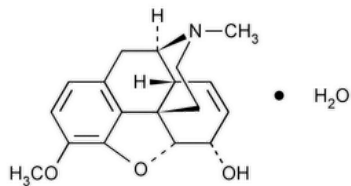


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Codeine

Change to read:



$C_{18}H_{21}NO_3 \cdot H_2O$ Δ 317.39 Δ (USP 1-Dec-2022)
Morphinan-6-ol, 7,8-didehydro-4,5-epoxy-3-methoxy-17-methyl-, monohydrate, (5 α ,6 α);
7,8-Didehydro-4,5 α -epoxy-3-methoxy-17-methylmorphinan-6 α -ol monohydrate CAS RN[®]: 6059-47-8; UNII: Q830PW7520.
Anhydrous 299.37 CAS RN[®]: 76-57-3; UNII: UX60WY2V7J.

Change to read:

DEFINITION

Codeine, dried at 80° for 4 h, contains NLT Δ 98.0% Δ (USP 1-Dec-2022) and NMT Δ 102.0% Δ (USP 1-Dec-2022) of codeine ($C_{18}H_{21}NO_3$).

IDENTIFICATION

Change to read:

- **A. [SPECTROSCOPIC IDENTIFICATION TESTS \(197\), Infrared Spectroscopy](#):** 197K Δ or 197A Δ (USP 1-Dec-2022)
Standard: Δ Dissolve about 33 mg of [USP Codeine Phosphate RS](#) in about 0.5 mL of [water](#) in a suitable glass tube. Add about 0.6 mL of a mixture of 50% (w/v) [sodium hydroxide](#) solution and [water](#) (50:50). Scratch the wall of the tube with a glass rod to initiate crystallization. Cool the solution in an ice bath to obtain the crystal. [NOTE—It is recommended to cool the solution for 2-3 h.] Wash the crystal with [water](#) and dry at 105° for 1 h. Δ (USP 1-Dec-2022)
Sample: Δ For codeine anhydrous, use as is; for codeine monohydrate, dry at 105° for 1 h. Δ (USP 1-Dec-2022)
Acceptance criteria: Meets the requirements

Delete the following:

- B. [SPECTROSCOPIC IDENTIFICATION TESTS \(197\), Ultraviolet-Visible Spectroscopy](#)** Δ (USP 1-Dec-2022)

Add the following:

- Δ • **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the Assay. Δ (USP 1-Dec-2022)

ASSAY

Change to read:

- **PROCEDURE**
 Δ **Solution A:** [Glacial acetic acid](#) and [water](#) (2:98). Adjust with 50% (w/v) [sodium hydroxide](#) solution to a pH of 4.5.
Solution B: [Acetonitrile](#)
Mobile phase: See [Table 1](#).

Table 1

Time (min)	Solution A (%)	Solution B (%)
---------------	-------------------	-------------------

Diluent: 0.5% (v/v) phosphoric acid in water	96	4
Standard solution: 4 mg/mL of USP Codeine Phosphate RS in <i>Diluent</i>		
Sample solution: 3 mg/mL of Codeine in <i>Diluent</i>	96	4
Chromatographic system (See Chromatography (621), System Suitability.)	89	11
Mode: LC		
Detector: UV 280 nm	63	37
Column: 4.6-mm × 15-cm; 3-μm packing L1		
Column temperature: 37°	96	4
Flow rate: 1.88 mL/min		
Injection volume: 10 μL	96	4

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: 1.5–5.0

Relative standard deviation: NMT 0.73%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of codeine ($C_{18}H_{21}NO_3$) in the portion of Codeine taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

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

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

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

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

M_{r1} = molecular weight of codeine, 299.37

M_{r2} = molecular weight of codeine phosphate, 397.36▲ (USP 1-Dec-2022)

Acceptance criteria: ▲98.0%–102.0%▲ (USP 1-Dec-2022) on the previously dried basis

IMPURITIES

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

Change to read:

- ORGANIC IMPURITIES

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

System suitability solution: 4 mg/mL of [USP Codeine System Suitability Mixture RS](#) in *Diluent*

Sensitivity solution: 2 μg/mL of [USP Codeine Phosphate RS](#) in *Diluent*

System suitability

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

Suitability requirements

Resolution: NLT 1.5 between norcodeine and codeine, *System suitability solution*

Relative standard deviation: NMT 0.73%, *Standard solution*

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

Analysis

Sample: *Sample solution*

Calculate the percentage of each impurity in the portion of Codeine taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times (1/F) \times 100$$

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

r_s = peak response of codeine from the *Standard solution*

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

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

M_{r1} = molecular weight of codeine, 299.37

M_{r2} = molecular weight of codeine phosphate, 397.36

F = relative response factor (see [Table 2](#))

Acceptance criteria: See [Table 2](#). The reporting threshold is 0.05%.

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Morphine	0.25	0.98	0.15
10-Hydroxycodeine ^a	0.40	1.12	0.15
14-Hydroxycodeine ^b	0.78	0.87	0.15
Norcodeine	0.88	0.98	0.15
Codeine	1.00	1.00	—
Codeine N-oxide	1.12	0.86	0.15
2,2'-Biscodeine ^c	1.15	1.42	0.15
Codeinone ^d	1.37	0.66	0.15
Codeine methyl ether	1.46	0.95	0.15
Thebaine ^e	1.60	4.78	0.15
Any unspecified impurity	—	1.00	0.10
Total impurities	—	—	1.0 ▲ (USP 1-Dec-2022)

^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 , 14-diol.

^c Also known as codeine dimer. 4,5 α :4',5' α -Diepoxy-3,3'-dimethoxy-17,17'-dimethyl-7,7',8,8'-tetrahydro-2,2'-bimorphinan-6 α ,6' α -diol.

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

^e 4,5 α -Epoxy-3,6-dimethoxy-17-methylmorphinan-6,8-diene.

Delete the following:

▲ **LIMIT OF MORPHINE** ▲ (USP 1-Dec-2022)

SPECIFIC TESTS

Delete the following:

▲ **MELTING RANGE OR TEMPERATURE** (741) ▲ (USP 1-Dec-2022)

• **LOSS ON DRYING** (731)

Analysis: Dry at 80° for 4 h.

Acceptance criteria: NMT 6.0%

Delete the following:

- ▲ [READILY CARBONIZABLE SUBSTANCES TEST \(271\)](#) ▲ (USP 1-Dec-2022)

ADDITIONAL REQUIREMENTS

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

Change to read:

- [USP REFERENCE STANDARDS \(11\)](#)

▲ [USP Codeine Phosphate RS](#)
[USP Codeine System Suitability Mixture RS](#)

Contains a mixture of the following five compounds:

Codeine phosphate.

Morphine: 7,8-Didehydro-4,5α-epoxy-17-methylmorphinan-3,6α-diol.



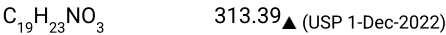
Codeine N-oxide: 7,8-Didehydro-4,5α-epoxy-3-methoxy-17-methylmorphinan-6α-ol N-oxide.



Norcodeine: 7,8-Didehydro-4,5α-epoxy-3-methoxymorphinan-6α-ol.



Codeine methyl ether: 7,8-Didehydro-4,5α-epoxy-3,6α-dimethoxy-17-methylmorphinan.



Auxiliary Information - Please [check for your question in the FAQs](#) before contacting USP.

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

Chromatographic Database Information: [Chromatographic Database](#)

Most Recently Appeared In:

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