Calcium Acetate Capsules

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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 (C₆H₅CaO₄).

**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 x 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 (C₆H₅CaO₄) in the portion of Capsules taken:

\[ \text{Result} = \left( \frac{r_s}{r_U} \right) \times \left( C_s / C_U \right) \times 100 \]

- **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 (C₆H₅CaO₄) dissolved at time point (i):

\[ \text{Result}_i = \left( \frac{r_s}{r_U} \right) \times C_s \times V \times D \times (1/L) \times 100 \]

- **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 (C₆H₅CaO₄) 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
2 Calcium

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\(_2\)H\(_4\)CaO\(_4\)) dissolved:

\[
\text{Result} = C \times V \times F \times D \times (M_1/M_2) \times (1/L) \times 100
\]

\[C = \text{concentration of calcium in the Sample solution determined (µg/mL)}\]

\[V = \text{volume of Medium, 900 mL}\]

\[F = \text{equivicacy factor, 0.001 mg/µg}\]

\[D = \text{dilution factor for the Sample solution, if needed}\]

\[M_1 = \text{molecular weight of calcium acetate, 158.17}\]

\[M_2 = \text{molecular weight of calcium, 40.08}\]

\[L = \text{label claim (mg/Capsule)}\]

Tolerances: NLT 85% (Q) of the labeled amount of calcium acetate (C\(_2\)H\(_4\)CaO\(_4\)) 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\(_2\)H\(_4\)CaO\(_4\)) dissolved:

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

\[C = \text{concentration of calcium acetate in the Sample solution determined (µg/mL)}\]

\[V = \text{volume of Medium, 900 mL}\]

\[F = \text{equivicacy factor, 0.001 mg/µg}\]

\[D = \text{dilution factor for the Sample solution, if needed}\]

\[L = \text{label claim (mg/Capsule)}\]

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 Titran, determining the endpoint photometrically using a suitable autotitrator.

Calculate the percentage of the labeled amount of calcium acetate (C\(_2\)H\(_4\)CaO\(_4\)) dissolved:

\[
\text{Result} = V_t \times M \times F \times (V_m/V_a) \times (1/L) \times 100
\]

\[V_t = \text{volume of Titrant consumed by the aliquot of Sample stock solution (mL)}\]

\[M = \text{actual Titrant concentration, in molarity (mmol/mL)}\]

\[F = \text{equivicacy factor of calcium acetate, 158.17 mg/mmol}\]

\[V_m = \text{volume of Medium, 900 mL}\]

\[V_a = \text{volume of the aliquot taken for Analysis (mL)}\]

\[L = \text{label claim (mg/Capsule)}\]

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 Titran 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\(_2\)H\(_4\)CaO\(_4\)) dissolved:

\[
\text{Result} = (V_1 - V_3) \times M \times F \times (V_m/V_a) \times (1/L) \times 100
\]

\[V_1 = \text{volume of Titrant consumed by the aliquot of Sample stock solution (mL)}\]

\[V_3 = \text{volume of Titrant consumed by the Blank (mL)}\]

\[M = \text{actual Titrant concentration, in molarity (mmol/mL)}\]
\( F \) = 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\(_4\)H\(_6\)CaO\(_4\)) 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\(_4\)H\(_6\)CaO\(_4\)) dissolved:

\[
\text{Result} = \left( \frac{r_U}{r_S} \right) \times C_S \times V \times \left( \frac{1}{L} \right) \times 100
\]

\( r_U \) = 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\(_4\)H\(_6\)CaO\(_4\)) is dissolved.

- **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