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Promethazine and Phenylephrine Hydrochloride and Codeine Phosphate Oral Solution

DEFINITION

Promethazine and Phenylephrine Hydrochloride and Codeine Phosphate Oral Solution contains NLT 90.0% and NMT 110.0% of the labeled amount of promethazine hydrochloride ($C_{17}H_{20}N_2S \cdot HCl$), phenylephrine hydrochloride ($C_9H_{13}NO_2 \cdot HCl$), and codeine phosphate ($C_{18}H_{21}NO_3 \cdot H_3PO_4 \cdot ½H_2O$). It may contain suitable preservatives.

IDENTIFICATION

• **A.** The retention times of the promethazine hydrochloride, phenylephrine hydrochloride, and codeine phosphate peaks from the *Sample solutions* correspond to those from the *Standard solution*, as obtained in the *Assay*.

ASSAY

• **Procedure**

At all times, protect the sample and the Standard solutions by using low-actinic glassware.

Solution A: Dissolve 2.0 g of monobasic potassium phosphate and 1.0 g of heptanesulfonic acid sodium salt monohydrate in 950 mL of water, and carefully add 50 mL of acetonitrile. Adjust with phosphoric acid to an apparent pH of 3.0.

Solution B: Dissolve 2.0 g of monobasic potassium phosphate and 1.0 g of heptanesulfonic acid sodium salt monohydrate in 500 mL of water, and carefully add 500 mL of acetonitrile. Adjust with phosphoric acid to an apparent pH of 3.0.

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	100	0
1.0	100	0
50.0	0	100
50.1	100	0
55.0	100	0

Standard stock solution A: 1.8 mg/mL of USP Promethazine Hydrochloride RS, 1.4 mg/mL of USP Phenylephrine Hydrochloride RS, and 2.8 mg/mL of USP Codeine Phosphate RS in *Solution A*

Standard stock solution B: 1.4 mg/mL of USP Sodium Benzoate RS, 2.5 mg/mL of USP Methylparaben RS, and 0.28 mg/mL of USP Propylparaben RS. Prepare by dissolving appropriate quantities of USP Methylparaben RS, USP Propylparaben RS, and USP Sodium Benzoate RS in a volume of acetonitrile equivalent to 40% of the total volume of the flask and diluting with *Solution A* to volume.

Standard solution: 0.18 mg/mL of USP Promethazine Hydrochloride RS, 0.14 mg/mL of USP Phenylephrine Hydrochloride RS, 0.28 mg/mL of USP Codeine Phosphate RS, 0.14 mg/mL of USP Sodium Benzoate RS, 0.25 mg/mL of USP Methylparaben RS, and 0.028 mg/mL of USP Propylparaben RS. Prepare by adding 5.0 mL each of *Standard stock solution A* and *Standard stock solution B* to a 50-mL volumetric flask and diluting with *Solution A* to volume.

Promethazine hydrochloride sample solution: Equivalent to 0.18 mg/mL, based on the label claim, of promethazine hydrochloride in *Solution A*

Phenylephrine hydrochloride sample solution: Equivalent to 0.14 mg/mL, based on the label claim, of phenylephrine hydrochloride in *Solution A*

Codeine phosphate sample solution: Equivalent to 0.28 mg/mL, based on the label claim, of codeine phosphate in *Solution A*

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: 1.5 mL/min

Injection volume: 15 µL

System suitability

Sample: *Standard solution*

[NOTE—The relative retention times for benzoate, methylparaben, and propylparaben are 0.59, 0.64, and 1.05, respectively.]

Suitability requirements

Resolution: NLT 4.5 between benzoate and methylparaben; NLT 1.5 between promethazine and propylparaben

Relative standard deviation: NMT 2.0% for promethazine, phenylephrine, and codeine

Analysis

Samples: *Standard solution* and *Promethazine hydrochloride sample solution*

Calculate the percentage of the labeled amount of promethazine hydrochloride ($C_{17}H_{20}N_2S \cdot HCl$) in the portion of sample taken:

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

r_U = promethazine peak response from the *Promethazine hydrochloride sample solution*

r_S = promethazine peak response from the *Standard solution*

C_S = concentration of USP Promethazine Hydrochloride RS in the *Standard solution* (mg/mL)

C_U = nominal concentration of promethazine hydrochloride in the *Promethazine hydrochloride sample solution* (mg/mL)

Samples: *Standard solution* and *Phenylephrine hydrochloride sample solution*

Calculate the percentage of the labeled amount of phenylephrine hydrochloride ($C_9H_{13}NO_2 \cdot HCl$) in the portion of sample taken:

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

r_U = phenylephrine peak response from the *Phenylephrine hydrochloride sample solution*

r_S = phenylephrine peak response from the *Standard solution*

C_S = concentration of USP Phenylephrine Hydrochloride RS in the *Standard solution* (mg/mL)

C_U = nominal concentration of phenylephrine hydrochloride in the *Phenylephrine hydrochloride sample solution* (mg/mL)

Samples: *Standard solution* and *Codeine phosphate sample solution*

Calculate the percentage of the labeled amount of codeine phosphate ($C_{18}H_{21}NO_3 \cdot H_3PO_4 \cdot ½H_2O$) in the portion of sample taken:

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

r_U = codeine peak response from the *Codeine phosphate sample solution*

r_S = codeine peak response from the *Standard solution*

C_S = concentration of USP Codeine Phosphate RS, on the dried basis, in the *Standard solution* (mg/mL)

C_U = nominal concentration of codeine phosphate in the *Codeine phosphate sample solution* (mg/mL)

M_{r1} = molecular weight of codeine phosphate, 406.37

M_{r2} = molecular weight of anhydrous codeine phosphate, 397.37

Acceptance criteria: 90.0%–110.0% for promethazine hydrochloride, phenylephrine hydrochloride, and codeine phosphate

IMPURITIES

• Organic Impurities, Procedure 1

At all times, protect the sample and the Standard solutions by using low-actinic glassware.

Solution C: Dissolve 4.36 g of dibasic potassium phosphate in 1 L of water, add 2.0 mL of triethylamine, and adjust with phosphoric acid to a pH of 6.4.

5 N phosphoric acid: Dilute 12 mL of phosphoric acid with water to 100 mL.

Diluent: Methanol, water, and *5 N phosphoric acid* (5:95:1)

Mobile phase: Acetonitrile, methanol, and *Solution C* (30:20:50)

Standard solution: 3.5 µg/mL of USP Promethazine Hydrochloride RS in *Diluent*

Sensitivity solution: 0.18 µg/mL of USP Promethazine Hydrochloride RS in *Diluent*, prepared from *Standard solution*. Prepare at time of use.

Sample solution: Equivalent to 175 µg/mL of promethazine hydrochloride in *Diluent*

Chromatographic system

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

Mode: LC

Detector: UV 254 nm

Column: 4.6-mm × 15-cm; 5-µm packing L1

Flow rate: 1.5 mL/min

Injection volume: 10 µL

Run time: 2 times the retention time of promethazine, *Standard solution*; 6 times the retention time of promethazine, *Sample solution*

System suitability

Samples: *Standard solution* and *Sensitivity solution*

Suitability requirements

Tailing factor: NMT 1.5 for promethazine, *Standard solution*

Relative standard deviation: NMT 7.5% for promethazine, *Standard solution*

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

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in the portion of Oral Solution taken:

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

r_U = impurity peak response from the *Sample solution*

r_S = promethazine hydrochloride peak response from the *Standard solution*

C_S = concentration of USP Promethazine Hydrochloride RS in the *Standard solution* (µg/mL)

C_U = nominal concentration of promethazine hydrochloride in the *Sample solution* (µg/mL)

F = relative response factor for each impurity (see *Table 2*)

Acceptance criteria: See *Table 2*.

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Promethazine	1.0	1.0	—
Phenothiazine	2.4	2.0	0.5
Methylphenothiazine[a]	4.2	2.0	0.5

[a] 10-Methylphenothiazine.

• Organic Impurities, Procedure 2

At all times, protect the sample and the Standard solutions by using low-actinic glassware.

Solution A, Solution B, Mobile phase, Standard stock solution B, Codeine phosphate sample solution, and **Phenylephrine hydrochloride sample solution:** Proceed as directed in the *Assay*.

Standard stock solution A: 88 µg/mL of USP Promethazine Hydrochloride RS in *Solution A*

Standard solution: 8.8 µg/mL of USP Promethazine Hydrochloride RS, 140 µg/mL of USP Sodium Benzoate RS, 250 µg/mL of USP Methylparaben RS, and 28 µg/mL of USP Propylparaben RS. Prepare by adding 5.0 mL of *Standard stock solution A* and 5.0 mL of *Standard stock solution B* to a 50-mL volumetric flask and diluting with *Solution A* to volume.

Sensitivity solution: 0.18 µg/mL of USP Promethazine Hydrochloride RS in *Solution A*, prepared from *Standard stock solution A*. Prepare at time of use.

Promethazine hydrochloride sample solution: Proceed as directed in the *Assay*. Use this solution to determine promethazine related compounds and specified and unknown impurities.

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: 1.5 mL/min

Injection volume: 50 µL

System suitability

Sample: *Standard solution* and *Sensitivity solution*

[NOTE—The relative retention times for benzoate, methylparaben, and propylparaben are 0.59, 0.64, and 1.05, respectively.]

Suitability requirements

Resolution: NLT 4.5 between benzoate and methylparaben, and NLT 1.5 between promethazine and propylparaben, *Standard solution*

Relative standard deviation: NMT 7.5% for promethazine, *Standard solution*

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

Analysis

Samples: *Phenylephrine hydrochloride sample solution* and *Standard solution*

Identify the phenylephrine impurities using the relative retention times listed in *Table 3*. Calculate the percentage of each phenylephrine impurity in the portion of sample taken:

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

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

r_S = promethazine hydrochloride peak response from the *Standard solution*

C_S = concentration of USP Promethazine Hydrochloride RS in the *Standard solution* (µg/mL)

C_U = nominal concentration of phenylephrine hydrochloride in the *Phenylephrine hydrochloride sample solution* (µg/mL)

F = relative response factor for each impurity (see *Table 3*)

Samples: *Standard solution* and *Promethazine hydrochloride sample solution*

Using the data in *Table 4*, calculate the percentage of each promethazine impurity, unspecified impurity, and unidentified impurity in the portion of sample taken:

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

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

r_S = promethazine hydrochloride peak response from the *Standard solution*

C_S = concentration of USP Promethazine Hydrochloride RS in the *Standard solution* (µg/mL)

C_U = nominal concentration of promethazine hydrochloride in the *Promethazine hydrochloride sample solution* (µg/mL)

F = relative response factor for each impurity (see *Table 4*)

Samples: *Codeine phosphate sample solution* and *Standard solution*

Identify the codeine impurities using the relative retention times given in *Table 4*. Calculate the percentage of each codeine impurity in the portion of sample taken:

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

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

r_S = promethazine hydrochloride peak response from the *Standard solution*

C_S = concentration of USP Promethazine Hydrochloride RS in the *Standard solution* (µg/mL)

C_U = nominal concentration of codeine phosphate in the *Codeine phosphate sample solution* (µg/mL)

F = relative response factor for each codeine impurity (see *Table 4*)

Acceptance criteria: See *Table 3* and *Table 4*.

Table 3

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Unidentified impurity 1	0.32	1.4	0.6
Unidentified impurity 2	0.33	1.4	0.5
3-Hydroxyindole dione[a]	0.34	1.4	2.6
Norphenylephrine[b]	0.37	1.4	3.5
7-Hydroxyindole trione[c]	0.38	1.4	3.5
Phenylephrine	0.40	—	—
Unidentified impurity 3	0.42	1.4	0.2
Unidentified impurity 4	0.43	1.4	0.5
4-Hydroxyindole trione and pyrocatecholyl phenylephrine[d]	0.44	1.4	0.6
Unidentified impurity 5	0.45	1.4	0.5
Unidentified impurity 6	0.46	1.4	0.5
Benzyl phenylephrine[e]	0.69	1.0	0.5
Benzyladrianone[f]	0.73	—	—
Promethazine	1.0	—	—
Any other unspecified impurity	—	1.0	0.2
Total phenylephrine impurities	—	—	10.0

[a] 3-Hydroxy-1-methyl-2,3-dihydro-1*H*-indole-5,6-dione.

[b] (*R*)-3-(2-Amino-1-hydroxyethyl)phenol.

[c] 7-Hydroxy-1-methyl-1*H*-indole-3,5,6(2*H*)-trione.

[d] 4-Hydroxy-1-methyl-1*H*-indole-3,5,6(2*H*)-trione, and two 3-{[2-hydroxy-2-(3-hydroxyphenyl)ethyl](methyl)amino}benzene-1,2-diol isomers.

[e] (*R*)-3-{2-[Benzyl(methyl)amino]-1-hydroxyethyl}phenol.

[f] Phenylephrine synthetic impurity. Do not quantify.

Table 4

Name	Source	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Codeine *N*-oxide[a]	Codeine	0.52	0.83	0.2
Norcodeine[b]	Codeine	0.53	0.83	0.2
Codeine	—	0.54	—	—
Codeinone[c]	Codeine	0.61	0.63	0.3
Codeine methyl ether[d]	Codeine	0.67	—	—
Total codeine impurities	Codeine	—	—	1.0
Phenothiazine sulfoxide[e]	Promethazine	0.71	1.0	0.5
Promethazine sulfoxide[f]	Promethazine	0.72	3.3	2.8
Unidentified impurity 1	Promethazine	0.77	1.0	0.2
Methylphenothiazine sulfoxide[g]	Promethazine	0.81	1.0	0.5
Unidentified impurity 2	Promethazine	0.85	1.0	0.2
Phenothiazinone[h]	Promethazine	0.98	10.0	0.2
Desmethyl promethazine[i]	Promethazine	0.99	1.0	0.2
Promethazine	Promethazine	1.0	—	—
Isopromethazine[j]	Promethazine	1.01	—	—
Unidentified impurity 3	Promethazine	1.09	1.0	0.2
Unidentified impurity 4	Promethazine	1.16	1.0	0.2
Any unspecified impurity	—	—	1.0	0.2
Total promethazine impurities	Promethazine	—	—	5.0[k]
Total impurities	Codeine, Promethazine, and Phenylephrine	—	—	17.0

[a] Morphinan-6-ol, 7-8-didehydro-4,5-epoxy-3-methoxy-17-methyl,17-oxide-(5α,6α).

[b] Morphinan-6-ol, 7,8-didehydro-4,5-epoxy-3-methoxy-(5α,6α).

[c] Morphinan-6-one, 7-8-didehydro-4,5-epoxy-3-methoxy-17-methyl-(5α).

[d] Codeine synthetic impurity. Do not quantitate.

[e] 10*H*-Phenothiazine sulfoxide.

[f] *N*,*N*-Dimethyl-1(10*H*-phenothiazin-10-yl)propan-2-amine sulfoxide.

[g] 10-Methyl-10*H*-phenothiazine sulfoxide.

[h] 1*H*-Phenothiazin-1-one.

[i] *N*-Methyl-1(10*H*-phenothiazin-10-yl)propan-2-amine.

[j] Promethazine synthetic impurity. Do not quantify.

[k] Includes phenothiazine and methylphenothiazine from *Procedure 1*.

SPECIFIC TESTS

• **Microbial Enumeration Tests ⟨61⟩** and **Tests for Specified Microorganisms ⟨62⟩:** The total aerobic microbial count does not exceed 10^2 cfu/mL. The total yeasts and molds count does not exceed 10^1 cfu/mL. It meets the requirements of the test for absence of *Escherichia coli*.

• **pH ⟨791⟩:** 3.7–4.7

• **Alcohol Determination, *Method II* ⟨611⟩** (if present)**:** 90.0%–110.0% of the labeled amount of C_2H_5OH

• **Deliverable Volume ⟨698⟩:** Meets the requirements

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in tight, light-resistant containers, and store at controlled room temperature.

• **USP Reference Standards ⟨11⟩**

USP Codeine Phosphate RS
USP Methylparaben RS
USP Phenylephrine Hydrochloride RS
USP Promethazine Hydrochloride RS
USP Propylparaben RS
USP Sodium Benzoate RS

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

Topic/Question	Contact	Expert Committee
PROMETHAZINE AND PHENYLEPHRINE HYDROCHLORIDE AND CODEINE PHOSPHATE ORAL SOLUTION	Documentary Standards Support	SM22020 Small Molecules 2
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM22020 Small Molecules 2

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