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Topiramate Tablets

DEFINITION
Topiramate Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of topiramate ($C_{12}H_{21}NO_8S$).

IDENTIFICATION

Change to read:

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

Wavenumber range: 4000–650 cm^{-1}

Standard solution: 20 mg/mL of USP Topiramate RS in acetone

Sample solution: Grind an appropriate number of Tablets to prepare a 20-mg/mL topiramate solution in acetone. Shake the solution for 30 min, and centrifuge for 10 min. Then pass an aliquot of the clear supernatant through a suitable nylon filter of 0.45-µm pore size, and use the filtrate for analysis.

Analysis: Apply 50 µL of the *Standard solution* to a sodium chloride plate, allow the solution to dry, and then obtain the IR spectrum. Wash the window with acetone, and repeat the same procedure using the *Sample solution*.

• **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: 1.54 g/L of ammonium acetate in water. Adjust with glacial acetic acid to a pH of 4.0.

Diluent: Methanol and water (1:4)

Mobile phase: Methanol and *Buffer* (1:4)

Standard solution: 6 mg/mL of USP Topiramate RS in *Diluent*

Sample solution: 6 mg/mL of topiramate in *Diluent* from NLT 12 Tablets, based on the label claim. [Note—Shake vigorously for at least 30 min, and pass a portion through a chemical-resistant filter (PTFE) of 0.45-µm pore size.]

Chromatographic system

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

Mode: LC

Detector: Refractive index

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

Temperature

Column: 35°

Detector: 35°

Flow rate: 1.5 mL/min

Injection size: 100 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of topiramate ($C_{12}H_{21}NO_8S$) 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 Topiramate RS in the *Standard solution* (mg/mL)

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

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

• **Dissolution ⟨711⟩**

Test 1

Medium: Water; 900 mL

Apparatus 2: 50 rpm

Time: 20 min

Mobile phase: 0.1% trifluoroacetic acid in water and methanol (1:1)

Standard solution: 0.1 mg/mL of USP Topiramate RS in *Medium*

Sample solution: Pass a portion of the solution under test through a suitable filter of 1-µm pore size.

Chromatographic system

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

Mode: LC

Detector: Refractive index

Guard column: 4.0-mm × 1-cm

Column: 4.6-mm × 25-cm; 5-µm packing L11

Temperature

Column: 40°

Detector: 40°

Flow rate: 1.2 mL/min

Injection size: 100 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of topiramate ($C_{12}H_{21}NO_8S$) 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 USP Topiramate RS in 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 topiramate is dissolved.

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

Medium: Water; 900 mL, deaerated

Apparatus 2: 50 rpm

Time: 40 min

Standard solution: (L/900) mg/mL of USP Topiramate RS in *Medium*, where L is the label claim in mg/Tablet

Sample solution: Pass a portion of the solution under test through a suitable filter, discarding the first few mL.

Mobile phase: Water and acetonitrile (1:1)

Chromatographic system

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

Mode: LC

Detector: Refractive index

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

Temperature

Column: 30°

Detector: 50°

Flow rate: 1.0 mL/min

Injection size: 100 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Column efficiency: NLT 5000 theoretical plates

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of topiramate ($C_{12}H_{21}NO_8S$) 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 USP Topiramate RS in 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 topiramate is dissolved.

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

Medium: Water; 900 mL

Apparatus 2: 50 rpm

Time: 30 min

Diluent: Acetonitrile and water (1:1)

Mobile phase: Water and acetonitrile (55:45)

Standard solution: 1.1 mg/mL of USP Topiramate RS in *Diluent*. Dilute with *Medium* to obtain a final concentration of about (L/900) mg/mL, where L is the label claim in mg/Tablet.

Sample solution: Pass a portion of the solution under test through a suitable filter, discarding the first few mL.

Chromatographic system

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

Mode: LC

Detector: Refractive index

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

Temperature

Column: 50°

Detector: 50°

Flow rate: 1.2 mL/min

Injection size: 100 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Column efficiency: NLT 2000 theoretical plates

Tailing factor: NMT 2.0

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of topiramate ($C_{12}H_{21}NO_8S$) 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 USP Topiramate RS in 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 topiramate is dissolved.

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

IMPURITIES

• **Related Compounds**

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

Standard solution: 1.2 mg/mL of USP Topiramate RS and 0.6 mg/mL of USP Topiramate Related Compound A RS in *Diluent*

Peak identification solution: 0.6 mg/mL each of USP Topiramate RS and USP Topiramate Related Compound A RS in *Diluent*

System suitability

Samples: *Standard solution* and *Peak identification solution*

[Note—Identify the peaks due to topiramate related compound A and topiramate using the relative retention times given in *Table 1*.]

Suitability requirements

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

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in the portion of Tablets taken:

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

r_U = peak response for the individual impurity from the *Sample solution*

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

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

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

F = relative response factor (see *Table 1*)

Acceptance criteria See *Table 1*.

Table 1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Topiramate related compound A	0.66	1.1	0.5
Topiramate	1.0	—	—
Individual unspecified degradation product	—	—	0.2
Total impurities	—	—	0.7

SPECIFIC TESTS

• Limit of Sulfamate and Sulfate

[Note—Use water with resistivity NLT 18 megohm-cm for preparation of the *Mobile phase*, *Standard solution*, and *Sample solution*.]

Buffer: 0.8 g/L of *p*-hydroxybenzoic acid in water

Mobile phase: Methanol and *Buffer* (2.5:97.5). Adjust with sodium hydroxide solution to a pH of 9.4 ± 0.5.

Standard solution: 0.015 mg/mL each of sodium sulfate and sulfamic acid in *Mobile phase* from anhydrous sodium sulfate and sulfamic acid, respectively

Sample solution: Transfer a suitable amount of ground powder from NLT 20 Tablets to a suitable volumetric flask to obtain a nominal concentration of 6 mg/mL of topiramate. Add 80% of the flask volume of *Mobile phase*, and shake for 30 min. Sonicate for 10 min, and dilute with *Mobile phase* to volume. Centrifuge, and pass through a polyethersulfone membrane filter of 0.45-µm pore size, discarding the first 3 mL of the filtrate.

Chromatographic system

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

Mode: LC

Detector: Conductivity

Column: 4.6-mm × 15-cm; 5-µm packing L47

Detector temperature: 30°

Flow rate: 1.5 mL/min

[Note—A suitable background suppression unit may be used.]

Injection size: 70 µL

System suitability

Sample: *Standard solution*

[Note—The approximate relative retention time of the sulfamate ion peak is 0.44 relative to the sulfate ion peak.]

Suitability requirements

Relative standard deviation: NMT 15.0% for the sulfamate and sulfate peaks

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of sulfate ion 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 sulfate ion from the *Sample solution*

r_S = peak response of sulfate ion from the *Standard solution*

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

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

M_{r1} = molecular weight of the sulfate anion, 96.04

M_{r2} = molecular weight of anhydrous sodium sulfate, 142.04

Calculate the percentage of sulfamate ion 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 sulfamate ion from the *Sample solution*

r_S = peak response of sulfamate ion from the *Standard solution*

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

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

M_{r1} = molecular weight of the sulfamate anion, 96.09

M_{r2} = molecular weight of sulfamic acid, 97.09

Acceptance criteria: NMT 0.25% of sulfate ion; NMT 0.25% of sulfamate ion

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Store in tightly closed containers at controlled room temperature, protected from moisture.
- **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 Topiramate RS

2,3:4,5-Di-*O*-isopropylidene-β-D-fructopyranose sulfamate.

$C_{12}H_{21}NO_8S$ 339.36

USP Topiramate Related Compound A RS

2,3:4,5-Bis-*O*-(1-methylethylidene)-β-D-fructopyranose.

$C_{12}H_{20}O_6$ 260.28

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

Topic/Question	Contact	Expert Committee
TOPIRAMATE TABLETS	Documentary Standards Support	SM42020 Small Molecules 4
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM42020 Small Molecules 4

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