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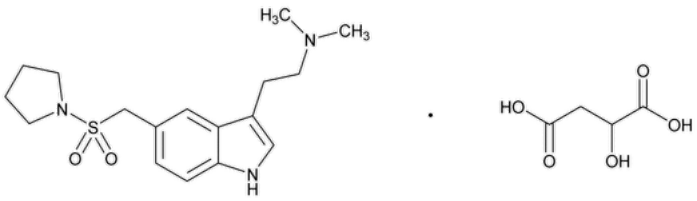
Almotriptan Malate



$C_{17}H_{25}N_3O_2S \cdot C_4H_6O_5$ 469.55

Pyrrolidine, 1-[[[3-[2-(dimethylamino)ethyl]-1*H*-indol-5-yl]methyl]sulfonyl]-, hydroxybutanedioate (1:1);
1-[({3-[2-(Dimethylamino)ethyl]indol-5-yl}methyl)sulfonyl]pyrrolidine malate (1:1) CAS RN®: 181183-52-8; UNII: PJP312605E.

DEFINITION

Almotriptan Malate contains NLT 98.0% and NMT 102.0% of almotriptan malate ($C_{17}H_{25}N_3O_2S \cdot C_4H_6O_5$), calculated on the anhydrous and solvent-free basis.

IDENTIFICATION

Change to read:

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

• **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: 2.72 g/L of monobasic potassium phosphate in water. Adjust with phosphoric acid to a pH of 3.5.

Mobile phase: Methanol and *Buffer* (40:60)

System suitability solution: 0.14 mg/mL each of USP Almotriptan Malate RS and USP Almotriptan Related Compound B RS in *Mobile phase*. Sonication may be used to promote dissolution.

Standard solution: 0.14 mg/mL of USP Almotriptan Malate RS in *Mobile phase*. Sonication may be used to promote dissolution.

Sample solution: 0.14 mg/mL of Almotriptan Malate in *Mobile phase*. Sonication may be used to promote dissolution.

Chromatographic system

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

Mode: LC

Detector: UV 230 nm

Column: 4.6-mm × 15-cm; 5-µm packing L10

Flow rate: 1 mL/min

Injection volume: 10 µL

Run time: NLT 2 times the retention time of almotriptan

System suitability

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

[Note—The relative retention times for almotriptan related compound B and almotriptan are 0.7 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 2.0 between almotriptan and almotriptan related compound B, *System suitability solution*

Tailing factor: NMT 2.0, *Standard solution*

Relative standard deviation: NMT 0.85% for six injections, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of almotriptan malate ($C_{17}H_{25}N_3O_2S \cdot C_4H_6O_5$) in the portion of Almotriptan Malate taken:

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

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

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

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

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

Acceptance criteria: 98.0%–102.0% on the anhydrous and solvent-free basis

IMPURITIES

- **Residue on Ignition ⟨281⟩:** NMT 0.10%
- **Limit of Almotriptan Related Compound D and Almotriptan *N*-Dimer**

Run buffer: 23.5 g/L of phosphoric acid in water. Adjust with triethanolamine to a pH of 3.0 and pass through a suitable filter of 0.45-µm pore size.

Diluent: Methanol and water (50:50)

Internal standard solution: 0.01 mg/mL of 4-hydroxy-4-phenylpiperidine in *Diluent*

System suitability solution: 0.005 mg/mL each of USP Almotriptan Related Compound B RS, USP Almotriptan Related Compound D RS, and USP Almotriptan Malate RS in the *Internal standard solution*. Pass through a suitable filter of 0.45-µm pore size.

Standard stock solution: 0.5 mg/mL of USP Almotriptan Malate RS in *Diluent*

Standard solution: 0.005 mg/mL of USP Almotriptan Malate RS from the *Standard stock solution* in the *Internal standard solution*. Pass through a suitable filter of 0.45-µm pore size.

Sample solution: 2.5 mg/mL of Almotriptan Malate in the *Internal standard solution*. Sonication may be used to promote dissolution. Pass the solution through a suitable filter of 0.45-µm pore size.

Capillary rinsing procedure: Use separate *Run buffer* vials for the capillary rinse and sample analysis. Condition the capillary by rinsing with water, 0.1 N sodium hydroxide, water, and the *Run buffer* before each injection. [Note—It may be suitable to rinse with water, 0.1 N sodium hydroxide, and water using a pressure of 20 psi for NLT 2 min each and then to rinse with the *Run buffer* using a pressure of 20 psi for NLT 5 min.]

Instrumental conditions

Mode: CE

Detector: UV 214 nm

Capillary, Capillary effective length, Capillary temperature, and **Voltage:** Use parameters described under *A* or *B* as indicated in *Table 1*.

Table 1

Parameter	A	B
Capillary	75-µm × 48.5-cm; uncoated fused silica	75-µm × 60-cm; uncoated fused silica
Capillary effective length	40 cm	47 cm
Capillary temperature	15°	25°
Voltage	A voltage of 15.5 kV may be suitable.	A voltage of 15.0 kV may be suitable.

Injection sequence: 0.5 psi for 8 s for the *Sample solution*, followed by 0.5 psi for 1 s for the *Run buffer*

Run time: NLT 2.5 times the migration time of almotriptan

System suitability

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

[Note—See *Table 2* for the relative migration times.]

Suitability requirements

Resolution: NLT 2.0 between almotriptan related compound B and almotriptan; NLT 2.0 between almotriptan and almotriptan related compound D, *System suitability solution*

Relative standard deviation: NMT 5.0% for the ratio of the peak response of almotriptan to the peak response of the internal standard, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the corrected peak response:

$$\text{Result} = (r/m)$$

r = peak response

m = migration time of the peak (min)

Calculate the percentage of almotriptan related compound D, almotriptan *N*-dimer, and other impurities in the portion of Almotriptan Malate taken:

$$\text{Result} = (R_U/R_S) \times (C_S/C_U) \times 100$$

R_U = corrected peak response ratio of the impurity to the internal standard from the *Sample solution*

R_S = corrected peak response ratio of almotriptan to the internal standard from the *Standard solution*

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

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

Acceptance criteria: See *Table 2*.

Table 2

Name	Relative Migration Time	Acceptance Criteria, NMT (%)
Almotriptan *N*-dimer[a]	0.71	0.3
Internal standard[b]	0.78	—
Almotriptan related compound B[c]	0.92	—
Almotriptan	1.0	—
Almotriptan related compound C[c]	1.02	—
Almotriptan related compound D	1.22	0.1
Any individual unspecified impurities	—	0.1

[a] 2-{1-({3-[2-(Dimethylamino)ethyl]-1*H*-indol-5-yl}methyl)-5-[(pyrrolidin-1-ylsulfonyl)methyl]-1*H*-indol-3-yl}-*N*,*N*-dimethylethan-1-amine.

[b] 4-Hydroxy-4-phenylpiperidine.

[c] If present, this impurity may not be fully resolved from almotriptan. It is quantified using the test for *Organic Impurities*.

• **Organic Impurities**

Buffer: Add 10 mL of triethylamine to every 1000 mL of 0.01 M phosphoric acid. Adjust with phosphoric acid to a pH of 6.5.

Mobile phase: Acetonitrile and *Buffer* (15:85)

System suitability stock solution: 0.5 mg/mL each of USP Almotriptan Related Compound B RS, USP Almotriptan Related Compound C RS, and USP Almotriptan Related Compound D RS in methanol

System suitability solution: 0.005 mg/mL each of USP Almotriptan Related Compound B RS, USP Almotriptan Related Compound C RS, and USP Almotriptan Related Compound D RS from the *System suitability stock solution* in water

Standard solution: 0.007 mg/mL of USP Almotriptan Malate RS in water

Sample solution: 3.5 mg/mL of Almotriptan Malate in water. Sonication may be used to promote dissolution.

Chromatographic system

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

Mode: LC

Detector: UV 210 nm

Column: 4.6-mm × 30-cm; 5-µm packing L1

Flow rate: 1 mL/min

Injection volume: 20 µL

Run time: NLT 3 times the retention time of almotriptan

System suitability

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

[Note—See *Table 3* for the relative retention times.]

Suitability requirements

Resolution: NLT 1.0 between almotriptan related compound C and almotriptan related compound D, *System suitability solution*

Relative standard deviation: NMT 5.0% for six replicate injections, *Standard solution*

Analysis

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

Chromatograph the *System suitability solution* and identify the components on the basis of their relative retention times, as shown in *Table 3*.

Calculate the percentage of each impurity in the portion of Almotriptan Malate taken:

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

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

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

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

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

Acceptance criteria: See *Table 3*.

Table 3

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Malic acid[a]	0.10	—
Almotriptan related compound B	0.62	0.1
Almotriptan related compound C	0.77	0.5
Almotriptan related compound D[b]	0.92	—
Almotriptan	1.00	—
Any other individual impurity	—	0.1
Total impurities[c]	—	1.0

[a] This peak is due to the malate counterion; hence it is not an impurity. It is not to be reported or included in the total impurities.

[b] This impurity is quantified using the *Limit of Almotriptan Related Compound D and Almotriptan N-Dimer* test.

[c] The sum of all impurities from the test for *Organic Impurities* and the *Limit of Almotriptan Related Compound D and Almotriptan N-Dimer* test.

• **Limit of Fumaric Acid**

Buffer: 6.8 g/L of monobasic potassium phosphate in water. Adjust with phosphoric acid to a pH of 2.8.

Mobile phase: Methanol and *Buffer* (5:95)

Standard solution: 0.0085 mg/mL of USP Fumaric Acid RS and 0.0017 mg/mL of USP Maleic Acid RS in water. Sonication may be used to promote dissolution.

Sample solution: 2.8 mg/mL of Almotriptan Malate in water. Sonication may be used to promote dissolution.

Chromatographic system

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

Mode: LC

Detector: UV 220 nm

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

Flow rate: 0.7 mL/min

Injection volume: 10 µL

Run time: NLT 1.6 times the retention time of fumaric acid

System suitability

Sample: *Standard solution*

[Note—See *Table 4* for the relative retention times.]

Suitability requirements

Resolution: NLT 2.0 between fumaric acid and maleic acid

Relative standard deviation: NMT 5.0% for fumaric acid from six injections

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of fumaric acid ($C_4H_4O_4$) in the portion of Almotriptan Malate taken:

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

r_U = peak response of fumaric acid from the *Sample solution*

r_S = peak response of fumaric acid from the *Standard solution*

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

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

Acceptance criteria: See *Table 4*.

Table 4

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Malic acid[a]	0.60	—
Maleic acid[a]	0.80	—
Fumaric acid	1.0	0.2

[a] Included for identification purposes only.

SPECIFIC TESTS

- **Water Determination ⟨921⟩, *Method I, Method Ia*:** NMT 0.5%

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in well-closed containers. Store at controlled room temperature.
- **USP Reference Standards ⟨11⟩**

USP Almotriptan Malate RS

USP Almotriptan Related Compound B RS

2-{5-[(Pyrrolidin-1-ylsulfonyl)methyl]-1*H*-indol-3-yl}ethanamine hemifumarate.

$C_{15}H_{21}N_3O_2S \cdot ½C_4H_4O_4$ 365.46

USP Almotriptan Related Compound C RS

N-Methyl-2-{5-[(pyrrolidin-1-ylsulfonyl)methyl]-1*H*-indol-3-yl}ethanamine.

$C_{16}H_{23}N_3O_2S$ 321.44

USP Almotriptan Related Compound D RS

1-[({3-[2-(Dimethylamino)ethyl]indol-5-yl}methyl)sulfonyl]pyrrolidine *N*-oxide hydrochloride.

$C_{17}H_{25}N_3O_3S \cdot HCl$ 387.92

USP Fumaric Acid RS

USP Maleic Acid RS

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

Topic/Question	Contact	Expert Committee
ALMOTRIPTAN MALATE	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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