Potassium Chloride Extended-Release Tablets

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Posting Date: 20–Aug–2019  
Official Date: 21–Aug–2019  
Expert Committee: Chemical Medicines Monographs 5  
Reason for Revision: Compliance

In accordance with the Rules and Procedures of the 2015–2020 Council of Experts, the Chemical Medicines Monographs 5 Expert Committee has revised the Potassium Chloride Extended-Release Tablets monograph. The purpose for the revision is to add Dissolution Test 3 to accommodate FDA-approved drug products with different dissolution conditions and tolerances than the existing dissolution tests.

- **Dissolution Test 3** was validated using a Dionex IonPac CS12A brand of L106 column from ThermoFisher. The typical retention time for potassium is about 5 min.

*USP Reference Standards* information has been incorporated to support the inclusion of **Dissolution Test 3**, which includes USP Potassium Chloride RS.

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

Should you have any questions, please contact Ren-Hwa Yeh, Senior Scientific Liaison (301-998-6818 or rhy@usp.org).
Potassium Chloride Extended-Release Tablets

DEFINITION
Potassium Chloride Extended-Release Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of potassium chloride (KCl).

IDENTIFICATION
A. IDENTIFICATION TESTS—GENERAL (191), Chemical Identification Tests, Potassium

Sample solution: A portion of the filtrate, obtained as directed for the designated Sample stock solution in the Assay

Acceptance criteria: Meet the requirements

B. IDENTIFICATION TESTS—GENERAL (191), Chemical Identification Tests, Chloride

Sample solution: A portion of the filtrate, obtained as directed for the designated Sample stock solution in the Assay

Acceptance criteria: Meet the requirements

ASSAY

PROCEDURE
[Note—If necessary, first score nonsugar-coated Tablets. Retain a portion of the filtrate of either Sample stock solution 1 or Sample stock solution 2 for use in Identification A and B.]

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: To separate 100-mL volumetric flasks transfer 10.0, 15.0, and 20.0 mL, respectively, of Standard stock solution. To each flask add 2.0 mL of sodium chloride solution (1 in 5) 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 preparation 1

Sample stock solution 1: Nominally 0.06 mg/mL of potassium chloride prepared as follows. Place NLT 20 Tablets in a suitable container with 400 mL of water, heat to boiling, and boil for 20 min. Allow to cool, transfer the solution to a 1000-mL volumetric flask, and dilute with water to volume. Filter and discard the first 20 mL of the filtrate. Transfer a measured volume of the subsequent filtrate, equivalent to 60 mg of potassium chloride, to a 1000-mL volumetric flask, and dilute with water to volume.

Sample stock solution 2: Nominally 3 µg/mL of potassium chloride prepared as follows. Place NLT 20 Tablets, prepared as follows. Transfer an appropriate amount of the powder, equivalent to about 5–6 Tablets, to a suitable volumetric flask, add 10% of the final flask volume of acetone, and sonicate for 45 min with intermittent shaking. Add 80% of the final flask volume of water and sonicate for 45 min with intermittent shaking. Cool to room temperature and dilute with water to volume. Centrifuge a portion of the solution at 5000 rpm for 10 min. Transfer an appropriate amount of the supernatant to a 100-mL volumetric flask and dilute with water to volume to obtain a solution with a concentration of 0.15 mg/mL.]

Sample solution 2: Nominally 3 µg/mL of potassium chloride prepared as follows. Transfer an appropriate amount of Sample stock solution 2 to a 100-mL volumetric flask, add 2.0 mL of sodium chloride solution (1 in 5) and 1.0 mL of hydrochloric acid, and dilute with water to volume.

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 1 or Sample solution 2, and Blank

Plot the absorbances 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, determine the concentration of potassium in the Sample solution (µg/mL).

Calculate the percentage of the labeled amount of potassium chloride (KCl) in each Tablet taken:

Result = \( \frac{C}{C_0} \times \frac{M_r}{A_r} \times 100 \)

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

\( C_0 \) = nominal concentration of potassium chloride in the Sample solution (µg/mL)

\( M_r \) = molecular weight of potassium chloride, 74.55

\( A_r \) = atomic weight of potassium, 39.10

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

Dissolution (711)

Test 1

Medium: Water; 900 mL

Apparatus 2: 50 rpm

Time: 2 h

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: To separate 100-mL volumetric flasks transfer 10.0, 15.0, and 20.0 mL, respectively, of Standard stock solution. To each flask add 2.0 mL of sodium chloride solution (1 in 5) and 1.0 mL of hydrochloric acid, and dilute with water to volume. The Standard solutions contain, respectively, 1.0, 1.5, and 2.0 µg/mL of potassium.
Sample stock solution: Filter the solution under test, and dilute with Medium to obtain a solution containing nominally 60 µg/mL of potassium chloride.

Sample solution: Transfer 5.0 mL of the Sample stock 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, and dilute with water to volume.

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 absorbances 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, determine the concentration of potassium in the Sample solution (µg/mL).

Calculate the percentage of the labeled amount of potassium chloride (KCl) dissolved:

\[ \text{Result} = \left( \frac{C \times D \times (V/L)}{A_1} \right) \times (M_r/A_r) \times 100 \]

where:
- \( C \) = concentration of potassium in the Sample solution as determined in this test (µg/mL)
- \( D \) = dilution factor of the Sample solution
- \( V \) = volume of Medium, 900 mL
- \( L \) = labeled amount of potassium chloride (µg/Tablet)
- \( M_r \) = molecular weight of potassium chloride, 74.55
- \( A_1 \) = atomic weight of potassium, 39.10
- \( A_r \) = concentration of potassium in the Sample solution
- \( S \) = absorbance of potassium in the Standard solution

Tolerances: NMT 35% (Q) of the labeled amount of potassium chloride (KCl) is dissolved in 2 h. The requirements are met if the quantities dissolved from the Tablets tested conform to Table 1 instead of the table shown in Dissolution (711).

<table>
<thead>
<tr>
<th>Stage</th>
<th>Number Tested</th>
<th>Acceptance Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6</td>
<td>Each unit is within the range Q ± 30%.</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>Average of 12 units (S, + S,) is within the range between Q – 30% and Q + 35%, and no unit is outside the range Q ± 40%.</td>
</tr>
<tr>
<td>3</td>
<td>12</td>
<td>Average of 24 units (S, + S,) is within the range between Q – 30% and Q + 35%, and NMT 2 units are outside the range Q ± 40%.</td>
</tr>
</tbody>
</table>

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

Standard stock solution and Standard solutions:
Prepare as directed in Test 1.

Medium: Water; 900 mL
Apparatus: 50 rpm
Times: 1, 2, 4, and 8 h

Sample solution: Transfer 4.0 mL of the solution under test into either a 50-mL volumetric flask (for 750-mg Tablet) or a 100-mL volumetric flask (for 1500-mg Tablet), dilute with water to volume, and filter.

Sample solution: Transfer 4.0 mL of the Sample stock 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, and dilute with water to volume.

Blank 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, and dilute with water to volume.

Instrumental conditions: Proceed as directed in Test 1, except do not use the Blank.

System suitability

Samples: Standard solutions
Suitability requirements

Linearity: Correlation coefficient NLT 0.99
Relative standard deviation: NMT 5.0% from 5 replicate analyses of the 1.5-µg/mL Standard solution

Analysis

Samples: 1.5-µg/mL Standard solution, Sample solution, and Blank solution

Calculate the percentage of the labeled amount of potassium chloride (KCl) dissolved:

\[ \text{Result} = \left( \frac{A_r}{A_1} \right) \times C \times D \times (V/L) \times (M_r/A_r) \times 100 \]

\( A_r \) = absorbance of potassium in the Sample solution
\( A_1 \) = absorbance of potassium in the Standard solution
\( C \) = concentration of potassium in the Standard solution (µg/mL)
\( D \) = dilution factor of the Sample solution
\( V \) = volume of Medium, 900 mL
\( L \) = labeled amount of potassium chloride (µg/Tablet)
\( M_r \) = molecular weight of potassium chloride, 74.55
\( A_r \) = atomic weight of potassium, 39.10

Tolerances: See Table 2.

<table>
<thead>
<tr>
<th>Time Point (h)</th>
<th>Time (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>10–30</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>30–50</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>60–80</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
<td>NLT 80</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of potassium chloride (KCl), dissolved at the times specified, conform to Dissolution (711), Acceptance Table 2.

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

Medium: Water; 900 mL
Apparatus: 50 rpm
Times: 0.5, 2, 4, and 10 h
Mobile phase: 20 mM methanesulfonic acid in water

Standard solution: \((L/900)\) mg/mL of USP Potassium Chloride RS in water, where \( L \) is the label claim of potassium chloride in mg/Tablet, prepared as follows. Transfer an appropriate quantity of USP Potassium Chloride RS to a suitable volumetric flask. Add 50% of the flask volume of water and sonicate to dissolve. Dilute with water to volume.

Sample solution: Pass a portion of the solution under test through a filter with a suitable pore size and use the filtrate.
Chromatographic system
(See Chromatography (621), System Suitability.)
Mode: LC
Detector: Conductivity with suppression
Column: 4.0-mm × 25-cm; 8.5-μm packing L1061
Column temperature: 30°
Flow rate: 1.0 mL/min
Injection volume: 5 μL
Run time: NLT 2 times the retention time of potassium

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 potassium chloride (KCl) dissolved at each time point (t):

\[
\text{Result, } \% = \left( \frac{r_i}{r_0} \times C_i \times V \times \left( \frac{1}{L} \right) \times 100 \right)
\]

where:
- \(r_0\) = peak response of potassium from the Sample solution
- \(r_i\) = peak response of potassium from the Standard solution
- \(C_i\) = concentration of USP Potassium Chloride RS in the Standard solution (mg/mL)
- \(V\) = volume of Medium, 900 mL
- \(L\) = label claim of potassium chloride (mg/Tablet)

Tolerances: See Table 3.

<table>
<thead>
<tr>
<th>Time Point (h)</th>
<th>Time (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.5</td>
<td>15–35</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>40–60</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>60–80</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>NLT 80</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of potassium chloride (KCl), dissolved at the times specified, conform to Dissolution (711), Acceptance Table 2.

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

Standard stock solution and Instrumental conditions:
Proceed as directed in Test 1, except Blank.
Medium: Water, 900 mL, degassed
Apparatus 2: 50 rpm
Times: 2, 4, and 8 h
Sodium chloride solution: 0.2 g/mL of sodium chloride in water

1 Weak cation-exchange resin consisting of ethylvinylenbenzene, 55% cross-linked with divinylenbenzene copolymer, 5–8 μm diameter; macroporous particles having an average pore size of 100 Å units; Substrate is surface grafted with carboxylic acid and phosphonic acid functional groups. Capacity NLT 2800 μeq/column (4-mm × 25-cm).

Hydrochloric acid solution: Dilute 100 mL of hydrochloric acid with 300 mL of water.

Standard solutions: To separate 100-mL volumetric flasks transfer 10.0, 15.0, and 20.0 mL, respectively, of Standard stock solution. To each flask add 2.0 mL of Sodium chloride solution and 4.0 mL of Hydrochloric acid solution, 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: Pass a portion of the solution under test through a filter with a suitable pore size and use the filtrate.

Sample solution: Transfer 1.0 mL of the Sample stock solution to a suitable volumetric flask and dilute with water if necessary. To the final dilution, add 2.0% flask volume of Sodium chloride solution and 4.0% flask volume of Hydrochloric acid solution, and dilute with water to volume.

Blank: To a suitable volumetric flask, add 2.0% flask volume of Sodium chloride solution and 4.0% flask volume of Hydrochloric acid solution, and dilute with water to volume.

System suitability
Samples: Standard solutions
Suitability requirements
Linearity: Correlation coefficient NLT 0.999
Relative standard deviation: NMT 1.5% from the absorbance responses of 5 replicate analyses of each Standard solution
Analysis: Proceed as directed in Test 1.
Tolerances: See Table 4.

<table>
<thead>
<tr>
<th>Time Point (h)</th>
<th>Time (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>22–42</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>44–64</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>NLT 80</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of potassium chloride (KCl), dissolved at the times specified, conform to Dissolution (711), Acceptance Table 2.

• **Uniformity of Dosage Units (905):** Meet the requirements

**ADDITIONAL REQUIREMENTS**

• **Packaging and Storage:** Preserve in tight containers, and store at a temperature not exceeding 30°.

• **Labeling:** The label states with which Sample preparation in the Assay the product complies only if Sample preparation 1 is not used. When more than one Dissolution test is given, the labeling states the Dissolution test used only if Test 1 is not used.

Add the following:

▲ **USP Reference Standards (11)**

USP Potassium Chloride RS
▲ (08 21-Aug-2019)