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Promethazine and Phenylephrine Hydrochloride Oral Solution

DEFINITION

Promethazine and Phenylephrine Hydrochloride Oral Solution contains NLT 90.0% and NMT 110.0% of the labeled amount of promethazine hydrochloride ($C_{17}H_{20}N_2S \cdot HCl$) and phenylephrine hydrochloride ($C_9H_{13}NO_2 \cdot HCl$). It may contain suitable preservatives.

IDENTIFICATION

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

Add the following:

▲• **B.** The UV absorption spectrum of both promethazine and phenylephrine peaks of the *Sample solution* exhibits maxima and minima at the same wavelengths as those of the *Standard solution*, as obtained in the *Assay*.▲ (USP 1-May-2019)

ASSAY

• **Procedure**

Protect the sample and Standard solutions by using low-actinic glassware.

Solution A: Dissolve 2.0 g of monobasic potassium phosphate and 1.0 g of heptane sulfonic 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 heptane sulfonic acid sodium salt monohydrate in 500 mL of water, and 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 and 1.4 mg/mL of USP Phenylephrine Hydrochloride 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 into 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, 0.14 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: Nominally equivalent to 0.18 mg/mL of promethazine hydrochloride in *Solution A*

Phenylephrine hydrochloride sample solution: Nominally equivalent to 0.14 mg/mL of phenylephrine hydrochloride 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 both promethazine and phenylephrine

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 Oral Solution taken:

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

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

r_S = peak response of promethazine 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 Oral Solution taken:

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

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

r_S = peak response of phenylephrine 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)

Acceptance criteria: 90.0%–110.0% for both promethazine hydrochloride and phenylephrine hydrochloride

IMPURITIES

Change to read:

• **ORGANIC IMPURITIES, PROCEDURE 1**

Protect the sample and 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* from the *Standard solution*. Prepare at time of use.

Promethazine hydrochloride sample solution: Nominally 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: ▲NLT▲ (USP 1-May-2019) 2 times the retention time of promethazine for Standards; ▲NLT▲ (USP 1-May-2019) 6 times the retention time of promethazine for samples

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 *Promethazine hydrochloride sample solution*

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

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

r_U = peak response of the impurity from the *Promethazine hydrochloride sample solution*

r_S = peak response of promethazine hydrochloride 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 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-Methyl-10*H*-phenothiazine.▲ (USP 1-May-2019)

Change to read:

• **Organic Impurities, Procedure 2**

Protect the sample and Standard solutions by using low-actinic glassware.

Solution A, Solution B, Mobile phase, Standard stock solution B, and **Phenylephrine hydrochloride sample solution:** Prepare 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* into a 50-mL volumetric flask, and dilute with *Solution A* to volume.

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

Promethazine hydrochloride sample solution: Prepare as directed in the *Assay*. Use this solution to determine the 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

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

Identify the phenylephrine impurities using the relative retention times given in *Table 3*.

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

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

r_U = peak response of the impurity from the *Phenylephrine hydrochloride sample solution*

r_S = peak response of promethazine hydrochloride 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 promethazine specified and unidentified impurities and any unspecified impurities in the portion of Oral Solution taken:

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

r_U = peak response of the impurity from the *Promethazine hydrochloride sample solution*

r_S = peak response of promethazine hydrochloride 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*)

Acceptance criteria

Individual impurities: See *Table 2*, *Table 3*, and *Table 4*.

Total impurities: NMT 16.0%. Sum of the total phenylephrine impurities from *Table 3* and total promethazine impurities from *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

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
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 ▲(*R*)-▲ (USP 1-May-2019) 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	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Phenothiazine sulfoxide[a]	0.71	1.0	0.5
Promethazine sulfoxide[b]	0.72	3.3	2.8
Unidentified impurity 1	0.77	1.0	0.2
Methylphenothiazine sulfoxide[c]	0.81	1.0	0.5
Unidentified impurity 2	0.85	1.0	0.2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Phenothiazinone[d]	0.98	10.0	0.2
Desmethyl promethazine[e]	0.99	1.0	0.2
Promethazine	1.0	—	—
Isopromethazine[f]	1.01	—	—
Unidentified impurity 3	1.09	1.0	0.2
Unidentified impurity 4	1.16	1.0	0.2
Any unspecified impurity	—	1.0	0.2
Total promethazine impurities	—	—	5.0[g]

[a] 10*H*-Phenothiazine sulfoxide.

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

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

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

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

[f] Promethazine synthetic impurity. Do not quantify.

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

SPECIFIC TESTS

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

• **pH ⟨791⟩:** 3.7–4.7

• **Alcohol Determination ⟨611⟩,** *Procedures, Method II—Gas Chromatographic Method* (if present)**:** 90.0%–110.0% of the labeled quantity of alcohol (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 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 ORAL SOLUTION	Documentary Standards Support	SM22020 Small Molecules 2
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM22020 Small Molecules 2

Chromatographic Database Information: Chromatographic Database

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