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Ciprofloxacin Extended-Release Tablets

DEFINITION
Ciprofloxacin Extended-Release Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of ciprofloxacin ($C_{17}H_{18}FN_3O_3$).

IDENTIFICATION
• **A.** 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: Dilute 2.9 mL of phosphoric acid in water to 1000 mL. Adjust with triethylamine to a pH of 3.0.

Mobile phase: Acetonitrile and *Buffer* (135:865)

System suitability solution: 0.58 mg/mL of USP Ciprofloxacin Hydrochloride RS and 0.5 mg/mL of USP Ciprofloxacin Ethylenediamine Analog RS in *Mobile phase*

Standard stock solution: 1.16 mg/mL of USP Ciprofloxacin Hydrochloride RS in *Mobile phase*

Standard solution: 0.058 mg/mL of USP Ciprofloxacin Hydrochloride RS in *Mobile phase* from *Standard stock solution*

Sample stock solution: Nominally 0.5 mg/mL in *Mobile phase* prepared as follows. Transfer an equivalent to 250 mg of ciprofloxacin from finely powdered Tablets (NLT 20) to a 500-mL volumetric flask. Add 400 mL of *Mobile phase*, place on a rotary shaker for 15 min, and sonicate for 25 min. Allow the solution to cool to room temperature, and dilute with *Mobile phase* to volume. Pass a portion of the solution through a suitable filter of 0.45-µm pore size.

Sample solution: Nominally 0.05 mg/mL of ciprofloxacin in water from *Sample stock solution*

Chromatographic system

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

Mode: LC

Detector: UV 278 nm

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

Column temperature: 30°

Flow rate: 1.5 mL/min

Injection volume: 10 µL

System suitability

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

Suitability requirements

Resolution: NLT 6 between the ciprofloxacin and ciprofloxacin ethylenediamine analog peaks, *System suitability solution*

Tailing factor: NMT 4.0 for the ciprofloxacin peak, *System suitability solution*

Relative standard deviation: NMT 2.0% for the ciprofloxacin peak, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of ciprofloxacin ($C_{17}H_{18}FN_3O_3$) in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

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

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

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

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

M_{r1} = molecular weight of ciprofloxacin, 331.34

M_{r2} = molecular weight of anhydrous ciprofloxacin hydrochloride, 367.81

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

- **Dissolution** ⟨711⟩

Test 1

Medium: pH 4.5 acetate buffer (transfer 3 g of sodium acetate and 14 mL of 2 N acetic acid to a 1-L volumetric flask, and dilute with water to volume); 900 mL, deaerated

Apparatus 2: 50 rpm

Times: 30, 60, and 120 min

Standard solution: 6.5 µg/mL of USP Ciprofloxacin Hydrochloride RS in *Medium*

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size. For 500-mg Tablets, transfer 2 mL of the filtrate to a 200-mL volumetric flask, and dilute with *Medium* to volume. For 1000-mg Tablets, transfer 1 mL of the filtrate to a 200-mL volumetric flask, and dilute with *Medium* to volume. Replace the aliquots withdrawn for analysis with fresh portions of *Medium*.

Instrumental conditions

Mode: UV

Analytical wavelength: 277 nm

Blank: *Medium*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of ciprofloxacin ($C_{17}H_{18}FN_3O_3$) dissolved at each time interval (D_i):

$$D_i = (A_U/A_S) \times (C_S/L) \times (M_{r1}/M_{r2}) \times V \times D \times 100$$

A_U = absorbance of the *Sample solution*

A_S = absorbance of the *Standard solution*

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

L = label claim (mg/Tablet)

M_{r1} = molecular weight of ciprofloxacin, 331.34

M_{r2} = molecular weight of anhydrous ciprofloxacin hydrochloride, 367.81

V = volume of *Medium*, 900 mL

D = dilution factor of the *Sample solution*

Percentage of ciprofloxacin dissolved at the first time interval = D_1

Percentage of ciprofloxacin dissolved at the second time interval = $D_2 + [D_1 \times (v/V)]$

Percentage of ciprofloxacin dissolved at the third time interval = $D_3 + [(D_2 + D_1) \times (v/V)]$

v = volume of solution under test removed at each time interval (mL)

Tolerances

For Tablets labeled to contain 500 mg, see *Table 1*.

Table 1

Time (min)	Amount Dissolved
30	42%–62%
60	62%–87%

Time (min)	Amount Dissolved
120	NLT 80%

For Tablets labeled to contain 1000 mg, see *Table 2*.

Table 2

Time (min)	Amount Dissolved
30	30%–50%
60	50%–70%
120	NLT 80%

The percentages of the labeled amount of ciprofloxacin ($C_{17}H_{18}FN_3O_3$) dissolved at the times specified conform to *Acceptance Table 2* in *Dissolution* ⟨711⟩.

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

Medium: 0.1 N hydrochloric acid; 900 mL

Apparatus 2: 50 rpm

Times: 30, 60, and 120 min

Standard solution: 0.62 mg/mL of USP Ciprofloxacin Hydrochloride RS in *Medium*

Sample solution: Pass a portion of the solution under test through a suitable filter. Dilute with *Medium* to a concentration similar to the *Standard solution*, if necessary.

Instrumental conditions

Mode: UV

Analytical wavelength: 276 nm

Cell length: 0.1 mm

Blank: *Medium*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of ciprofloxacin ($C_{17}H_{18}FN_3O_3$) dissolved at each time interval (D_i):

$$D_i = (A_U/A_S) \times (C_S/L) \times (M_{r1}/M_{r2}) \times V \times D \times 100$$

A_U = absorbance of the *Sample solution*

A_S = absorbance of the *Standard solution*

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

L = label claim (mg/Tablet)

M_{r1} = molecular weight of ciprofloxacin, 331.34

M_{r2} = molecular weight of anhydrous ciprofloxacin hydrochloride, 367.81

V = volume of *Medium*, 900 mL

D = dilution factor of the *Sample solution*

Percentage of ciprofloxacin dissolved at the first time interval = D_1

Percentage of ciprofloxacin dissolved at the second time interval = $D_2 + [D_1 \times (v/V)]$

Percentage of ciprofloxacin dissolved at the third time interval = $D_3 + [(D_2 + D_1) \times (v/V)]$

v = volume of solution under test removed at each time interval (mL)

Tolerances: See *Table 3*.

Table 3

Time Point (*i*)	Time (min)	Amount Dissolved
1	30	40%–65%
2	60	NLT 60%
3	120	NLT 80%

The percentages of the labeled amount of ciprofloxacin ($C_{17}H_{18}FN_3O_3$) dissolved at the times specified conform to *Acceptance Table 2* in *Dissolution* ⟨711⟩.

Test 3: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 3*.

Medium: 0.1 N hydrochloric acid; 900 mL

Apparatus 2: 50 rpm

Times: 30, 60, and 120 min

Standard solution: 0.65 mg/mL of USP Ciprofloxacin Hydrochloride RS in *Medium*

Sample solution: Pass a portion of the solution under test through a suitable filter. Dilute with *Medium* to a concentration similar to the *Standard solution*, if necessary.

Instrumental conditions

Mode: UV

Analytical wavelength: 350 nm

Cell length

For 500-mg Tablet strength: 2 mm

For 1000-mg Tablet strength: 1 mm

Blank: *Medium*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of ciprofloxacin ($C_{17}H_{18}FN_3O_3$) dissolved at each time interval (D_i):

$$D_i = (A_U/A_S) \times (C_S/L) \times (M_{r1}/M_{r2}) \times V \times D \times 100$$

A_U = absorbance of the *Sample solution*

A_S = absorbance of the *Standard solution*

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

L = label claim (mg/Tablet)

M_{r1} = molecular weight of ciprofloxacin, 331.34

M_{r2} = molecular weight of anhydrous ciprofloxacin hydrochloride, 367.81

V = volume of *Medium*, 900 mL

D = dilution factor of the *Sample solution*

Percentage of ciprofloxacin dissolved at the first time interval = D_1

Percentage of ciprofloxacin dissolved at the second time interval = $D_2 + [D_1 \times (v/V)]$

Percentage of ciprofloxacin dissolved at the third time interval = $D_3 + [(D_2 + D_1) \times (v/V)]$

v = volume of solution under test removed at each time interval (mL)

Tolerances: See *Table 4*.

Table 4

Time Point (*i*)	Time (min)	Amount Dissolved
1	30	37%–57%
2	60	55%–75%
3	120	NLT 80%

The percentages of the labeled amount of ciprofloxacin ($C_{17}H_{18}FN_3O_3$) dissolved at the times specified conform to *Acceptance Table 2* in *Dissolution* ⟨711⟩.

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

IMPURITIES

• **Organic Impurities**

Buffer, Mobile phase, and **System suitability solution:** Prepare as directed in the *Assay*.

Standard stock solution: 0.5 mg/mL of USP Ciprofloxacin Hydrochloride RS in *Mobile phase*

Standard solution: 1.25 µg/mL of USP Ciprofloxacin Hydrochloride RS in *Mobile phase* from *Standard stock solution*

Sample solution: Nominally 0.5 mg/mL of ciprofloxacin in *Mobile phase* prepared as follows. Transfer an equivalent to 250 mg of ciprofloxacin from finely powdered Tablets (NLT 20) to a 500-mL volumetric flask. Add 400 mL of *Mobile phase*, place on a rotary shaker for 15 min, and sonicate for 25 min with intermittent shaking. Allow the solution to cool to room temperature, and dilute with *Mobile phase* to volume. Pass a portion of the solution through a suitable filter of 0.45-µm pore size.

Chromatographic system

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

Mode: LC

Detector: UV 263 and 278 nm

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

Column temperature: 30°

Flow rate: 1.5 mL/min

Injection volume: 10 µL

System suitability

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

Suitability requirements

Resolution: NLT 6 between the ciprofloxacin and ciprofloxacin ethylenediamine analog peaks at 278 nm, *System suitability solution*

Tailing factor: NMT 2.0 for the ciprofloxacin peak at 278 nm, *Standard solution*

Relative standard deviation: NMT 10.0% for the ciprofloxacin peak at 278 nm, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of decarboxyciprofloxacin in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times (1/F) \times 100$$

r_U = peak response of decarboxyciprofloxacin at 263 nm from the *Sample solution*

r_S = peak response of ciprofloxacin at 263 nm from the *Standard solution*

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

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

M_{r1} = molecular weight of ciprofloxacin, 331.34

M_{r2} = molecular weight of anhydrous ciprofloxacin hydrochloride, 367.81

F = relative response factor of decarboxyciprofloxacin (see *Table 5*)

Calculate the percentage of the other impurities in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times (1/F) \times 100$$

r_U = peak response of each impurity at 278 nm from the *Sample solution*

r_S = peak response of ciprofloxacin at 278 nm from the *Standard solution*

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

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

M_{r1} = molecular weight of ciprofloxacin, 331.34

M_{r2} = molecular weight of anhydrous ciprofloxacin hydrochloride, 367.81

F = relative response factor (see *Table 5*)

Acceptance criteria: See *Table 5*.

Table 5

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Decarboxyciprofloxacin[a]	0.36	1.6	0.2
Desfluorociprofloxacin[b]	0.59	1.0	0.2
Ciprofloxacin ethylenediamine analog[c]	0.68	1.2	0.2
Ciprofloxacin	1.00	—	—
7-Chloro-6-piperazinyl analog[d]	1.20	0.45	0.2
Chlorociprofloxacin[e]	2.10	0.75	0.2
Any unspecified impurity	—	1.0	0.2
Total impurities	—	—	0.6

[a] 1-Cyclopropyl-6-fluoro-7-(piperazin-1-yl)quinolin-4(1*H*)-one.

[b] 1-Cyclopropyl-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid.

[c] 7-(2-Aminoethylamino)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid.

[d] 7-Chloro-1-cyclopropyl-4-oxo-6-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid.

[e] 6-Chloro-1-cyclopropyl-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid.

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in tight containers. Store at controlled room temperature.
- **Labeling:** 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 Ciprofloxacin Ethylenediamine Analog RS

7-(2-Aminoethylamino)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid.

$C_{15}H_{16}FN_3O_3$ 305.30

USP Ciprofloxacin Hydrochloride RS

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

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