Potassium Citrate Extended-Release Tablets

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<thead>
<tr>
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<tr>
<td>Expert Committee</td>
<td>Non-Botanical Dietary Supplements</td>
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</tbody>
</table>

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 Davydo, Senior Scientific Liaison (301-816-8328 or nd@usp.org).
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 (C₆H₅K₃O₇·H₂O).

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 (C₆H₅K₃O₇·H₂O) in the portion of Tablets taken:

  \[ \text{Result} = \left( \frac{r_U}{r_S} \right) \times \left( \frac{C_S}{C_U} \right) \times \left( \frac{M_{r_1}}{M_{r_2}} \right) \times 100 \]

  \[ r_U = \text{citric acid peak area from the Sample solution} \]
**PERFORMANCE TESTS**

**Change to read:**

Dissolution (711)

Test 1

1. **Apparatus**: Water bath, 900 mL, times: 0, 1, 3 h; without Medium replacement (Note: Withdraw the same volume at each time point.)
2. **Medium**: 2.5% w/v of sodium chloride solution, 100 mL

**Acceptance criteria**: 36.4%–40.2%

**Calculation**

\[ C = \frac{C_u}{C_b} \times 100\% \]

- \( C \) = concentration of potassium in the Sample solution as determined in this test (μg/mL)
- \( C_u \) = concentration of potassium citrate anhydrous (C₆H₅K₂O₇) in the Sample solution calculated from the Assay of potassium citrate monohydrate (C₆H₅K₂O₇·H₂O) (μg/mL)
- \( C_b \) = concentration of potassium in the Blank solution (μg/mL)

- Calculate the percentage of potassium in the Sample solution (μg/mL).
- Plot the straight line best fitting the three plotted points. From the graph obtained, determine the concentration of potassium in the Sample solution.

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

**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 mL of the Sample stock solution to 100 mL volumetric flask.

**Other Components**

**USP Citric Acid RS** in the Standard solution (mg/mL)

- **M₃**: Molecular weight of potassium citrate monohydrate, 324.13
- **C₃**: Nominal concentration of potassium citrate monohydrate in the sample solution (mg/mL)

**Standard stock solutions**: Transfer 0.10, 15.0, and 20.0 mL, respectively, to separate 100 mL volumetric flasks. Add 10 mL of hydrochloric acid, and dilute with water to volume. The standard solutions contain 1.0, 15, and 20 μg/mL of potassium, respectively.

**Lamp**: Potassium hollow cathode

**Flame**: Air-acetylene

**Analytical wavelength**: 766 nm

**Model**: Atomic absorption spectrophotometry

**Instrumental conditions**

- **Sample**
  - **Sample solution**: Transfer 3 mL of the Sample stock solution to 100 mL volumetric flask.
  - **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.
**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 (C₆H₅K₃O₇·H₂O) 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:

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

\[ C = \text{as } C_1, C_2, C_3, \text{ concentration of potassium in the } \text{Sample solution} \text{ at each time point (µg/mL)} \]

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

\[ R = \text{ratio of the molecular weight of potassium citrate monohydrate to 3 times the atomic weight of potassium, 2.765} \]

\[ F = \text{dilution factor of the } \text{Sample solution} \]

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

\[ V_S = \text{volume of sample withdrawn at each time point (mL)} \]

**Tolerances**: The percentages of the labeled amount of potassium citrate monohydrate (C₆H₅K₃O₇·H₂O) 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**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Number Tested</th>
<th>Acceptance Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>S₁</td>
<td>6</td>
<td>Each unit is within the range between Q ± 10% and Q’ ± 10%, and is NLT Q” + 5% at the stated times.</td>
</tr>
<tr>
<td>Stage</td>
<td>Number Tested</td>
<td>Acceptance Criteria</td>
</tr>
<tr>
<td>-------</td>
<td>--------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>$S_2$</td>
<td>6</td>
<td>Average of 12 units ($S_1 + S_2$) is within the range between $Q \pm 10%$ and $Q' \pm 10%$ and is NLT $Q''$; no unit is outside the range between $Q \pm 15%$ and $Q' \pm 15%$, and no unit is less than $Q'' - 5%$ at the stated times.</td>
</tr>
<tr>
<td>$S_3$</td>
<td>12</td>
<td>Average of 24 units ($S_1 + S_2 + S_3$) is within the range between $Q \pm 10%$ and $Q' \pm 10%$ and is NLT $Q''$; NMT 1 unit is outside the range between $Q \pm 15%$, NMT 1 unit is outside the range between $Q' \pm 15%$, and NMT 1 unit is less than $Q'' - 5%$ at the stated times.</td>
</tr>
</tbody>
</table>

**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°C.

**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

<table>
<thead>
<tr>
<th>Tablet Strength (mg, as potassium citrate monohydrate)</th>
<th>Concentration of Citric Acid (mg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>540</td>
<td>0.35</td>
</tr>
<tr>
<td>1080</td>
<td>0.70</td>
</tr>
<tr>
<td>1620</td>
<td>1.05</td>
</tr>
</tbody>
</table>

**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°C

**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 (C₆H₅K₃O₇ ⋅ H₂O) in the sample withdrawn from the vessel at each time point:

\[
\text{Result} = \left(\frac{r_U}{r_S}\right) \times C_S \times \left(\frac{M_{r1}}{M_{r2}}\right)
\]

- \(r_U\) = 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 (C₆H₅K₃O₇ ⋅ H₂O), 324.41
- \(M_{r2}\) = molecular weight of citric acid (C₆H₈O₇), 192.13

Calculate the percentage of the labeled amount of potassium citrate monohydrate (C₆H₅K₃O₇ ⋅ H₂O) 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 (C₆H₅K₃O₇ ⋅ H₂O) dissolved at the times specified in Table 3 conform to Dissolution (711), Acceptance Table 2.

**Table 3**

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>25–50</td>
</tr>
<tr>
<td>1</td>
<td>40–65</td>
</tr>
<tr>
<td>4</td>
<td>NLT 70</td>
</tr>
<tr>
<td>6</td>
<td>NLT 80</td>
</tr>
</tbody>
</table>

**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

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>5 mEq Tablet Dilution</th>
<th>10 mEq Tablet Dilution</th>
<th>15 mEq Tablet Dilution</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>6.0 mL into 25 mL</td>
<td>6.0 mL into 50 mL</td>
<td>4.0 mL into 50 mL</td>
</tr>
<tr>
<td>1</td>
<td>5.0 mL into 25 mL</td>
<td>5.0 mL into 50 mL</td>
<td>3.0 mL into 50 mL</td>
</tr>
<tr>
<td>5</td>
<td>7.0 mL into 50 mL</td>
<td>7.0 mL into 100 mL</td>
<td>2.0 mL into 50 mL</td>
</tr>
</tbody>
</table>

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:

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

\( C \) is the concentration of potassium in the Sample solution at each time point.
(mg/mL)

\[D = \text{as } D_1, D_2, D_3, \text{ dilution factor of the Sample solution at each point}\]

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

\[L = \text{label claim (mEq/Tablet)}\]

\[A = \text{atomic weight of potassium, 39.1}\]

\[V_s = \text{volume of sample withdrawn at each time point (mL)}\]

**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

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>30–50</td>
</tr>
<tr>
<td>1</td>
<td>45–65</td>
</tr>
<tr>
<td>5</td>
<td>NLT 85</td>
</tr>
</tbody>
</table>

**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°C.

> [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

<table>
<thead>
<tr>
<th>Tablet Strength (mg, as potassium citrate monohydrate)</th>
<th>Concentration of Citric Acid (mg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1080</td>
<td>0.70</td>
</tr>
<tr>
<td>1620</td>
<td>1.05</td>
</tr>
</tbody>
</table>

**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:

\[
\text{Result} = \left(\frac{r_U}{r_S}\right) \times C_S \times \left(\frac{M_{r1}}{M_{r2}}\right)
\]
\[ r_U \] = 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:

\[
\text{Result}_1 = C_I \times V \times (100/L)
\]

At 1 h:

\[
\text{Result}_2 = (C_2 \times V + C_I \times V_S) \times (100/L)
\]

At 6 h:

\[
\text{Result}_3 = [C_3 \times V + (C_4 + C_2) \times V_S] \times 100/L
\]

\[ C_I \] = 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

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>30–50</td>
</tr>
<tr>
<td>1</td>
<td>45–65</td>
</tr>
<tr>
<td>6</td>
<td>NLT 80</td>
</tr>
</tbody>
</table>

**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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