## Potassium Chloride Extended-Release Capsules

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| **Expert Committee** | Small Molecules 5 |

In accordance with the Rules and Procedures of the Council of Experts, the Small Molecules 5 Expert Committee has revised the Potassium Chloride Extended-Release Capsules monograph. The purpose for the revision is to add *Dissolution Test 4* to accommodate FDA-approved drug products with different dissolution conditions and/or tolerances than the existing dissolution tests.

- *Dissolution Test 4* was validated using a Dionex Ion Pac CS12A-Analytical brand of column with L106 packing. The typical retention time for potassium is about 5.6 min.

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

Should you have any questions, please contact Josan Thomas, Scientific Liaison (+91-4044488948 or josan.thomas@usp.org).

*Revision Bulletin*
Official: January 1, 2021

# 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 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/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 4:** If the product complies with this procedure, the labeling indicates that it meets USP *Dissolution Test 4*.

[NOTE—Use water with a conductivity of NMT 1 µS/cm to prepare solutions, except *Medium*.]

**Medium:** Water; 900 mL

**Apparatus 1:** 100 rpm

**Times:** 1, 2, 4, and 8 h

**Solution A:** 100 mM methanesulfonic acid prepared as follows. Transfer 6.5 mL of methanesulfonic acid to a 1000-mL volumetric flask and dilute with water to volume.

**Mobile phase:** *Solution A* and water (20:80)

**Standard stock solution:** 600 µg/mL of USP Potassium Chloride RS in water

**Standard solution A:** 3 µg/mL of USP Potassium Chloride RS in water from *Standard stock solution*

**Standard solution B:** 12 µg/mL of USP Potassium Chloride RS in water from *Standard stock solution*

**Standard solution C:** 30 µg/mL of USP Potassium Chloride RS in water from *Standard stock solution*

**Standard solution D:** 48 µg/mL of USP Potassium Chloride RS in water from *Standard stock solution*

**Standard solution E:** 60 µg/mL of USP Potassium Chloride RS in water from *Standard stock solution*

**Standard solution F:** 72 µg/mL of USP Potassium Chloride RS in water from *Standard stock solution*

**Standard solution G:** 90 µg/mL of USP Potassium Chloride RS in water from *Standard stock solution*

**Sample solution:** Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size at the times specified, discarding the first few milliliters of the filtrate. Replace the portion removed with same volume of *Medium*. Dilute the filtrate with water, if necessary, to obtain a solution with a concentration similar to that of *Standard solution E*.

**Chromatographic system**

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

**Mode:** LC

**Detector:** Conductivity with suppression

**Columns**

**Guard:** 4-mm × 5-cm; 8.5-µm packing L106

**Analytical:** 4-mm × 25-cm; 8.5-µm packing L106

**Suppressor:** 4-mm cation or a suitable suppressor

**Column temperature:** 30°

**Flow rate:** 1 mL/min

**Injection volume:** 50 µL

**Run time:** NLT 2.5 times the retention time of potassium

**System suitability**

**Samples:** *Standard solution A*, *Standard solution B*, *Standard solution C*, *Standard solution D*, *Standard solution E*, *Standard solution F*, and *Standard solution G*

**Suitability requirements**

**Tailing factor:** NMT 2.0, *Standard solution E*

**Relative standard deviation:** NMT 2.0%, *Standard solution E*

**Correlation coefficient:** NLT 0.999, from the linear regression in the *Analysis*

**Y-intercept:** ±2% of *Standard solution E* response, from the calibration curve in the *Analysis*

**Analysis**

**Samples:** *Standard solution A*, *Standard solution B*, *Standard solution C*, *Standard solution D*, *Standard solution E*, *Standard solution F*, *Standard solution G*, and *Sample solution*

Determine the responses for *Standard solution A*, *Standard solution B*, *Standard solution C*, *Standard solution D*, *Standard solution E*, *Standard solution F*, and *Standard solution G*. Construct a linear calibration curve by plotting response values of *Standard solution A*, *Standard solution B*, *Standard solution C*, *Standard solution D*, *Standard solution E*, *Standard solution F*, and *Standard solution G* versus their corresponding concentrations in mg/mL.

From the linear calibration curve, determine the C*orrelation coefficient* and *Y-intercept*.

Calculate the concentration ($C_i$) of potassium chloride (KCl) in the sample withdrawn from the vessel at time point *i*:

$$\text{Result} = (r_U/r_S) \times C_S \times D$$

$r_U$ = peak response of potassium from the *Sample solution* at time point *i*

$r_S$ = peak response of potassium from *Standard solution E*

$C_S$ = concentration of USP Potassium Chloride RS in *Standard solution E* (mg/mL)

$D$ = dilution factor of the *Sample solution*, if needed

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

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$

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

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

$$\text{Result}_4 = \{(C_4 \times V) + [(C_3 + C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$

$C_i$ = concentration of potassium chloride in the portion of sample withdrawn at time point *i* (mg/mL)

$V$ = volume of *Medium*, 900 mL

$L$ = label claim (mg/capsule)

$V_S$ = volume of the *Sample solution* withdrawn at each time point (mL)

**Tolerances:** See *Table 3*.

**Table 3**

| Time Point (*i*) | Time (h) | Amount Dissolved (%) |
|---|---|---|
| 1 | 1 | NMT 20 |
| 2 | 2 | 25–45 |
| 3 | 4 | 55–80 |
| 4 | 8 | NLT 80 |

The percentage of the labeled amount of potassium chloride (KCl) dissolved at the times specified conforms to *Dissolution* ⟨711⟩, *Acceptance Table 2*. ▲ (RB 1-Jan-2021)

- **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.

***Add the following:***

▲● **USP Reference Standards** ⟨11⟩

USP Potassium Chloride RS ▲ (RB 1-Jan-2021)

**Page Information:**

Not Applicable

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