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 (C₁₇H₂₁NO·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

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.
- 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**

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Solution C (%)</th>
<th>Solution D (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>14.0</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>20.0</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>20.1</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>25.0</td>
<td>100</td>
<td>0</td>
</tr>
</tbody>
</table>

  **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°C

  **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 (C₁₇H₂₁NO·HCl) in the portion of Oral Solution taken:

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

  **Acceptance criteria:** 90.0%–110.0%

**OTHER COMPONENTS**

- **ALCOHOL DETERMINATION** (611) (if present): 90.0%–110.0% of the labeled amount of ethanol (C₂H₅OH)

**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:

Result = \( \frac{r_0}{r_1} \times \frac{C_1}{C_0} \times 100 \)

\( r_0 \) = peak response of each specified degradation product from the Sample solution

\( r_1 \) = peak response of the corresponding USP Reference Standard from the Standard solution

\( C_0 \) = concentration of the appropriate USP Reference Standard in the Standard solution (mg/mL)

\( C_1 \) = 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:

Result = \( \frac{r_0}{r_3} \times \frac{C_1}{C_0} \times 100 \)

\( r_0 \) = peak response of each unspecified degradation product from the Sample solution

\( r_3 \) = peak response of diphenhydramine from the Standard solution

\( C_0 \) = concentration of USP Diphenhydramine Hydrochloride RS in the Standard solution (mg/mL)

\( C_1 \) = 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

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium benzoate(^a)</td>
<td>0.50</td>
<td>—</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>1.00</td>
<td>—</td>
</tr>
<tr>
<td>Diphenhydramine N-oxide</td>
<td>1.07</td>
<td>3.0</td>
</tr>
<tr>
<td>Benzhydrol</td>
<td>1.12</td>
<td>2.0</td>
</tr>
<tr>
<td>Benzophenone</td>
<td>1.45</td>
<td>0.4</td>
</tr>
<tr>
<td>Diphenhydramine related compound B(^b)</td>
<td>0.93</td>
<td>0.2 each</td>
</tr>
<tr>
<td>Diphenhydramine related compound A</td>
<td>0.96</td>
<td></td>
</tr>
<tr>
<td>Any individual unspecified degradation product</td>
<td>—</td>
<td></td>
</tr>
</tbody>
</table>

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)\(^\text{USP39})*

PERFORMANCE TESTS

Add the following:

**\(^\bullet\) DELIVERABLE VOLUME (698):** Meets the requirements\(^\text{USP39}\)

SPECIFIC TESTS

Add the following:

**\(^\bullet\) PH (791):** 3.5–5.5\(^\text{USP39}\)

Add the following:

**\(^\bullet\) 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\(^4\) cfu/mL. The total yeasts and molds count does not exceed 10\(^1\) cfu/mL\(^\text{USP39}\)

ADDITIONAL REQUIREMENTS

Change to read:

**• PACKAGING AND STORAGE:** Store at controlled room temperature.\(^\text{USP39}\)
Change to read:

- **USP Reference Standards (11)**
  - USP Benzhydrol RS
    - Diphenylmethanol. \( \text{C}_{16}\text{H}_{19}\text{NO} \cdot \text{HCl} 277.79 \) \( \text{Postponed indefinitely} \) \( \text{(RB 1-May-2016)} \)
  - USP Benzophenone RS
    - Diphenylmethylmethane. \( \text{C}_{16}\text{H}_{18}\text{O} \cdot \text{HCl} 258.32 \) \( \text{Postponed indefinitely} \) \( \text{(RB 1-May-2016)} \)
  - USP Diphenhydramine Hydrochloride RS
    - USP Diphenhydramine N-Oxide RS
      - 2-(Benzhydryloxy)-N,N-dimethylethan-1-amine oxide hydrochloride.