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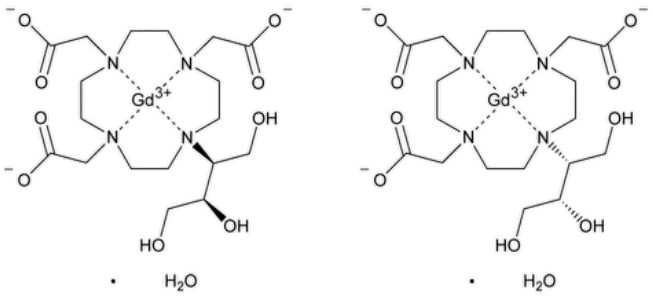
Add the following:

▲Gadobutrol



$C_{18}H_{31}GdN_4O_9 \cdot H_2O$ 622.73
$C_{18}H_{31}GdN_4O_9$ 604.72

Gadolinium, [10-[2-(hydroxy-κ*O*)-3-hydroxy-1-(hydroxymethyl)propyl]-1,4,7,10-tetraazacyclododecane-1,4,7-triacetato(3-)-κN^1, κN^4, κN^7, κN^{10}, κO^1, κO^4, κO^7]-, monohydrate, [SA-8-1425362'5'-(*R**,*S**)]-;

Gadolinium(III) [10-[(2*RS*,3*SR*)-1,3,4-trihydroxybutan-2-yl]-1,4,7,10-tetraazacyclododecane-1,4,7-triacetate] monohydrate CAS RN®: 198637-52-4.

Anhydrous CAS RN®: 770691-21-9.

DEFINITION

Gadobutrol contains NLT 98.0% and NMT 102.0% of gadobutrol ($C_{18}H_{31}GdN_4O_9$) on the anhydrous basis.

IDENTIFICATION

• **A. Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*:** 197A or 197K. If the spectra obtained show differences, dissolve Gadobutrol and USP Gadobutrol RS separately in 0.5 mL of water. Add 5 mL of absolute alcohol. Evaporate to dryness and record the spectra of residues.

• **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**

[Note—Plastic labware and plastic vials may be suitable for the preparation of solutions.]

Diluted formic acid: Anhydrous formic acid and water (50:50)

Solution A: Adjust 995 mL of water with *Diluted formic acid* to a pH of 3.6. Add 5 mL of acetonitrile.

Solution B: Acetonitrile

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	100	0
15	100	0
30	75	25
30.1	100	0

Time (min)	Solution A (%)	Solution B (%)
40	100	0

Standard solution: 1.0 mg/mL of USP Gadobutrol RS in *Solution A*

Sample solution: 1.0 mg/mL of Gadobutrol in *Solution A*

Chromatographic system

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

Mode: LC

Detector: UV 195 nm

Column: 4.6-mm × 25-cm; 3-µm packing L11

Temperatures

Autosampler: 10°

Column: 50°

Flow rate: 1 mL/min

Injection volume: 40 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.5 for gadobutrol

Relative standard deviation: NMT 0.73% for gadobutrol

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of gadobutrol ($C_{18}H_{31}GdN_4O_9$) on the anhydrous basis in the portion of Gadobutrol taken:

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

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

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

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

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

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

IMPURITIES

• **Limit of Free Gadolinium**

Buffer: Dissolve 50.0 g of sodium acetate in 10.0 mL of glacial acetic acid and add water. Adjust with a suitable concentration of sodium hydroxide or glacial acetic acid to a pH of 5.0, and dilute with water to 1000.0 mL.

Xylenol orange solution: 0.5 mg/mL of xylenol orange in water

Indicator solution: Transfer 30.0 mL of *Buffer* to a suitable flask. Add 1.5 mL of *Xylenol orange solution*. Dilute with water to 200 mL.

0.25 mM sodium edetate solution: Transfer 5.0 mL of 0.05 M edetate sodium VS to a 1-L volumetric flask. Dilute with water to volume.

Standard solution: 93.4 mg/L of gadolinium sulfate octahydrate in water

Titrimetric system

Mode: Direct titration

Titrant: *0.25 mM sodium edetate solution*

Endpoint detection: Photometric at 570–574 nm

Analysis

Sample titration: Dissolve 250 mg of Gadobutrol in 5.0 mL of the *Standard solution* and 30 mL of water with sonication. Add 10.0 mL of the *Indicator solution* and adjust with 0.1 N hydrochloric acid or 1 N sodium hydroxide to a pH of 5.0. Titrate with *Titrant*, determining the endpoint photometrically using a suitable autotitrator (V_U).

Blank titration: Transfer 5.0 mL of the *Standard solution* and 30 mL of water to the titration vessel. Add 10.0 mL of the *Indicator solution* and adjust with 0.1 N hydrochloric acid or 1 N sodium hydroxide to a pH of 5.0. Titrate with *Titrant*, determining the endpoint photometrically using a suitable autotitrator (V_B).

Calculate the percentage of free gadolinium (Gd) in the portion of Gadobutrol taken on the anhydrous basis:

$$\text{Result} = (V_U - V_B) \times C \times (1/W) \times A \times 100$$

V_U = volume of *Titrant* required for the *Sample titration* (mL)

V_B = volume of *Titrant* required for the *Blank titration* (mL)

C = concentration of *Titrant* (0.00025 mmol/mL)

W = weight of Gadobutrol in the *Sample titration* (mg)

A = atomic weight of gadolinium (157.25 mg/mmol)

Acceptance criteria: NMT 0.01% on the anhydrous basis

- **Organic Impurities**

Solution A, Solution B, and **Mobile phase:** Prepare as directed in the *Assay*.

System suitability solution: 10 mg/mL of USP Gadobutrol System Suitability Mixture RS in *Solution A*

Standard solution: 0.005 mg/mL of USP Gadobutrol RS in *Solution A*

Sensitivity solution: 0.003 mg/mL of USP Gadobutrol RS from the *Standard solution* in *Solution A*

Sample solution: 10.0 mg/mL of Gadobutrol in *Solution A*

Chromatographic system

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

Mode: LC

Detector: Charged aerosol detector (CAD)

Column: 4.6-mm × 25-cm; 3-µm packing L11

Temperatures

Autosampler: 10°

Column: 50°

Flow rate: 1 mL/min

Injection volume: 40 µL

System suitability

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

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

Suitability requirements

Peak-to-valley ratio: NLT 2.0 for the ratio of the height of the gadobutrol dealkyl analog peak to the height above the baseline of the lowest point of the curve separating the gadobutrol dealkyl analog peak from the gadobutrol peak, *System suitability solution*

Tailing factor: NMT 1.5 for gadobutrol, *Standard solution*

Relative standard deviation: NMT 10.0% for gadobutrol, *Standard solution*

Signal-to-noise ratio: NLT 10 for gadobutrol, *Sensitivity solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in the portion of Gadobutrol 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 USP Gadobutrol RS from the *Standard solution*

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

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

Acceptance criteria: See *Table 2*. The reporting threshold is 0.03%.

Table 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Butrol diacid analog[a]	0.25	0.05
Butrol[b]	0.36	0.05
Gadobutrol	1.0	—
Gadobutrol dealkyl analog[c]	1.1	0.05
Any individual unspecified impurity	—	0.05
Total impurities	—	0.3

[a] 2,2'-[4,10-Bis(1,3,4-trihydroxybutan-2-yl)-1,4,7,10-tetraazacyclododecane-1,7-diyl]diacetic acid.

[b] 2,2',2"-{10-[(2*RS*,3*SR*)-1,3,4-Trihydroxybutan-2-yl]-1,4,7,10-tetraazacyclododecane-1,4,7-triyl}triacetic acid.

[c] Gadolinium(III) 2,2',2"-(1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetate.

SPECIFIC TESTS

• **Water Determination ⟨921⟩, *Method I, Method Ic***

Sample: 10 mg of Gadobutrol

Analysis: Use the evaporation technique in which water is released and evaporated from the *Sample* by heating it in an external oven at 220° and transferring it to the reaction cell with the aid of an inert gas.

Acceptance criteria: 2.0%–7.0%

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in well-closed containers. Store at room temperature.

• **USP Reference Standards ⟨11⟩**

USP Gadobutrol RS

USP Gadobutrol System Suitability Mixture RS▲ (USP 1-Aug-2021)

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

Topic/Question	Contact	Expert Committee
GADOBUTROL	Documentary Standards Support	SM42020 Small Molecules 4

Chromatographic Database Information: Chromatographic Database

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