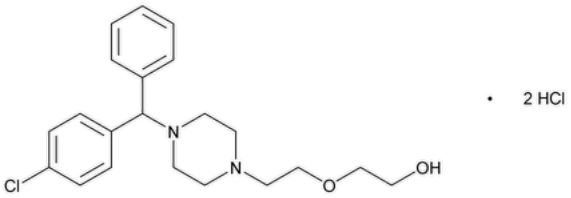
Status: Currently Official on 14-Feb-2025
Official Date: Official as of 01-May-2022
Document Type: USP Monographs
DocId: GUID-75440BE6-2C8E-48EC-98EF-600D71D6EB97_6_en-US
DOI: https://doi.org/10.31003/USPNF_M39460_06_01
DOI Ref: 9f04r

Hydroxyzine Hydrochloride



$C_{21}H_{27}ClN_2O_2 \cdot 2HCl$ 447.83

Ethanol, 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-, dihydrochloride, (±)-;
(±)-2-[2-[4-(*p*-Chloro-α-phenylbenzyl)-1-piperazinyl]ethoxy]ethanol dihydrochloride CAS RN®: 2192-20-3; UNII: 76755771U3.

DEFINITION

Hydroxyzine Hydrochloride contains NLT 98.0% and NMT 102.0% of hydroxyzine hydrochloride ($C_{21}H_{27}ClN_2O_2 \cdot 2HCl$), calculated on the anhydrous basis.

IDENTIFICATION

• **A. Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*:** 197A or 197K

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

Change to read:

• **C.**

Sample solution: 2.5 mg/mL of Hydroxyzine Hydrochloride in water

Analysis: To 10 mL of the *Sample solution*, add 2 drops of nitric acid and 1 mL of silver nitrate TS.

Acceptance criteria: A curdy, white precipitate, insoluble in 2 N nitric acid ▲TS▲ (USP 1-May-2022) but soluble in 6 N ammonium hydroxide, separates (presence of chloride).

ASSAY

• **Procedure**

Solution A: Trifluoroacetic acid and water (0.1: 99.9)

Solution B: Trifluoroacetic acid and acetonitrile (0.05: 99.95)

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	90	10
4	90	10
12	55	45
16	55	45
21	20	80
25	20	80
26	90	10
30	90	10

Diluent: Acetonitrile and water (30:70)

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

Sample solution: 0.05 mg/mL of Hydroxyzine Hydrochloride in *Diluent*

Chromatographic system

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

Mode: LC

Detector: UV 230 nm

Column: 2.1-mm × 15-cm; 1.8-µm packing L1

Flow rate: 0.3 mL/min

Injection volume: 2 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 0.73%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of hydroxyzine hydrochloride ($C_{21}H_{27}ClN_2O_2 \cdot 2HCl$) in the portion of Hydroxyzine Hydrochloride taken:

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

r_U = peak response of hydroxyzine from the *Sample solution*

r_S = peak response of hydroxyzine from the *Standard solution*

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

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

Acceptance criteria: 98.0%–102.0% on the anhydrous basis

IMPURITIES

• **Residue on Ignition ⟨281⟩:** NMT 0.5%

Change to read:

• **Organic Impurities**

Solution A, Solution B, Mobile phase, and **Diluent:** Prepare as directed in the *Assay*.

Standard solution: 1.5 µg/mL each of USP Hydroxyzine Hydrochloride RS, USP Hydroxyzine Related Compound A RS, and USP 4-Chlorobenzophenone RS in *Diluent*

Sample solution: 500 µg/mL of Hydroxyzine Hydrochloride in *Diluent*

Chromatographic system

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

Mode: LC

Detectors

Decloxizine, hydroxyzine related compound A, and hydroxyzine: UV 230 nm

4-Chlorobenzophenone: UV 254 nm

Column: 2.1-mm × 15-cm; 1.8-µm packing L1

Flow rate: 0.3 mL/min

Injection volume: 2 µL

System suitability

Sample: *Standard solution*

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

Suitability requirements

Resolution: NLT 5.0 between hydroxyzine related compound A and hydroxyzine

Relative standard deviation: NMT 3.0% for hydroxyzine related compound A, hydroxyzine, and 4-chlorobenzophenone

Analysis

Samples: *Standard solution* and *Sample solution*

For impurities detected at UV 230 nm

Calculate the percentage of hydroxyzine related compound A in the portion of Hydroxyzine Hydrochloride taken:

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

r_U = peak response of hydroxyzine related compound A from the *Sample solution*

r_S = peak response of hydroxyzine related compound A from the *Standard solution*

C_S = concentration of USP Hydroxyzine Related Compound A RS in the *Standard solution* (µg/mL)

C_U = concentration of Hydroxyzine Hydrochloride in the *Sample solution* (µg/mL)

Calculate the percentage of decloxizine or any individual unspecified impurity in the portion of Hydroxyzine Hydrochloride taken:

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

r_U = peak response of decloxizine or any other individual impurity from the *Sample solution*

r_S = peak response of hydroxyzine from the *Standard solution*

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

C_U = concentration of Hydroxyzine Hydrochloride in the *Sample solution* (µg/mL)

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

For 4-chlorobenzophenone detected at UV 254 nm

Calculate the percentage of 4-chlorobenzophenone in the portion of Hydroxyzine Hydrochloride taken:

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

r_U = peak response of 4-chlorobenzophenone from the *Sample solution*

r_S = peak response of 4-chlorobenzophenone from the *Standard solution*

C_S = concentration of USP 4-Chlorobenzophenone RS in the *Standard solution* (µg/mL)

C_U = concentration of Hydroxyzine Hydrochloride in the *Sample solution* (µg/mL)

Acceptance criteria: See *Table 2*. ▲The reporting threshold is 0.05%.▲ (USP 1-May-2022)

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Decloxizine[a]	0.87	0.68	0.3
Hydroxyzine related compound A	0.96	—	0.3
Hydroxyzine	1.0	—	—
4-Chlorobenzophenone	1.4	—	0.2
Any individual unspecified impurity	—	1.0	0.2
Total impurities	—	—	0.75

[a] 2-[2-(4-Benzhydrylpiperazin-1-yl)ethoxy]ethanol; also known as 2-{2-[4-(diphenylmethyl)piperazin-1-yl]ethoxy}ethanol.

SPECIFIC TESTS

Change to read:

• **Water Determination** ⟨921⟩, ▲*Method I*:▲ (USP 1-May-2022) NMT 5.0%

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in tight containers. Store at controlled room temperature. Protect from light.

• **USP Reference Standards** ⟨11⟩

USP 4-Chlorobenzophenone RS

4-Chlorobenzophenone.

$C_{13}H_9ClO$ 216.66

USP Hydroxyzine Hydrochloride RS

USP Hydroxyzine Related Compound A RS

1-[(4-Chlorophenyl)phenylmethyl]piperazine;
Also known as *p*-Chlorobenzhydrylpiperazine.

$C_{17}H_{19}ClN_2$ 286.80

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

Topic/Question	Contact	Expert Committee
HYDROXYZINE HYDROCHLORIDE	Documentary Standards Support	SM42020 Small Molecules 4

Chromatographic Database Information: Chromatographic Database

Most Recently Appeared In:
Pharmacopeial Forum: Volume No. 46(6)

Current DocID: GUID-75440BE6-2C8E-48EC-98EF-600D71D6EB97_6_en-US

DOI: https://doi.org/10.31003/USPNF_M39460_06_01

DOI ref: 9f04r