl$ 307.82 •(Postponed indefinitely)• (RB 1-May-2016)

USP Diphenhydramine Related Compound A RS
2-(Diphenylmethoxy)-*N*-methylethanamine hydrochloride.
$C_{16}H_{19}NO \cdot HCl$ 277.79

USP Diphenhydramine Related Compound B RS
3-(Benzhydryloxy)propane-1,2-diol.
$C_{16}H_{18}O_3$ 258.32 •(Postponed indefinitely)• (RB 1-May-2016)
▲*USP39*