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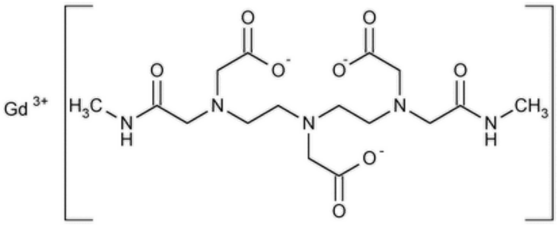
Gadodiamide



$C_{16}H_{26}GdN_5O_8$ 573.66

[5,8-Bis(carboxymethyl)-11-[2-(methylamino)-2-oxoethyl]-3-oxo-2,5,8,11-tetraazatridecan-13-oato(3-)]gadolinium.

[*N*,*N*-Bis[2-[(carboxymethyl)](methylcarbamoyl)methyl]-amino]ethyl]glycinato(3-)]gadolinium CAS RN®: 131410-48-5; UNII: 84F6U3J2R6.

» Gadodiamide contains not less than 97.0 percent and not more than 103.0 percent of $C_{16}H_{26}GdN_5O_8$, calculated on the anhydrous basis.

Packaging and storage—Preserve in tight containers, and store at controlled room temperature.

USP Reference Standards ⟨11⟩—

USP Gadodiamide RS

USP Gadodiamide Related Compound A RS

Gadolinium sodium diethylenetriamine pentaacetic acid monomethylamide.

$C_{15}H_{22}GdN_4NaO_9$ 582.60

USP Gadodiamide Related Compound B RS

Gadolinium disodium diethylenetriamine pentaacetic acid.

$C_{14}H_{18}GdN_3Na_2O_{10}$ 591.54

Clarity of solution—

Reference solution—

REFERENCE SOLUTION A— Transfer 1.0 g of hydrazine sulfate to a 100-mL volumetric flask, dissolve in and dilute with water to volume, and mix. Allow to stand for 4 to 6 hours. [**Caution—**Hydrazine sulfate is highly toxic. Avoid skin contact.]

REFERENCE SOLUTION B— Transfer 2.5 g of methenamine to a 100-mL glass-stoppered flask, add 25 mL of water, and mix to dissolve.

PRIMARY OPALESCENT MIXTURE— To the flask containing *Reference solution B*, add 25.0 mL of *Reference solution A,* mix, and allow to stand for 24 hours. [Note—The suspension is stable for 2 months. Mix before use, and do not use if it adheres to the container.]

OPALESCENCE STANDARD— Dilute 15.0 mL of the *Primary opalescent mixture* with water to 1000.0 mL, and mix. This standard must be freshly prepared.

PROCEDURE— Transfer 10.0 mL of the *Opalescence standard* to a 100-mL volumetric flask, dilute with water to volume, and mix. Transfer 40 mL of this solution (*Reference solution*) to a 50-mL color comparison tube.

Test solution—Transfer an accurately weighed quantity of Gadodiamide, equivalent to about 15 g of anhydrous gadodiamide, to a 50-mL volumetric flask, dissolve in and dilute with water to volume, and mix. Transfer 40 mL of this solution to a 50-mL color comparison tube.

Blank—Transfer 40 mL of water to a 50-mL color comparison tube.

Procedure—Five minutes after preparation of the *Reference solution,* view the *Reference solution*, the *Test solution,* and the *Blank* against a black background: the *Test solution* is not more opalescent than the *Reference solution*. [Note—If the *Test solution* is more opalescent than the *Reference solution*, heat the *Test solution* to 60° to 70° for 2 to 3 minutes, cool to room temperature, and view again.]

Identification—

Change to read:

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

B: It exhibits the maximum absorption at the relevant wavelength specified when tested as directed under the test for *Content of gadolinium*.

Microbial enumeration tests ⟨61⟩ and Tests for specified microorganisms ⟨62⟩—The total aerobic microbial count is not more than 500 cfu per g. The total combined molds and yeasts count is not more than 50 cfu per g.

Bacterial Endotoxins Test ⟨85⟩ —It contains not more than 3.5 USP Endotoxin Units per g.

Water Determination, *Method I* **⟨921⟩**: between 3.0% and 14.0%.

Limit of free gadolinium (III)—

Arsenazo III indicator—Transfer 150 mg of arsenazo III disodium to a 100-mL volumetric flask, dilute with water to volume, and mix.

MES buffer—Transfer 48.8 g of 2-(*N*-morpholino)ethanesulfonic acid (MES) to a 250-mL volumetric flask. Add 180 mL of water and 25 mL of 2 N sodium hydroxide, and mix. Adjust with 2 N sodium hydroxide to a pH of 6.0, dilute with water to volume, and mix.

Edetate disodium titrant—Pipet 100 mL of 0.02 M edetate disodium VS into a 1000-mL volumetric flask, dilute with water to volume, and mix.

Test solution—Transfer about 1 g of Gadodiamide, accurately weighed, to a 125-mL conical flask, add 25 mL of *MES buffer* and 0.1 mL of *Arsenazo III indicator,* and mix. A turquoise color indicates the presence of excess gadolinium.

Procedure—Titrate the *Test solution* with *Edetate disodium titrant* to a violet-pink endpoint. Each mL of *Edetate disodium titrant* is equivalent to 0.3145 mg of excess gadolinium: not more than 0.3% of free gadolinium is found, calculated on the anhydrous basis.

Limit of free diethylenetriamine pentaacetic acid bismethylamide—

Arsenazo III indicator and *MES buffer*—Proceed as directed for *Limit of free gadolinium* (*III*).

0.002 M gadolinium (*III*) *titrant*—Transfer 18.6 g of gadolinium chloride to a 1000-mL volumetric flask, dilute with 0.1 N hydrochloric acid to volume, and mix. Pipet 10 mL of this solution into a conical flask, and add 25 mL of *MES buffer* and 0.1 mL of *Arsenazo III indicator*. Titrate with 0.02 M edetate disodium VS to a violet-pink endpoint, and determine the molarity. Pipet 40 mL of this solution into a 1000-mL volumetric flask, dilute with water to volume, and mix.

Blank solution—Transfer 25 mL of *MES buffer* and 0.1 mL of *Arsenazo III indicator* into a suitable flask, and mix.

Test solution—Transfer about 1 g of Gadodiamide, accurately weighed, to a 125-mL conical flask. Add 25 mL of *MES buffer* and 0.1 mL of *Arsenazo III indicator*, and mix. A violet-pink color indicates the presence of excess diethylenetriamine pentaacetic acid bismethylamide.

Procedure—Concomitantly titrate the *Blank solution* and the *Test solution* with *0.002 M gadolinium* (*III*) *titrant* to a turquoise endpoint. Calculate the percentage of free diethylenetriamine pentaacetic acid bismethylamide in the portion of Gadodiamide taken by the formula:

$$100(V_U - V_B)M_T(419.43)/W$$

in which V_U is the volume of gadolinium (III) in the *Test solution;* V_B is the volume of gadolinium (III) in the *Blank solution;* M_T is the molarity of the *0.002 M gadolinium* (*III*) *titrant;* 419.43 is the molecular weight of diethylenetriamine pentaacetic acid bismethylamide; and W is the weight, in mg, of Gadodiamide taken to prepare the *Test solution:* not more than 0.7% of diethylenetriamine pentaacetic acid bismethylamide is found, calculated on the anhydrous basis.

Limit of methylamine—

Borate buffer—Transfer 12.4 g of boric acid to a 500-mL volumetric flask, and suspend it in 300 mL of water. Add 100 mL of 1 N potassium hydroxide, and mix. Adjust with 1 N potassium hydroxide to a pH of 10.0, dilute with water to volume, and mix. Store in a closed plastic container.

OPA reagent—Transfer 100 mg of *o*-phthalaldehyde to an amber bottle, add 3 mL of methanol, and mix. Add 220 mL of *Borate buffer* and 0.1 mL of mercaptoethanol, and mix. [Note—This solution must be freshly prepared.]

Standard solutions—Transfer about 110 mg of methylamine hydrochloride, accurately weighed, to a 500-mL volumetric flask, and dilute with water to volume to obtain a solution having a concentration of about 100 µg of methylamine per mL. Pipet 1, 5, 10, and 20 mL of this solution into separate 100-mL volumetric flasks, dilute the contents of each flask with water to volume, and mix.

Test solution—Transfer about 1.5 g of Gadodiamide, accurately weighed, to a 10-mL volumetric flask, dilute with water to volume, and mix.

Procedure—Proceed as follows for each of the *Standard solutions*. Add 3.0 mL of *OPA reagent*, mix, and within 1 minute measure the absorbance at 335 nm. Compare to a blank consisting of 3.0 mL of water and 3.0 mL of *OPA reagent*. Plot a calibration curve of absorbance versus standard concentration, in µg of methylamine per mL. Mix 3.0 mL of the *Test solution* with 3.0 mL of *OPA reagent*, and proceed as directed above. [Note—If the absorbance obtained with the *Test solution* exceeds the absorbance of the highest *Standard solution*, perform an additional quantitative dilution of the *Test solution*, and repeat the analysis.] Determine the concentration, in µg per mL, of methylamine in the *Test solution* by interpolation from the calibration curve. Calculate the amount of methylamine in the portion of Gadodiamide taken: not more than 0.05% of methylamine is found.

Limit of acetone, ethyl alcohol, and isopropyl alcohol—

Internal standard solution—Transfer about 500 mg of methyl ethyl ketone to a 100-mL volumetric flask, dilute with water to volume, and mix. Pipet 5 mL of this solution into a 100-mL volumetric flask, dilute with water to volume, and mix.

Stock solution—Transfer about 1000 mg each of acetone, ethyl alcohol, and isopropyl alcohol, accurately weighed, to a 100-mL volumetric flask, dilute with water to volume, and mix.

Diluted stock solution A—Pipet 5 mL of the *Stock solution* into a 100-mL volumetric flask, dilute with water to volume, and mix.

Diluted stock solution B—Pipet 10 mL of the *Stock solution* into a 100-mL volumetric flask, dilute with water to volume, and mix.

System suitability solution—Pipet 10 mL of the *Internal standard solution* and 15 mL of *Diluted stock solution A* into a 100-mL volumetric flask, dilute with water to volume, and mix.

Test solution 1—Pipet 10 mL of the *Internal standard solution* into a 100-mL volumetric flask, dilute with water to volume, and mix. Transfer 7.0 mL of this solution to a 10-mL gas chromatographic headspace vial, add about 1300 mg of Gadodiamide, accurately weighed, and cap immediately. Swirl to dissolve.

Test solution 2—Pipet 10 mL of the *Internal standard solution* and 2.5 mL of *Diluted stock solution A* into a 100-mL volumetric flask, dilute with water to volume, and mix. Transfer 7.0 mL of this solution to a 10-mL gas chromatographic headspace vial, add about 1300 mg of Gadodiamide, accurately weighed, and cap immediately. Swirl to dissolve.

Test solution 3—Pipet 10 mL of the *Internal standard solution* and 15 mL of *Diluted stock solution A* into a 100-mL volumetric flask, dilute with water to volume, and mix. Transfer 7.0 mL of this solution to a 10-mL gas chromatographic headspace vial, add about 1300 mg of Gadodiamide, accurately weighed, and cap immediately. Swirl to dissolve.

Test solution 4—Pipet 10 mL of the *Internal standard solution* and 25 mL of *Diluted stock solution B* into a 100-mL volumetric flask, dilute with water to volume, and mix. Transfer 7.0 mL of this solution to a 10-mL gas chromatographic headspace vial, add about 1300 mg of Gadodiamide, accurately weighed, and cap immediately. Swirl to dissolve.

Chromatographic system (see Chromatography ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector and a 0.32-mm × 30-m capillary column coated with a 1.8-µm phase G43. The column temperature is maintained at 40°. Helium is used as the carrier gas at a flow rate of about 1.5 mL per minute, and the split ratio is 1:15. The injection port and detector block are maintained at about 250°. Chromatograph the *System suitability solution* as directed for *Procedure:* the order of elution is ethyl alcohol, acetone, isopropyl alcohol, and methyl ethyl ketone; the resolution, *R,* between the ethyl alcohol and acetone peaks is not less than 1.0 and between the acetone and isopropyl alcohol peaks is not less than 1.0; and the relative standard deviation is not more than 3.0% for each of the three analytes.

Procedure—Separately inject equal volumes (about 1 µL) of each of the four *Test solutions* into the chromatograph, record the chromatograms, and measure the areas for the major peaks relative to the area for the internal standard peak. Plot the responses of the *Test solutions* versus the content, in µg per mL, of the relevant analyte in each vial, draw the straight line best fitting the four points, and calculate the correlation coefficient for the line. A suitable system is one that yields a line having a correlation coefficient of not less than 0.99. Calculate the percentage of each analyte in the portion of Gadodiamide taken by the formula:

$$a/(10{,}000b)$$

in which *a* is the intercept and *b* is the slope of the straight line, evaluated by linear regression analysis. [Note—If *a* is negative, report the result as none detected.] Not more than 0.2% of acetone, ethyl alcohol, and isopropyl alcohol is found, calculated on the anhydrous basis; and the sum of all three analytes is not more than 0.2%, calculated on the anhydrous basis.

Related compounds—

Mobile phase—Prepare as directed in the *Assay*.

Postcolumn reagent—Dissolve 120 mg of arsenazo III acid in 400 mL of water previously acidifed with 6.3 mL of nitric acid. Add 650 mg of urea, and mix to dissolve. Pass the solution through a 0.45-µm porosity filter, washing the filter with 600 mL of water. Dilute with water to 1000 mL, mix, and degas.

System suitability solution—Prepare an aqueous solution containing about 0.01 mg of USP Gadodiamide Related Compound A RS, 0.01 mg of USP Gadodiamide Related Compound B RS, and 2 mg of USP Gadodiamide RS in each mL.

Test solution—Transfer about 200 mg of Gadodiamide, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with water to volume, and mix.

Chromatographic system (see Chromatography ⟨621⟩)—Proceed as directed in the *Assay*, except to use the *Postcolumn reagent* prepared as directed above. Chromatograph the *System suitability solution*, and record the peak responses as directed for *Procedure:* the resolution, *R,* between the gadodiamide and gadodiamide related compound A peaks is not less than 1.0, and between gadodiamide related compound A and gadodiamide related compound B peaks is not less than 1.5; and the relative standard deviation for replicate injections is not more than 10%.

Procedure—Inject about 10 µL of the *Test solution* into the chromatograph, record the chromatogram, and measure the peak responses. [Note—The tail of the gadodiamide peak may contain a small shoulder due to an isomer; the area of the shoulder should be included in the gadodiamide peak area.] Calculate the percentage of each impurity in the portion of Gadodiamide taken by the formula:

$$100(r_i/r_s)$$

in which r_i is the response of each impurity; and r_s is the sum of all peaks having a percentage greater than 0.10%: not more than 2.0% of gadodiamide related compounds A and B is found; no individual impurity is more than 0.2%; and the sum of all impurities, other than gadodiamide related compounds A and B, is not more than 0.5%.

Content of gadolinium—

Standard solutions—Prepare three separate solutions in 0.2 M nitric acid to obtain concentrations of 100, 150, and 200 µg of gadolinium per mL.

Test solution—Transfer about 600 mg of Gadodiamide, accurately weighed, to a 100-mL volumetric flask, dilute with water to volume, and mix. Pipet 10 mL of this solution into a 100-mL volumetric flask, dilute with 0.2 M nitric acid to volume, and mix.

Procedure—Concomitantly determine the absorbances of the *Standard solutions* and the *Test solution* at the gado linium resonance line of 342.3 nm with a suitable atomic absorption spectrophotometer (see *Atomic Absorption Spectroscopy ⟨852⟩*), using 0.2 M nitric acid as the blank. Plot the absorbances of the *Standard solutions* versus concentration, in µg per mL, of gadolinium, and draw the straight line best fitting the three plotted points. From the graph so obtained, determine the concentration, in µg per mL, of gadolinium in the *Test solution:* the content of gadolinium is between 26.0% and 29.0%, calculated on the anhydrous basis.

Assay—

Mobile phase—Transfer 14.0 mL of triethylamine, 5.7 mL of glacial acetic acid, and 5.7 mL of water to a 1000-mL volumetric flask, dilute with water to volume, and mix. Transfer 50 mL of this solution to a 1000-mL volumetric flask, add 900 mL of water, and mix. Adjust with 1 N acetic acid or 1 N sodium hydroxide to a pH between 6.5 and 7.0. Dilute with water to volume, mix, filter, and degas (see *System Suitability* under *Chromatography ⟨621⟩*).

Postcolumn reagent—Dissolve 325 mg of urea in a solution of 60 mg of arsenazo III acid in 550 mL of water previously acidified with 3.2 mL of nitric acid. Pass the solution through a 0.45-µm porosity filter, wash the filter with 400 mL of water, dilute with water to 1000 mL, mix, and degas.

Standard preparation—Prepare an aqueous solution of USP Gadodiamide RS having a known concentration of about 0.6 mg per mL.

Assay preparation—Transfer about 60 mg of Gado diamide, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with water to volume, and mix.

Chromatographic system (see *Chromatography* 〈621〉)—The liquid chromatograph is equipped with a 658-nm detector and a 4.6-mm × 25-cm column that contains 5-µm base-deactivated packing L1. A second pump mixes the *Mobile phase* with the *Postcolumn reagent* prior to detection via a T-junction. The system is maintained at a constant temperature between 20° and 35°. The flow rate is about 1.5 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 2.5%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of $C_{16}H_{26}GdN_5O_8$ in the portion of Gadodiamide taken by the formula:

$$100C(r_U/r_S)$$

in which C is the concentration, in mg per mL, of USP Gadodiamide RS in the *Standard preparation;* and r_U and r_S are the gadodiamide peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

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

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

Chromatographic Database Information: Chromatographic Database

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