Calcium Acetate Capsules

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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 4* to accommodate FDA-approved drug products with different dissolution conditions and/or tolerances than the existing dissolution tests.

- *Dissolution Test 4* was validated using a YMC-Pack ODS-A C18 brand of L1 column. The typical retention time for calcium acetate is about 4.3 min.

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

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

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
  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 milliliter.
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.

▲**Test 4:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 4*.
Medium: Water; 900 mL, deaerated
Apparatus 2: 50 rpm
Time: 20 min
Solution A: 0.07% (v/v) phosphoric acid in water
Mobile phase: Methanol and *Solution A* (5:95)
Standard solution: 0.74 mg/mL of USP Calcium Acetate RS in *Medium*
Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size.
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 202 nm
Column: 4.6-mm × 25-cm; 5-µm packing L1
Flow rate: 1 mL/min
Injection volume: 10 µL
Run time: NLT 2 times the retention time of the acetate peak
System suitability
Sample: *Standard solution*
Suitability requirements
Tailing factor: NMT 2.0
Relative standard deviation: NMT 2.0%
Analysis
Samples: *Standard solution* and *Sample solution*

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

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

r_U = peak response of acetate from the *Sample solution*
r_S = peak response of acetate from the *Standard solution*
C_S = concentration of USP Calcium Acetate RS in the *Standard solution* (mg/mL)
V = volume of *Medium*, 900 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-Jan-2020)

- **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.
- **Labeling:** When more than one *Dissolution* test is given, the labeling states the *Dissolution* test used only if *Test 1* is not used.
- **USP Reference Standards** ⟨11⟩
USP Calcium Acetate RS