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Codeine Sulfate Tablets

DEFINITION
Codeine Sulfate Tablets contain NLT 93.0% and NMT 107.0% of the labeled amount of codeine sulfate trihydrate $[(C_{18}H_{21}NO_3)_2 \cdot H_2SO_4 \cdot 3H_2O]$.

IDENTIFICATION

- **A.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.
- **B.**

Standard solution and **Sample solution:** Proceed as directed in the *Assay*.

Analysis: Inject 2 µL each of the *Standard solution* and the *Sample solution* using the *Chromatographic system* in the *Assay*.

Acceptance criteria: The spectrum of the codeine peak of the *Sample solution* exhibits maxima and minima at the same wavelengths as those of the corresponding peaks of the *Standard solution*, as obtained in the *Assay*.

ASSAY

- **Procedure**

Solution A: Acetonitrile and 0.1% ammonium hydroxide (1.0 mL of concentrated ammonium hydroxide and 1000 mL of water) (1:19)

Solution B: Acetonitrile and 0.1% ammonium hydroxide (9:11)

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	100	0
40	0	100
41	100	0
50	100	0

[Note—The *Standard solution* and *Sample solution*, for the degradation products, are stable for 4 days when stored at room temperature in amber vials.]

Diluent: 0.5% phosphoric acid (5 mL of concentrated phosphoric acid and 1000 mL of water)

Standard solution: 1.2 mg/mL of USP Codeine Sulfate RS in *Diluent*

Sample solution: Nominally 1.2 mg/mL of codeine sulfate trihydrate in *Diluent*. Dissolve 20 Tablets in 80% of the flask volume of *Diluent* and sonicate for 15–30 min with occasional swirling before diluting with *Diluent* to volume.

Chromatographic system

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

Mode: LC

Detector: UV 282 nm. For *Identification* test *B*, use a diode-array detector in the range of 210–400 nm.

Column: 4.6-mm × 15-cm; 3-µm packing L1

Column temperature: 40°

Flow rate: 1.2 mL/min

Injection volume: 40 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 the labeled amount of codeine sulfate trihydrate $[(C_{18}H_{21}NO_3)_2 \cdot H_2SO_4 \cdot 3H_2O]$ in the portion of Tablets taken:

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

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 = nominal concentration of codeine sulfate trihydrate in the *Sample solution* (mg/mL)

M_{r1} = molecular weight of codeine sulfate trihydrate, 750.85

M_{r2} = molecular weight of codeine sulfate, anhydrous, 696.81

Acceptance criteria: 93.0%–107.0%

PERFORMANCE TESTS

• **Dissolution ⟨711⟩**

Medium: Water; 500 mL

Apparatus 2: 25 rpm

Time: 45 min

Detector: UV maxima at about 284 nm

Cell: 1 cm

Blank: *Medium*

Standard solution: USP Codeine Sulfate RS in *Medium*

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.8-µm pore size.

Tolerances: NLT 75% (*Q*) of the labeled amount of codeine sulfate trihydrate $[(C_{18}H_{21}NO_3)_2 \cdot H_2SO_4 \cdot 3H_2O]$ is dissolved.

• **Uniformity of Dosage Units ⟨905⟩:** Meet the requirements

IMPURITIES

• **Organic Impurities**

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

Sensitivity solution: 0.6 µg/mL of USP Codeine Sulfate RS from the *Standard solution* in *Diluent*

System suitability

Samples: *Standard solution* and *Sensitivity solution*

Suitability requirements

Tailing factor: NMT 2.0, *Standard solution*

Relative standard deviation: NMT 2.0%, *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 Tablets 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 = nominal concentration of codeine sulfate trihydrate in the *Sample solution* (mg/mL)

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

Acceptance criteria: See *Table 2*. Disregard any impurity peak less than 0.05%.

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Codeine-*N*-oxide[a]	0.39	1.25	0.2
Codeine sulfate	1.00	—	—
Codeinone[b]	1.10	1.0	0.3
Individual unspecified degradant	—	1.0	0.2
Total impurities	—	—	0.5

[a] 7,8-Didehydro-4,5α-epoxy-3-methoxy-17-methylmorphinan-6α-ol *N*-oxide.

[b] 7,8-Didehydro-4,5α-epoxy-3-methoxy-17-methylmorphinan-6α-one.

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in well-closed containers. Store at controlled room temperature. Protect from moisture and light.
- **USP Reference Standards** ⟨11⟩
  USP Codeine Sulfate RS

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

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

Chromatographic Database Information: Chromatographic Database

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