Diphenhydramine Hydrochloride and Ibuprofen Capsules

Type of Posting	Revision Bulletin
Posting Date	24–Apr–2020
Official Date	01–May–2020
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 ($C_{17}H_{21}NO \cdot HCl$) 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 the final volume of water, and sonicate for 20 min. Dissolve and dilute with *Mobile phase* to volume. Pass a portion through a suitable filter of 0.45-µm pore size.
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 × 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 ($C_{17}H_{21}NO \cdot HCl$) and ibuprofen ($C_{13}H_{18}O_2$) in the portion of Capsules taken:

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

r_U = peak response of diphenhydramine or ibuprofen from the *Sample solution*
r_S = peak response of diphenhydramine or ibuprofen from the *Standard solution*
C_S = concentration of USP Diphenhydramine Hydrochloride RS or USP Ibuprofen RS in the *Standard solution* (mg/mL)
C_U = 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 1▲ (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 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 × 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 ($C_{17}H_{21}NO \cdot HCl$) and ibuprofen ($C_{13}H_{18}O_2$) dissolved:

$$\text{Result} = (r_U/r_S) \times C_S \times V \times (1/L) \times 100$$

r_U = peak response of diphenhydramine or ibuprofen from the *Sample solution*
r_S = peak response of diphenhydramine or ibuprofen from the *Standard solution*
C_S = concentration of USP Diphenhydramine Hydrochloride RS or USP Ibuprofen RS in the *Standard solution* (mg/mL)
V = volume of *Medium*, 900 mL

L = label claim of diphenhydramine or ibuprofen (mg/Capsule)

Tolerances: NLT 75% (Q) of the labeled amounts of diphenhydramine hydrochloride ($C_{17}H_{21}NO \cdot HCl$) and ibuprofen ($C_{13}H_{18}O_2$) is dissolved.

▲**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

Times

Medium A: 20 min

Medium A and Medium B (see *Procedure*): 10 min

Procedure: Perform the test using the conditions under *Tier 1*. In the presence of cross-linking, repeat the test with new capsules using the conditions under *Tier 2* as follows. After 20 min with 450-mL of *Medium A*, stop the dissolution bath and timer and carefully add 450-mL of *Medium B*, pre-equilibrated at 37°. Restart the bath and timer, and continue the dissolution for an additional 10 min.

Solution A: 2.72 g/L of potassium phosphate, monobasic in water;adjusted with 10% phosphoric acid to a pH of 3.0

Solution B: Acetonitrile

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	58	42
3	58	42
8	30	70
14	30	70
15	58	42
20	58	42

Diluent: *0.2 M phosphate buffer pH 7.2* and *0.2 M phosphate buffer pH 7.2 with pancreatin* (50:50)

Standard stock solution A: 0.7 mg/mL of USP Diphenhydramine Hydrochloride RS in *Medium* for *Tier 1*, or in *Diluent* for *Tier 2*. Sonicate to dissolve.

Standard stock solution B: 1.1 mg/mL of USP Ibuprofen RS. Transfer a suitable quantity of USP Ibuprofen RS to a suitable volumetric flask. Add about 10% of the flask volume of acetonitrile and sonicate to dissolve. Dilute with *Medium* for *Tier 1*, or *Diluent* for *Tier 2*, to volume.

Standard solution: 0.028 mg/mL of USP Diphenhydramine Hydrochloride RS and 0.22 mg/mL of USP Ibuprofen RS in *Medium* for *Tier 1*, or *Diluent* for *Tier 2*

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 × 25-cm, 5-µm packing L7

Column temperature: 40°

Flow rate: 1.2 mL/min

Injection volume: 20 µL

System suitability

Sample: *Standard solution*

[NOTE—The relative retention times for diphenhydramine and ibuprofen are 0.3 and 1.0 respectively.]

Suitability requirements

Tailing factor: NMT 2.0 for both diphenhydramine and ibuprofen

Relative standard deviation: NMT 2.0% for diphenhydramine and ibuprofen

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amounts of diphenhydramine hydrochloride ($C_{17}H_{21}NO \cdot HCl$) and ibuprofen ($C_{13}H_{18}O_2$) dissolved:

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

r_U = peak response of diphenhydramine or ibuprofen from the *Sample solution*

r_S = peak response of diphenhydramine or ibuprofen from the *Standard solution*

C_S = concentration of USP Diphenhydramine Hydrochloride RS or USP Ibuprofen RS in the *Standard solution* (mg/mL)

L = label claim of diphenhydramine hydrochloride or ibuprofen (mg/Capsule)

V = volume of appropriate *Medium* (*Tier 1* or *Tier 2*), 900 mL

Tolerances:

NLT 80% (Q) of the labeled amount of diphenhydramine hydrochloride ($C_{17}H_{21}NO \cdot HCl$) is dissolved; NLT 80% (Q) of the labeled amount of ibuprofen ($C_{13}H_{18}O_2$) is dissolved.▲ (RB 1-May-2020)

• **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 Diphenhydramine Hydrochloride 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

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 × 10-cm; 3-µm packing L11
Column temperature: 25°
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*
Suitability requirements
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:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (1/F) \times 100$$

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* ▲2▲ (RB 1-May-2020))

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

Table ▲2▲ (RB 1-May-2020)

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Diphenhydramine related compound A	0.9	1.0	0.2
Diphenhydramine	1.0	1.0	—
4-Methyldiphenhydramine[a]	1.3	1.0	0.2
4-Bromodiphenhydramine[b]	1.7	0.9	0.2
Benzhydrol[c]	2.3	1.6	0.2
Ibuprofen	4.1	—	—
Any other individual impurity	—	1.0	0.20
Total impurities	—	—	1.0

[a] *N,N*-Dimethyl-2-[phenyl(*p*-tolyl)methoxy]ethanamine.
[b] 2-[(4-Bromophenyl)(phenyl)methoxy]-*N,N*-dimethylethanamine.
[c] Diphenylmethanol.

SPECIFIC TESTS

- **Microbial Enumeration Tests** ⟨61⟩ and **Tests for Specified Microorganisms** ⟨62⟩**:** NMT 5×10^2 cfu/g for the total aerobic microbial count; NMT 10^2 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*-methylethanamine hydrochloride.
$C_{16}H_{19}NO \cdot HCl$ 277.79
USP Ibuprofen RS