Potassium Chloride Extended-Release Tablets

Type of Posting	Notice of Intent to Revise
Posting Date	27–Sep–2019
Targeted Official Date	To Be Determined, Revision Bulletin
Expert Committee	Chemical Medicines Monographs 5

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 *Test 6* in the *Dissolution* section of the monograph.

- *Dissolution Test 6* was validated using the Dionex IonPac CS12A brand of L106 column from Thermo Fisher. The typical retention time for potassium is about 7 min.

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 Pavani Jagu, Associate Scientific Liaison (+91 40 44488968 or Pavani.jagu@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 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:

$$\text{Result} = (C/C_U) \times (M_r/A_r) \times 100$$

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

C_U = 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:

$$\text{Result} = [C \times D \times (V/L)] \times (M_r/A_r) \times 100$$

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_r = 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

Stage	Number Tested	Acceptance Criteria
S_1	6	Each unit is within the range $Q \pm 30\%$.
S_2	6	Average of 12 units ($S_1 + S_2$) is within the range between $Q - 30\%$ and $Q + 35\%$, and no unit is outside the range $Q \pm 40\%$.
S_3	12	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 $Q \pm 40\%$.

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:

$$\text{Result}_i = [(A_U/A_S) \times C_S \times D \times (V/L)] \times (M_r/A_r) \times 100$$

A_U = absorbance of potassium in the *Sample solution*
A_S = absorbance of potassium in the *Standard solution*
C_S = 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

Time Point (i)	Time (h)	Amount Dissolved (%)	
		750 mg/Tablet	1500 mg/Tablet
1	1	10–30	5–25
2	2	30–50	25–45
3	4	60–80	55–75
4	8	NLT 80	NLT 85

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
Column: 4.0-mm × 25-cm; 8.5-µm packing L106[1]
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 (*i*):

$$\text{Result}_i = (r_U/r_S) \times C_S \times V \times (1/L) \times 100$$

r_U = peak response of potassium from the *Sample solution*
r_S = peak response of potassium from the *Standard solution*
C_S = 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 3

Time Point (*i*)	Time (h)	Amount Dissolved (%)
1	0.5	15–35
2	2	40–60
3	4	60–80
4	10	NLT 80

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
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 4

Time Point (*i*)	Time (h)	Amount Dissolved (%)
1	2	22–42
2	4	44–64
3	8	NLT 80

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: (*L*/900) mg/mL of potassium chloride, previously dried at 105° 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 volume 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*

[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 µEq/column (4-mm × 25-cm).

acid solution, and 0.1 mL of *Saturated potassium sulfate solution* to the vessel. Titrate with *Titrant* and determine the endpoint potentiometrically.

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_i) 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 = volume of *Titrant* used to titrate the *Sample solution*
V_B = volume of *Titrant* used to titrate the *Blank*
N = actual normality of *Titrant* (mEq/mL)
F = equivalency factor, 74.55 mg/mEq
V_S = 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*):

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$
$$\text{Result}_2 = [(C_2 \times V) + (C_1 \times V_W)] \times (1/L) \times 100$$
$$\text{Result}_3 = [(C_3 \times V) + (C_2 + C_1) \times V_W] \times (1/L) \times 100$$

C_i = concentration of potassium chloride in the portion of sample withdrawn at the specific time point
V = volume of *Medium*, 900 mL
L = labeled amount of potassium chloride (mg/Tablet)
V_W = volume of *Sample solution* withdrawn from vessel, 10 mL

Tolerances: See *Table 5*.

Table 5

Time Point (*i*)	Time (h)	Amount Dissolved (%)
1	1	22–42
2	2	38–58
3	8	NLT 80

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

▲**Test 6:** If the product complies with this procedure, the labeling indicates that it meets USP *Dissolution Test 6*.

Use water with a resistivity of NLT 18 megohm-cm to prepare the solutions.

Medium: Water; 900 mL

Apparatus 2: 50 rpm

Times: 1, 2, and 8 h

0.1 M sulfuric acid solution: Transfer 10 mL of 1 M sulfuric acid TS into a 100-mL volumetric flask and dilute with water to volume.

Mobile phase: 0.01 M sulfuric acid in water, from *0.1 M sulfuric acid solution*

Standard solution: 0.83 mg/mL of USP Potassium Chloride RS in water

Sample solution: Pass a portion of the solution under test through a filter with a suitable pore size and use the filtrate. Discard the first 2 mL of the filtrate.

Blank solution: *Medium*

Chromatographic system

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

Mode: LC

Detector: Conductivity with suppression

Columns

Guard: 4.0-mm × 5-cm; 8.5-µm packing L106[1]

Analytical: 4.0-mm × 25-cm; 8.5-µm packing L106[1]

Temperatures

Column: 30°

Cell: 35°

Flow rate: 1.0 mL/min

Injection volume: 10 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 concentration (C_i) of potassium chloride (KCl) in the sample withdrawn from the vessel at each time point (*i*):

$$C_i = (r_U/r_S) \times C_S$$

r_U = peak response of potassium from the *Sample solution*
r_S = peak response of potassium from the *Standard solution*
C_S = concentration of USP Potassium Chloride RS in the *Standard solution* (mg/mL)

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

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$
$$\text{Result}_2 = \{[C_2 \times (V - V_S)] + (C_1 \times V_S)\} \times (1/L) \times 100$$
$$\text{Result}_3 = \{C_3 \times [(V - (2 \times V_S)] + [(C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$

C_i = concentration of potassium chloride in the portion of the 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 solution* withdrawn at each time point (mL)

Tolerances: See *Table 6*.

Table 6

Time Point (*i*)	Time (h)	Amount Dissolved (%)
1	1	23–43
2	2	40–60
3	8	NLT 80

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

- **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.
- **USP REFERENCE STANDARDS** ⟨11⟩
  USP Potassium Chloride RS