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Diphenhydramine Hydrochloride and Ibuprofen Capsules

To view the Notice from the Expert Committee that posted in conjunction with this accelerated revision, please click https://www.uspnf.com/rb/diphenhydramine-hcl-ibuprofen-caps-20200424.

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

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
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

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
DIPHENHYDRAMINE HYDROCHLORIDE AND IBUPROFEN CAPSULES	Documentary Standards Support	SM22020 Small Molecules 2

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