Calcium Acetate Capsules

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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.
Calcium Acetate Capsules

**DEFINITION**
Calcium Acetate Capsules contain NLT 90.0% and NMT 110.0% of the labeled amount of calcium acetate (C$_4$H$_6$CaO$_4$).

**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:

$$\text{Result} = \left(\frac{r_U}{r_S}\right) \times \left(\frac{C_S}{C_U}\right) \times 100$$

- $r_U$ = 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

**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:

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

- $r_U$ = 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)
- $V$ = 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 calcium¹ in the Blank
**Standard solution B**: 5.0 µg/mL of calcium¹ in the Blank
**Standard solution C**: 6.0 µg/mL of calcium¹ in the Blank
**Standard solution D**: 7.0 µg/mL of calcium¹ in the Blank
**Standard solution E**: 8.0 µg/mL of calcium¹ 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

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

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 (C₄H₆CaO₄) dissolved:

Result = C × V × F × D × (Mₑ₁/Mₑ₂) × (1/L) × 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
Mₑ₁ = molecular weight of calcium acetate, 158.17
Mₑ₂ = molecular weight of calcium, 40.08
L = label claim (mg/Capsule)

Tolerances: NLT 85% (Q) of the labeled amount of calcium acetate (C₄H₆CaO₄) 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

C317339-M11403-SM52020, rev. 00 20230127
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**


- **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 (C₄H₆CaO₄) dissolved:
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:

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

$V_S$ = 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:

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

$V_S$ = 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 \(\times\) 25-cm; 5-µm packing \(L_1\)
- **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:

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

\(r_U\) = 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 \((C_4H_6CaO_4)\) 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 (C₉H₆CaO₄) dissolved:

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

  - \( r_U \) = 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)
  - \( V \) = 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 (C₉H₆CaO₄) 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

C317339-M11403-SM52020, rev. 00 20230127
From commercially available, National Institute of Standards and Technology (NIST)-traceable standard solution for calcium.