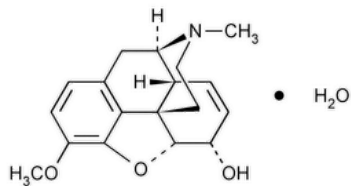


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Codeine

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*