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Loperamide Hydrochloride Tablets

DEFINITION

Loperamide Hydrochloride Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of loperamide hydrochloride ($C_{29}H_{33}ClN_2O_2 \cdot HCl$).

IDENTIFICATION

Change to read:

• **A.** ▲**Spectroscopic Identification Tests ⟨197⟩, *Ultraviolet-Visible Spectroscopy*:** 197U▲ (CN 1-May-2020)

[Note—This procedure is not applicable for Tablets labeled as chewable.]

Wavelength range: 250–300 nm

Standard solution: About 0.4 mg/mL of USP Loperamide Hydrochloride RS, prepared as follows. Transfer an amount of USP Loperamide Hydrochloride RS to a suitable volumetric flask, dissolve first in isopropyl alcohol, using 50% of the final volume. Add 0.1 N hydrochloric acid equivalent to 10% of the final volume, and dilute with isopropyl alcohol to volume.

Sample solution: Transfer a quantity of finely powdered Tablets equivalent to about 10 mg of loperamide hydrochloride to a test tube. Add 20.0 mL of isopropyl alcohol, shake by mechanical means for 1 min, and allow to settle. Pipet 9.0 mL of the supernatant into a 10-mL volumetric flask, and dilute with 0.1 N hydrochloric acid to volume.

Acceptance criteria: The spectrum of the *Sample solution* exhibits maxima and minima at the same wavelengths as those of the *Standard solution*, concomitantly measured.

Thin-Layer Chromatographic Identification Test ⟨201⟩

[Note—For Tablets labeled as chewable, use the following procedure.]

Standard solution: 1.0 mg/mL of USP Loperamide Hydrochloride RS in methanol

Sample solution: Grind a number of Tablets, equivalent to 10 mg of loperamide hydrochloride, with 10 mL of methanol for about 2 min. Centrifuge the mixture, and use the supernatant.

Application volume: 10 µL

Developing solvent system: Chloroform, methanol, and formic acid (75:25:1)

Analysis: Visualize the spots by using Dragendorff's TS.

Acceptance criteria: Meet the requirements

• **B.** 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**

Solvent mixture: Methanol and acetonitrile (3:1)

Ion pairing solution: Solution containing 2.35 g/L of sodium 1-hexanesulfonate and 2.88 g/L of monobasic ammonium phosphate in water, adjusted with phosphoric acid to a pH of 3.2

Mobile phase: *Solvent mixture* and *Ion pairing solution* (55:45)

System suitability solution: 0.2 mg/mL of USP Loperamide Hydrochloride RS and 0.002 mg/mL of USP Loperamide Related Compound F RS in *Mobile phase*

Standard solution: 0.2 mg/mL of USP Loperamide Hydrochloride RS in *Mobile phase*

Sample solution: Fill a 100-mL volumetric flask with *Mobile phase*. Immediately transfer a number of Tablets equivalent to 20 mg of loperamide hydrochloride to the flask, and cap tightly. Sonicate for 15–30 min with intermittent shaking. Allow the contents to settle, and use a clear supernatant.

Chromatographic system

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

Mode: LC

Detector: UV 219 nm

Column: 3.9-mm × 15-cm; 5-µm or 10-µm packing L1

Flow rate: 2 mL/min

Injection volume: 50 µL

System suitability

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

Suitability requirements

Resolution: NLT 3.0 between loperamide and loperamide related compound F, *System suitability solution*

Tailing factor: NMT 2.0 for both peaks, *System suitability solution*

Relative standard deviation: NMT 2.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of loperamide hydrochloride ($C_{29}H_{33}ClN_2O_2 \cdot HCl$) in the portion of Tablets 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 Loperamide Hydrochloride RS in the *Standard solution* (mg/mL)

C_U = nominal concentration of loperamide hydrochloride in the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

• **Dissolution ⟨711⟩**

Test 1

Medium: 0.01 N hydrochloric acid; 900 mL

Apparatus 2: 50 rpm

Time: 30 min

Standard solution: USP Loperamide Hydrochloride RS at a known concentration in *Medium*. [Note—If necessary, dissolve USP Loperamide Hydrochloride RS in a minimal amount of methanol, and then dilute with *Medium* to final concentration.]

Sample solution: Filtered solution under test

Buffer: Transfer 3.0 g of triethylamine hydrochloride and 1.0 mL of phosphoric acid to a 1-L flask, and add 550 mL of water.

Mobile phase: Acetonitrile and *Buffer* (45:55)

Chromatographic system

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

Mode: LC

Detector: UV 214 nm

Column: 4.6-mm × 7.5-cm; 3.5-µm packing L7 or 4.6-mm × 12.5-cm; 5-µm packing L7

Flow rate: 1.5 mL/min

Injection volume: 50 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of loperamide hydrochloride ($C_{29}H_{33}ClN_2O_2 \cdot HCl$) dissolved:

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

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of the *Standard solution* (mg/mL)

L = label claim (mg/Tablet)

V = volume of *Medium*, 900 mL

Tolerances: NLT 80% (*Q*) of the labeled amount of loperamide hydrochloride ($C_{29}H_{33}ClN_2O_2 \cdot HCl$) is dissolved.

Test 2: If the product complies with this test, the labeling indicates that the product meets USP *Dissolution Test 2*.

Medium: 0.01 N hydrochloric acid; 900 mL

Apparatus 2: 50 rpm

Time: 10 min

Standard stock solution: 0.44 mg/mL of USP Loperamide Hydrochloride RS in methanol. Use sonication as necessary to dissolve.

Standard solution: 0.0022 mg/mL of USP Loperamide Hydrochloride RS in *Medium*, from the *Standard stock solution*

Sample solution: Pass a portion of the solution under test through a suitable membrane filter of 0.45-µm pore size, discarding first few milliliters of the filtrate.

Buffer: Transfer 3.0 g of triethylamine hydrochloride and 1.0 mL of phosphoric acid to a 1-L flask, and add 550 mL of water.

Mobile phase: Acetonitrile and *Buffer* (40:60)

Chromatographic system

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

Mode: LC

Detector: UV 214 nm

Column: 4.6-mm × 15-cm; 5-µm packing L7

Flow rate: 2.0 mL/min

Injection volume: 50 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of loperamide hydrochloride ($C_{29}H_{33}ClN_2O_2 \cdot HCl$) dissolved:

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

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of the *Standard solution* (mg/mL)

L = label claim (mg/Tablet)

V = volume of *Medium*, 900 mL

Tolerances: NLT 80% (*Q*) of the labeled amount of loperamide hydrochloride ($C_{29}H_{33}ClN_2O_2 \cdot HCl$) is dissolved.

• **Uniformity of Dosage Units ⟨905⟩:** Meet the requirements

IMPURITIES

• **Organic Impurities**

Solvent mixture, Ion pairing solution, Mobile phase, System suitability solution, Sample solution, and **Chromatographic system:** Proceed as directed in the *Assay*.

Standard solution: 0.002 mg/mL of USP Loperamide Related Compound F RS in *Mobile phase*

System suitability

Sample: *System suitability solution*

Suitability requirements

Resolution: NLT 3.0 between loperamide and loperamide related compound F

Tailing factor: NMT 2.0 for both peaks

Analysis

Samples: *Sample solution* and *Standard solution*

Calculate the percentage of loperamide *N*-oxide in the portion of Tablets taken:

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

r_T = sum of the peak responses of the *cis* and *trans* isomers of *N*-oxide from the *Sample solution*

r_S = peak response of loperamide related compound F from the *Standard solution*

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

C_U = nominal concentration of loperamide hydrochloride in the *Sample solution* (mg/mL)

Acceptance criteria: See *Table 1*.

Table 1

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Loperamide	1.0	—
Loperamide *trans*-*N*-oxide (loperamide related compound F)	1.5	2.0[a]
Loperamide *cis*-*N*-oxide[b]	1.7	

[a] For the sum of *trans* and *cis* isomers.

[b] (1*s*,4*r*)-4-(4-Chlorophenyl)-1-[4-(dimethylamino)-4-oxo-3,3-diphenylbutyl]-4-hydroxypiperidine 1-oxide.

ADDITIONAL REQUIREMENTS

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

• **Labeling:** Label chewable Tablets to indicate that they are to be chewed before swallowing. When more than one *Dissolution* test is given, the labeling states the *Dissolution* test used only if *Test 1* is not used.

• **USP Reference Standards** ⟨11⟩

USP Loperamide Hydrochloride RS

USP Loperamide Related Compound F RS

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

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

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

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