Status: Currently Official on 14-Feb-2025
Official Date: Official as of 01-Feb-2018
Document Type: USP Monographs
DocId: GUID-DAA72BDC-0466-4CF4-B5C1-06B08FB251D5_4_en-US
DOI: https://doi.org/10.31003/USPNF_M1148_04_01
DOI Ref: 5aia3

Ezetimibe Tablets

DEFINITION

Ezetimibe Tablets contain NLT 93.0% and NMT 107.0% of the labeled amount of ezetimibe ($C_{24}H_{21}F_2NO_3$).

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*.

• **B.** The UV absorption spectrum of the ezetimibe peak of the *Sample solution* exhibits maxima and minima at the same wavelengths as those of the corresponding peak of the *Standard solution*, as obtained in the *Assay*.

ASSAY

• **Procedure**

Buffer: Dissolve 6.8 g of monobasic potassium phosphate in 1 L of water.

Mobile phase: Tetrahydrofuran, acetonitrile, and *Buffer* (100:250:650)

Diluent: Acetonitrile, glacial acetic acid, and water (600:1:400)

Standard solution: 0.2 mg/mL of USP Ezetimibe RS in *Diluent*. Pass through a suitable filter of 0.45-µm pore size and discard the first 3 mL of the filtrate.

Sample solution: Nominally 0.2 mg/mL of ezetimibe in *Diluent* prepared as follows. Place NLT 10 powdered Tablets in a suitable volumetric flask, add *Diluent* to fill about 60% of the total volume, sonicate for about 30 min, and shake on a wrist shaker for about 45 min. Dilute with *Diluent* to volume, pass through a suitable filter of 0.45-µm pore size, and discard the first 3 mL of the filtrate.

Chromatographic system

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

Mode: LC

Detector: UV 232 nm. For *Identification B*, use a diode array detector in the range of 200–400 nm.

Column: 4.6-mm × 15-cm; 5-µm packing L1

Flow rate: 1 mL/min

Injection volume: 30 µL

Run time: NLT 2.4 times the retention time of the ezetimibe peak

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 1.5

Relative standard deviation: NMT 1.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of ezetimibe ($C_{24}H_{21}F_2NO_3$) in the portion of Tablets taken:

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

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

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

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

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

Acceptance criteria: 93.0%–107.0%

PERFORMANCE TESTS

• **Dissolution ⟨711⟩**

Test 1

Do not refrigerate solutions containing ezetimibe.

Medium: 0.45% sodium lauryl sulfate in 0.05 M sodium acetate buffer, pH 4.5, prepared as follows. To 6 L of water in a suitable flask, add about 27 g of sodium lauryl sulfate and 24.6 g of sodium acetate. Dissolve the reagents by stirring until the solution is clear. Adjust with either hydrochloric acid or sodium hydroxide to a pH of 4.5; 500 mL.

Apparatus 2: 50 rpm

Time: 30 min

Standard solution: 0.02 mg/mL of USP Ezetimibe RS in *Medium* prepared as follows. To a suitable amount of USP Ezetimibe RS in an appropriate volumetric flask, add methanol to fill about 1% of the total volume, and shake until completely dissolved. Dilute with *Medium* to volume.

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size. Discard the first 3 mL of the filtrate.

Instrumental conditions

(See *Ultraviolet-Visible Spectroscopy* ⟨857⟩.)

Mode: UV

Analytical wavelength: 233 nm

Cell: 1.0 cm

Blank: *Medium*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of ezetimibe ($C_{24}H_{21}F_2NO_3$) dissolved:

$$\text{Result} = (A_U/A_S) \times C_S \times V \times (1/L) \times 100$$

A_U = absorbance of the *Sample solution*

A_S = absorbance of the *Standard solution*

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

V = volume of *Medium*, 500 mL

L = label claim (mg/Tablet)

Tolerances: NLT 80% (*Q*) of the labeled amount of ezetimibe ($C_{24}H_{21}F_2NO_3$) is dissolved.

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

Apparatus 2, Standard solution, Sample solution, Instrumental conditions, and **Analysis:** Proceed as directed in *Test 1*.

Buffer: 6.8 g/L of sodium acetate pH 4.5 prepared as follows. Dissolve 6.8 g of sodium acetate in 1 L of water. Add 3 mL of glacial acetic acid and mix. If necessary, adjust with 2 N acetic acid or 0.2 N sodium hydroxide to a pH of 4.5.

Medium: 0.45% (w/v) sodium dodecyl sulfate in *Buffer*, 500 mL

Time: 20 min

System suitability

Sample: *Standard solution*

Suitability requirements

Relative standard deviation: NMT 2.0% for 5 replicate readings

Tolerances: NLT 80% (*Q*) of the labeled amount of ezetimibe ($C_{24}H_{21}F_2NO_3$) is dissolved.

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

IMPURITIES

• **Organic Impurities**

Buffer, Mobile phase, Diluent, Sample solution, and **Chromatographic system:** Proceed as directed in the *Assay*.

System suitability solution: Weigh about 20 mg of USP Ezetimibe RS into a 100-mL volumetric flask. Dissolve in 10 mL of 0.01 N alcoholic sodium hydroxide. Place the capped volumetric flask into a 55° oven for 15 min. Remove from the oven and immediately add 2 mL of 0.1 N hydrochloric acid and about 50 mL of *Diluent*. Mix, allow to cool to room temperature, and dilute with *Diluent* to volume. Pass through a suitable filter of 0.45-µm pore size and discard the first 3 mL of the filtrate. [Note—Unidentified peak 2 with a relative retention time of about 1.14 is generated during hydrolysis.]

Sensitivity solution: 0.1 µg/mL of USP Ezetimibe RS in *Diluent*

System suitability

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

Suitability requirements

Resolution: NLT 1.5 between the ezetimibe peak and unidentified peak 2, *System suitability solution*

Signal-to-noise ratio: NLT 10, *Sensitivity solution*

Analysis

Sample: *Sample solution*

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

$$\text{Result} = (r_U/r_T) \times 100$$

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

r_T = sum of all the peak responses from the *Sample solution*

Acceptance criteria: See *Table 1*.

Table 1

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Unidentified peak 1	0.64	—
S,S,S-Ezetimibe and *R,R,R*-Ezetimibe[a,b]	0.78	—
Ezetimibe	1.00	—
Unidentified peak 2	1.14	—
Ezetimibe tetrahydropyran analog[c]	1.53	0.2
Ezetimibe ketone[d]	1.75	0.2
Any unspecified impurity	—	0.2
Total impurities[e]	—	0.5

[a] (3*S*,4*S*)-1-(4-Fluorophenyl)-3-[(*S*)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)azetidin-2-one and (3*R*,4*R*)-1-(4-Fluorophenyl)-3-[(*R*)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)azetidin-2-one.

[b] Process-related impurity and controlled in the drug substance.

[c] *N*,6-Bis(4-fluorophenyl)-2-(4-hydroxyphenyl)tetrahydro-2*H*-pyran-3-carboxamide.

[d] (3*R*,4*S*)-1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-oxopropyl]-4-(4-hydroxyphenyl)azetidin-2-one.

[e] Total impurities include specified and unspecified degradation products. Process impurities are not included.

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Protect from moisture. 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 Ezetimibe RS

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

Topic/Question	Contact	Expert Committee
EZETIMIBE TABLETS	Documentary Standards Support	SM22020 Small Molecules 2

Chromatographic Database Information: Chromatographic Database

Most Recently Appeared In:
Pharmacopeial Forum: Volume No. PF 42(3)

Current DocID: GUID-DAA72BDC-0466-4CF4-B5C1-06B08FB251D5_4_en-US
Previous DocID: GUID-DAA72BDC-0466-4CF4-B5C1-06B08FB251D5_2_en-US
DOI: https://doi.org/10.31003/USPNF_M1148_04_01
DOI ref: 5aia3