Potassium Chloride Extended-Release Tablets

<table>
<thead>
<tr>
<th>Type of Posting</th>
<th>Notice of Intent to Revise</th>
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<tr>
<td>Posting Date</td>
<td>To Be Determined, Revision Bulletin</td>
</tr>
<tr>
<td>Expert Committee</td>
<td>Chemical Medicines Monographs 5</td>
</tr>
</tbody>
</table>

In accordance with section 7.04 (c) of the 2015–2020 Rules and Procedures of the Council of Experts and the Pending Monograph Guideline, this is to provide notice that the Chemical Medicines Monographs 5 Expert Committee intends to revise the Potassium Chloride Extended-Release Tablets monograph.

Based on the supporting data received from a manufacturer awaiting FDA approval, the Expert Committee proposes to add Dissolution Test 7 to the monograph. The Notice of Intent to Revise regarding Dissolution Test 6 is previously posted.

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 Ren-Hwa Yeh, Senior Scientific Liaison to the Chemical Medicines Monographs 5 Expert Committee (301-998-6818 or rhy@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.
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 the solution under test, and add 80% of the final flask volume of acetone, and sonicate for 45 min with intermittent shaking. Add 20% 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 stock 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 = \[(C/C_0) \times (M/A) \times 100\]

\[C\] = 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)

\[M\] = molecular weight 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.

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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 Spectrophotometry (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:

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

\( C \) = 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)
\( M_i \) = molecular weight of potassium chloride, 74.55
\( A_r \) = atomic weight of potassium, 39.10

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>4</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>1</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 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:

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

\( A_1 \) = absorbance of potassium in the Sample solution
\( A_r \) = absorbance of potassium in the Standard solution
\( C_s \) = concentration of potassium in the Sample 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></td>
<td></td>
<td>750 mg/Tablet</td>
</tr>
<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>
<tr>
<td></td>
<td></td>
<td>1500 mg/Tablet</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>5–25</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>25–45</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>55–75</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.

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

Medium: Water; 900 mL
Apparatus 2: 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

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Potassium 3

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 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>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 5: If the product complies with this procedure, the labeling indicates that it meets USP Dissolution Test 5.

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

Dilute glacial acetic acid solution: Dilute 25 mL of glacial acetic acid with 75 mL of water.

Saturated potassium sulfate solution: Dissolve sufficient quantities of potassium sulfate in a suitable volume of water until undissolved particles appear in the solution.

0.01 N silver nitrate solution: Transfer 10 mL of 0.1 N silver nitrate VS to a 100-mL volumetric flask and dilute with water to volume.

Standard solution: Transfer 0.01 N/mg/mL of potassium chloride, previously dried at 105°C for 2 h, in water, where L is the label claim in mg/Tablet. Pass the solution through a suitable filter.

Sample solution: Withdraw 10 mL of the solution under test at the specified time points and pass a suitable portion of the solution through a suitable filter. Replace each of the volumes withdrawn with an equal volume of the Medium.

Blank: Medium
Titrimetric system
(See Titrimetry (541).)
Mode: Direct titration
Titrant: 0.01 N silver nitrate solution
Endpoint detection: Potentiometric
System suitability
Sample: Standard solution
Transfer 5 mL of Standard solution into a titration vessel and add 25 mL of water, 5 mL of Dilute glacial acetic acid solution, and 0.1 mL of Saturated potassium sulfate solution to the vessel. Titrate with Titrant and determine the endpoint potentiometrically.

1 Weak cation-exchange resin consisting of ethylvinylbenzene, 55% cross-linked with divinylbenzene 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 μg/column (4-mm × 25-cm).
4 Potassium

Suitability requirements
Relative standard deviation: NMT 2.0% from 5 replicate analyses

Analysis
Samples: Sample solution and Blank
Transfer 5 mL of each solution into separate titration vessels and add 25 mL of water, 5 mL of Dilute glacial acetic acid solution, and 0.1 mL of Saturated potassium sulfate solution to each vessel. Titrate with Titrant and determine the endpoint potentiometrically.

Calculate the concentration (C) of potassium chloride (KCl) in the sample withdrawn from the vessel at each time point (i):

\[
\text{Result}_i = (V_U - V_B) \times N \times F \times (1/V_S)
\]

\[V_U = \text{volume of Titrant used to titrate the Sample solution}\]
\[V_B = \text{volume of Titrant used to titrate the Blank}\]
\[N = \text{actual normality of Titrant (mEq/mL)}\]
\[F = \text{equivalency factor, 75.53 mg/mEq}\]
\[V_S = \text{volume of Sample solution used in the test, 5 mL}\]

Calculate the percentage of the labeled amount of potassium chloride (KCl) dissolved at each time point (i):

\[
\text{Result}_1 = C_i \times V \times (1/L) \times 100
\]
\[
\text{Result}_2 = ((C_i \times V) + (C_i \times V_W)) \times (1/L) \times 100
\]
\[
\text{Result}_3 = ((C_i \times V) + (C_i \times V_W)) \times (1/L) \times (M_i/A_i) \times 100
\]

\[C_i = \text{concentration of potassium chloride in the sample withdrawn at the specified time point}\]
\[V = \text{volume of Medium, 900 mL}\]
\[L = \text{labeled amount of potassium chloride (mg/Tablet)}\]
\[V_W = \text{volume of Sample solution withdrawn from vessel, 10 mL}\]

Tolerances: See Table 5.

<table>
<thead>
<tr>
<th>Time Point (i)</th>
<th>Time (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>22–42</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>38–58</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.

Test 7: If the product complies with this procedure, the labeling indicates that it meets USP Dissolution Test 7.


Medium: Water; 900 mL, degassed
Times: 1, 3, and 8 h

Sample stock solution: At each specified time point, withdraw 15 mL of the solution under test and pass a portion of the solution through a filter with a suitable pore size, discard the first 2 mL, and use the filtrate. Further dilute the filtrate with water as appropriate, ensuring the concentration of Sample solution is within the linearity range of the Standard solutions. [Note—Do not replace the Medium at the time of sampling.]

System suitability
Samples: Standard solutions
Suitability requirement
Linearity: Correlation coefficient NLT 0.995
Recovery: 90%–110%, back calculated from the 1.5 µg/mL Standard solution

Analysis: Proceed as directed in Test 1.
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 at each time point (i):

\[
\text{Result}_1 = C_i \times V \times (1/L) \times (M_i/A_i) \times 100
\]
\[
\text{Result}_2 = ((C_i \times V) + (C_i \times V_W)) \times (1/L) \times (M_i/A_i) \times 100
\]
\[
\text{Result}_3 = ((C_i \times V) + (C_i \times V_W)) \times (1/L) \times (M_i/A_i) \times 100
\]

\[C_i = \text{concentration of potassium in the Sample solution at the specified time point (µg/mL)}\]
\[D_i = \text{dilution factor of the Sample solution at the specified time point}\]
\[V = \text{volume of Medium, 900 mL}\]
\[L = \text{labeled amount of potassium chloride (µg/Tablet)}\]
\[M_i = \text{molecular weight of potassium chloride, 74.55}\]
\[A_i = \text{atomic weight of potassium, 39.10}\]
\[V_W = \text{volume of Sample solution withdrawn at each time point, 15 mL}\]

Tolerances: See Table 6.

<table>
<thead>
<tr>
<th>Time Point (i)</th>
<th>Time (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>NLT 22</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>37–57</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. Additional Requirements

+ 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°C
+ Labeling: The label states the proper conditions of 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.
+ USP Reference Standards (11): USP Potassium Chloride RS