Potassium Chloride Extended-Release Tablets

Type of Posting	Revision Bulletin
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 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*.▲ (RB 21-Aug-2019)

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*.
• **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
▲ (RB 21-Aug-2019)

[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).