Potassium Citrate Extended-Release Tablets

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In accordance with the Rules and Procedures of the Council of Experts, the Non-Botanical Dietary Supplements Expert Committee has revised the Potassium Citrate Extended-Release Tablets 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.

The Potassium Citrate Extended-Release Tablets Revision Bulletin supersedes the currently official monograph.

Should you have any questions, please contact Natalia Davydova, Senior Scientific Liaison (301-816-8328 or nd@usp.org).

Revision Bulletin
Official: November 1, 2020

Potassium Citrate Extended-Release Tablets

DEFINITION

Potassium Citrate Extended-Release Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of potassium citrate as monohydrate ($C_6H_5K_3O_7 \cdot H_2O$).

IDENTIFICATION

- **A. Identification Tests—General ⟨191⟩, *Chemical Identification Tests, Potassium***
  Sample solution: Powder 5 Tablets, mix with 20 mL of water, and filter.
  Acceptance criteria: The filtrate meets the requirements.
- **B. Identification Tests—General ⟨191⟩, *Chemical Identification Tests, Citrate***
  Sample: A portion of powdered Tablets containing about 50 mg of potassium citrate
  Acceptance criteria: Meet the requirements

ASSAY

- **Procedure**
  Buffer: 3.4 g/L of monobasic potassium phosphate in water. Adjust with phosphoric acid to a pH of 2.2.
  Mobile phase: *Buffer*
  Standard solution: 0.4 mg/mL of USP Citric Acid RS in *Mobile phase*
  Sample stock solution: Weigh and finely powder NLT 20 Tablets. Transfer a portion of the powder, equivalent to 2000 mg of potassium citrate monohydrate, to a 250-mL volumetric flask, and add 150 mL of hot water (60°–70°). Sonicate for 20 min with occasional shaking. Allow to cool to room temperature, dilute with water to volume, and mix.
  Sample solution: Pass a portion of the *Sample stock solution* through a suitable filter of 0.45-µm pore size, discarding the first 5 mL of filtrate. Transfer 4 mL of the filtrate to a 50-mL volumetric flask, dilute with *Mobile phase* to volume, and mix. [Note—Reserve the remaining filtrate for use in the *Content of Potassium* test.]
  Chromatographic system
  (See *Chromatography ⟨621⟩, System Suitability*.)
  Mode: LC
  Detector: UV 210 nm
  Column: 4.6-mm × 25-cm; 5-µm packing L1
  Column temperature: 55°
  Flow rate: 1 mL/min
  Injection volume: 20 µL
  System suitability
  Sample: *Standard solution*
  Suitability requirements
  Relative standard deviation: NMT 2.0%
  Analysis
  Samples: *Standard solution* and *Sample solution*
  Calculate the percentage of the labeled amount of potassium citrate monohydrate ($C_6H_5K_3O_7 \cdot H_2O$) in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

r_U = citric acid peak area from the *Sample solution*

r_S = citric acid peak area from the *Standard solution*

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

C_U = nominal concentration of potassium citrate monohydrate in the *Sample solution* (mg/mL)

M_{r1} = molecular weight of potassium citrate monohydrate, 324.41

M_{r2} = molecular weight of citric acid ($C_6H_8O_7$), 192.13

Acceptance criteria: 90.0%–110.0%

OTHER COMPONENTS

- **Content of Potassium**

Standard stock solution: 19.07 µg/mL of potassium chloride, previously dried at 105° for 2 h, in water. This solution contains 10 µg/mL of potassium.

Standard solutions: Transfer 10.0, 15.0, and 20.0 mL, respectively, to separate 100-mL volumetric flasks of the *Standard stock solution*. To each flask, add 2.0 mL of sodium chloride solution (200 mg/mL) and 1.0 mL of hydrochloric acid, and dilute with water to volume. The *Standard solutions* contain 1.0, 1.5, and 2.0 µg/mL of potassium, respectively.

Sample stock solution: Dilute the clear filtrate, reserved from the *Assay*, with water to obtain a solution containing about 160 µg/mL of potassium citrate monohydrate.

Sample solution: Transfer 3.0 mL of the *Sample stock solution* to a 100-mL volumetric flask.

Instrumental conditions

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

Mode: Atomic absorption spectrophotometry

Analytical wavelength: Potassium emission line at 766.5 nm

Lamp: Potassium hollow-cathode

Flame: Air–acetylene

Blank: Water

Analysis

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

Plot the absorbance of the *Standard solutions* versus the concentration of potassium, in µg/mL, and draw the straight line best fitting the three plotted points. From the graph obtained, determine the concentration of potassium in the *Sample solution* (µg/mL).

Calculate the percentage of potassium (K) in the portion of Tablets taken:

$$\text{Result} = C \times 100/C_U$$

C = concentration of potassium in the *Sample solution* as determined in this test (µg/mL)

C_U = concentration of potassium citrate anhydrous ($C_6H_5K_3O_7$) in the *Sample solution* calculated from the *Assay* value of potassium citrate monohydrate ($C_6H_5K_3O_7 \cdot H_2O$) (µg/mL)

Acceptance criteria: 36.4%–40.2%

PERFORMANCE TESTS

Change to read:

- **Dissolution** ⟨711⟩

Test 1

Medium: Water; 900 mL

Apparatus 2: 50 rpm

Times: 0.5, 1, and 3 h; without *Medium* replacement

[Note—Withdraw the same volume at each time point.]

Standard stock solution and **Standard solutions:** Prepare as directed in the *Content of Potassium* test.

Sample solution: Filter the solution under test and dilute quantitatively with *Medium* to obtain a solution containing about 60 µg of potassium citrate per mL. Transfer 5.0 mL of this solution to a 100-mL volumetric flask, add 2.0 mL of sodium chloride solution (1 in 5) and 1.0 mL of hydrochloric acid. Dilute with water to volume, and mix.

Instrumental conditions

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

Mode: Atomic absorption spectrophotometry

Analytical wavelength: Potassium emission line at 766.5 nm

Lamp: Potassium hollow-cathode

Flame: Air–acetylene

Blank: Water

Analysis

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

Determine the concentration, in µg/mL, of potassium in the *Sample solution* at each time point.

Calculate the percentage of the labeled amount of potassium citrate monohydrate ($C_6H_5K_3O_7 \cdot H_2O$) dissolved at each time point: At 0.5 h:

$$\text{Result}_1 = C_1 \times V \times R \times F \times 100/L$$

At 1 h:

$$\text{Result}_2 = [C_2 \times (V - V_S) + C_1 \times V_S] \times R \times F \times 100/L$$

At 3 h:

$$\text{Result}_3 = \{C_3 \times [V - 2 \times V_S] + (C_1 + C_2) \times V_S\} \times R \times F \times 100/L$$

C = as C_1, C_2, C_3, concentration of potassium in the *Sample solution* at each time point (µg/mL)

V = volume of *Medium*, 900 mL

R = ratio of the molecular weight of potassium citrate monohydrate to 3 times the atomic weight of potassium, 2.765

F = dilution factor of the *Sample solution*

L = label claim (mg/Tablet)

V_S = volume of sample withdrawn at each time point (mL)

Tolerances: The percentages of the labeled amount of potassium citrate monohydrate ($C_6H_5K_3O_7 \cdot H_2O$) dissolved from the Tablets are NMT 45% (Q) in 30 min, NMT 60% (Q') in 1 h, and NLT 80% (Q'') in 3 h. The requirements are met if the quantities dissolved from the Tablets tested conform to *Table 1* instead of the table shown under *Dissolution* ⟨711⟩.

Table 1

Stage	Number Tested	Acceptance Criteria
S_1	6	Each unit is within the range between Q ± 10% and Q' ± 10%, and is NLT Q'' + 5% at the stated times.

Stage	Number Tested	Acceptance Criteria
S_2	6	Average of 12 units (S_1 + S_2) is within the range between Q ± 10% and Q' ± 10% and is NLT Q''; no unit is outside the range between Q ± 15% and Q' ± 15%, and no unit is less than Q'' − 5% at the stated times.
S_3	12	Average of 24 units (S_1 + S_2 + S_3) is within the range between Q ± 10% and Q' ± 10% and is NLT Q''; NMT 1 unit is outside the range between Q ± 15%, NMT 1 unit is outside the range between Q' ± 15%, and NMT 1 unit is less than Q'' − 5% at the stated times.

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

Medium: Water; 900 mL

Apparatus 2: 50 rpm

Times: 0.5, 1, 4, and 6 h. Replace the volume withdrawn with the equal volume of *Medium* preheated to 37 ± 0.5°.

Buffer: 3.4 g/L of monobasic potassium phosphate in water. Adjust with phosphoric acid to a pH of 2.2.

Mobile phase: *Buffer*

Standard solution: Prepare a solution of USP Citric Acid RS in *Medium* as directed in *Table 2*.

Table 2

Tablet Strength (mg, as potassium citrate monohydrate)	Concentration of Citric Acid (mg/mL)
540	0.35
1080	0.70
1620	1.05

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size, discarding the first 5 mL of filtrate.

Chromatographic system

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

Mode: LC

Detector: UV 210 nm

Column: 4.6-mm × 25-cm; 5-µm packing L1

Column temperature: 55°

Flow rate: 1.0 mL/min

Injection volume: 20 µL

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*

Determine the concentration, in mg/mL, of potassium citrate monohydrate ($C_6H_5K_3O_7 \cdot H_2O$) in the sample withdrawn from the vessel at each time point:

$$\text{Result} = (r_U/r_S) \times C_S \times (M_{r1}/M_{r2})$$

r_U = citric acid peak area from the *Sample solution*

r_S = citric acid peak area from the *Standard solution*

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

M_{r1} = molecular weight of potassium citrate monohydrate ($C_6H_5K_3O_7 \cdot H_2O$), 324.41

M_{r2} = molecular weight of citric acid ($C_6H_8O_7$), 192.13

Calculate the percentage of the labeled amount of potassium citrate monohydrate ($C_6H_5K_3O_7 \cdot H_2O$) dissolved at each time point: At 0.5 h:

$$\text{Result}_1 = C_1 \times V \times 100/L$$

At 1 h:

$$\text{Result}_2 = (C_2 \times V + C_1 \times V_S) \times 100/L$$

At 4 h:

$$\text{Result}_3 = [C_3 \times V + (C_1 + C_2) \times V_S] \times 100/L$$

At 6 h:

$$\text{Result}_4 = [C_4 \times V + (C_1 + C_2 + C_3) \times V_S] \times 100/L$$

C = as C_1, C_2, C_3, C_4, concentration of potassium citrate monohydrate in the portion of sample withdrawn at the specified time point (mg/mL)

V = volume of *Medium*, 900 mL

L = label claim (mg/Tablet)

V_S = volume of sample withdrawn at each time point (mL)

Tolerances: The percentages of the labeled amount of potassium citrate monohydrate ($C_6H_5K_3O_7 \cdot H_2O$) dissolved at the times specified in *Table 3* conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.

Table 3

Time (h)	Amount Dissolved (%)
0.5	25–50
1	40–65
4	NLT 70
6	NLT 80

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

Medium: Deaerated water; 900 mL

Apparatus 2: 50 rpm

[Note—Employ sinker if necessary to ensure that the Tablets do not float.]

Times: 0.5, 1, and 5 h; without *Medium* replacement

[Note—Withdraw the same volume at each time point. Pass a portion of the solution through a 0.45-µm membrane filter, discarding the first 2 mL of the filtrate.]

Diluent: Transfer 5 g of sodium chloride to a 100-mL volumetric flask, add 25 mL of water and 25 mL of concentrated hydrochloric acid, shake until dissolved, cool to room temperature, and dilute with water to volume.

Standard stock solution: 19.07 µg/mL of potassium chloride, previously dried at 105° for 2 h, in water. This solution contains 10 µg/mL of potassium.

Standard solutions: Transfer 5.0, 7.0, 10.0, 15.0, and 20.0 mL of *Standard stock solution* to separate 100-mL volumetric flasks. Add 4.0 mL of *Diluent* to each flask, dilute with water to volume, and mix well. The *Standard solutions* contain 0.5, 0.7, 1.0, 1.5, and 2.0 µg/mL of potassium, respectively.

Sample stock solution: Filter the solution under test, and dilute quantitatively with water as stated in *Table 4*.

Table 4

Time (h)	5 mEq Tablet Dilution	10 mEq Tablet Dilution	15 mEq Tablet Dilution
0.5	6.0 mL into 25 mL	6.0 mL into 50 mL	4.0 mL into 50 mL
1	5.0 mL into 25 mL	5.0 mL into 50 mL	3.0 mL into 50 mL
5	7.0 mL into 50 mL	7.0 mL into 100 mL	2.0 mL into 50 mL

Sample solution: Transfer 5.0 mL of respective *Sample stock solution* into 100-mL volumetric flasks. Add 4.0 mL of *Diluent*, dilute with water to volume, and mix well.

Instrumental conditions

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

Mode: Atomic absorption spectrophotometry

Analytical wavelength: Potassium emission line at 766.5 nm

Lamp: Potassium hollow-cathode

Flame: Air–acetylene

Blank: Dilute *Diluent* with water (4:96)

Analysis

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

Determine the concentration, in µg/mL, of potassium in the *Sample solution* at each time point.

Calculate the percentage of the labeled amount of potassium dissolved at each time point: At 0.5 h:

$$\text{Result}_1 = C_1 \times D_1 \times V \times 100/(L \times A)$$

At 1 h:

$$\text{Result}_2 = [C_2 \times D_2 \times (V - V_S) + C_1 \times D_1 \times V_S] \times 100/(L \times A)$$

At 5 h:

$$\text{Result}_3 = \{C_3 \times D_3 \times [V - 2 \times V_S] + (C_1 \times D_1 + C_2 \times D_2) \times V_S\} \times D \times 100/(L \times A)$$

C = as C_1, C_2, C_3, concentration of potassium in the *Sample solution* at each time point

(mg/mL)

D = as D_1, D_2, D_3, dilution factor of the *Sample solution* at each point

V = volume of *Medium*, 900 mL

L = label claim (mEq/Tablet)

A = atomic weight of potassium, 39.1

V_S = volume of sample withdrawn at each time point (mL)

Tolerances: The percentages of the labeled amount of potassium dissolved at the times specified in *Table 5* conform to *Dissolution ⟨711⟩*, *Acceptance Table 2*.

Table 5

Time (h)	Amount Dissolved (%)
0.5	30–50
1	45–65
5	NLT 85

▲**Test 4:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 4*.

Medium: Water; 900 mL

Apparatus 2: 50 rpm.

[NOTE—Use tablet sinkers if necessary.]

Times: 0.5, 1, and 6 h. Replace the volume withdrawn with the equal volume of *Medium* preheated to 37 ± 0.5°.

[NOTE—Withdraw the same volume at each time point. Pass a portion of the withdrawn solution through a 0.45-µm nylon filter, discarding the first 5 mL of filtrate.]

Buffer and **Mobile phase:** Prepare as directed in *Test 2*.

Standard solution: Prepare a solution of USP Citric Acid RS in *Medium* as directed in *Table 6*.

Table 6

Tablet Strength (mg, as potassium citrate monohydrate)	Concentration of Citric Acid (mg/mL)
1080	0.70
1620	1.05

Sample solution: Filtered portion of the solution under test

Chromatographic system and **System suitability:** Proceed as directed in *Test 2*.

Analysis

Samples: *Standard solution* and *Sample solution*

Determine the concentration, in mg/mL, of potassium citrate monohydrate ($C_6H_5K_3O_7 \cdot H_2O$) in the sample withdrawn from the vessel at each time point:

$$\text{Result} = (r_U/r_S) \times C_S \times (M_{r1}/M_{r2})$$

r_U = peak area of citric acid from the *Sample solution*

r_S = peak area of citric acid from the *Standard solution*

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

M_{r1} = molecular weight of potassium citrate monohydrate ($C_6H_5K_3O_7 \cdot H_2O$), 324.41

M_{r2} = molecular weight of citric acid ($C_6H_8O_7$), 192.13

Calculate the percentage of the labeled amount of potassium citrate monohydrate ($C_6H_5K_3O_7 \cdot H_2O$) dissolved at each time point:

At 0.5 h:

$$\text{Result}_1 = C_1 \times V \times (100/L)$$

At 1 h:

$$\text{Result}_2 = (C_2 \times V + C_1 \times V_S) \times (100/L)$$

At 6 h:

$$\text{Result}_3 = [C_3 \times V + (C_1 + C_2) \times V_S] \times 100/L$$

C_i = concentration of potassium citrate monohydrate in the portion of sample withdrawn at the specified time point (mg/mL)

V = volume of *Medium*, 900 mL

L = label claim (mg/Tablet)

V_S = volume of sample withdrawn at each time point (mL)

Tolerances: The percentages of the labeled amount of potassium citrate monohydrate ($C_6H_5K_3O_7 \cdot H_2O$) dissolved at the times specified in *Table 7* conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.

Table 7

Time (h)	Amount Dissolved (%)
0.5	30–50
1	45–65
6	NLT 80

▲ (RB 1-Nov-2020)

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

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in tight containers.
- **Labeling:** The label states the amount of potassium citrate as monohydrate ($C_6H_5K_3O_7 \cdot H_2O$) in mEq and in g/Tablet. The label indicates the *Dissolution* test with which the product complies.
- **USP Reference Standards** ⟨11⟩

  USP Citric Acid RS

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