Diphenhydramine Hydrochloride Capsules

Type of Posting  Revision Bulletin
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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 (C17H21NO·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>
<thead>
<tr>
<th>Table 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time (min)</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>7</td>
</tr>
<tr>
<td>9</td>
</tr>
<tr>
<td>13</td>
</tr>
</tbody>
</table>

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.**

**PERFORMANCE TESTS**

- **DISSOLUTION (711)**
  Procedure for a pooled sample
  Medium: Water; 500 mL
  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 (C17H21NO·HCl) dissolved.
  Tolerances: NLT 80% of the labeled amount of diphenhydramine hydrochloride (C17H21NO·HCl) is dissolved.

**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.
Diphenhydramine

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:

\[
\text{Result} = \left( \frac{r_U}{r_S} \right) \times \left( \frac{C_S}{C_U} \right) \times 100
\]

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

Calculate the percentage of each degradation product in the portion of Capsule contents taken:

\[
\text{Result} = \left( \frac{r_U}{r_S} \right) \times \left( \frac{C_S}{C_U} \right) \times \left( \frac{1}{F} \right) \times 100
\]

\[r_U = \text{peak response of each degradation product from the Sample solution}\]
\[r_S = \text{peak response of diphenhydramine from the Standard solution}\]
\[C_S = \text{concentration of USP Diphenhydramine Hydrochloride RS in the Standard solution (mg/mL)}\]

\[C_U = \text{nominal concentration of diphenhydramine hydrochloride in the Sample solution (mg/mL)}\]

\[F = \text{relative response factor (see Table 2)}\]

Acceptance criteria: See Table 2. Disregard any impurity peak less than 0.05%.

Table 2

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Relative Response Factor</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphenhydramine related compound A</td>
<td>0.9</td>
<td>1.0</td>
<td>0.5</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>1.0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Diphenhydramine N-oxide</td>
<td>1.2</td>
<td>1.0</td>
<td>3.0</td>
</tr>
<tr>
<td>Benzhydrol</td>
<td>4.7</td>
<td>1.5</td>
<td>2.0</td>
</tr>
<tr>
<td>Benzophenone</td>
<td>9.3</td>
<td>0.8</td>
<td>0.4</td>
</tr>
<tr>
<td>Individual unspecified impurity</td>
<td>—</td>
<td>—</td>
<td>1.0</td>
</tr>
</tbody>
</table>

\[\text{USP REFERENCE STANDARDS (11)}\]
USP Diphenhydramine Hydrochloride RS
\[\text{USP Diphenhydramine Related Compound A RS} \]
2-(Diphenylmethoxy)-N-methylethanamine hydrochloride.
\[\text{C}_{16}H_{19}NO \cdot HCl \quad 277.79\text{USP39}\]

**ADDITIONAL REQUIREMENTS**

**Change to read:**

- **Packaging and Storage:** Preserve in tight containers. ▲ Store at controlled room temperature. ▲ USP39

**ADD**

**Change to read:**

- **USP Reference Standards (11)**
USP Diphenhydramine Hydrochloride RS
▲ USP Diphenhydramine Related Compound A RS
2-(Diphenylmethoxy)-N-methylethanamine hydrochloride.
\[\text{C}_{16}H_{19}NO \cdot HCl \quad 277.79\text{USP39}\]