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Promethazine Hydrochloride Oral Solution

To view the Notice from the Expert Committee that posted in conjunction with this accelerated revision, please click www.uspnf.com/rb-promethazine-hcl-os-20231027.

DEFINITION

Promethazine Hydrochloride Oral Solution contains NLT 90.0% and NMT 110.0% of the labeled amount of promethazine hydrochloride ($C_{17}H_{20}N_2S \cdot HCl$).

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

ASSAY

- **Procedure**

Buffer: 3.7 g/L of ammonium acetate in water

Solution A: Acetonitrile and *Buffer* (30:70)

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

Diluent: 0.1% triethylamine in methanol

System suitability solution: 1.0 µg/mL each of USP Promethazine Hydrochloride RS and USP Promethazine Related Compound B RS in *Diluent*

Standard solution: 0.05 mg/mL of USP Promethazine Hydrochloride RS in *Diluent*

Sample solution: Nominally 0.05 mg/mL of promethazine hydrochloride from a volume of Oral Solution in *Diluent*. Centrifuge for 10 min and use the supernatant.

[Note—Sonication may be used in the preparation of the *System suitability solution*, *Standard solution*, and *Sample solution*.]

Chromatographic system

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

Mode: LC

Detector: UV 254 nm. For *Identification* test *B*, use a diode array detector in the range of 200–400 nm.

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

Temperatures

Autosampler: 4°

Column: 30°

Flow rate: 1.4 mL/min

Injection volume: 15 µL

System suitability

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

[NOTE—The relative retention times for promethazine and promethazine related compound B are 1.0 and 1.3, respectively.]

Suitability requirements

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

Tailing factor: NMT 2.0, *Standard solution*

Relative standard deviation: NMT 1.0%, *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 Oral Solution 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: 90.0%–110.0%

IMPURITIES

Change to read:

• **ORGANIC IMPURITIES**

Buffer, Solution A, Solution B, Mobile phase, Diluent, and **Chromatographic system:** Proceed as directed in the *Assay*.

Standard solution: 1.0 µg/mL each of USP Promethazine Hydrochloride RS and USP Promethazine Related Compound B RS in *Diluent*

Sample solution: Nominally 500 µg/mL of promethazine hydrochloride from a volume of Oral Solution in *Diluent*. Centrifuge for 10 min and use the supernatant.

[NOTE—Sonication may be used in the preparation of the *Standard solution* and the *Sample solution*.]

System suitability

Sample: *Standard solution*

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

Suitability requirements

Resolution: NLT 5.0 between promethazine and promethazine related compound B peaks

Relative standard deviation: NMT 5.0% for promethazine

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each degradation product 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 each degradation product from the *Sample solution*

r_S = peak response of promethazine 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 (see *Table 2*)

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

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Promethazine sulfoxide[a]	0.3	0.26	▲2.5▲ (RB 1-Nov-2023)
Desmethyl promethazine[b]	0.6	1.0	0.2
Promethazine	1.0	—	—
Promethazine related compound B[c]	1.3	—	—
Phenothiazine[d]	1.5	2.2	0.2
Any individual unspecified degradation product	—	1.0	0.2

[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.

[c] This is a process impurity which is controlled in the drug substance and is included in the table for identification only.

[d] 10*H*-Phenothiazine.

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 ORAL SOLUTION	Documentary Standards Support	SM52020 Small Molecules 5
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM52020 Small Molecules 5

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