Potassium Chloride Extended-Release Tablets

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Posting Date: 31–Jul–2019
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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 4* to accommodate FDA-approved drug products with different dissolution conditions and tolerances than the existing dissolution tests.

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

The addition of *Dissolution Test 3* to the Potassium Chloride Extended-Release Tablets monograph is currently being proposed under the Pending Monograph process.

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 solution 1: Nominally 3 µg/mL of potassium chloride prepared as follows. Transfer 5.0 mL of Sample stock solution 1 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.

Sample preparation 2 (for formulations containing crystals coated with hydrophobic polymers)

Sample stock solution 2: Nominally 0.06 mg/mL of potassium chloride prepared as follows. Place NLT 20 Tablets in a 2000-mL volumetric flask. Add 1200 mL of a mixture of acetonitrile and water (1:1), and shake by mechanical means, or stir using a magnetic bar for 90 min. Dilute with the mixture of acetonitrile and water (1:1) to volume. Allow to stand for 90 min. Pass through a filter of 0.2-µm pore size. Transfer a measured volume of the filtrate, and quantitatively dilute with water to obtain a solution with a concentration of 0.06 mg/mL. [Note—Alternatively, Sample stock solution 2 can be prepared by the following procedure. Nominally 0.15 mg/mL of potassium chloride from NLT 20 finely powdered 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 = \( \frac{C}{C_0} \times \frac{M_r}{A} \times 100 \)

\( C \) = 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 concentration of potassium chloride, 74.55

\( A \) = 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 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:

$$\text{Result} = \frac{C \times D \times (V/L)}{(M/A)} \times 100$$

**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 1**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Number Tested</th>
<th>Acceptance Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>$S_1$</td>
<td>6</td>
<td>Each unit is within the range Q ± 30%.</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 – 30% and Q + 33%, and no unit is outside the range Q ± 40%.</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 – 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 2:** 50 rpm

**Times:** 1, 2, 4, and 8 h

**Sample stock 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:

$$\text{Result} = \frac{(A_i/A_r) \times C_r \times D \times (V/L) \times (M/A)}{100}$$

$A_i$ = absorbance of potassium in the Sample solution

$A_r$ = absorbance of potassium in the Standard solution

$C_r$ = 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 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.

**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 85</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.

*A 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 do not use the 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

**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 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>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 Z* ⁎ (88 1-Aug-2019)

- **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.