Diphenhydramine Hydrochloride Capsules

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 Capsules 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 Capsules Revision Bulletin supersedes the currently official Diphenhydramine Hydrochloride Capsules 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 Capsules

DEFINITION

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

IDENTIFICATION

- **A. IDENTIFICATION—ORGANIC NITROGENOUS BASES ⟨181⟩:** The contents of the Capsules meet 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

Change to read:

- **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: Nominally 0.07 mg/mL of USP Diphenhydramine Hydrochloride RS in *Diluent*
Sample stock solution: Weigh and combine the contents of NLT 20 Capsules. Transfer an accurately weighed portion of the combined Capsule contents, equivalent to about 50 mg of diphenhydramine hydrochloride, to a 100-mL volumetric flask. Dissolve in and dilute with water to volume, and filter. Alternatively, dissolve NLT 20 Capsules in water at 50° and pipet the solution equivalent to about 50 mg of diphenhydramine hydrochloride to a 100-mL volumetric flask. Dissolve in and dilute with water to volume, and filter.
Sample solution: 0.07 mg/mL of diphenhydramine hydrochloride in *Diluent* from the *Sample stock solution*
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 Capsule contents 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)▲*USP39*
Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

- **DISSOLUTION ⟨711⟩**

Procedure for a pooled sample
Medium: Water; 500 mL
Apparatus 1: 100 rpm
Time: 30 min
Mobile phase and **Chromatographic system:** Proceed as directed in the *Assay*.
Injection volume: 50 µL
Standard solution: USP Diphenhydramine Hydrochloride RS in *Medium*, at a known concentration similar to that of the *Sample solution*
Sample solution: Dilute with *Medium* to a concentration that is similar to that of the *Standard solution*.
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of diphenhydramine hydrochloride ($C_{17}H_{21}NO \cdot HCl$) dissolved.
Tolerances: NLT 80% (*Q*) of the labeled amount of diphenhydramine hydrochloride ($C_{17}H_{21}NO \cdot HCl$) is dissolved.

- **UNIFORMITY OF DOSAGE UNITS ⟨905⟩:** Meet the requirements

IMPURITIES

Change to read:

▲• ORGANIC IMPURITIES
Buffer, Diluent, and **System suitability solution:** Prepare as directed in the *Assay*.
Mobile phase: Acetonitrile and *Buffer* (35:65)
Standard solution: 0.02 mg/mL of USP Diphenhydramine Hydrochloride RS and 0.01 mg/mL of USP Diphenhydramine Related Compound A RS in *Diluent*
Sample solution: Nominally equivalent to 2 mg/mL of diphenhydramine hydrochloride in *Diluent* prepared as follows. Remove the contents of NLT 20 Capsules as completely as possible, and weigh. Transfer a portion of the powder, nominally equivalent to 100 mg of diphenhydramine hydrochloride, to a 50-mL volumetric flask. Dilute with *Diluent* to volume. Sonicate the solution for 5 min.

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: 10 times the retention time of diphenhydramine
System suitability
Sample: *System suitability solution*
[NOTE—See *Table 2* for the relative retention times.]
Suitability requirements
Resolution: NLT 2.0 between diphenhydramine and diphenhydramine related compound A
Relative standard deviation: NMT 5.0% for diphenhydramine and diphenhydramine related compound A
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of diphenhydramine related compound A in the portion of Capsule contents taken:

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

r_U = peak response of diphenhydramine related compound A from the *Sample solution*
r_S = peak response of diphenhydramine related compound A from the *Standard solution*
C_S = concentration of USP Diphenhydramine Related Compound A RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of diphenhydramine hydrochloride in the *Sample solution* (mg/mL)

Calculate the percentage of each degradation product in the portion of Capsule contents 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 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)
F = relative response factor (see *Table 2*)
Acceptance criteria: See *Table 2*. Disregard any impurity peak less than 0.05%.

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Diphenhydramine related compound A	0.9	1.0	0.5
Diphenhydramine	1.0	—	—
Diphenhydramine *N*-oxide[a]	1.2	1.0	3.0
Benzhydrol[b]	4.7	1.5	2.0
Benzophenone[c]	9.3	0.8	0.4
Individual unspecified impurity	—	—	1.0

[a] 2-(Benzhydryloxy)-*N*,*N*-dimethylethan-1-amine oxide.
[b] Diphenylmethanol.
[c] Diphenylmethanone.

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

ADDITIONAL REQUIREMENTS

Change to read:

• **PACKAGING AND STORAGE:** Preserve in tight containers. ▲ Store at controlled room temperature.▲*USP39*

Change to read:

• **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▲*USP39*