Calcium Acetate Capsules

Type of Posting	Notice of Intent to Revise
Posting Date	27-Jan-2023
Targeted Official Date	To Be Determined, Revision Bulletin
Expert Committee	Small Molecules 5

In accordance with the Rules and Procedures of the Council of Experts and the Pending Monograph Guideline, this is to provide notice that the Small Molecules 5 Expert Committee intends to revise the Calcium Acetate Capsules monograph.

Based on the supporting data received from a manufacturer awaiting FDA approval, the Expert Committee proposes to revise the Calcium Acetate Capsules monograph to add *Dissolution Test 5*.

The proposed revision is contingent on FDA approval of a product that meets the proposed monograph specifications. The proposed revision will be published as a Revision Bulletin and an official date will be assigned to coincide as closely as possible with the FDA approval of the associated product.

See below for additional information about the proposed text.[1]

Should you have any questions, please contact Yanyin Yang, Senior Scientist II (301-692-3623 or yanyin.yang@usp.org).

[1] This text is not the official version of a *USP–NF* monograph and may not reflect the full and accurate contents of the currently official monograph. Please refer to the current edition of the *USP–NF* for official text.

USP provides this text to indicate changes that we anticipate will be made official once the product subject to this proposed revision under the Pending Monograph Program receives FDA approval. Once FDA approval is granted for the associated revision request, a Revision Bulletin will be posted that will include the changes indicated herein, as well as any changes indicated in the product's final approval, combined with the text of the monograph as effective on the date of approval. Any revisions made to a monograph under the Pending Monograph Program that are posted without prior publication for comment in the *Pharmacopeial Forum* must also meet the requirements outlined in the USP Guideline on Use of Accelerated Processes for Revisions to the *USP–NF*.

Notice of Intent to Revise
Official: To Be Determined

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* (10:90). 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

Solution A, 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:

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

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 of 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 solution A: 4.0 µg/mL of calcium[1] in the *Blank*

Standard solution B: 5.0 µg/mL of calcium[1] in the *Blank*

Standard solution C: 6.0 µg/mL of calcium[1] in the *Blank*

Standard solution D: 7.0 µg/mL of calcium[1] in the *Blank*

Standard solution E: 8.0 µg/mL of calcium[1] in the *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 *Standard solution C*, 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*, *Standard solution A*, *Standard solution B*, *Standard solution C*, *Standard solution D*, and *Standard solution E*

Suitability requirements

Correlation coefficient: NLT 0.995, from the linear regression in the *Analysis*

Drift: Within ±2%, *Standard solution D*. (See *Atomic Absorption Spectroscopy* ⟨852⟩*, Procedure, Analysis*.)

Analysis

Samples: *Blank*, *Standard solution A*, *Standard solution B*, *Standard solution C*, *Standard solution D*, *Standard solution E*, and *Sample solution*

Use the *Blank* to set the instrument to zero. Concomitantly determine the responses for *Standard solution A*, *Standard solution B*, *Standard solution C*, *Standard solution D*, and *Standard solution E*. Construct a linear calibration curve by plotting the absorbance values of *Standard solution A*, *Standard solution B*, *Standard solution C*, *Standard solution D*, and *Standard solution E* versus their corresponding concentrations, in µg/mL. 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* (µg/mL)
V	= volume of *Medium*, 900 mL
F	= conversion factor, 0.001 mg/µg
D	= dilution factor of 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 in *Tier 1*. In the presence of cross-linking, repeat the test with a new set of Capsules using the conditions in *Tier 2*.

Analytical procedure 1

Blank: 0.02 N nitric acid

Standard solution A: 2.4 µg/mL of USP Calcium Acetate RS in the *Blank*

Standard solution B: 3.2 µg/mL of USP Calcium Acetate RS in the *Blank*

Standard solution C: 4.0 µg/mL of USP Calcium Acetate RS in the *Blank*

Standard solution D: 4.8 µg/mL of USP Calcium Acetate RS in the *Blank*

Standard solution E: 5.6 µg/mL of USP Calcium Acetate RS in the *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 solution A*, *Standard solution B*, *Standard solution C*, *Standard solution D*, *Standard solution E*, and *Sample solution*

Suitability requirements

Relative standard deviation: NMT 3.0% in 4 replicate measurements, *Standard solution A*, *Standard solution B*, *Standard solution C*, *Standard solution D*, *Standard solution E*, and *Sample solution*

Correlation coefficient: NLT 0.995, from the linear regression in the *Analysis*

Drift: Within ±5%, the absorbance value of *Standard solution E*. (See *Atomic Absorption Spectroscopy* ⟨852⟩*, Procedure, Analysis*.)

Analysis

Samples: *Blank*, *Standard solution A*, *Standard solution B*, *Standard solution C*, *Standard solution D*, *Standard solution E*, and *Sample solution*

Use the *Blank* to set the instrument to zero. Concomitantly determine the responses for *Standard solution A*, *Standard solution B*, *Standard solution C*, *Standard solution D*, and *Standard solution E*. Construct a quadratic calibration curve by plotting the absorbance values of *Standard solution A*, *Standard solution B*, *Standard solution C*, *Standard solution D*, and *Standard solution E* versus their corresponding concentrations, in µg/mL. From the quadratic calibration curve, 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* (µg/mL)
V = volume of *Medium 1*, 900 mL
F = conversion factor, 0.001 mg/µg
D = dilution factor of 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 molarity of the *Titrant* (mmol/mL)
F = equivalency factor of calcium acetate, 158.17 mg/mmol
V_M = volume of *Medium 1*, 900 mL
V_A = volume of the aliquot taken (mL)
L = label claim (mg/Capsule)

Analytical procedure 3

Blank: *Medium 2*

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 molarity of the *Titrant* (mmol/mL)
F = equivalency factor of calcium acetate, 158.17 mg/mmol
V_M = volume of *Medium 2*, 900 mL
V_A = volume of the aliquot taken (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, with appropriate sinkers, if necessary

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.

▲**Test 5:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 5*.

Medium: 0.1 N hydrochloric acid; 500 mL

Apparatus 2: 50 rpm with sinkers. [NOTE—A suitable sinker is available as catalog No. PSCAPWST-31 from *https://www.dissolutionaccessories.com*.]

Time: 30 min

Solution A: 10.82 mL/L of nitric acid in water

Solution B: 0.75 mM dipicolinic acid and 1.7 mM nitric acid in water prepared as follows. Dissolve 0.125 g of dipicolinic acid in 700 mL of water and add 10 mL of *Solution A*. Dilute with water to 1000 mL. [Note—Warm water may be required to dissolve dipicolinic acid.]

Mobile phase: Acetone and *Solution B* (10:90)

Standard stock solution: 1.32 mg/mL of USP Calcium Acetate RS in *Medium*. Sonicate to dissolve.

Standard solution: 0.08 mg/mL of USP Calcium Acetate RS from the *Standard stock solution* in water. Pass through a suitable filter of 0.22-µm pore size and discard the first 5 mL.

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.22-µm pore size, discarding the first 5 mL. Dilute with water to a concentration that is similar to that of the *Standard 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 calcium

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:

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

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*, 500 mL

D = dilution factor of the *Sample solution*

L = label claim (mg/Capsule)

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

- **Uniformity of Dosage Units** ⟨905⟩**:** Meet the requirements

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

[1] From commercially available, National Institute of Standards and Technology (NIST)-traceable standard solution for calcium.

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