Potassium Chloride Extended-Release Tablets

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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 6* to accommodate FDA-approved drug products with different dissolution conditions and/or tolerances than the existing dissolution test(s).

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

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

Should you have any questions, please contact Pavani Jagu, Associate Scientific Liaison (+91 40 44488968 or pavani.jagu@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:

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

  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 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 µEq/column (4-mm × 25-cm).

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*.▲ (RB 24-Mar-2020)

- **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