Potassium Chloride Extended-Release Capsules

Type of Posting	Notice of Intent to Revise
Posting Date	31–May–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 Capsules monograph.

Based on the supporting data received from a manufacturer awaiting FDA approval, the Expert Committee proposes to add *Dissolution Test 3* to the monograph.

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, 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 Capsules

DEFINITION

Potassium Chloride Extended-Release Capsules 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 *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 *Sample stock solution* in the *Assay*

Acceptance criteria: Meet the requirements

ASSAY

• **PROCEDURE**

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 (200 mg/mL) 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: Place NLT 20 Capsules 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, discarding 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. [NOTE—Retain a portion of the filtrate for use in the *Identification* tests.]

Sample solution: Transfer 5.0 mL of *Sample stock solution* to a 100-mL volumetric flask. Add 2.0 mL of sodium chloride solution (200 mg/mL) 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 absorbance 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 Capsule 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 = 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 1: 100 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 (200 mg/mL) 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 quantitatively with *Medium* to obtain a solution containing 60 µg/mL of potassium chloride.

Sample solution: Add 5.0 mL of the *Sample stock solution* to a 100-mL volumetric flask, add 2.0 mL of sodium chloride solution (200 mg/mL) 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 absorbance 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/Capsule)

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 Capsules tested conform to *Table 1* instead of to the table shown in *Dissolution* ⟨711⟩.

Table 1

Stage	Number Tested	Acceptance Criteria
S_1	6	Each unit is within the range Q ± 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 ± 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 ± 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 1: 100 rpm
Times: 1, 2, 4, and 6 h
Sample stock solution: Transfer 4.0 mL of the solution under test into a 50-mL volumetric flask, 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 (200 mg/mL) 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 (200 mg/mL) 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 sutability
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/Capsule)
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/Capsule
1	1	25–45
2	2	45–65
3	4	70–90
4	6	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, Apparatus, and **Standard stock solution:** Prepare as directed in *Test 1*.
Times: 0.5, 2, and 6 h
Sodium chloride solution: 200 mg/mL of sodium chloride in water
Hydrochloric acid solution: Hydrochloric acid in water (1:3)
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, respectively, 1.0, 1.5, and 2.0 µg/mL of potassium.
Sample solution: Transfer an appropriate portion of the filtered solution under test into a suitable volumetric flask. Add 2.0% of flask volume of *Sodium chloride solution* and 4.0% of *Hydrochloric acid solution*, and dilute with water to volume.
Blank solution: To a 100-mL volumetric flask, add 2.0 mL of *Sodium chloride solution* and 4.0 mL of *Hydrochloric acid solution*, and dilute with water to volume.
Instrumental conditions: Proceed as directed in *Test 1*, except do not use the *Blank*.
System sutability
Samples: *Standard solutions*
Suitability requirements
Linearity: Correlation coefficient NLT 0.999
Relative standard deviation: NMT 1.5% from 5 replicate analyses of each *Standard solution*
Analysis: Proceed as directed in *Test 1*.
Tolerances: See *Table 3*.

Table 3

Time Point (*i*)	Time (h)	Amount Dissolved (%)
1	0.5	2–22
2	2	38–58
3	6	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:** When more than one *Dissolution* test is given, the labeling states the *Dissolution* test used only if *Test 1* is not used.