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Codeine Sulfate

$(C_{18}H_{21}NO_3)_2 \cdot H_2SO_4 \cdot 3H_2O$ 750.85
 $(C_{18}H_{21}NO_3)_2 \cdot H_2SO_4$ 696.82
Morphinan-6-ol, 7,8-didehydro-4,5-epoxy-3-methoxy-17-methyl-, (5 α ,6 α)-, sulfate (2:1) (salt), trihydrate;
7,8-Didehydro-4,5 α -epoxy-3-methoxy-17-methylmorphinan-6 α -ol sulfate (2:1) (salt) trihydrate CAS RN[®]: 6854-40-6; UNII: 11QV9BS0CB.
Anhydrous CAS RN[®]: 1420-53-7; UNII: AVW5HY4N2E.

DEFINITION
Codeine Sulfate, dried at 105° for 3 h, contains NLT 98.0% and NMT 102.0% of $(C_{18}H_{21}NO_3)_2 \cdot H_2SO_4$.

IDENTIFICATION

Change to read:

- A. [▲SPECTROSCOPIC IDENTIFICATION TESTS \(197\), Infrared Spectroscopy: 197K▲](#) (CN 1-MAY-2020)

Change to read:

- B. [▲SPECTROSCOPIC IDENTIFICATION TESTS \(197\), Ultraviolet-Visible Spectroscopy: 197U▲](#) (CN 1-MAY-2020)

Sample solution: 100 µg/mL in water
Acceptance criteria: Absorptivities at 284 nm do not differ by more than 3.0%, calculated on the dried basis.

- C. [IDENTIFICATION TESTS—GENERAL, Sulfate\(191\)](#): Meets the requirements

ASSAY

• **PROCEDURE**

Buffer: Dissolve 4.0 g of potassium phosphate monobasic in 2000 mL of water, and adjust with phosphoric acid to a pH of 3.0 ± 0.1.
Solution A: 5 mM sodium heptane sulfonate in methanol and *Buffer* (3:7). [NOTE—Dissolve 1.0 g sodium heptane sulfonate for each L of *Mobile phase* produced, and filter.]
Solution B: 5 mM sodium heptane sulfonate in methanol and *Buffer* (11:9). [NOTE—Dissolve 1.0 g sodium heptane sulfonate for each L of *Mobile phase* produced, and filter.]
Diluent: *Solution A*
Mobile phase: See the gradient table below.

Time (min)	Solution A (%)	Solution B (%)
0	100	0
16	0	100
16.5	100	0
24	100	0

Standard solution: 1 mg/mL of [USP Codeine Sulfate RS](#) in *Diluent*
Sample solution: 1 mg/mL of Codeine Sulfate in *Diluent*
Chromatographic system
(See [Chromatography \(621\), System Suitability](#).)
Mode: LC
Detector: UV 280 nm
Column: 4.6-mm × 25-cm; 5-µm packing L1

Column temperature: 40°

Flow rate: 1.0 mL/min

Injection size: 20 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of codeine sulfate $[(C_{18}H_{21}NO_{3/2} \cdot H_2SO_4)]$ in the portion of Codeine Sulfate taken:

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

r_U = peak area of codeine sulfate from the *Sample solution*

r_S = peak area of codeine sulfate from the *Standard solution*

C_S = concentration of [USP Codeine Sulfate RS](#) in the *Standard solution* (mg/mL)

C_U = concentration of Codeine Sulfate in the *Sample solution* (mg/mL)

Acceptance criteria: 98.0%–102.0%

IMPURITIES

INORGANIC IMPURITIES

- [RESIDUE ON IGNITION \(281\)](#): NMT 0.1%

ORGANIC IMPURITIES

• PROCEDURE 1

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

Standard stock solution: 1 mg/mL of [USP Codeine Sulfate RS](#) in *Diluent*

Standard solution: 0.01 mg/mL of [USP Codeine Sulfate RS](#) in *Diluent* from *Standard stock solution*

Sensitivity solution: 0.5 µg/mL of [USP Codeine Sulfate RS](#) in *Diluent* from *Standard stock solution*

Sample solution: 1 mg/mL of Codeine Sulfate in *Diluent*

System suitability

Samples: *Standard solution* and *Sensitivity solution*

Suitability requirements

Tailing factor: NLT 0.5 and NMT 1.5, *Standard 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 individual impurity in the portion of Codeine Sulfate 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 codeine sulfate from the *Standard solution*

C_S = concentration of [USP Codeine Sulfate RS](#) in the *Standard solution* (mg/mL)

C_U = concentration of Codeine Sulfate in the *Sample solution* (mg/mL)

F = relative response factor of the related compounds (see [Impurity Table 1](#))

Acceptance criteria

Individual impurities: See [Impurity Table 1](#).

Impurity Table 1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria NMT (%)
10-Hydroxy codeine ^a	0.81	1.35	0.15
Codeine- <i>N</i> -oxide ^b	0.90	1.0	0.15
Codeine sulfate	1.00	—	—
Norcodeine ^c	1.09	1.0	0.15
Codeinone ^d	1.16	1.0	0.15
Codeine methyl ether ^e	1.34	1.0	1.0
Individual unspecified impurities	—	—	0.10

^a 7,8-Didehydro-4,5 α -epoxy-3-methoxy-17-methylmorphinan-6 α ,10-diol.

^b 7,8-Didehydro-4,5 α -epoxy-3-methoxy-17-methylmorphinan-6 α -ol *N*-oxide.

^c 7,8-Didehydro-4,5 α -epoxy-3-methoxymorphinan-6 α -ol.

^d 7,8-Didehydro-4,5 α -epoxy-3-methoxy-17-methylmorphinan-6 α -one.

^e 7,8-Didehydro-4,5 α -epoxy-3,6 α -dimethoxy-17-methylmorphinan.

• **PROCEDURE 2: LIMIT OF MORPHINE**

Analysis: Dissolve 50 mg of potassium ferricyanide in 10 mL of water, and add 1 drop of ferric chloride TS and 1 mL of a 10 mg/mL solution of Codeine Sulfate.

Acceptance criteria: No blue color is produced immediately.

SPECIFIC TESTS

• **OPTICAL ROTATION, *Specific Rotation*(781S).**

Sample solution: 20 mg/mL, in water

Acceptance criteria: -112.5° to -115.0°

• **ACIDITY**

Analysis: Dissolve 500 mg in 15 mL of water, add 1 drop of methyl red TS, and titrate with 0.020 N sodium hydroxide.

Acceptance criteria: NMT 0.30 mL is required for neutralization.

• **WATER DETERMINATION, *Method III*(921):** Dry 500 mg at 105° for 3 h: it loses between 6.0% and 7.5% of its weight.

• **READILY CARBONIZABLE SUBSTANCES TEST (271).**

Sample solution: Dissolve 10 mg in 5 mL of sulfuric acid.

Acceptance criteria: The solution has no more color than *Matching Fluid S*.

ADDITIONAL REQUIREMENTS

• **PACKAGING AND STORAGE:** Preserve in tight, light-resistant containers.

• **USP REFERENCE STANDARDS (11).**

[USP Codeine Sulfate RS](#)

Topic/Question	Contact	Expert Committee
CODEINE SULFATE	Documentary Standards Support	SM22020 Small Molecules 2

Chromatographic Database Information: [Chromatographic Database](#)

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