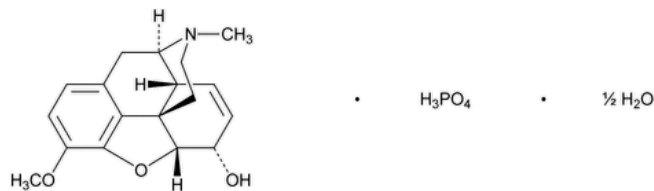


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Codeine Phosphate

To view the Notice from the Expert Committee that posted in conjunction with this accelerated revision, please click <https://www.uspnf.com/rb-codeine-phosphate-notice-20210430>.



$C_{18}H_{21}NO_3 \cdot H_3PO_4 \cdot \frac{1}{2}H_2O$ 406.37
 Morphinan-6-ol, 7,8-didehydro-4,5-epoxy-3-methoxy-17-methyl-, (5 α ,6 α)-, phosphate (1:1) (salt), hemihydrate;
 7,8-Didehydro-4,5 α -epoxy-3-methoxy-17-methylmorphinan-6 α -ol phosphate (1:1) (salt) hemihydrate CAS RN[®]: 41444-62-6.
 Anhydrous CAS RN[®]: 52-28-8.

DEFINITION

Change to read:

Codeine Phosphate contains ▲NLT 98.0% and NMT 102.0%▲ (USP 1-May-2021) of codeine phosphate ($C_{18}H_{21}NO_3 \cdot H_3PO_4$), calculated on the anhydrous basis.

IDENTIFICATION

Change to read:

- **A.** [SPECTROSCOPIC IDENTIFICATION TESTS \(197\)](#), [Infrared Spectroscopy](#): 197K or ▲197A▲ (USP 1-May-2021)

Add the following:

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

(USP 1-May-2021)

Change to read:

- ▲**C.**▲ (USP 1-MAY-2021)

Analysis: Neutralize 20 mg/mL of Codeine Phosphate in [water](#) with [6 N ammonium hydroxide](#) and add [silver nitrate TS](#).
Acceptance criteria: A yellow precipitate of silver phosphate is formed, and it is soluble in 2 N [nitric acid](#) and [6 N ammonium hydroxide](#).

ASSAY

Change to read:

- **PROCEDURE**

▲**Solution A:** 2% [acetic acid](#) in [water](#). 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 (%)
0	96	4

Time (min)	Solution A (%)	Solution B (%)
15	96	4
22	89	11
31	63	37
31.1	96	4
36	96	4

Diluent: 0.5% (v/v) [phosphoric acid](#) in [water](#)

Standard solution: 4 mg/mL of [USP Codeine Phosphate RS](#) in *Diluent*

Sample solution: 4 mg/mL of Codeine Phosphate in *Diluent*

Chromatographic system

(See [Chromatography \(621\), System Suitability](#).)

Mode: LC

Detector: UV 280 nm

Column: 4.6-mm × 15-cm; 3.0-μm packing [L1](#)

Column temperature: 37°

Flow rate: 1.88 mL/min

Injection volume: 10 μL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: 0.8–3.0

Relative standard deviation: NMT 0.73%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of codeine phosphate ($C_{18}H_{21}NO_3 \cdot H_3PO_4$) in the portion of Codeine Phosphate taken:

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

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 Phosphate in the *Sample solution* (mg/mL)

Acceptance criteria: 98.0%–102.0% on the anhydrous basis ▲ (USP 1-May-2021)

IMPURITIES

Delete the following:

▲ • **LIMIT OF MORPHINE**

Analysis: Dissolve about 50 mg of [potassium ferricyanide](#) in 10 mL of [water](#), add 1 drop of [ferric chloride](#) TS, and 1 mL of 10 mg/mL Codeine Phosphate solution.

Acceptance criteria: No blue color is produced immediately. ▲ (USP 1-May-2021)

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.

Sensitivity solution: 0.002 mg/mL of [USP Codeine Phosphate RS](#) in *Diluent*

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

System suitability

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

$$\text{Result} = (r_U/r_T) \times (1/F) \times 100$$

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

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

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	0.97	0.15
10-Hydroxycodeine ^a	0.40	1.13	0.15
14-Hydroxycodeine ^b	0.78	0.88	0.15
Norcodeine	0.88	0.97	0.15
Codeine	1.00	1.00	—
Codeine N-oxide	1.12	1.14	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	0.96	▲0.45▲ (RB 1-May-2021)
Thebaine ^e	1.60	4.83	0.15
Any unspecified impurity	—	1.00	0.10
Total impurities	—	—	1.0▲ (USP 1-May-2021)

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

^b 7,8-Didehydro-4,5α-epoxy-3-methoxy-17-methylmorphinan-6α, 14-diol.

^c 7,7',8,8'-Tetradhydro-4,5α:4',5'α-diepoxy-3,3'-dimethoxy-17,17'-dimethyl-2,2'-bimorphinan-6α,6'α-diol.

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

^e 6,7,8,14-Tetradhydro-4,5α-epoxy-3,6-dimethoxy-17-methylmorphinan.

SPECIFIC TESTS

• ACIDITY

Sample: 100 mg of Codeine Phosphate

Titrant: 0.010 N [sodium hydroxide](#)

Analysis: Dissolve the *Sample* in 20 mL of [water](#), and titrate with *Titrant* to a pH of 5.4, using a pH meter.

Acceptance criteria: NMT 1.0 mL of *Titrant* is required.

• [WATER DETERMINATION \(921\)](#), [Method I](#): NMT 3.0%

• CHLORIDE

Sample solution: 10 mg/mL of Codeine Phosphate in [water](#)

Analysis: Acidify 10 mL of *Sample solution* with [nitric acid](#) and add a few drops of [silver nitrate TS](#).

Acceptance criteria: No opalescence is produced immediately.

• SULFATE

Sample solution: 10 mg/mL of Codeine Phosphate in [water](#)

Analysis: To 10 mL of the *Sample solution* add a few drops of [barium chloride TS](#).

Acceptance criteria: No turbidity is produced immediately.

ADDITIONAL REQUIREMENTS

• **PACKAGING AND STORAGE:** Preserve in tight, light-resistant containers. Store up to 40° as permitted by the manufacturer.

Change to read:

• [USP REFERENCE STANDARDS \(11\)](#).

[USP Codeine Phosphate RS](#)

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

It contains codeine phosphate hemihydrate, morphine, codeine *N*-oxide, norcodeine, and codeine methyl ether.

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

C₁₇H₁₉NO₃ 285.34

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

C₁₈H₂₁NO₄ 315.36

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

C₁₇H₁₉NO₃ 285.34

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

C₁₉H₂₃NO₃ 313.39▲ (USP 1-May-2021)

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

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

Chromatographic Database Information: [Chromatographic Database](#)

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