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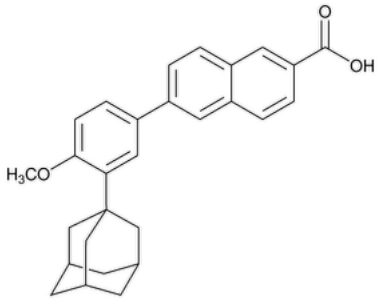
Adapalene



$C_{28}H_{28}O_3$ 412.52

2-Naphthalenecarboxylic acid, 6-(4-methoxy-3-tricyclo [3.3.1.1^{3,7}]dec-1-ylphenyl)-;

6-[3-(1-Adamantyl)-4-methoxyphenyl]-2-naphthoic acid. CAS RN®: 106685-40-9; UNII: 1L4806J2QF.

DEFINITION

Adapalene contains NLT 98.0% and NMT 102.0% of adapalene ($C_{28}H_{28}O_3$), calculated on the dried 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**

Mobile phase: Acetonitrile, tetrahydrofuran, trifluoroacetic acid, and water (21:16:0.01:13)

Standard stock solution: 0.2 mg/mL of USP Adapalene RS in *Mobile phase*. Dissolve USP Adapalene RS in a minimal amount of tetrahydrofuran (about 1%–5% of the final volume), using sonication as needed, and dilute with *Mobile phase* to volume.

Standard solution: 40 µg/mL of USP Adapalene RS in *Mobile phase* from the *Standard stock solution*

Sample stock solution: 0.2 mg/mL of Adapalene in *Mobile phase*. Dissolve Adapalene in a minimal amount of tetrahydrofuran (about 1%–5% of the final volume), using sonication as needed, and dilute with *Mobile phase* to volume.

Sample solution: 40 µg/mL of Adapalene in *Mobile phase* from the *Sample stock solution*

Chromatographic system

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

Mode: LC

Detector: UV 235 nm

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

Flow rate: 1 mL/min

Injection volume: 20 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Relative standard deviation: NMT 1.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of adapalene ($C_{28}H_{28}O_3$) in the portion of Adapalene 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 Adapalene RS in the *Standard solution* (µg/mL)

C_U = concentration of Adapalene in the *Sample solution* (µg/mL)

Acceptance criteria: 98.0%–102.0% on the dried basis

IMPURITIES

• **Residue on Ignition ⟨281⟩:** NMT 0.20%

[Note—On the basis of the synthetic route, perform either *Organic Impurities, Procedure 1* or *Organic Impurities, Procedure 2*.]

• **Organic Impurities, Procedure 1**

Procedure 1 is recommended if adapalene related compounds A and B may be present.

Mobile phase: Proceed as directed in the *Assay*.

Standard stock solution: 0.2 mg/mL of USP Adapalene RS, 0.3 mg/mL of USP Adapalene Related Compound A RS, and 0.2 mg/mL of USP Adapalene Related Compound B RS in *Mobile phase*. Dissolve USP Adapalene RS, USP Adapalene Related Compound A RS, and USP Adapalene Related Compound B RS in a minimal amount of tetrahydrofuran (about 1%–5% of the final volume), using sonication as needed, and dilute with *Mobile phase* to volume.

Standard solution: 0.2 µg/mL of USP Adapalene RS, 0.3 µg/mL of USP Adapalene Related Compound A RS, and 0.2 µg/mL of USP Adapalene Related Compound B RS in *Mobile phase* from the *Standard stock solution*

Sample solution: 0.2 mg/mL of Adapalene in *Mobile phase*. Dissolve Adapalene in a minimal amount of tetrahydrofuran (about 1%–5% of the final volume), using sonication as needed, and dilute with *Mobile phase* to volume.

Chromatographic system: Proceed as directed in the *Assay*, except use a run time of NLT two times the retention time of adapalene peak for *Standard solution* and NLT six times the retention time of adapalene peak for *Sample solution*.

System suitability

Sample: *Standard solution*

Suitability requirements

Relative standard deviation: NMT 3.0% for the adapalene peak

Column efficiency: NLT 3000 theoretical plates for the adapalene peak

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of adapalene related compounds A and B in the portion of Adapalene taken:

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

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

r_S = peak area of corresponding adapalene related compound A or adapalene related compound B from the *Standard solution*

C_S = concentration of corresponding USP Adapalene Related Compound A RS or USP Adapalene Related Compound B RS in the *Standard solution* (mg/mL)

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

Calculate the percentage of each unspecified impurity in the portion of Adapalene taken:

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

r_U = peak area of each unspecified impurity from the *Sample solution*

r_S = peak area of adapalene from the *Standard solution*

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

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

Acceptance criteria: See *Table 1*. Disregard any impurity peaks less than 0.05%.

Table 1

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Adapalene related compound A[a]	0.52	0.10
Adapalene	1.0	—

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Adapalene related compound B[b]	1.57	0.10
Any individual unspecified impurity	—	0.10
Total impurities	—	0.50

[a] Methyl 6-bromo-2-naphthoate.

[b] Methyl 6-[3-(1-Adamantyl)-4-methoxyphenyl]-2-naphthoate.

• **Organic Impurities, Procedure 2**

Procedure 2 is recommended if adapalene related compounds E, C, and D may be present.

Solution A: Glacial acetic acid and water (0.1:100)

Solution B: Acetonitrile and tetrahydrofuran (65:35)

Mobile phase: See *Table 2*.

Table 2

Time (min)	Solution A (%)	Solution B (%)
0	50	50
2.5	50	50
40	28	72
42	28	72
42.1	50	50
50	50	50

Diluent: Acetonitrile, tetrahydrofuran, and water (37:20:43)

Standard stock solution: 0.2 mg/mL of USP Adapalene RS in tetrahydrofuran

Standard solution: 2.0 µg/mL of USP Adapalene RS in *Diluent* from the *Standard stock solution*

System suitability solution: 0.2 mg/mL of USP Adapalene RS and 1.2 µg/mL each of USP Adapalene Related Compound C RS, USP Adapalene Related Compound D RS, and USP Adapalene Related Compound E RS prepared by dissolving the standards in tetrahydrofuran equivalent to 50% of the final volume, and diluting with *Diluent* to volume

Sample solution: 2.0 mg/mL of Adapalene prepared by dissolving in tetrahydrofuran equivalent to 50% of the final volume, and diluting with *Diluent* to volume

Chromatographic system

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

Mode: LC

Detector: UV 270 nm

Column: 4.6-mm × 25-cm; 5-µm packing L11 with 7.5% carbon loading

Column temperature: 30°

Flow rate: 1.2 mL/min

Injection volume: 25 µL

System suitability

Sample: *System suitability solution*

Suitability requirements

Resolution: NLT 4.5 between the adapalene and adapalene related compound C peaks

Signal-to-noise ratio: NLT 10 for the adapalene related compound C peak

Analysis

Samples: *Standard solution* and *Sample solution*

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

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

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

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

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

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

F = relative response factor for each individual impurity (see *Table 3*)

Acceptance criteria: See *Table 3*. Disregard any impurity peaks less than 0.05%.

Table 3

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Adapalene related compound E[a]	0.3	1.4	0.3
Hydroxyadapalene[b]	0.5	0.91	0.1
Adapalene related compound C[c]	0.9	0.14	0.1
Adapalene	1.0	—	—
Adapalene related compound D[d]	1.9	0.71	0.2
Any individual unspecified impurity	—	1.0	0.1
Total impurities	—	—	0.5

[a] 2,2′-Binaphthyl-6,6′-dicarboxylic acid.

[b] 6-[3-(3-Hydroxyadamant-1-yl)-4-methoxyphenyl]-2-naphthoic acid.

[c] 2-(Adamant-1-yl)methoxybenzene.

[d] 4,4′-Dimethoxy-3,3′-di(adamant-1-yl)biphenyl.

• **Residual Solvent: Limit of Triethylamine**

[Note—This test should be performed if triethylamine is used in the manufacturing process.]

Diluent: Dimethyl sulfoxide

Standard solution: 4.0 µg/mL of USP Triethylamine RS in *Diluent*. Transfer 4.0 mL of this solution to a 20-mL headspace vial, and add 1.0 mL of 1 N NaOH solution.

Sample solution: 50 mg/mL of Adapalene in *Diluent*. Transfer 4.0 mL of this solution to a 20-mL headspace vial, and add 1.0 mL of 1 N NaOH solution.

Chromatographic system

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

Mode: GC

Detector: Flame ionization

Column: 30-m × 0.53-mm; 3.0-µm coating of G27

Temperatures

Injection port: 250°

Detector: 300°

Column: See *Table 4*.

Table 4

Initial Temperature (°)	Temperature Ramp (°/min)	Final Temperature (°)	Hold Time at Final Temperature (min)
40	0	40	5
40	40	240	5

Headspace operating parameters

[Note—Headspace operating parameters can be modified in order to optimize the performance.]

Equilibration temperature: 95°

Equilibration time: 15 min

Transfer line temperature: 125°

Pressurization time: 3 min

Carrier gas: Nitrogen

Flow rate: 4.8 mL/min

Injection volume: 1 mL

System suitability

Sample: *Standard solution*

Suitability requirements

Relative standard deviation: NMT 15%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the content, in ppm, of triethylamine in the portion of Adapalene taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 10^6$$

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

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

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

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

Acceptance criteria: NMT 80 ppm

SPECIFIC TESTS

- **Loss on Drying ⟨731⟩**

Analysis: Dry a sample at 105° for 4 h.

Acceptance criteria: NMT 0.6%

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in tight, light-resistant containers, and store at room temperature.
- **Labeling:** If a test for *Organic Impurities* other than *Procedure 1* is used, the labeling states the test with which the article complies.
- **USP Reference Standards ⟨11⟩**

USP Adapalene RS

USP Adapalene Related Compound A RS

Methyl 6-bromo-2-naphthoate.

$C_{12}H_9BrO_2$ 265.10

USP Adapalene Related Compound B RS

Methyl 6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoate.

$C_{29}H_{30}O_3$ 426.55

USP Adapalene Related Compound C RS

2-(Adamant-1-yl)methoxybenzene.

$C_{17}H_{22}O$ 242.36

USP Adapalene Related Compound D RS

4,4′-Dimethoxy-3,3′-di(adamant-1-yl)biphenyl.

$C_{34}H_{42}O_2$ 482.70

USP Adapalene Related Compound E RS

2,2′-Binaphthyl-6,6′-dicarboxylic acid.

$C_{22}H_{14}O_4$ 342.34

USP Triethylamine RS

Triethylamine.

$C_6H_{15}N$ 101.19

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

Topic/Question	Contact	Expert Committee
ADAPALENE	Documentary Standards Support	SM32020 Small Molecules 3
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM32020 Small Molecules 3

Chromatographic Database Information: Chromatographic Database

Most Recently Appeared In:
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