Loperamide Hydrochloride Tablets

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Expert Committee	Chemical Medicines Monographs 3
Reason for Revision	Compliance

In accordance with the Rules and Procedures of the 2015-2020 Council of Experts, the Chemical Medicines Monographs 3 Expert Committee has revised the Loperamide Hydrochloride Tablets monograph. The purpose for the revision is to add *Dissolution Test* 2 for a drug product approved by the FDA. This analytical procedure was validated using Zorbax RX-C8 brand of L7 column. The typical retention time for loperamide is about 4 min.

The Loperamide Hydrochloride Tablets Revision Bulletin supersedes the currently official monograph. The Revision Bulletin will be incorporated in the *First Supplement* to *USP 40–NF 35*.

Should you have any questions, please contact Elena Gonikberg, Ph.D., Principal Scientific Liaison, (301-816-8251 or eg@usp.org).

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

- **A.**

ULTRAVIOLET ABSORPTION ⟨197U⟩

[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

Change to read:

- **DISSOLUTION ⟨711⟩**

•Test 1• (RB 1-Oct-2016)

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.● (RB 1-Oct-2016)

• **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	
Loperamide *cis-N*-oxide[b]	1.7	2.0[a]

[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.

Change to read:

• **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.● (RB 1-Oct-2016)

• **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