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Promethazine Hydrochloride Tablets

DEFINITION

Promethazine Hydrochloride Tablets contain NLT 95.0% and NMT 110.0% of the labeled amount of promethazine hydrochloride ($C_{17}H_{20}N_2S \cdot HCl$).

[Note—Throughout the following procedures, protect the samples, the Reference Standards, and the solutions containing them, by conducting the procedures without delay under subdued light or using low-actinic glassware.]

IDENTIFICATION

• **A.**

Standard solution: In a separator, dissolve 50 mg of USP Promethazine Hydrochloride RS in 40 mL of dilute hydrochloric acid (1 in 1000).

Sample solution: Shake a quantity of powdered Tablets, equivalent to 50 mg of promethazine hydrochloride, with 30 mL of chloroform, and filter into a beaker. Evaporate the chloroform, dissolve the residue in 40 mL of dilute hydrochloric acid (1 in 1000), and transfer the liquid to a separator.

Analysis: Separately treat the *Sample solution* and the *Standard solution* as follows. Add 2 mL of 1 N sodium hydroxide and 15 mL of carbon disulfide to the separators, and shake for 2 min. Centrifuge if necessary to clarify the lower phase, and pass through a dry filter, collecting the filtrate from each separator in a small flask provided with a glass stopper. Reduce the volume of the carbon disulfide extracts to 4–5 mL, and proceed as directed in *Identification—Organic Nitrogenous Bases* ⟨181⟩, beginning with "Determine the absorption spectra".

Acceptance criteria: Meet the requirements

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

ASSAY

• **Procedure**

Diluent: Dissolve 8.2 mL of hydrochloric acid in 1000 mL of water.

Mobile phase: Acetonitrile, water, and triethylamine (850:270:1)

System suitability stock solution: 1.2 mg/mL of USP Promethazine Related Compound B RS in *Diluent*. Sonicate to dissolve.

Standard solution: 0.1 mg/mL of USP Promethazine Hydrochloride RS in *Diluent*. Sonicate to dissolve.

System suitability solution: 0.09 mg/mL of USP Promethazine Hydrochloride RS and 0.12 mg/mL of USP Promethazine Related Compound B RS in *Diluent* from the *Standard solution* and *System suitability stock solution*, respectively

Sample stock solution: Nominally 2.5–5.0 mg/mL of promethazine hydrochloride prepared as follows. Transfer 20 Tablets to a volumetric flask of an appropriate size and add 50% of the flask volume of *Diluent*. Sonicate with swirling for NLT 20 min, or until the Tablets have fully disintegrated. Shake the flask for NLT 15 min and dilute with *Diluent* to volume.

Sample solution: Nominally 0.1 mg/mL of promethazine hydrochloride in *Diluent* from the *Sample stock solution*. Pass a portion through a filter of 0.45-µm pore size and use the clear filtrate.

Chromatographic system

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

Mode: LC

Detector: UV 254 nm

Column: 3.9-mm × 30-cm; 10-µm packing L1

Flow rate: 2.5 mL/min

Injection volume: 20 µL

Run time: NLT 2.5 times the retention time of promethazine

System suitability

Samples: *System suitability solution* and *Standard solution*

[Note—The relative retention times for promethazine related compound B and promethazine are 0.82 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 1.5 between promethazine and promethazine related compound B, *System suitability solution*

Tailing factor: NMT 1.5, *Standard solution*

Relative standard deviation: NMT 2.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

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

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

r_U = peak response from the *Sample solution*

r_S = 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 *Sample solution* (mg/mL)

Acceptance criteria: 95.0%–110.0%

PERFORMANCE TESTS

• **Dissolution ⟨711⟩**

Test 1

Medium: 0.01 N hydrochloric acid; 900 mL

Apparatus 1: 100 rpm

Time: 45 min

Standard solution: Prepare a solution with a known concentration of USP Promethazine Hydrochloride RS in *Medium*.

Sample solution: A filtered portion of the solution under test, suitably diluted with *Medium*

Instrumental conditions

Mode: UV

Analytical wavelength: Absorption maximum at about 249 nm

Analysis

Samples: *Standard solution* and *Sample solution*

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

$$\text{Result} = (A_U/A_S) \times (C_S/C_U) \times D \times 100$$

A_U = absorbance of the *Sample solution*

A_S = absorbance of 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 *Sample solution* (mg/mL)

D = dilution factor for the *Sample solution*

Tolerances: NLT 75% (Q) of the labeled amount of promethazine hydrochloride ($C_{17}H_{20}N_2S \cdot HCl$) is dissolved.

Test 2: If the product complies with this test, the labeling indicates that the product meets USP *Dissolution Test 2*.

Medium: 0.01 N hydrochloric acid; 900 mL

Apparatus 1: 100 rpm

Time: 15 min

Standard solution: (L/900) mg/mL of USP Promethazine Hydrochloride RS in *Medium*, where L is the label claim (mg/Tablet)

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size.

Instrumental conditions

Mode: UV

Analytical wavelength: Absorption maximum at about 249 nm

Cell: 0.2 cm

Blank: *Medium*

Analysis

Samples: *Standard solution* and *Sample solution*

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

$$\text{Result} = (A_U/A_S) \times C_S \times V \times (1/L) \times 100$$

A_U = absorbance of the *Sample solution*

A_S = absorbance of the *Standard solution*

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

V = volume of *Medium*, 900 mL

L = label claim (mg/Tablet)

Tolerances: NLT 80% (Q) of the labeled amount of promethazine hydrochloride ($C_{17}H_{20}N_2S \cdot HCl$) is dissolved.

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

IMPURITIES

Change to read:

• **Organic Impurities**

Diluent: Methanol and triethylamine (999:1)

Buffer: 3.7 g/L of ammonium acetate in water

Solution A: *Buffer* and acetonitrile (700:300)

Solution B: Acetonitrile

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	100	0
10	60	40
18	60	40
18.1	100	0
25	100	0

System suitability stock solution: 0.5 mg/mL of USP Promethazine Related Compound B RS in *Diluent*

Standard stock solution: 0.5 mg/mL of USP Promethazine Hydrochloride RS in *Diluent*

System suitability solution: 5 µg/mL each of USP Promethazine Hydrochloride RS and USP Promethazine Related Compound B RS from the *Standard stock solution* and *System suitability stock solution*, respectively▲, in *Diluent*▲ (ERR 1-Sep-2022)

Standard solution: 5 µg/mL of USP Promethazine Hydrochloride RS from the *Standard stock solution*▲in *Diluent*▲ (ERR 1-Sep-2022)

Sensitivity solution: 0.25 µg/mL of USP Promethazine Hydrochloride RS from the *Standard solution*▲in *Diluent*▲ (ERR 1-Sep-2022)

Sample solution: Nominally 0.5 mg/mL of promethazine hydrochloride from powdered Tablets (NLT 20) prepared as follows. Transfer a quantity of powdered Tablets, equivalent to 50 mg of promethazine hydrochloride, to a volumetric flask of appropriate size and add 75% of the flask volume of *Diluent*. Shake the flask for NLT 5 min and dilute with *Diluent* to volume. Pass a portion through a suitable filter.

Chromatographic system

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

Mode: LC

Detector: UV 234 and 249 nm

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

Column temperature: 30°

Flow rate: 1.4 mL/min

Injection volume: 15 µL

System suitability

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

[NOTE—See *Table 2* for the relative retention times.]

Suitability requirements

Resolution: NLT 5.0 between promethazine and promethazine related compound B, *System suitability solution*

Relative standard deviation: NMT 3.0% at 234 and 249 nm, *Standard solution*

Signal-to-noise ratio: NLT 10 at 234 and 249 nm, *Sensitivity solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of promethazine sulfoxide 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 promethazine sulfoxide at 234 nm from the *Sample solution*

r_S = peak response of promethazine hydrochloride at 234 nm 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 *Sample solution* (mg/mL)

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

Calculate the percentage of all other degradation products 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 degradation product at 249 nm from the *Sample solution*

r_S = peak response of promethazine hydrochloride at 249 nm 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 *Sample solution* (mg/mL)

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

Acceptance criteria: See *Table 2*. Disregard peaks that are less than 0.05%.

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Promethazine sulfoxide[a]	0.28	2.1	0.5
Desmethyl promethazine[b]	0.71	1.0	0.5
Promethazine	1.0	—	—
Promethazine related compound B[c]	1.3	—	—
Phenothiazine	1.7	2.0	0.5

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Any individual unspecified degradation product	—	1.0	0.2
Total degradation products	—	—	1.0

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

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

[c] This is a process impurity and is included for identification only. It is not to be reported and not to be included in the total degradation products.

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in tight, light-resistant containers. Store at controlled room temperature.
- **Labeling:** When more than one *Dissolution* test is given, the labeling states the test used only if *Test 1* is not used.
- **USP Reference Standards** ⟨11⟩

USP Promethazine Hydrochloride RS

USP Promethazine Related Compound B RS

Isopromethazine hydrochloride;
N,*N*-Dimethyl-2-(10*H*-phenothiazin-10-yl)propan-1-amine hydrochloride.
$C_{17}H_{20}N_2S \cdot HCl$ 320.88

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

Topic/Question	Contact	Expert Committee
PROMETHAZINE HYDROCHLORIDE TABLETS	Documentary Standards Support	SM52020 Small Molecules 5
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM52020 Small Molecules 5

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