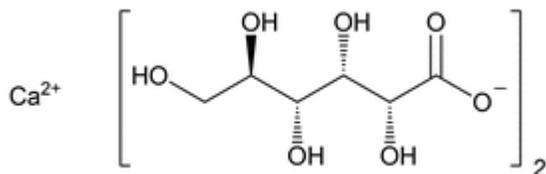


Calcium Gluconate



$C_{12}H_{22}CaO_{14}$ 430.37
 $C_{12}H_{22}CaO_{14} \cdot H_2O$ 448.39
 D-Gluconic acid, calcium salt (2:1);
 Calcium D-gluconate (1:2) [299-28-5].
 Monohydrate [66905-23-5].

DEFINITION

Calcium Gluconate is anhydrous or contains one molecule of water of hydration. The anhydrous form contains NLT 98.0% and NMT 102.0% of calcium gluconate ($C_{12}H_{22}CaO_{14}$), calculated on the dried basis. The monohydrate form contains NLT 99.0% and NMT 101.0% of calcium gluconate monohydrate ($C_{12}H_{22}CaO_{14} \cdot H_2O$) where labeled as intended for use in preparing injectable dosage forms, and NLT 98.5% and NMT 102.0% of calcium gluconate monohydrate ($C_{12}H_{22}CaO_{14} \cdot H_2O$) where labeled as not intended for use in preparing injectable dosage forms.

IDENTIFICATION

A. IDENTIFICATION TESTS—GENERAL (191), *Calcium*

Sample solution: 20 mg/mL

Acceptance criteria: Meets the requirements

B. INFRARED ABSORPTION

Standard preparation: Prepare USP Calcium Gluconate Anhydrous RS or USP Calcium Gluconate Monohydrate RS in the form of a potassium bromide pellet.

Sample preparation: Prepare calcium gluconate anhydrous or calcium gluconate monohydrate in the form of a potassium bromide pellet.

Analysis

Samples: *Standard preparation* and *Sample preparation*
 Record the spectra over the range from about 2.6 to 15 μ m (3800–650 cm^{-1}).

Acceptance criteria: The spectrum of Calcium Gluconate labeled as anhydrous exhibits the differential maxima at the wavenumbers in *Table 1* that are consistent with those of the spectrum of USP Calcium Gluconate Anhydrous RS. The spectrum of Calcium Gluconate labeled as monohydrate exhibits the differential maxima at the wavenumbers in *Table 1* that are consistent with those of the spectrum of USP Calcium Gluconate Monohydrate RS.

Table 1

Spectral Region	Wavenumber (cm^{-1}) of Characteristic Absorptions for Anhydrous	Wavenumber (cm^{-1}) of Characteristic Absorptions for Monohydrate
O-H stretching	No sharp band at about 3485, only broad absorption	At about 3485 (medium sharp over broad absorption)
C=O stretching	1618 (strong)	1595 (strong)

Table 1 (continued)

Spectral Region	Wavenumber (cm^{-1}) of Characteristic Absorptions for Anhydrous	Wavenumber (cm^{-1}) of Characteristic Absorptions for Monohydrate
Fingerprint	1329 (medium)	Not observed
	Not observed	1305 (medium)
	1263–1250 (strong, two fused bands)	Not observed
	Not observed	1236 (medium)
	1007 (medium)	Not observed
	Not observed	1045 (medium)
	948 (duplet, medium)	Not observed
	Not observed	972 (weak)
	865 (weak)	Not observed
	Not observed	878 (weak)
	766 (medium)	Not observed

ASSAY

PROCEDURE

Sample: 800 mg of calcium gluconate anhydrous or calcium gluconate monohydrate

Blank: 150 mL of water containing 2 mL of 3 N hydrochloric acid

Titrimetric system

(See *Titrimetry* (541).)

Mode: Direct titration

Titrant: 0.05 M edetate disodium VS

Endpoint detection: Visual

Analysis: Dissolve the *Sample* in 150 mL of water containing 2 mL of 3 N hydrochloric acid. While stirring, add 30 mL of *Titrant* from the titration buret. Add 15 mL of 1 N sodium hydroxide and 300 mg of hydroxy naphthol blue, and continue the titration to a blue endpoint. Perform the *Blank* determination.

Calculate the percentage of calcium gluconate ($C_{12}H_{22}CaO_{14}$) or calcium gluconate monohydrate ($C_{12}H_{22}CaO_{14} \cdot H_2O$) in the *Sample* taken:

$$\text{Result (anhydrous form)} = \left\{ \frac{(V_s - V_b) \times M \times F}{W} \right\} \times 100$$

$$\text{Result (monohydrate form)} = \left\{ \frac{(V_s - V_b) \times M \times F}{W} \right\} \times \left(\frac{M_{r2}}{M_{r1}} \right) \times 100$$

V_s = *Titrant* volume consumed by the *Sample* (mL)

V_b = *Titrant* volume consumed by the *Blank* (mL)

M = *Titrant* molarity (mmol/mL)

F = equivalency factor, 430.4 mg/mmol

W = *Sample* weight (mg)

M_{r2} = molecular weight of calcium gluconate monohydrate, 448.4

M_{r1} = molecular weight of calcium gluconate anhydrous, 430.4

Acceptance criteria

Anhydrous: 98.0%–102.0% on the dried basis

Monohydrate: 99.0%–101.0% where labeled as intended for use in preparing injectable dosage forms; 98.5%–102.0% where labeled as not intended for use in preparing injectable dosage forms

IMPURITIES• **ARSENIC** (211), *Method I*

Test preparation: Dissolve 1.0 g in a mixture of 10 mL of hydrochloric acid and 20 mL of water, and dilute with water to 55 mL.

Analysis: Proceed as directed in the chapter, except to omit the addition of 20 mL of 7 N sulfuric acid.

Acceptance criteria: NMT 3 ppm

- **CHLORIDE AND SULFATE** (221), *Chloride:* A 1.0-g portion shows no more chloride than corresponds to 0.07 mL of 0.020 N hydrochloric acid (0.005%). Where it is labeled as not intended for use in the preparation of injectable dosage forms, a 1.0-g portion shows no more chloride than corresponds to 1 mL of 0.020 N hydrochloric acid (0.07%).
- **CHLORIDE AND SULFATE** (221), *Sulfate:* A 2.0-g portion dissolved in boiling water shows no more sulfate than corresponds to 0.1 mL of 0.020 N sulfuric acid (0.005%). Where it is labeled as not intended for use in the preparation of injectable dosage forms, a 2.0-g portion dissolved in boiling water shows no more sulfate than corresponds to 1 mL of 0.020 N sulfuric acid (0.05%).

• **LIMIT OF IRON**

[NOTE—Calcium Gluconate labeled as not intended for use in the preparation of injectable dosage forms is exempt from this requirement.]

Internal standard solution: 2 µg/mL of yttrium in 10% nitric acid, prepared from commercially prepared yttrium standard suitable for ICP–OES. [NOTE—The yttrium concentration can be varied to optimize the analysis.]

Standard solutions: 0.05, 0.1, 0.2, and 0.4 µg/mL of iron in 10% nitric acid, prepared from commercially prepared iron standard suitable for ICP–OES

Sample solution: 40 mg/mL of Calcium Gluconate in 10% nitric acid

Blank solution: 10% Nitric acid solution

Instrumental conditions

(See *Plasma Spectrochemistry* (730).)

Mode: Inductively coupled plasma–optical emission spectroscopy (ICP–OES)

Emission wavelengths: 239.562 nm or optimized wavelength for iron; 371.029 nm or optimized wavelength for yttrium

System suitability

Samples: *Internal standard solution, Standard solutions, and Blank solution*

Instrument performance must be verified to conform to the manufacturer's specifications for resolution and sensitivity. Before analyzing samples, the instrument must pass a suitable performance check. Generate the calibration curve using the *Blank solution* and *Standard solutions* as follows. Scan the *Internal standard solution* while running the *Blank solution* to measure the intensity of the yttrium emission. Hold this value constant throughout the remainder of the test. Separately scan the *Blank solution; Standard solutions* of 0.05, 0.1, 0.2, and 0.4 µg/mL of iron; and *Internal standard solution*. [NOTE—Add the *Internal standard solution* via an in-line mixing chamber.] Normalize the yttrium intensity to the value of the *Internal standard solution*. Apply this normalization factor to the iron intensity, which is then referred to as the corrected iron intensity. Construct a calibration curve by plotting the corrected iron intensity versus the known concentrations, in µg/mL, of the iron: the linear regression coefficient is NLT 0.999.

Analysis

Sample: *Sample solution*

Similarly, analyze the *Sample solution* on the ICP. Plot the intensity of the emission of the *Sample solution* on the calibration curve. Obtain the concentration of iron, *C*, in

µg/mL, in the *Sample solution* through the calibration curve.

Calculate the content, in µg/g (ppm), of iron in the portion of Calcium Gluconate taken:

$$\text{Result} = (C \times V)/W$$

- C* = concentration of iron in the *Sample solution* obtained from the calibration curve (µg/mL)
V = volume of the *Sample solution* (mL)
W = weight of Calcium Gluconate taken to prepare the *Sample solution* (g)

Acceptance criteria: NMT 5 ppm

• **LIMIT OF MAGNESIUM AND ALKALI METALS**

[NOTE—Calcium Gluconate labeled as not intended for use in preparing injectable dosage forms is exempt from this requirement.]

Sample: 1.0 g

Analysis: Dissolve the *Sample* completely in 100 mL of boiling water. Add 10 mL of ammonium chloride TS, 1 mL of ammonium hydroxide, and 50 mL of hot (maintained at 70°–80°) ammonium oxalate TS. Allow to stand for 4 h, dilute with water to 200 mL, and filter. Evaporate 100 mL of the filtrate to dryness, and ignite to constant weight.

Acceptance criteria: NMT 0.4%; the weight of the residue does not exceed 2 mg.

• **LIMIT OF PHOSPHATE**

[NOTE—Calcium Gluconate labeled as not intended for use in the preparation of injectable dosage forms is exempt from this requirement.]

Standard stock solution 1: 0.716 mg/mL of monobasic potassium phosphate

Standard stock solution 2: Dilute 1.0 mL of *Standard stock solution 1* with water to 100 mL.

Standard solution: Dilute 2.0 mL of *Standard stock solution 2* with water to 100 mL.

Sample stock solution: To 10.0 g of Calcium Gluconate add 90 mL of hot water (70°–80°), and heat to boiling, with swirling, for 10 s to obtain a clear solution.

Sample solution: Dilute 1 mL of the hot *Sample stock solution* with water to 100 mL.

Analysis

Samples: *Standard solution* and *Sample solution*

To the *Standard solution* and *Sample solution* add 4 mL of sulfomolybdic acid TS, and mix. To both solutions add 0.1 mL of a freshly prepared mixture of 3 N hydrochloric acid and stronger acid stannous chloride TS (10:1), and mix.

Acceptance criteria: NMT 0.01%; after 10 min any color in the *Sample solution* is not more intense than that in the *Standard solution*.

• **LIMIT OF OXALATE**

[NOTE—Calcium Gluconate labeled as not intended for use in the preparation of injectable dosage forms is exempt from this requirement.]

[NOTE—Use deionized water where water is indicated.]

Solution A: 0.0125 M sulfuric acid in water

Solution B: Dilute 1 mL of hydrochloric acid with water to 1200 mL.

Mobile phase: 0.0017 M sodium bicarbonate and 0.0018 M sodium carbonate in water

Standard solution: 1.5 µg/mL of sodium oxalate in *Solution B*

Sample solution: 20 mg/mL of Calcium Gluconate in *Solution B*. Sonicate if necessary.

Chromatographic system

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

Mode: Ion chromatography

Detector: Conductance

Columns**Guard:** 4-mm × 5-cm; 15-μm packing L12**Analytical:** 4-mm × 25-cm; 15-μm packing L12**Anion suppressor:** The micromembrane anion suppressor column is connected in series with the guard and analytical columns. The anion suppressor column is equipped with a micromembrane that separates *Mobile phase* from *Solution A* flowing countercurrent to *Mobile phase* at a rate of about 7 mL/min.[NOTE—Condition the system for about 15 min with *Mobile phase* at a flow rate of 2 mL/min.]**Flow rate:** 2 mL/min**Injection volume:** 50 μL**System suitability****Sample:** *Standard solution***Suitability requirements****Column efficiency:** NLT 2500 theoretical plates**Tailing factor:** NMT 1.2**Relative standard deviation:** NMT 2.0%**Analysis****Samples:** *Standard solution* and *Sample solution*

Calculate the percentage of oxalate in the portion of Calcium Gluconate taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times F \times 100$$

 r_U = peak response of oxalate from the *Sample solution* r_S = peak response of oxalate from the *Standard solution* C_S = concentration of sodium oxalate in the *Standard solution* (μg/mL) C_U = concentration of Calcium Gluconate in the *Sample solution* (mg/mL) M_{r1} = molecular weight of oxalate, 88.03 M_{r2} = molecular weight of sodium oxalate, 134.00 F = conversion factor, 0.001 mg/μg**Acceptance criteria:** NMT 0.01%**• REDUCING SUBSTANCES****Sample:** 1.0 g of Calcium Gluconate**Blank:** 20 mL of water**Titrimetric system**(See *Titrimetry* <541>.)**Mode:** Residual titration**Titrant:** 0.1 N iodine VS**Back titrant:** 0.1 N sodium thiosulfate VS**Endpoint detection:** Visual**Analysis:** Transfer the *Sample* to a 250-mL conical flask, dissolve in 20 mL of hot water, cool, and add 25 mL ofalkaline cupric citrate TS. Cover the flask, boil gently for 5 min, accurately timed, and cool rapidly to room temperature. Add 25 mL of 0.6 N acetic acid, 10.0 mL of *Titrant*, and 10 mL of 3 N hydrochloric acid. Titrate with the *Back titrant*, adding 3 mL of starch TS as the endpoint is approached. Perform the *Blank* determination. Calculate the percentage of reducing substances (as dextrose) in the *Sample* taken:

$$\text{Result} = \{(V_B - V_S) \times N \times F/W\} \times 100$$

 V_B = *Back titrant* volume consumed by the *Blank* (mL) V_S = *Back titrant* volume consumed by the *Sample* (mL) N = *Back titrant* normality (mEq/mL) F = equivalency factor, 27 mg/mEq W = *Sample* weight (mg)**Acceptance criteria:** NMT 1.0%**SPECIFIC TESTS****• LOSS ON DRYING** <731>**Analysis:** Dry at 105° for 16 h.**Acceptance criteria****Anhydrous:** NMT 3.0%**Monohydrate:** NMT 1.0%, where labeled as intended for use in preparing injectable dosage forms; NMT 2.0%, where labeled as not intended for use in preparing injectable dosage forms**ADDITIONAL REQUIREMENTS****• PACKAGING AND STORAGE:** Preserve in well-closed containers.**• LABELING:** Label it to indicate whether it is anhydrous or monohydrate. Where the quantity of calcium gluconate is indicated in the labeling of any solution containing Calcium Gluconate, this shall be understood to be in terms of anhydrous calcium gluconate (C₁₂H₂₂CaO₁₄). Calcium Gluconate intended for use in preparing injectable dosage forms is so labeled. Calcium Gluconate not intended for use in preparing injectable dosage forms is so labeled; in addition, it may be labeled also as intended for use in preparing oral dosage forms.**• USP REFERENCE STANDARDS** <11>

USP Calcium Gluconate Anhydrous RS

USP Calcium Gluconate Monohydrate RS