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Paricalcitol Capsules

DEFINITION

Paricalcitol Capsules contain NLT 90.0% and NMT 110.0% of the labeled amount of paricalcitol ($C_{27}H_{44}O_3$). They may contain butylated hydroxytoluene or other suitable antioxidant.

IDENTIFICATION

• **A.** 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**

[Note—Protect paricalcitol solutions from light.]

Solution A: Acetonitrile, isopropyl alcohol, and water (50:15:35)

Solution B: Acetonitrile and isopropyl alcohol (50:50)

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	100	0
20	100	0
21	0	100
29	0	100
30	100	0
35	100	0

Internal standard solution: 0.75 µg/mL of triphenylene in acetonitrile

Standard stock solution: 10 µg/mL of paricalcitol from USP Paricalcitol Solution RS in acetonitrile

Standard solution: A mixture of 0.5 µg/mL of paricalcitol from *Standard stock solution* and 0.15 µg/mL of triphenylene from *Internal standard solution* in acetonitrile

Sample solution: Nominally 0.5 µg/mL of paricalcitol from Capsules and 0.15 µg/mL of triphenylene from *Internal standard solution*, prepared as follows. Transfer 10 Capsules to a suitable container. Transfer the volume of acetonitrile specified in *Table 2* to a separate beaker. Cut each Capsule to allow the oil to flow freely from the shell. Rinse any tools used to open the shells by pouring in portions of acetonitrile from the beaker into the sample container. When the rinsing is complete, add the remainder of the acetonitrile to the sample container, add the volume of *Internal standard solution* specified in *Table 2*, and mix well. [Note—To facilitate cutting the Capsules open, soften them in a suitable microwave oven for NMT 10 s; taking care not to melt the Capsules. A microwave oven of 600–825 watts was found to be suitable for this procedure.]

Table 2

Capsule Strength (µg/Capsule)	Volume of Acetonitrile (mL)	Volume of Internal Standard Solution (mL)	Internal Standard Correction Factor (*F*)
1	16.0	4.0	1
2	32.0	8.0	1
4	65.0	15.0	0.9375

Chromatographic system

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

Mode: LC

Detector: UV 252 nm

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

Flow rate: 2.0 mL/min

Injection volume: 50 µL

Run time: 20 min

System suitability

Sample: *Standard solution*

[NOTE—The relative retention times for paricalcitol and triphenylene are 1.0 and 2.0, respectively.]

Suitability requirements

Resolution: NLT 4.0 between paricalcitol and triphenylene

Tailing factor: NMT 2.0 for the paricalcitol peak

Relative standard deviation: NMT 2.0% for the peak response ratios of paricalcitol to triphenylene

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of paricalcitol ($C_{27}H_{44}O_3$) in the portion of Capsules taken:

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

R_U = peak response ratio of paricalcitol to triphenylene from the *Sample solution*

R_S = peak response ratio of paricalcitol to triphenylene from the *Standard solution*

C_S = concentration of paricalcitol from USP Paricalcitol Solution RS in the *Standard solution* (µg/mL)

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

F = internal standard correction factor (see *Table 2*)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

• **RUPTURE TEST**

Apparatus: Disintegration apparatus with mesh wire, as described in *Disintegration ⟨701⟩*

Medium: Water

Procedure: Preheat disintegration apparatus water bath to 37 ± 2°. Transfer an appropriate volume of water such that at the highest point of the upward stroke the wire mesh of the basket-rack assembly remains at least 15 mm below the surface of the fluid and descends to NLT 25 mm from the bottom of the vessel on the downward stroke. Place the beakers in the water bath and allow the contents to warm to 37 ± 2°; the fluid must be maintained at this temperature for the duration of the test. Place one Capsule in each of the six tubes of the basket-rack assembly, adding a mesh wire screen to each tube, then start the action of the lifting apparatus and timing simultaneously. Observe the units at 5-min intervals.

Tolerances: The requirements are met if all of the Capsules tested rupture in NMT 15 min.

• **UNIFORMITY OF DOSAGE UNITS ⟨905⟩:** Meet the requirements

IMPURITIES

• **Organic Impurities**

[Note—Unless otherwise specified, protect paricalcitol solutions from light.]

Solution A: Water

Solution B: Acetonitrile

Solution C: Acetonitrile and isopropyl alcohol (50:50)

Mobile phase: See *Table 3*.

Table 3

Time (min)	Solution A (%)	Solution B (%)	Solution C (%)
0	85	15	0
55	5	95	0
56	0	0	100
60	0	0	100
61	85	15	0
70	85	15	0

Diluent: Acetonitrile and water (50:50)

Degradation stock solution: Dilute 1 mL of USP Paricalcitol Solution RS with *Diluent* to 5 mL.

Degradation solution A: Transfer 1 mL of the *Degradation stock solution* and 0.1 mL of 30% hydrogen peroxide to a suitable container, and allow to stand at room temperature for 1 h. Dilute with *Diluent* to 10 mL, and mix. This solution contains paricalcitol and related compounds A and B.

Degradation solution B: Mix 1 mL of the *Degradation stock solution* and 1 mL of 0.1 N hydrochloric acid, and heat at 70° for 1 h. Cool to room temperature, dilute with *Diluent* to 10 mL, and mix. This solution contains paricalcitol and related compounds C, D, G, H, and I.

Internal standard solution: 0.08 µg/mL of calcitriol from USP Calcitriol Solution RS in acetonitrile

Standard solution: 0.01 µg/mL of paricalcitol from USP Paricalcitol Solution RS and 0.016 µg/mL of calcitriol from *Internal standard solution* in *Diluent*

Sample solution: Nominally 1.8 µg/mL of paricalcitol from Capsules, prepared as follows. Remove the contents of a suitable number of Capsules using a syringe or cut the Capsules open with scissors and transfer the contents to a suitable container. Transfer a portion of mixed Capsule contents containing nominally 18 µg of paricalcitol to a 10-mL volumetric flask. Add acetonitrile to obtain a total mass of 5 g. Transfer 2.0 mL of *Internal standard solution* to the flask and dilute with water to volume. Mix using a vortex mixer. Centrifuge for 5-min intervals until the top layer is clear, then transfer the supernatant to a suitable chromatographic vial within 2 min.

Chromatographic system

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

Mode: LC

Detector: UV 252 nm

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

Flow rate: 1.5 mL/min

Injection volume: 300 µL

Run time: 55 min

System suitability

Sample: *Standard solution*

[Note—The relative retention times for paricalcitol and calcitriol are 1.0 and 1.03, respectively. See *Table 4* for all other relative retention times.]

Suitability requirements

Resolution: NLT 2.0 between paricalcitol and calcitriol

Relative standard deviation: NMT 7.0% for the peak response ratio of paricalcitol to calcitriol

Analysis

Samples: *Degradation solution A*, *Degradation solution B*, *Standard solution*, and *Sample solution*

Identify the impurities in the *Sample solution* on the basis of the relative retention times of the components of *Degradation solution A* and *Degradation solution B* in Table 4.

Table 4

Name[a]	Degradation Solution	Relative Retention Time
Related compound A	A	0.74
Related compound B	A	0.84
Related compound C	B	0.91
Related compound D	B	0.97
7*Z*-Paricalcitol[b]	—	1.01
Related compound G	B	1.47
Related compound H	B	1.50
Related compound I	B	1.51
Total impurities	—	—

[a] Related compounds A, B, C, D, G, H, and I are specified unidentified degradation products. No information is available about chemical structures or chemical names for these impurities.

[b] (7*Z*,22*E*)-19-Nor-9,10-secoergosta-5,7,22-triene-1α,3β,25-triol.

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

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

R_U = peak response ratio of each impurity to calcitriol from the *Sample solution*

R_S = peak response ratio of paricalcitol to calcitriol from the *Standard solution*

C_S = concentration of paricalcitol from USP Paricalcitol Solution RS in the *Standard solution* (µg/mL)

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

Acceptance criteria

Any individual impurity: NMT 2.0%

Total impurities: NMT 3.0%

SPECIFIC TESTS

• **Microbial Enumeration Tests ⟨61⟩** and **Tests for Specified Microorganisms ⟨62⟩:** The total aerobic microbial count is NMT 10^3 cfu/g, and the total combined yeasts and molds count is NMT 10^2 cfu/g. Meet the requirements of the test for absence of *Escherichia coli*.

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in a tight container. Store at controlled room temperature.

• **USP Reference Standards ⟨11⟩**

USP Calcitriol Solution RS

USP Paricalcitol Solution RS

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

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