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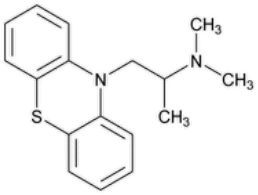
# Promethazine Hydrochloride




• HCl

$C_{17}H_{20}N_2S \cdot HCl$ 320.88

10*H*-Phenothiazine-10-ethanamine, *N*,*N*,α-trimethyl-, monohydrochloride, (±)-;

(±)-10-[2-(Dimethylamino)propyl]phenothiazine monohydrochloride CAS RN®: 58-33-3; UNII: R61ZEH7I1I.

## DEFINITION

Promethazine Hydrochloride contains NLT 97.0% and NMT 101.5% of promethazine hydrochloride ($C_{17}H_{20}N_2S \cdot HCl$), calculated on the dried basis.

[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. Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*:** 197A or 197K
- **B. Identification Tests—General ⟨191⟩, *Chloride***
- **C.** 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 solution:** 0.1 mg/mL of Promethazine Hydrochloride in *Diluent*. Sonicate to dissolve.

**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 promethazine hydrochloride ($C_{17}H_{20}N_2S \cdot HCl$) in the portion of Promethazine Hydrochloride 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)

$C_U$ = concentration of Promethazine Hydrochloride in the *Sample solution* (mg/mL)

**Acceptance criteria:** 97.0%–101.5% on the dried basis

## IMPURITIES

• **Residue on Ignition ⟨281⟩:** NMT 0.1%

***Change to read:***

• **Organic Impurities**

**Diluent:** Methanol and triethylamine (999:1)

**Buffer:** 3.7 g/L of ammonium acetate in water

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

**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:** 0.5 mg/mL of Promethazine Hydrochloride in *Diluent*

**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 Promethazine Hydrochloride 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)

$C_U$ = concentration of Promethazine Hydrochloride in the *Sample solution* (mg/mL)

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

Calculate the percentage of all other impurities in the portion of Promethazine Hydrochloride taken:

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

$r_U$ = peak response of each impurity 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)

$C_U$ = 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 | 0.1 |
| Desmethyl promethazine[b] | 0.71 | 1.0 | 0.2 |
| Promethazine | 1.0 | — | — |
| Promethazine related compound B | 1.3 | 1.0 | 0.8 |
| Phenothiazine | 1.7 | 2.0 | 0.1 |
| Any individual unspecified impurity | — | 1.0 | 0.10 |
| Total impurities | — | — | 1.2 |

[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.

**SPECIFIC TESTS**

- **pH** ⟨791⟩

  **Sample solution:** 50 mg/mL of Promethazine Hydrochloride

  **Acceptance criteria:** 4.0–5.0

- **Loss on Drying** ⟨731⟩

  **Analysis:** Dry at 105° for 4 h.

  **Acceptance criteria:** NMT 0.5%

**ADDITIONAL REQUIREMENTS**

- **Packaging and Storage:** Preserve in tight, light-resistant containers.
- **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 | Documentary Standards Support | SM52020 Small Molecules 5 |
| REFERENCE STANDARD SUPPORT | RS Technical Services<br>RSTECH@usp.org | SM52020 Small Molecules 5 |

**Chromatographic Database Information:** Chromatographic Database

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