Calcium Acetate Capsules

Type of Posting	Revision Bulletin
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Expert Committee	Chemical Medicines Monographs 6
Reason for Revision	Compliance

In accordance with the Rules and Procedures of the 2015–2020 Council of Experts, the Chemical Medicines Monographs 6 Expert Committee has revised the Calcium Acetate Capsules monograph. The purpose for the revision is to add *Dissolution Test 2* and *Dissolution Test 3* to accommodate FDA-approved drug products with different dissolution conditions and tolerances than the existing dissolution test. A *Labeling* section has also been incorporated to support the inclusion of *Dissolution Test 2* and *Dissolution Test 3*.

The Calcium Acetate Capsules Revision Bulletin supersedes the currently official monograph.

Should you have any questions, please contact Michael Chang, Scientific Liason (301-230-3217 or mxc@usp.org).

Add the following:

▲Calcium Acetate Capsules

DEFINITION

Calcium Acetate Capsules contain NLT 90.0% and NMT 110.0% of the labeled amount of calcium acetate ($C_4H_6CaO_4$).

IDENTIFICATION

- **A.** The retention time of the calcium peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.
- **B. IDENTIFICATION TESTS—GENERAL** ⟨191⟩**,** *Chemical Identification Tests, Acetate*

Sample solution: 67 mg/mL of calcium acetate from Capsule contents

Acceptance criteria: Meet the requirements for test *B*

ASSAY

- **PROCEDURE**

Solution A: 0.75 mM dipicolinic acid and 1.7 mM nitric acid in water. [NOTE—Warm water may be required to dissolve dipicolinic acid.]

Mobile phase: Acetone and *Solution A* (100:900). Pass through a suitable filter of 0.2-µm pore size.

Standard solution: 0.08 mg/mL of USP Calcium Acetate RS in water

Sample stock solution: Nominally 6.7 mg/mL of calcium acetate prepared as follows. Transfer an appropriate portion of the contents of NLT 20 Capsules to a suitable volumetric flask. Add water to about 40% of the final volume of the flask and sonicate for 20 min with intermittent shaking. Dilute with water to volume. Pass through a suitable filter of 0.45-µm pore size.

Sample solution: Nominally 0.08 mg/mL of calcium acetate in water from the *Sample stock solution*

Chromatographic system

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

Mode: Ion chromatography

Detector: Conductivity

Column: 4.0-mm × 15-cm; 5-µm packing L76

Column temperature: 35°

Flow rate: 0.9 mL/min

Injection volume: 10 µL

Run time: NLT 1.5 times the retention time of the calcium peak

System suitability

Sample: *Standard solution*

Suitability requirements

Column efficiency: NLT 1000 theoretical plates

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of calcium acetate ($C_4H_6CaO_4$) in the portion of Capsules taken:

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

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

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

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

C_U = nominal concentration of calcium acetate in the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

- **DISSOLUTION** ⟨711⟩

▲Test 1▲ (RB 1-May-2019)

Medium: Water; 900 mL

Apparatus 2: 50 rpm, with sinkers

Time: 10 min

Mobile phase, Standard solution, Chromatographic system, and **System suitability:** Proceed as directed in the *Assay*.

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size. Dilute with *Medium* to a concentration similar to the *Standard solution*, if necessary.

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of calcium acetate ($C_4H_6CaO_4$) dissolved at time point (*i*):

$$\text{Result}_i = (r_U/r_S) \times C_S \times V \times D \times (1/L) \times 100$$

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

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

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

V = volume of *Medium*, 900 mL

D = dilution factor for the *Sample solution*, if needed

L = label claim (mg/Capsule)

Tolerances: NLT 80% (*Q*) of the labeled amount of calcium acetate ($C_4H_6CaO_4$) is dissolved.

▲Test 2: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.

Medium: 0.1 N hydrochloric acid; 900 mL

Apparatus 1: 100 rpm

Time: 15 min

Blank: 0.2% (v/v) nitric acid

Standard solutions: 4.0, 5.0, 6.0, 7.0, and 8.0 µg/mL of calcium [from commercially available, National Institute of Standards and Technology (NIST) traceable standard solution for calcium] in *Blank*

Sample solution: Pass a portion of the solution under test through a suitable filter of 1.0-µm pore size. Dilute with *Blank* to a concentration similar to 6.0-µg/mL *Standard solution*, if necessary.

Instrumental conditions

(See *Atomic Absorption Spectroscopy* ⟨852⟩.)

Mode: Atomic absorption spectrometry

Analytical wavelength: 422.8 nm

Lamp: Calcium hollow-cathode

Flame: Air–acetylene oxidizing flame

System suitability

Samples: *Blank* and *Standard solutions*

Suitability requirements

Linearity: Use the *Blank* to set the instrument to zero. Concomitantly determine the responses for each of the *Standard solutions*. Construct a linear calibration curve by plotting the absorbance values of the *Standard solutions* versus their corresponding concentrations, in micrograms per milliliter.

Correlation coefficient: NLT 0.995

Drift: Within ±2%, 7.0-µg/mL *Standard solution*. See *Atomic Absorption Spectroscopy* ⟨852⟩, *Procedure, Analysis*.

Analysis

Sample: *Sample solution*

From the linear calibration curve, determine the concentration (*C*), in µg/mL, for calcium in the *Sample solution*.

Calculate the percentage of the labeled amount of calcium acetate ($C_4H_6CaO_4$) dissolved:

$$\text{Result} = C \times V \times F \times D \times (M_{r1}/M_{r2}) \times (1/L) \times 100$$

C = concentration of calcium in the *Sample solution* determined (µg/mL)
V = volume of *Medium*, 900 mL
F = equivalency factor, 0.001 mg/µg
D = dilution factor for the *Sample solution*, if needed
M_{r1} = molecular weight of calcium acetate, 158.17
M_{r2} = molecular weight of calcium, 40.08
L = label claim (mg/Capsule)

Tolerances: NLT 85% (*Q*) of the labeled amount of calcium acetate ($C_4H_6CaO_4$) is dissolved.

Test 3: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 3*.

Tier 1

Medium 1: Water; 900 mL
Apparatus 2: 100 rpm, with sinkers
Time: 15 min

Tier 2

Medium 2: Simulated gastric fluid TS; 900 mL
Apparatus 2: 100 rpm, with sinkers
Time: 15 min

Determine the amount of calcium acetate dissolved using *Analytical procedure 1* or *Analytical procedure 2* for *Tier 1* and *Analytical procedure 3* for *Tier 2*.

Sample stock solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size.

Dissolution procedure: Perform the test using the conditions under *Tier 1*. In the presence of cross-linking, repeat the test with a new set of Capsules using the conditions under *Tier 2*.

Analytical procedure 1

Blank: 0.02 N nitric acid

Standard solutions: 2.4, 3.2, 4.0, 4.8, and 5.6 µg/mL of USP Calcium Acetate RS in *Blank*

Sample solution: Nominally 3.7 µg/mL of calcium acetate from *Sample stock solution*, dilute with *Blank* if necessary

Instrumental conditions

(See *Atomic Absorption Spectroscopy* ⟨852⟩.)
Mode: Atomic absorption spectrometry
Analytical wavelength: 422.8 nm
Lamp: Calcium hollow-cathode
Flame: Nitrous oxide–acetylene
Replicates: 4

System suitability

Samples: *Blank*, *Standard solutions*, and *Sample solution*

Suitability requirements

Relative standard deviation: NMT 3.0% in 4 replicate measurements, *Standard solutions* and *Sample solution*

Correlation coefficient: NLT 0.995, use the *Blank* to set the instrument to zero. Concomitantly determine the responses for each of the *Standard solutions*. Construct a quadratic calibration curve by plotting the absorbance values of the *Standard solutions* versus their corresponding concentrations, in micrograms per milliter.

Drift: Within ±5%, the absorbance value of 5.6 µg/mL of USP Calcium Acetate RS from the *Standard solutions*. See *Atomic Absorption Spectroscopy* ⟨852⟩, *Procedure, Analysis*.

Analysis

Sample: *Sample solution*

From the quadratic calibration curve obtained from the *Correlation coefficient*, determine the concentration (*C*), in µg/mL, for calcium acetate in the *Sample solution*.

Calculate the percentage of the labeled amount of calcium acetate ($C_4H_6CaO_4$) dissolved:

$$\text{Result} = C \times V \times F \times D \times (1/L) \times 100$$

C = concentration of calcium acetate in the *Sample solution* determined (µg/mL)
V = volume of *Medium*, 900 mL
F = equivalency factor, 0.001 mg/µg
D = dilution factor for the *Sample solution*, if needed
L = label claim (mg/Capsule)

Analytical procedure 2

Titrimetric system

(See *Titrimetry* ⟨541⟩.)
Mode: Complexometric titration
Titrant: 0.005 M edetic acid (EDTA)
Endpoint detection: Photometric at 610 nm

Analysis: To an aliquot of the *Sample stock solution* equivalent to about 7.4 mg of calcium acetate, add 60 mL of 0.1 N sodium hydroxide and 0.2 g of hydroxynaphthol blue indicator. Titrate with *Titrant*, determining the endpoint photometrically using a suitable autotitrator.

Calculate the percentage of the labeled amount of calcium acetate ($C_4H_6CaO_4$) dissolved:

$$\text{Result} = V_S \times M \times F \times (V_M/V_A) \times (1/L) \times 100$$

V_S = volume of *Titrant* consumed by the aliquot of *Sample stock solution* (mL)
M = actual *Titrant* concentration, in molarity (mmol/mL)
F = equivalency factor of calcium acetate, 158.17 mg/mmol
V_M = volume of *Medium*, 900 mL
V_A = volume of the aliquot taken for *Analysis* (mL)
L = label claim (mg/Capsule)

Analytical procedure 3

Blank: *Medium*

Titrimetric system

(See *Titrimetry* ⟨541⟩.)
Mode: Complexometric titration
Titrant: 0.005 M edetic acid (EDTA)
Endpoint detection: Visual

Analysis: To an aliquot of the *Sample stock solution* equivalent to about 7.4 mg of calcium acetate, add 50 mL of water, 10 mL of 0.1 N sodium hydroxide, and 0.2 g of hydroxynaphthol blue indicator. Titrate with *Titrant* to a blue endpoint while stirring using a

magnetic stirring bar. Perform a *Blank* determination in the same manner.

Calculate the percentage of the labeled amount of calcium acetate ($C_4H_6CaO_4$) dissolved:

$$\text{Result} = (V_S - V_B) \times M \times F \times (V_M/V_A) \times (1/L) \times 100$$

V_S = volume of *Titrant* consumed by the aliquot of *Sample stock solution* (mL)
V_B = volume of *Titrant* consumed by the *Blank* (mL)
M = actual *Titrant* concentration, in molarity (mmol/mL)
F = equivalency factor of calcium acetate, 158.17 mg/mmol
V_M = volume of *Medium*, 900 mL
V_A = volume of the aliquot taken for *Analysis* (mL)
L = label claim (mg/Capsule)

Tolerances: NLT 85% (Q) of the labeled amount of calcium acetate ($C_4H_6CaO_4$) is dissolved. ▲ (RB 1-May-2019)

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

SPECIFIC TESTS

- **MICROBIAL ENUMERATION TESTS** ⟨61⟩ and **TESTS FOR SPECIFIED MICROORGANISMS** ⟨62⟩**:** The total aerobic microbial count does not exceed 10^3 cfu/g, and the total combined molds and yeast count does not exceed 10^2 cfu/g. It meets the requirements of the test for the absence of *Escherichia coli*.

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in well-closed containers and store at controlled room temperature.

Add the following:

▲• **LABELING:** When more than one *Dissolution* test is given, the labeling states the *Dissolution* test used only if *Test 1* is not used. ▲ (RB 1-May-2019)

- **USP REFERENCE STANDARDS** ⟨11⟩
  USP Calcium Acetate RS

▲ USP 1-May-2019