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Metronidazole Extended-Release Tablets

DEFINITION

Metronidazole Extended-Release Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of metronidazole ($C_6H_9N_3O_3$).

IDENTIFICATION

Change to read:

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

Diluent: Methanol and sulfuric acid (350:1)

Standard stock solution: 15 mg/mL of USP Metronidazole RS in dilute hydrochloric acid (1 in 100). Sonicate to dissolve and pass through a suitable filter.

Standard solution: 18.8 µg/mL of USP Metronidazole RS in *Diluent* from *Standard stock solution*

Sample stock solution: Nominally 15 mg/mL of metronidazole prepared as follows. Finely powder NLT 5 Tablets and transfer an amount equivalent to 300 mg of metronidazole into a 20-mL volumetric flask. Add about 15 mL of dilute hydrochloric acid (1 in 100) and shake mechanically for 30 min. Dilute with dilute hydrochloric acid (1 in 100) to volume and shake well. Pass through a suitable filter.

Sample solution: Nominally equivalent to 18.8 µg/mL of metronidazole in *Diluent* from *Sample stock solution*

Wavelength range: 200–400 nm

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**

Buffer: 1.4 g/L of monobasic potassium phosphate in water

Mobile phase: Methanol and *Buffer* (30:70)

Standard solution: 0.1 mg/mL of USP Metronidazole RS in *Mobile phase*

Sample stock solution: Nominally 2.0 mg/mL of metronidazole from NLT 20 finely powdered Tablets in *Mobile phase*, prepared as follows. Transfer a suitable amount of the powder to a suitable volumetric flask. Add 60% of the flask volume with *Mobile phase*, and shake by mechanical means for 30 min. Dilute with *Mobile phase* to volume. Allow the solution to stand until the insoluble material settles.

Sample solution: Nominally 0.1 mg/mL of metronidazole in *Mobile phase* from the *Sample stock solution* supernatant. Pass the solution through a suitable filter of 0.45-µm pore size.

Chromatographic system

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

Mode: LC

Detector: UV 315 nm

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

Temperatures

Column: 30°

Autosampler: 15°

Flow rate: 1 mL/min

Injection volume: 10 µL

Run time: 15 min

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 metronidazole ($C_6H_9N_3O_3$) in the portion of Tablets taken:

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

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

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

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

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

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

• **Dissolution** ⟨711⟩

Medium: Water; 900 mL

Apparatus 2: 50 rpm

Times: 2, 6, 10, and 16 h

Standard solution: 16.65 µg/mL of USP Metronidazole RS in *Medium*

Sample solution: At the times specified, withdraw 10 mL of the solution under test and pass through a suitable filter of 0.45-µm pore size. Replace the aliquots withdrawn for analysis with equal volumes of fresh portions of *Medium* maintained at 37°. Dilute with *Medium* to a concentration similar to that of the *Standard solution*.

Blank: *Medium*

Instrumental conditions

Mode: UV

Analytical wavelength: 320 nm

Cell: 1 cm

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the concentration (C_i) of metronidazole ($C_6H_9N_3O_3$) in the sample withdrawn from the vessel at each time point (*i*).

$$\text{Result} = (A_U/A_S) \times C_S \times D$$

A_U = absorbance of the *Sample solution*

A_S = absorbance of the *Standard solution*

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

D = dilution factor, if needed

Calculate the percentage of the labeled amount (Q_i) of metronidazole ($C_6H_9N_3O_3$) dissolved at each time point (*i*).

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$

$$\text{Result}_2 = [(C_2 \times V) + (C_1 \times V_S)] \times (1/L) \times 100$$

$$\text{Result}_3 = \{[C_3 \times V] + [(C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$

$$\text{Result}_4 = \{(C_4 \times V) + [(C_3 + C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$

C_i = concentration of metronidazole in the portion of sample withdrawn at the specified time point (mg/mL)

V = volume of the *Medium*, 900 mL

L = label claim (mg/Tablet)

V_S = volume of the *Sample solution* withdrawn at each time point and replaced with *Medium* (mL)

Tolerances: See *Table 1*.

Table 1

Time Point (*i*)	Time (h)	Amount Dissolved (%)
1	2	20–35
2	6	45–60

Time Point (*i*)	Time (h)	Amount Dissolved (%)
3	10	60–75
4	16	NLT 75

The percentages (*Q*) of the labeled amount of metronidazole ($C_6H_9N_3O_3$) released at the times specified conform to *Dissolution ⟨711⟩, Acceptance Table 2*.

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

IMPURITIES

- **Organic Impurities**

Buffer: Dissolve 1.5 g of monobasic potassium phosphate in 900 mL of water, adjust with phosphoric acid to a pH of 3.2, and dilute with water to 1000 mL.

Diluent: Acetonitrile and *Buffer* (45:55)

Mobile phase: See *Table 2*.

Table 2

Time (min)	Buffer (%)	Acetonitrile (%)
0	95	5
5	95	5
25	50	50
30	95	5
35	95	5

System suitability solution: 0.5 mg/mL of USP Metronidazole RS and 2.5 µg/mL of USP Tinidazole Related Compound A RS in *Diluent*. Sonicate, if necessary, to dissolve.

Standard solution: 0.75 µg/mL of USP Metronidazole RS in *Diluent*

Sample solution: Nominally 0.5 mg/mL of metronidazole from NLT 20 finely powdered Tablets in *Diluent*, prepared as follows. Transfer a suitable amount of the powder to a suitable volumetric flask. Add *Diluent* equivalent to 70% of the flask volume, sonicate for 15 min with intermittent shaking, and dilute with *Diluent* to volume. Allow the solution to stand until the insoluble material settles, and pass the supernatant through a suitable filter of 0.45-µm pore size.

Chromatographic system

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

Mode: LC

Detector: UV 315 nm

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

Autosampler temperature: 20°

Flow rate: 1 mL/min

Injection volume: 10 µL

System suitability

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

Suitability requirements

Resolution: NLT 2.0 between tinidazole related compound A and metronidazole, *System suitability solution*

Relative standard deviation: NMT 5.0% for metronidazole, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each individual degradation product in the portion of Tablets taken:

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

r_U = peak response of each individual degradation product from the *Sample solution*

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

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

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

Acceptance criteria: See *Table 3*. Disregard any impurity peaks less than 0.05%.

Table 3

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Tinidazole related compound A	0.79	0.15
Metronidazole	1.0	—
Any individual unspecified degradation product	—	0.10
Total degradation products	—	0.50

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in well-closed containers. Store at controlled room temperature.
- **USP Reference Standards** (11)
  USP Metronidazole RS
  USP Tinidazole Related Compound A RS
  2-Methyl-5-nitroimidazole.
  $C_4H_5N_3O_2$ 127.10

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

Topic/Question	Contact	Expert Committee
METRONIDAZOLE EXTENDED-RELEASE TABLETS	Documentary Standards Support	SM12020 Small Molecules 1

Chromatographic Database Information: Chromatographic Database

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