Diphenhydramine Hydrochloride and Ibuprofen Capsules

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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 and Ibuprofen Capsules monograph. The purpose for the revision is to add **Dissolution Test 2** to accommodate FDA-approved drug products with different dissolution conditions and/or tolerances than the existing dissolution test. This revision also necessitates a change in the table numbering in the test for **Organic Impurities**. A **Labeling** section has also been added.

- **Dissolution Test 2** was validated using a GL Sciences Inertsil C8-3 brand of L7 column. The typical retention times for diphenhydramine and ibuprofen are about 3.3 min and 10.8 min, respectively.

The Diphenhydramine Hydrochloride and Ibuprofen Capsules Revision Bulletin supersedes the currently official monograph.

Should you have any questions, please contact Mark Tiedje, Scientific Liaison (301-816-8535 or mark.tiedje@usp.org).
**Diphenhydramine Hydrochloride and Ibuprofen Capsules**

**DEFINITION**

Diphenhydramine Hydrochloride and Ibuprofen Capsules contain NLT 95.0% and NMT 105.0% of the labeled amounts of diphenhydramine hydrochloride (C_{17}H_{21}NO·HCl) and ibuprofen (C_{13}H_{18}O_{2}).

**IDENTIFICATION**

- **A.** The retention times of the diphenhydramine and ibuprofen peaks of the *Sample solution* correspond to those of the *Standard solution*, as obtained in the *Assay*.
- **B.** The UV absorption spectra of the diphenhydramine and ibuprofen peaks of the *Sample solution* and those of the *Standard solution* exhibit maxima at the same wavelengths of 265 and 273 nm, as obtained in the *Assay*.

**ASSAY**

**PROCEDURE**

- **Buffer:** 6.8 g/L of monobasic potassium phosphate in water. Adjust with phosphoric acid to a pH of 3.0.

- **Mobile phase:** Acetonitrile and Buffer (38:62).

- **Standard solution:** 0.05 mg/mL of USP Diphenhydramine Hydrochloride RS and 0.4 mg/mL of USP Ibuprofen RS in Mobile phase

- **Sample stock solution:** Nominally 0.25 mg/mL of diphenhydramine hydrochloride and 2.0 mg/mL of ibuprofen, prepared as follows. Transfer NLT 5 Capsules (including shells) to a suitable volumetric flask, add 4% of amounts of USP Diphenhydramine Hydrochloride RS and 2.2 mg/mL of USP Ibuprofen RS, prepared as follows. Transfer known amounts of USP Diphenhydramine Hydrochloride RS and 0.22 mg/mL of USP Ibuprofen RS to a suitable volumetric flask. Add 5% of the final volume of methanol and sonicate to dissolve. Dilute with Medium to volume.

- **Sample solution:** Nominally 0.05 mg/mL of diphenhydramine hydrochloride and 0.4 mg/mL of ibuprofen in Mobile phase from Sample stock solution

**Chromatographic system**

(See Chromatography (621), System Suitability.)

- **Mode:** LC
- **Detectors:** Assay: UV 220 nm
- **Identification B:** Diode array, UV 200–400 nm
- **Column:** 4.6-mm x 10-cm; 3-μm packing L11
- **Column temperature:** 25°
- **Flow rate:** 1.0 mL/min
- **Injection volume:** 5 μL
- **Run time:** NLT 4 times the retention time of diphenhydramine

**System suitability**

- **Sample:** Standard solution
- **Suitability requirements**
  - **Tailing factor:** NMT 2.0 for both diphenhydramine and ibuprofen
  - **Relative standard deviation:** NMT 2.0% for both diphenhydramine and ibuprofen

**Analysis**

- **Samples:** Standard solution and Sample solution

Calculate the percentage of the labeled amounts of diphenhydramine hydrochloride (C_{17}H_{21}NO·HCl) and ibuprofen (C_{13}H_{18}O_{2}) in the portion of Capsules taken:

\[
\text{Result} = \left( \frac{r_d}{r_s} \right) \times \left( \frac{C_j}{C_i} \right) \times 100
\]

- **r_{d}** = peak response of diphenhydramine or ibuprofen from the *Sample solution*
- **r_{s}** = peak response of diphenhydramine or ibuprofen from the *Standard solution*
- **C_{j}** = concentration of USP Diphenhydramine Hydrochloride RS or USP Ibuprofen RS in the *Standard solution* (mg/mL)
- **C_{i}** = nominal concentration of diphenhydramine hydrochloride or ibuprofen in the *Sample solution* (mg/mL)

**Acceptance criteria:** 95.0%–105.0%

**PERFORMANCE TESTS**

**Change to read:**

- **DISSOLUTION (711)**
- **Test 1a** (RB 1-May-2020)

**Medium:** Phosphate buffer, pH 7.2 (27.22 mg/mL of monobasic potassium phosphate in water and adjust with 100 mg/mL of sodium hydroxide to a pH of 7.2); 900 mL

**Apparatus 1:** 100 rpm

**Time:** 45 min

**Buffer:** 6.8 g/L of monobasic potassium phosphate in water. Adjust with 100 mg/mL of sodium hydroxide to a pH of 6.6.

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

**Standard stock solution:** 0.27 mg/mL of USP Diphenhydramine Hydrochloride RS and 2.2 mg/mL of USP Ibuprofen RS, prepared as follows. Transfer known amounts of USP Diphenhydramine Hydrochloride RS and 0.22 mg/mL of USP Ibuprofen RS to a suitable volumetric flask. Add 5% of the final volume of methanol and sonicate to dissolve. Dilute with Medium to volume.

**Standard solution:** 0.027 mg/mL of USP Diphenhydramine Hydrochloride RS and 0.22 mg/mL of USP Ibuprofen RS in Medium from Standard stock solution

**Sample solution:** Pass a portion of the solution under test through a suitable filter of 0.45-μm pore size and discard the first few mL of the filtrate.

**Chromatographic system**

(See Chromatography (621), System Suitability.)

- **Mode:** LC
- **Detector:** UV 220 nm
- **Column:** 4.6-mm x 15-cm; 5-μm packing L7
- **Column temperature:** 35°
- **Flow rate:** 1.0 mL/min
- **Injection volume:** 5 μL
- **Run time:** NLT 2.3 times the retention time of ibuprofen

**System suitability**

- **Sample:** Standard solution
- **Suitability requirements**
  - **Tailing factor:** NMT 2.0 for both diphenhydramine and ibuprofen
  - **Relative standard deviation:** NMT 2.0% for both diphenhydramine and ibuprofen

**Analysis**

- **Samples:** Standard solution and Sample solution

Calculate the percentage of the labeled amounts of diphenhydramine hydrochloride (C_{17}H_{21}NO·HCl) and ibuprofen (C_{13}H_{18}O_{2}) dissolved:

\[
\text{Result} = \left( \frac{r_d}{r_s} \right) \times \left( \frac{C_j}{C_i} \right) \times V \times \left( \frac{1}{L} \right) \times 100
\]

- **r_{d}** = peak response of diphenhydramine or ibuprofen from the *Sample solution*
- **r_{s}** = peak response of diphenhydramine or ibuprofen from the *Standard solution*
- **C_{j}** = concentration of USP Diphenhydramine Hydrochloride RS or USP Ibuprofen RS in the *Standard solution* (mg/mL)
- **V** = volume of Medium, 900 mL

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2 Diphenhydramine

If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 2.

**Test 2:** If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 2.

### Tier 1
- **0.2 M phosphate buffer pH 7.2:** Dissolve 27.22 g/L of potassium phosphate, monobasic in water and add 5.52 g/L of sodium hydroxide pellets, and mix. Adjust with 0.2 N sodium hydroxide or 0.2 N hydrochloric acid to a pH of 7.2
- **Medium:** 0.2 M phosphate buffer pH 7.2; 900 mL
- **Apparatus 1:** 100 rpm
- **Time:** 30 min

### Tier 2
- **0.2 M phosphate buffer pH 7.2 with pancreatin:** 160 mg/L of pancreatin in 0.2 M phosphate buffer pH 7.2
- **Medium A:** 0.2 M phosphate buffer pH 7.2 with pancreatin; 450 mL
- **Medium B:** 0.2 M phosphate buffer pH 7.2; 450 mL
- **Apparatus 1:** 10 mesh, 100 rpm

#### Procedure

**Tolerances:**
- NLT 75% (Q) of the labeled amounts of diphenhydramine hydrochloride (C\textsubscript{17}H\textsubscript{21}NO · HCl) and ibuprofen (C\textsubscript{13}H\textsubscript{18}O\textsubscript{2}) is dissolved.

**Sample solution:** Pass a portion of the solution through a suitable filter of 0.45-μm pore size.

**Chromatographic system**

(See Chromatography (621), System Suitability.)

- **Mode:** LC
- **Detector:** UV 220 nm
- **Column:** 4.6-mm x 25-cm, 5-μm packing L7
- **Column temperature:** 40°C
- **Flow rate:** 1.2 mL/min

**Injection volume:** 20 μL

**System suitability**

- **Sample:** Standard solution
- **Sample solution:** Standard solution
- **Relative standard deviation:** NMT 2.0% for diphenhydramine and ibuprofen

**Analysis**

- **Samples:** Standard solution and Sample solution
- **Samples:** Standard solution and Sample solution

**Tolerances:**
- NLT 80% (Q) of the labeled amounts of diphenhydramine hydrochloride (C\textsubscript{17}H\textsubscript{21}NO · HCl) and ibuprofen (C\textsubscript{13}H\textsubscript{18}O\textsubscript{2}) is dissolved.

### UNIFORMITY OF DOSAGE UNITS (905): Meet the requirements

**IMPURITIES**

**Change to read:**

- **ORGANIC IMPURITIES**
  - **Buffer:** Proceed as directed in the Assay.
  - **Mobile phase:** Acetonitrile and Buffer (32:68)
  - **Diluent:** Acetonitrile and Buffer (40:60)
  - **System suitability solution:** 0.0005 mg/mL of USP Diphenhydramine Related Compound A RS and 0.25 mg/mL of USP Ibuprofen RS in Diluent. Sonicate if necessary to dissolve.
  - **Standard solution:** 0.00125 mg/mL of USP Diphenhydramine Hydrochloride RS and 0.01 mg/mL of USP Ibuprofen RS in Diluent. Sonicate to dissolve.
  - **Sample solution:** Nominally 0.25 mg/mL of diphenhydramine hydrochloride and 2 mg/mL of ibuprofen, prepared as follows. Transfer a suitable amount of Capsule contents from NLT 10 Capsules to a dry volumetric flask. Add about 60% of the final volume of Diluent and dissolve the contents completely by using a suitable filter of 0.45-μm pore size.
vortex. Dilute with Diluent to volume. Pass a portion through a suitable filter of 0.45-μm pore size.

**Chromatographic system**
(See Chromatography (621), System Suitability.)
Mode: LC
Detector: UV 220 nm
Column: 4.6-mm x 10-cm; 3-μm packing L11
Flow rate: 1.0 mL/min
Injection volume: 20 μL
Run time: NLT 20 times the retention time of diphenhydramine

**System suitability**
Samples: System suitability solution and Standard solution
Resolution: NLT 1.5 between diphenhydramine related compound A and diphenhydramine, System suitability solution
Relative standard deviation: NMT 5.0% for both diphenhydramine and ibuprofen, Standard solution

**Analysis**
Samples: Standard solution and Sample solution
Calculate the percentage of each individual impurity in the portion of Capsules taken:

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

\( r_U \) = peak response of each individual impurity 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 of each individual impurity (see Table 2A (RB 1-May-2020))

**Acceptance criteria:** See Table 2A (RB 1-May-2020).

### Table 2A (RB 1-May-2020)

<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>0.2</td>
</tr>
</tbody>
</table>

**SPECIFIC TESTS**
- **Microbial Enumeration Tests** (61) and **Tests for Specified Microorganisms** (62): NMT 5 x 10² cfu/g for the total aerobic microbial count; NMT 10² cfu/g for total combined yeasts and molds count. It meets the requirements for absence of Escherichia coli, Salmonella species, Staphylococcus aureus, and Pseudomonas aeruginosa.

**ADDITIONAL REQUIREMENTS**
- **Packaging and Storage:** Preserve in tight containers and store at 20°–25°. Protect from light and excessive heat above 40°.

**Add the following:**

**LABELING:** When more than one Dissolution test is given, the labeling states the Dissolution test used only if Test 1 is not used. **(RB 1-May-2020)**

**USP Reference Standards** (11)
USP Diphenhydramine Hydrochloride RS
USP Diphenhydramine Related Compound A RS
2-(Diphenylmethoxy)-N,N-dimethylethanamine hydrochloride, C16H19NO · HCl 277.79
USP Ibuprofen RS

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