Status: Currently Official on 14-Feb-2025
Official Date: Official as of 01-Aug-2018
Document Type: USP Monographs
DocId: GUID-967EDB57-BB82-4E32-8247-478606B6F4C4_6_en-US
DOI: https://doi.org/10.31003/USPNF_M11535_06_01
DOI Ref: q8fol

Add the following:

▲Calcium Citrate Malate

$Ca_3(C_6H_5O_7)_2 \cdot 3CaC_4H_4O_5 \cdot 6H_2O$ 1122.97

1,2,3-Propanetricarboxylic acid, 2-hydroxy-, calcium salt mixture with 2-hydroxybutanedioic acid calcium salt (2:3:6), hexahydrate;
Calcium citrate malate (6:2:3), hexahydrate.

DEFINITION

Calcium Citrate Malate is a complex of calcium, citrate, and malate. It contains NLT 23.0% and NMT 24.2% of calcium, calculated on the dried basis. The sum of citrate and malate is NLT 73.0%, calculated on the dried basis.

IDENTIFICATION

• **A.**

Sample: 0.5 g of Calcium Citrate Malate

Analysis: Ignite completely the *Sample* at as low a temperature as possible, cool, and dissolve the residue in dilute glacial acetic acid (1:10). Filter, and add 10 mL of ammonium oxalate TS to the filtrate.

Acceptance criteria: A voluminous white precipitate that is soluble in hydrochloric acid is formed.

• **B.** The retention times of the citric acid peak and the malic acid peak of the *Sample solution* correspond to those of the *System suitability solution*, as obtained in the test for *Content of Citrate, Malate, and Fumarate*.

ASSAY

• **Procedure**

Sample: 350 mg of Calcium Citrate Malate

Titrimetric system

(See *Titrimetry* ⟨541⟩.)

Mode: Direct titration

Titrant: 0.05 M edetate disodium VS

Endpoint detection: Visual

Analysis: Transfer the *Sample* into a 250-mL beaker, add 10 mL of water, 3 mL of 3 N hydrochloric acid, and swirl to dissolve. Add 90 mL of water and stir using a magnetic stirring bar. While stirring, add 30 mL of *Titrant* from the titration buret, and 25 mL of 1 N sodium hydroxide. Add 150 mg of hydroxy naphthol blue, and continue the titration to a blue endpoint. Perform a blank determination.

Calculate the percentage of calcium in the portion of Calcium Citrate Malate taken:

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

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

V_B = *Titrant* volume consumed by the blank (mL)

M_A = actual molarity of the *Titrant* (mmol/mL)

F = equivalency factor, 40.08 mg/mmol

W = *Sample* weight (mg)

Acceptance criteria: 23.0%–24.2% on the dried basis

IMPURITIES

Change to read:

• **Limit of Fluoride**

[Note—Prepare and store all solutions in plastic containers.]

Buffer solution: 294 mg/mL of sodium citrate dihydrate in water

Standard stock solution: 1.1052 mg/mL of USP Sodium Fluoride RS in water

Standard solution: Transfer ▲2.0 mL▲ (ERR 1-Aug-2018) of *Standard stock solution* to a 1000-mL volumetric flask, dilute with water to volume, and mix. Each milliliter of this solution contains 1 µg of fluoride ion.

Sample solution: Transfer 1.0 g of Calcium Citrate Malate to a 100-mL beaker containing a plastic-coated stirring bar. Add 10 mL of water and place on a hot plate (medium heat). While stirring, add 10 mL of 1 N hydrochloric acid to dissolve. When dissolved, boil rapidly for 1 min, and transfer the solution to a 250-mL beaker. Cool rapidly to room temperature in an ice bath. Add 15 mL of *Buffer solution* and 10 mL of 0.2 M edetic acid, and mix. Adjust with 1 N hydrochloric acid or 1 N sodium hydroxide to a pH of 5.5 ± 0.1. Transfer the solution to a 100-mL volumetric flask, dilute with water to volume, and mix. Pour the solution back to the 250-mL beaker for performing the titration.

Electrode system: Use a fluoride-specific ion-indicating electrode and a silver–silver chloride reference electrode connected to a pH meter capable of measuring potentials with a minimum reproducibility of ±0.2 mV (see *pH* ⟨791⟩).

Analysis

Samples: *Standard solution* and *Sample solution*

Standard response line: Transfer 5.0, 25.0, and 50.0 mL of the *Standard solution* to three individual 250-mL beakers containing a plastic-coated stirring bar. Add 10 mL of 1 N hydrochloric acid, 15 mL of *Buffer solution*, and 0.2 M edetic acid to each beaker and mix. Adjust with 1 N hydrochloric acid or 1 N sodium hydroxide to a pH of 5.5 ± 0.1. Transfer the solutions to individual 100-mL volumetric flasks, dilute with water to volume, and mix. Pour the solutions back to the individual 250-mL beakers for performing the titration. Insert the electrodes into the solutions starting with the lowest concentration, stir for 15 min, and read the potential in millivolts. Between measurements, wash both reference and ion-selective electrodes with water and dry with cloth or paper towel. Plot the logarithms of the fluoride ion concentrations (0.05, 0.25, and 0.5 µg/mL) versus potential, in millivolts.

Rinse and dry the electrodes, insert them into the *Sample solution*, stir for 5 min, and read the potential, in millivolts. From the measured potential and the *Standard response line* determine the concentration (*C*), in µg/mL, of fluoride ion in the *Sample solution*.

Calculate the content of fluoride in the portion of Calcium Citrate Malate taken:

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

V = volume of the *Sample solution* (mL)

C = concentration of fluoride ion in the *Sample solution* determined from the *Standard response line* (µg/mL)

W = weight of Calcium Citrate Malate taken to prepare the *Sample solution* (g)

Acceptance criteria: NMT 30 µg/g

• **Elemental Impurities—Procedures** ⟨233⟩

Acceptance criteria

Arsenic: NMT 3.0 µg/g

Lead: NMT 1.0 µg/g

SPECIFIC TESTS

• **Content of Citrate, Malate, and Fumarate**

Diluent: 0.2 N hydrochloric acid

Mobile phase: 50 mM of monobasic potassium phosphate in water. Adjust with phosphoric acid to a pH of 2.5.

System suitability solution: 5 mg/mL of USP Calcium Citrate Malate RS in *Diluent*

Citric acid standard solution: 1.8 mg/mL of USP Citric Acid RS in *Diluent*

Malic acid standard solution: 1.8 mg/mL of USP Malic Acid RS in *Diluent*

Fumaric acid standard solution: 20 µg/mL of USP Fumaric Acid RS in *Diluent*

Sample solution: 5 mg/mL of Calcium Citrate Malate in *Diluent*

Chromatographic system

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

Mode: LC

Detector: UV 226 nm

Column: 4.6-mm × 15-cm; 5-µm packing L1

Column temperature: 35°

Flow rate: 1.0 mL/min

Injection volume: 10 µL

System suitability

Samples: *System suitability solution*, *Citric acid standard solution*, *Malic acid standard solution*, and *Fumaric acid standard solution*

[Note—The relative retention times for malic acid, citric acid, and fumaric acid are 0.6, 1.0, and 1.4, respectively.]

Suitability requirements

Resolution: NLT 8.0 between malic acid and citric acid, *System suitability solution*

Relative standard deviation: NMT 2.0% for each *Standard solution*

Chromatogram similarity: The chromatogram of the *System suitability solution* is similar to the reference chromatogram provided with the lot of USP Calcium Citrate Malate RS being used.

Analysis

Samples: *Citric acid standard solution*, *Malic acid standard solution*, *Fumaric acid standard solution*, and *Sample solution*

Separately calculate the percentage of citrate, malate, and fumarate in the portion of Calcium Citrate Malate taken:

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

r_U = peak response of citric acid, malic acid, or fumaric acid from the *Sample solution*

r_S = peak response of citric acid, malic acid, or fumaric acid from the respective *Standard solutions*

C_S = concentration of USP Citric Acid RS, USP Malic Acid RS, or USP Fumaric Acid RS in the respective *Standard solutions* (mg/mL)

C_U = concentration of Calcium Citrate Malate in the *Sample solution* (mg/mL)

F = factor for converting molecular weight of the acid form to that of the salt form, 0.98

Acceptance criteria

Sum of citrate and malate: NLT 73.0% on the dried basis

Fumarate: NMT 0.1% on the dried basis

- **pH** ⟨791⟩

Sample solution: 30 mg/mL in water. [NOTE—The solution is a slurry.]

Acceptance criteria: 4.0–8.0

- **Loss on Drying** ⟨731⟩

Analysis: Dry at 150° for 4 h.

Acceptance criteria: 8.0%–11.0%

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in tight containers.
- **USP Reference Standards** ⟨11⟩

USP Calcium Citrate Malate RS
USP Citric Acid RS
USP Fumaric Acid RS
USP Malic Acid RS
USP Sodium Fluoride RS▲1S *(USP41)*

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

Topic/Question	Contact	Expert Committee
CALCIUM CITRATE MALATE	Nagaphani Batchu Senior Scientist I, Documentary Standards	NBDS2020 Non-botanical Dietary Supplements

Chromatographic Database Information: Chromatographic Database

Most Recently Appeared In:
Pharmacopeial Forum: Volume No. PF 43(2)

Current DocID: GUID-967EDB57-BB82-4E32-8247-478606B6F4C4_6_en-US
Previous DocID: GUID-967EDB57-BB82-4E32-8247-478606B6F4C4_5_en-US
DOI: https://doi.org/10.31003/USPNF_M11535_06_01
DOI ref: q8fol