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Topiramate Capsules

DEFINITION
Topiramate Capsules 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 to 650 cm^{-1}

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

Sample solution: Open an appropriate number of Capsules 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 0.2-µm pore size, and use the filtrate for analysis.

Analysis

Samples: *Standard solution* and *Sample solution*

Apply 50 µL to an NaCl plate, allow the solution to dry, then obtain the IR spectrum.

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

Diluent: Acetonitrile and water (20:80)

Mobile phase: Methanol and *Buffer* (20:80)

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

Sample solution: Nominally 6 mg/mL of topiramate in *Diluent* from NLT 20 Capsules. [Note—Shake vigorously for at least 60 min, and pass a portion through a PTFE chemical-resistant filter 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

Flow rate: 1.5 mL/min

Injection volume: 100 µL

Temperatures

Column: 35°

Detector: 35°

System suitability

Sample: *Standard solution*

Suitability requirements

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of topiramate ($C_{12}H_{21}NO_8S$) in the portion of Capsules taken:

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

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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. Use an appropriate sinker as necessary.

Time: 45 min

Standard stock solution: 0.56 mg/mL of USP Topiramate RS in *Medium* prepared as follows. Transfer a suitable amount to a suitable volumetric flask. Add 2% of the flask volume of acetone to dissolve the solid. Dilute with *Medium* to volume.

Standard solution: (*L*/900) mg/mL of USP Topiramate RS in *Medium*, where *L* is the label claim, in mg of topiramate per Capsule from the *Standard stock solution*

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

Mobile phase: Methanol and water (32:68)

Chromatographic system

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

Mode: LC

Detector: Refractive index

Column: 4.6-mm × 15-cm; 5-µm packing L7

Flow rate: 2 mL/min

Injection volume: 200 µL

Temperatures

Column: 35°

Detector: 35°

System suitability

Sample: *Standard solution*

Suitability requirements

Relative standard deviation: NMT 2.0% for Capsules labeled to contain more than 15 mg of topiramate; NMT 3.0% for Capsules labeled to contain less than or equal to 15 mg of topiramate

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of topiramate ($C_{12}H_{21}NO_8S$) dissolved:

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

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)

V = volume of *Medium*, 900 mL

L = label claim (mg/Capsule)

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

Apparatus 2: 50 rpm. Use an appropriate sinker as necessary.

Time: 60 min

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

Sample solution: Pass a portion of the solution under test through a suitable filter.

Mobile phase: Methanol and water (40:60)

Chromatographic system

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

Mode: LC

Detector: Refractive index

Column: 4.6-mm × 25-cm; 5-µm packing L7

Flow rate: 1.5 mL/min

Injection volume: 100 µL

Temperatures

Column: 35°

Detector: 35°

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 topiramate ($C_{12}H_{21}NO_8S$) dissolved:

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

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)

V = volume of *Medium*, 900 mL

L = label claim (mg/Capsule)

Tolerances: NLT 75% (*Q*) of the labeled amount of topiramate ($C_{12}H_{21}NO_8S$) is dissolved.

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

IMPURITIES

• **Limit of Sulfamate and Sulfate:** Use water with a resistivity of NLT 18 megohm-cm for the 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: Grind the contents of NLT 20 Capsules. Transfer an amount of powder equivalent to 300 mg of topiramate to a 50-mL volumetric flask. Add about 40 mL of *Mobile phase*, and stir 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

Flow rate: 1.5 mL/min. [Note—A suitable background suppression unit may be used.]

Detector temperature: 30°

Injection volume: 70 µL

System suitability

Sample: *Standard solution*

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

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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 in the portion of Capsules 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 from the *Sample solution*

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

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

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

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

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

Calculate the percentage of sulfamate in the portion of Capsules 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 from the *Sample solution*

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

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

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

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

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

Acceptance criteria: NMT 0.25% (w/w) of sulfate and NMT 0.25% (w/w) of sulfamate

- **Organic Impurities**

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*

System suitability

Sample: *Standard 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%

Analysis

Samples: *Sample solution* and *Standard solution*

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

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

r_U = peak response of 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*)

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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

ADDITIONAL REQUIREMENTS

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

• **Labeling:** Topiramate Capsules may be swallowed whole or may be administered by carefully opening the Capsule and sprinkling the entire contents on a teaspoon of soft food. This drug-food mixture should be swallowed immediately and not chewed. It should not be stored for future use. 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

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 CAPSULES	Documentary Standards Support	SM42020 Small Molecules 4
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM42020 Small Molecules 4

Chromatographic Database Information: Chromatographic Database

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