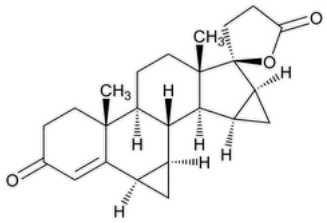
Status: Currently Official on 14-Feb-2025
Official Date: Official as of 01-May-2020
Document Type: USP Monographs
DocId: GUID-5BEE116E-8504-43F1-A92B-65594677DE98_4_en-US
DOI: https://doi.org/10.31003/USPNF_M28560_04_01
DOI Ref: ne9he

Drospirenone



$C_{24}H_{30}O_3$ 366.49

(6*R*,7*R*,8*R*,9*S*,10*R*,13*S*,14*S*,15*S*,16*S*,17*S*)-1,3',4',6,6a,7,8,9,10, 11,12,13,14,15,15a,16-Hexadecahydro-10,13-dimethylspiro-[17*H*-dicyclopropa[6,7:15,16]cyclopenta[*a*]phenanthrene-17,2'(5'*H*)-furan]-3,5'(2*H*)-dione;

17-Hydroxy-6β,7β:15β,16β-dimethylene-3-oxo-17 α-pregn-4-ene-21-carboxylic acid, γ-lactone CAS RN®: 67392-87-4; UNII: N295J34A25.

DEFINITION

Drospirenone contains NLT 98.0% and NMT 102.0% of $C_{24}H_{30}O_3$, calculated on the anhydrous and solvent-free basis.

IDENTIFICATION

Change to read:

• **A.** ▲**Spectroscopic Identification Tests** ⟨197⟩, *Infrared Spectroscopy*: **197M**▲ (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**

Solution A: Water

Solution B: Acetonitrile

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	63	37
2.0	63	37
16.0	52	48
23.0	52	48
31.0	20	80
39.0	20	80
39.1	63	37
49.0	63	37

Diluent: Acetonitrile and water (1:1)

System suitability solution: 60 µg/mL of USP Drospirenone RS and 60 µg/mL of USP Drospirenone Related Compound A RS in *Diluent*

Standard solution: 0.6 mg/mL of USP Drospirenone RS in *Diluent*

Sample solution: 0.6 mg/mL of Drospirenone in *Diluent*

Chromatographic system

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

Mode: LC

Detector: UV 245 nm

Column: 4.6-mm × 25-cm; 3-µm packing L1

Column temperature: 35°

Flow rate: 1 mL/min

Injection size: 10 µL

System suitability

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

Suitability requirements

Resolution: NLT 5.0 between drospirenone and drospirenone related compound A, *System suitability solution*

Tailing factor: Between 0.8 and 1.5, *Standard solution*

Relative standard deviation: NMT 2.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of drospirenone ($C_{24}H_{30}O_3$) in the portion of Drospirenone 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 Drospirenone RS in the *Standard solution* (mg/mL)

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

Acceptance criteria: 98.0%–102.0%

IMPURITIES

Inorganic Impurities

- **Residue on Ignition ⟨281⟩:** NMT 0.1%

Organic Impurities

- **Procedure 1: Limit of 1,2-Dimethoxyethane and Diisopropyl Ether** (if present)

Standard solution: 0.1 mg/mL of 1,2-dimethoxyethane and 0.05 mg/mL of diisopropyl ether in dimethylformamide

Sample solution: 50 mg/mL of Drospirenone in dimethylformamide

Chromatographic system

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

Mode: GC

Detector: Flame ionization

Column: 0.25-mm × 30-m; 1.4-µm coating of phase G43

Temperature

Injector: 160°

Detector: 250°

Column: See *Table 2*.

Table 2

Initial Temperature (°)	Temperature Ramp (°/min)	Final Temperature (°)	Hold Time at Final Temperature (min)
40	0	40	10
40	5	70	0
70	30	220	0

Carrier gas: Helium

Flow rate: 32 ± 8 cm/s. [Note—For pressure- controlled systems, a column pressure of about 130 kPa is necessary.]

Injector type: Headspace

Sample volume: 2.0 mL/vial

Vial treatment: Maintain at 80° for 60 min before injection.

System suitability

Sample: *Standard solution*

[NOTE—The relative retention times for diisopropyl ether and 1,2-dimethoxyethane are about 0.6 and 1.0, respectively.]

Suitability requirements

Relative standard deviation: NMT 4.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of 1,2-dimethoxyethane and diisopropyl ether in the portion of Drospirenone taken:

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

r_U = peak response of 1,2-dimethoxyethane or diisopropyl ether from the *Sample solution*

r_S = peak response of 1,2-dimethoxyethane or diisopropyl ether from the *Standard solution*

C_S = concentration of 1,2-dimethoxyethane or diisopropyl ether in the *Standard solution* (mg/mL)

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

Acceptance criteria

Individual impurities: NMT 0.2% of 1,2-dimethoxyethane and NMT 0.1% of diisopropyl ether

- **PROCEDURE 2**

Solution A: Water

Solution B: Acetonitrile

Mobile phase: See *Table 3*.

Table 3

Time (min)	Solution A (%)	Solution B (%)
0	63	37
2.0	63	37
16.0	52	48
23.0	52	48
31.0	20	80
39.0	20	80
39.1	63	37
49.0	63	37

Diluent: Acetonitrile and water (1:1)

System suitability solution: 60 µg/mL of USP Drospirenone RS and 60 µg/mL of USP Drospirenone Related Compound A RS in *Diluent*

Standard solution: 0.6 µg/mL of USP Drospirenone RS in *Diluent*

Sample solution: 0.6 mg/mL of Drospirenone in *Diluent*

Chromatographic system

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

Mode: LC

Detector: UV 195 nm and 245 nm

Column: 4.6-mm × 25-cm; 3-µm packing L1

Column temperature: 35 ± 5°

Flow rate: 1 mL/min

Injection size: 10 µL

System suitability

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

Suitability requirements

Resolution: NLT 5.0 between drospirenone and drospirenone related compound A, *System suitability solution*

Tailing factor: Between 0.8 and 1.5, *Standard solution*

Relative standard deviation: NMT 15.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

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

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

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

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

C_S = concentration of USP Drospirenone RS in the *Standard solution* (µg/mL)

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

F = relative response factor for each individual impurity (see *Table 4*)

[NOTE—The percentage of hydroxydrospirenone is calculated at 195 nm.]

Acceptance criteria

[NOTE—Disregard any peaks that are less than 0.05% of the drospirenone peak.]

Individual impurities: See *Table 4*.

Table 4

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
7-Hydroxymethyl drospirenone at 245 nm[a]	0.43	1.9	0.1
5-Hydroxydros pirenone at 195 nm[b]	0.57	0.57	0.1
17-Keto drospirenone at 245 nm[c]	0.77	1.2	0.1
Drospirenone at 245 and 195 nm	1.00	—	—
Drospirenone 6-ene at 245 nm[d]	1.04	0.30	0.1
Drospirenone related compound A at 245 nm[e]	1.11	1.0	0.1
6,7-Epidrospirenone at 245 nm[f]	1.14	1.3	0.1
6,7-Desmethylene drospirenone at 245 nm[g]	1.18	2.2	0.1
15-Methyl drospirenone at 245 nm[h]	1.34	0.99	0.1
7-Chloromethyl drospirenone at 245 nm[i]	1.38	1.6	0.1
7-Chloromethyl 17-epidrospirenone at 245 nm[j]	1.51	1.9	0.1
7-Hydroxymethyl 3,5(6)-diene drospirenone at 245 nm[k]	1.55	1.4	0.1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Any unspecified impurity at 245 nm	—	1.0	0.1
Total impurities	—	—	0.4

[a] 17-Hydroxy-7β-hydroxymethyl-15β,16β-methylene-3-oxo-17α-pregn-4-ene-21-carboxylic acid, γ-lactone.

[b] 5β,17-Dihydroxy-6β,7β:15β,16β-dimethylene-3-oxo-17α-pregnan-21-carboxylic acid, γ-lactone.

[c] 6β,7β:15β,16β-Dimethyleneandrost-4-ene-3,17-dione.

[d] 17-Hydroxy-15β,16β-methylene-3-oxo-17α-pregn-4,6-diene-21-carboxylic acid, γ-lactone.

[e] 17-Hydroxy-6β,7β:15β,16β-dimethylene-3-oxo-17β-pregn-4-ene-21-carboxylic acid, γ-lactone; 17-epidrospirenone.

[f] 17-Hydroxy-6α,7α:15β,16β-dimethylene-3-oxo-17α-pregn-4-ene-21-carboxylic acid, γ-lactone.

[g] 17-Hydroxy-15β,16β-methylene-3-oxo-17α-pregn-4-ene-21-carboxylic acid, γ-lactone.

[h] 17-Hydroxy-15β-methyl-6β,7β-methylene-3-oxo-17α-pregn-4-ene-21-carboxylic acid, γ-lactone.

[i] 17-Hydroxy-7β-chloromethyl-15β,16β-methylene-3-oxo-17α-pregn-4-ene-21-carboxylic acid, γ-lactone.

[j] 17-Hydroxy-7β-chloromethyl-15β,16β-methylene-3-oxo-17β-pregn-4-ene-21-carboxylic acid, γ-lactone.

[k] 17-Hydroxy-7β-hydroxymethyl-15β,16β-methylene-17α-pregn-3,5(6)-diene-21-carboxylic acid, γ-lactone.

SPECIFIC TESTS

- **Optical Rotation,** *Specific Rotation* ⟨781S⟩

  Sample solution: 10 mg/mL in methanol

  Acceptance criteria: −187° to −193° at 20° on the anhydrous and solvent-free basis
- **Melting Range or Temperature,** *Class 1* ⟨741⟩**:** 198°–203°. [Note—Dry over silica gel for NLT 24 h before testing.]
- **Water Determination,** *Method I* ⟨921⟩**:** NMT 0.2%

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in tight containers, and store at controlled room temperature.
- **USP Reference Standards** ⟨11⟩

  USP Drospirenone RS

  USP Drospirenone Related Compound A RS

  17-Hydroxy-6β,7β:15β,16β-dimethylene-3-oxo-17β-pregn-4-ene-21-carboxylic acid, γ-lactone.

  $C_{24}H_{30}O_3$ 366.49

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

Topic/Question	Contact	Expert Committee
DROSPIRENONE	Documentary Standards Support	SM52020 Small Molecules 5

Chromatographic Database Information: Chromatographic Database

Most Recently Appeared In:
Pharmacopeial Forum: Volume No. PF 36(6)

Current DocID: GUID-5BEE116E-8504-43F1-A92B-65594677DE98_4_en-US

DOI: https://doi.org/10.31003/USPNF_M28560_04_01

DOI ref: ne9he