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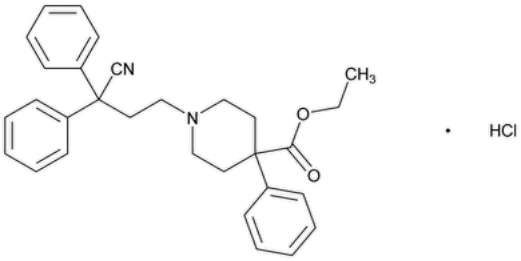
Diphenoxylate Hydrochloride



$C_{30}H_{32}N_2O_2 \cdot HCl$ 489.05

4-Piperidinecarboxylic acid, 1-(3-cyano-3,3-diphenylpropyl)-4-phenyl-, ethyl ester, hydrochloride;

Ethyl 1-(3-cyano-3,3-diphenylpropyl)-4-phenylpiperidine-4-carboxylate hydrochloride CAS RN®: 3810-80-8; UNII: W24OD7YW48.

DEFINITION

Diphenoxylate Hydrochloride contains NLT 98.0% and NMT 102.0% of diphenoxylate hydrochloride ($C_{30}H_{32}N_2O_2 \cdot HCl$), calculated on the dried basis.

IDENTIFICATION

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

• **B. Identification Tests—General ⟨191⟩, *Chemical Identification Tests, Chloride*:** A saturated solution meets the requirements.

Add the following:

▲• **C.** The retention time of the diphenoxylate peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.▲ (USP 1-Dec-2021)

ASSAY

Change to read:

• **Procedure**

▲**Solution A:** Adjust 900 mL of water with phosphoric acid to a pH of 2.3, and dilute with water to 1000 mL.

Solution B: Acetonitrile

Mobile phase: See *Table 1*. Return to original conditions and re-equilibrate the system for NLT 5 min.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	75	25
5	75	25
40	15	85

Diluent: Acetonitrile and *Solution A* (50:50)

System suitability solution: 1.0 mg/mL of USP Diphenoxylate Hydrochloride RS and 0.005 mg/mL of USP Diphenoxylate Related Compound A RS in *Diluent*. Sonicate to dissolve, if necessary.

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

Sample solution: 0.05 mg/mL of Diphenoxylate Hydrochloride in *Diluent*. Sonicate to dissolve, if necessary.

Chromatographic system

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

Mode: LC

Detector: UV 210 nm

Column: 4.6-mm × 25-cm; 5-µm packing L1

Flow rate: 2 mL/min

Injection volume: 20 µL

System suitability

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

[NOTE—The relative retention times for diphenoxylate related compound A and diphenoxylate are about 0.8 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 5.0 between diphenoxylate related compound A and diphenoxylate, *System suitability solution*

Tailing factor: NMT 2.0, *Standard solution*

Relative standard deviation: NMT 0.73%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of diphenoxylate hydrochloride ($C_{30}H_{32}N_2O_2 \cdot HCl$) in the portion of Diphenoxylate Hydrochloride taken:

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

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

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

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

C_U = concentration of Diphenoxylate Hydrochloride in the *Sample solution* (mg/mL)▲ (USP 1-Dec-2021)

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

IMPURITIES

Change to read:

• **ORGANIC IMPURITIES**

▲**Solution A, Solution B, Mobile phase, Diluent, System suitability solution,** and **Chromatographic system:** Proceed as directed in the *Assay*.▲ (USP 1-Dec-2021)

Standard solution: ▲0.001 mg/mL▲ (USP 1-Dec-2021) of USP Diphenoxylate Hydrochloride RS in *Diluent*

Sensitivity solution: 0.5 µg/mL of USP Diphenoxylate Hydrochloride RS from *Standard solution* in *Diluent*

Sample solution: 1.0 mg/mL of Diphenoxylate Hydrochloride in *Diluent*. Sonicate for about 2 min to dissolve.

▲▲ (USP 1-Dec-2021)

System suitability

Samples: *System suitability solution*, ▲*Standard solution*,▲ (USP 1-Dec-2021) and *Sensitivity solution*

Suitability requirements

Resolution: NLT 5.0 between diphenoxylate related compound A and diphenoxylate, *System suitability solution*

▲**Relative standard deviation:** NMT 5.0%, *Standard solution*▲ (USP 1-Dec-2021)

Signal-to-noise ratio: NLT 10, *Sensitivity solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each individual impurity in the portion of Diphenoxylate Hydrochloride taken:

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

r_U = peak response of each ▲individual▲ (USP 1-Dec-2021) impurity from the *Sample solution*

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

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

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

Acceptance criteria: See *Table 2*. ▲The reporting threshold is▲ (USP 1-Dec-2021) 0.05%.

Table 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
▲▲ (USP 1-Dec-2021) Diphenoxylate related compound A	0.8	0.50
Diphenoxylate	1.0	—
Any other individual impurity	—	0.10
Total impurities	—	0.5

SPECIFIC TESTS

• **Loss on Drying** ⟨731⟩

Analysis: Dry at 105° for 2 h.

Acceptance criteria: NMT 0.5%

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in well-closed containers, protected from light. Store at room temperature.

• **USP Reference Standards** ⟨11⟩

USP Diphenoxylate Hydrochloride RS

USP Diphenoxylate Related Compound A RS

Diphenoxylic acid;
1-(3-Cyano-3,3-diphenylpropyl)-4-phenylpiperidine-4-carboxylic acid.
$C_{28}H_{28}N_2O_2$ 424.53

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

Topic/Question	Contact	Expert Committee
DIPHENOXYLATE HYDROCHLORIDE	Documentary Standards Support	SM32020 Small Molecules 3
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM32020 Small Molecules 3

Chromatographic Database Information: Chromatographic Database

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