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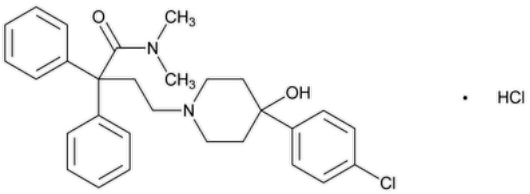
Loperamide Hydrochloride

To view the Notice from the Expert Committee that posted in conjunction with this accelerated revision, please click https://www.uspnf.com/rb/loperamide-hcl-20200529.



$C_{29}H_{33}ClN_2O_2 \cdot HCl$ 513.50

1-Piperidinebutanamide, 4-(4-chlorophenyl)-4-hydroxy-*N*,*N*-dimethyl-α,α-diphenyl-, monohydrochloride;

4-[4-(4-Chlorophenyl)-4-hydroxypiperidin-1-yl]-*N*,*N*-dimethyl-2,2-diphenylbutanamide hydrochloride CAS RN®: 34552-83-5.

DEFINITION

Loperamide Hydrochloride contains NLT 98.0% and NMT 102.0% of loperamide hydrochloride ($C_{29}H_{33}ClN_2O_2 \cdot HCl$), calculated on the dried basis.

IDENTIFICATION

- **A. Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*:** 197A or 197K
- **B. Identification Tests—General ⟨191⟩, *Chemical Identification Tests, Chloride***

Sample solution: Dissolve about 30 mg of Loperamide Hydrochloride in 0.5 mL of methanol. Add 1.5 mL of water and 1 mL of 6 N ammonium hydroxide. A precipitate forms. Centrifuge, decant, and acidify the supernatant with diluted nitric acid.

Acceptance criteria: Meets the requirements

ASSAY

Change to read:

- **Procedure**

▲**Sample solution:** Dissolve 400 mg of Loperamide Hydrochloride in 50 mL of alcohol and add 5.0 mL of 0.01 N hydrochloric acid.

Analysis: Titrate the *Sample solution* with 0.1 N sodium hydroxide VS (see *Titrimetry ⟨541⟩*), determining the endpoint potentiometrically. Read the volume of 0.1 N sodium hydroxide added between the two points of inflection. Each milliliter of 0.1 N sodium hydroxide is equivalent to 51.35 mg of loperamide hydrochloride ($C_{29}H_{33}ClN_2O_2 \cdot HCl$).▲ (USP 1-May-2020)

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

IMPURITIES

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

Change to read:

- **Organic Impurities**

▲**Solution A:** 17.0 g/L of tetrabutylammonium hydrogen sulfate in water

Solution B: Acetonitrile

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

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	90	10
15	30	70
17	30	70

System suitability solution: 10 mg/mL of USP Loperamide System Suitability Mixture RS in methanol. See *Table 2* for the relative retention times of the main components of the mixture.

Standard solution: 20 µg/mL of USP Loperamide Hydrochloride RS in methanol

Sensitivity solution: 5 µg/mL of USP Loperamide Hydrochloride RS in methanol, from the *Standard solution*

Sample solution: 10 mg/mL of Loperamide Hydrochloride in methanol

Chromatographic system

(See *Chromatography ⟨621⟩, System Suitability (RB-1-Nov-2020).*)

Mode: LC

Detector: UV 220 nm

Column: 4.6-mm × 10-cm; 3-µm packing L1

Column temperature: 35°

Flow rate: 1.5 mL/min

Injection volume: 10 µL

System suitability

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

Suitability requirements

Peak-to-valley ratio: NLT 1.5 for loperamide *cis-N*-oxide and anhydroloperamide; NLT 1.5 for loperamide piperidinolamide and loperamide biphenyl analog, *System suitability solution*

Relative standard deviation: NMT 10.0%, *Standard solution*

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 Loperamide 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 from the *Sample solution*

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

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

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

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

Acceptance criteria: See *Table 2*.

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Chlorophenylpiperidinol	0.2	1.0	0.2
Deschloroloperamide	0.8	0.59	0.2
Loperamide	1.0	—	—
Loperamide *trans-N*-oxide	1.1	1.0	0.2
Loperamide *cis-N*-oxide	1.16	1.0	0.2
Anhydroloperamide	1.18	1.0	0.2
Loperamide piperidinolamide	1.3	1.0	0.2
Loperamide biphenyl analog	1.4	0.77	0.2
Loperamide quaternary salt	1.7	1.0	0.2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Any other individual impurity	—	1.0	0.10▲ (USP 1-May-2020)
▲Total impurities	—	—	0.3▲ (RB 1-Nov-2020)

SPECIFIC TESTS

• **Loss on Drying** ⟨731⟩

Analysis: Dry at 105° for 4 h.

Acceptance criteria: NMT 0.5%

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in well-closed containers.

Change to read:

• **USP Reference Standards** ⟨11⟩

USP Loperamide Hydrochloride RS

▲USP Loperamide System Suitability Mixture RS

The mixture contains loperamide hydrochloride and the following impurities (other impurities may also be present):

Chlorophenylpiperidinol;
4-(4-Chlorophenyl)piperidin-4-ol. $C_{11}H_{14}ClNO$ 211.69

Deschloroloperamide;
4-(4-Hydroxy-4-phenylpiperidin-1-yl)-*N*,*N*-dimethyl-2,2-diphenylbutanamide. $C_{29}H_{34}N_2O_2$ 442.59

Loperamide *trans*-*N*-oxide;
(1*r*,4*s*)-4-(4-Chlorophenyl)-1-[4-(dimethylamino)-4-oxo-3,3-diphenylbutyl]-4-hydroxypiperidine 1-oxide. $C_{29}H_{33}ClN_2O_3$ 493.04

Loperamide *cis*-*N*-oxide;
(1*s*,4*r*)-4-(4-Chlorophenyl)-1-[4-(dimethylamino)-4-oxo-3,3-diphenylbutyl]-4-hydroxypiperidine 1-oxide. $C_{29}H_{33}ClN_2O_3$ 493.04

Anhydroloperamide;
4-[4-(4-Chlorophenyl)-5,6-dihydropyridin-1(2*H*)-yl]-*N*,*N*-dimethyl-2,2-diphenylbutanamide. $C_{29}H_{31}ClN_2O$ 459.02

Loperamide piperidinolamide;
1,4-Bis[4-(4-chlorophenyl)-4-hydroxypiperidin-1-yl]-2,2-diphenylbutan-1-one. $C_{38}H_{40}Cl_2N_2O_3$ 643.64

Loperamide biphenyl analog;
4-[4-(4′-Chlorobiphenyl-4-yl)-4-hydroxypiperidin-1-yl]-*N*,*N*-dimethyl-2,2-diphenylbutanamide. $C_{35}H_{37}ClN_2O_2$ 553.13

Loperamide quaternary salt;
4-(4-Chlorophenyl)-1,1-bis[4-(dimethylamino)-4-oxo-3,3-diphenylbutyl]-4-hydroxypiperidin-1-ium chloride. $C_{47}H_{53}Cl_2N_3O_3$ 778.85▲

(USP 1-May-2020)

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

Topic/Question	Contact	Expert Committee
LOPERAMIDE HYDROCHLORIDE	Documentary Standards Support	SM32020 Small Molecules 3

Chromatographic Database Information: Chromatographic Database

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