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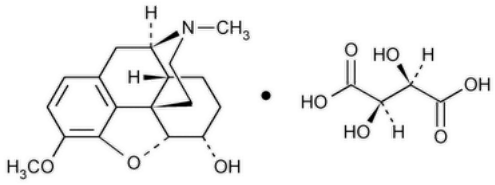
Dihydrocodeine Bitartrate

Change to read:



$C_{18}H_{23}NO_3 \cdot C_4H_6O_6$ 451.47
Morphinan-6-ol, 4,5-epoxy-3-methoxy-17-methyl-, (5α,6α)-2,3-dihydroxybutanedioate (1:1) (salt);
4,5α-Epoxy-3-methoxy-17-methylmorphinan-6α-ol (+)-tartrate (salt) CAS RN®: ▲5965-13-9.
Dihydrocodeine (free base)
$C_{18}H_{23}NO_3$ 301.39 CAS RN®: 125-28-0.▲ (USP 1-May-2019)

DEFINITION

Dihydrocodeine Bitartrate contains NLT 98.0% and NMT 102.0% of dihydrocodeine bitartrate ($C_{18}H_{23}NO_3 \cdot C_4H_6O_6$), calculated on the dried basis.

IDENTIFICATION

Change to read:

• **A.** ▲**Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*:** 197A or 197K▲ (CN 1-May-2020)

Change to read:

• ▲**B.**▲ (USP 1-May-2019) The retention time of the dihydrocodeine peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

Change to read:

• ▲**C.**▲ (USP 1-May-2019) **Identification Tests—General ⟨191⟩, *Chemical Identification Tests, Tartrate*:** Meets the requirements

Delete the following:

▲• **C.**

Analysis: To a solution of 20 mg in 5 mL of sulfuric acid in a test tube, add 1 drop of ferric chloride TS, and heat in a boiling water bath for 2 min.

Acceptance criteria: Although the solution may darken, no blue color is produced (distinction from codeine and morphine).▲ (USP 1-May-2019)

ASSAY

Change to read:

• **Procedure**

▲**Buffer:** Dissolve 2.0 g of monobasic potassium phosphate and 1.0 g of sodium 1-heptanesulfonate in 1000 mL of water. Adjust with 50% sodium hydroxide to a pH of 7.0.

Solution A: Acetonitrile and *Buffer* (5:195)

Solution B: Acetonitrile, *Buffer*, and water (140:35:10)

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	75	25
10	65	35

Time (min)	Solution A (%)	Solution B (%)
13	40	60
16	40	60
16.5	75	25
23	75	25

Standard solution: 2.25 mg/mL of USP Dihydrocodeine Bitartrate RS in *Solution A*. Sonicate to dissolve, if necessary.

Sample solution: 2.25 mg/mL of Dihydrocodeine Bitartrate in *Solution A*. Sonicate to dissolve, if necessary.

Chromatographic system

(See *Chromatography ⟨621⟩, System Suitability*.)

Mode: LC

Detector: UV 280 nm

Column: 4.6-mm × 15-cm; 3.5-µm packing L1

Column temperature: 45°

Flow rate: 1.0 mL/min

Injection volume: 20 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 0.73%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of dihydrocodeine bitartrate ($C_{18}H_{23}NO_3 \cdot C_4H_6O_6$) in the portion of Dihydrocodeine Bitartrate taken:

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

r_U = peak response of dihydrocodeine from the *Sample solution*

r_S = peak response of dihydrocodeine from the *Standard solution*

C_S = concentration of USP Dihydrocodeine Bitartrate RS in the *Standard solution* (mg/mL)

C_U = concentration of Dihydrocodeine Bitartrate in the *Sample solution* (mg/mL)▲ (USP 1-May-2019)

Acceptance criteria: 98.0%–102.0% on the dried basis

IMPURITIES

• **Residue on Ignition ⟨281⟩:** NMT 0.1%

Delete the following:

▲• **Ordinary Impurities ⟨466⟩**

Standard solution and **Sample solution:** Water

Eluant: A mixture of methylene chloride, methanol, and ammonium hydroxide (90:10:1)

Visualization: 17, and view under short-wavelength UV light

Acceptance criteria: Meet the requirements▲ (USP 1-May-2019)

Add the following:

▲• **Organic Impurities**

Buffer, Solution A, Solution B, Mobile phase, Sample solution, and **Chromatographic system:** Proceed as directed in the *Assay*.

Sensitivity solution: 0.00113 mg/mL of USP Dihydrocodeine Bitartrate RS in *Solution A*. Sonicate to dissolve, if necessary.

System suitability stock solution A: 0.3 mg/mL each of USP Morphine Sulfate RS and USP Codeine Sulfate RS prepared as follows. Dissolve suitable amounts of USP Morphine Sulfate RS and USP Codeine Sulfate RS with 20% of the final volume of methanol in a suitable volumetric flask. Dilute with *Solution A* to volume. Sonicate to dissolve, if necessary.

System suitability stock solution B: Prepare as directed for the *Standard solution* in the *Assay*.

System suitability solution: 0.015 mg/mL each of USP Morphine Sulfate RS and USP Codeine Sulfate RS, and 2.25 mg/mL of USP Dihydrocodeine Bitartrate RS prepared as follows. Dilute *System suitability stock solution A* with *System suitability stock solution B*.

Standard solution: 0.00225 mg/mL of USP Dihydrocodeine Bitartrate RS in *Solution A*. Sonicate to dissolve, if necessary.

System suitability

Samples: *Sensitivity solution*, *System suitability solution*, and *Standard solution*

[NOTE—See *Table 2* for relative retention times.]

Suitability requirements

Resolution: NLT 2 between morphine and dihydrocodeine; NLT 2 between dihydrocodeine and codeine, *System suitability solution*

Relative standard deviation: NMT 5.0%, *Standard solution*

Signal-to-noise ratio: NLT 10, *Sensitivity solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in the portion of Dihydrocodeine Bitartrate taken:

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

r_U = peak response of each impurity from the *Sample solution*

r_S = peak response of dihydrocodeine from the *Standard solution*

C_S = concentration of USP Dihydrocodeine Bitartrate RS in the *Standard solution* (mg/mL)

C_U = concentration of Dihydrocodeine Bitartrate in the *Sample solution* (mg/mL)

F = relative response factor (see *Table 2*)

Acceptance criteria: See *Table 2*.

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Tartaric acid[a]	0.33	—	—
Dihydromorphine[b]	0.52	1.4	0.50
Morphine	0.64	1.3	0.50
Dihydrocodeine bitartrate	1.00	1.0	—
Codeine	1.39	1.4	0.50
Hydrocodone	1.84	1.0	0.50
Tetrahydrothebaine[c]	2.15	1.4	0.15
Individual unspecified impurities	—	1.0	0.10
Total impurities	—	—	1.5▲ (USP 1-May-2019)

[a] Counter ion; not to be included in the total impurities.

[b] 4,5α-Epoxy-17-methylmorphinan-3,6α-diol.

[c] 4,5α-Epoxy-3,6-dimethoxy-17-methylmorphinan.

SPECIFIC TESTS

Delete the following:

▲• **AMMONIUM SALTS**

Analysis: To about 100 mg of Dihydrocodeine Bitartrate in a suitable test tube, add 5 mL of 1 N sodium hydroxide, and heat on a steam bath

Acceptance criteria: The odor of ammonia is not detected▲ (USP 1-May-2019)

• **LOSS ON DRYING ⟨731⟩**

Analysis: Dry Dihydrocodeine Bitartrate at 105° for 4 h.

Acceptance criteria: NMT 0.5%

Delete the following:

▲• **MELTING RANGE OR TEMPERATURE ⟨741⟩, *Class I*:** 186°–190°, but the range between beginning and end of melting does not exceed 2.5°▲ (USP 1-May-2019)

- **Optical Rotation** ⟨781S⟩, *Procedures, Specific Rotation*

  Sample solution: 10 mg/mL of Dihydrocodeine Bitartrate in water

  Acceptance criteria: Between −72° and −75°

- **pH** ⟨791⟩

  Sample solution: 100 mg/mL of Dihydrocodeine Bitartrate in water

  Acceptance criteria: 3.2–4.2

ADDITIONAL REQUIREMENTS

Change to read:

- **Packaging and Storage:** Preserve in tight containers. ▲Protect from light.▲ (USP 1-May-2019)

Change to read:

- **USP Reference Standards** ⟨11⟩

▲USP Codeine Sulfate RS▲ (USP 1-May-2019)

USP Dihydrocodeine Bitartrate RS

▲USP Morphine Sulfate RS▲ (USP 1-May-2019)

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

Topic/Question	Contact	Expert Committee
DIHYDROCODEINE BITARTRATE	Documentary Standards Support	SM22020 Small Molecules 2

Chromatographic Database Information: Chromatographic Database

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