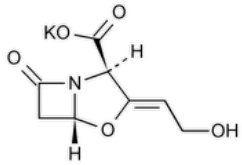
Status: Currently Official on 14-Feb-2025
Official Date: Official as of 01-May-2018
Document Type: USP Monographs
DocId: GUID-A984DC58-903F-4577-B7E4-A108B988F1E0_3_en-US
DOI: https://doi.org/10.31003/USPNF_M18000_03_01
DOI Ref: 94sn9

Clavulanate Potassium



$C_8H_8KNO_5$ 237.25

4-Oxa-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 3-(2-hydroxyethylidene)-7-oxo-, monopotassium salt, 2*R*-(2α,3*Z*,5α)-;

Potassium (*Z*)-(2*R*,5*R*)-3-(2-hydroxyethylidene)-7-oxo-4-oxa-1-azabicyclo[3.2.0]heptane-2-carboxylate CAS RN®: 61177-45-5; UNII: Q42OMW3AT8.

DEFINITION

Clavulanate Potassium contains the equivalent of NLT 75.5% and NMT 92.0% of clavulanic acid ($C_8H_9NO_5$), calculated on the anhydrous basis.

IDENTIFICATION

• **A.** The retention time of the major peak for clavulanic acid of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

• **B.** **Identification Tests—General ⟨191⟩, *Chemical Identification Tests, Potassium*:** Meets the requirements

ASSAY

• **Procedure**

Solution A: 7.8 mg/mL of monobasic sodium phosphate in water. Adjust with phosphoric acid or 10 N sodium hydroxide to a pH of 4.4 ± 0.1 before final dilution.

Mobile phase: Methanol and *Solution A* (1:19)

Standard solution: 0.25 mg/mL of USP Clavulanate Lithium RS in water

System suitability solution: 0.5 mg/mL of amoxicillin dissolved in *Standard solution*

Sample solution: 0.25 mg/mL of Clavulanate Potassium in water

Chromatographic system

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

Mode: LC

Detector: UV 220 nm

Column: 4-mm × 30-cm; 3- to 10-µm packing L1

Flow rate: 2 mL/min

Injection volume: 20 µL

System suitability

Samples: *Standard solution* and *System suitability solution*

[Note—The relative retention times for clavulanic acid and amoxicillin are about 0.5 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 3.5 between the amoxicillin and clavulanic acid peaks, *System suitability solution*

Tailing factor: NMT 1.5, *Standard solution*

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

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of clavulanic acid ($C_8H_9NO_5$) in each mg of Clavulanate Potassium taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times P \times F \times 100$$

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of USP Clavulanate Lithium RS in the *Standard solution* (mg/mL)

C_U = concentration of Clavulanate Potassium in the *Sample solution* (mg/mL)

P = designated potency of USP Clavulanate Lithium RS, in µg/mg of clavulanic acid

F = unit conversion factor, 0.001 mg/µg

Acceptance criteria: 75.5%–92.0% on the anhydrous basis

IMPURITIES

• **Procedure 1**

Solution A: 0.05 M monobasic sodium phosphate. Adjust with phosphoric acid to a pH of 4.0 ± 0.1.

Solution B: Methanol and *Solution A* (1:1)

System suitability solution: 0.1 mg/mL each of USP Clavulanate Lithium RS and amoxicillin in *Solution A*

Mobile phase: See *Table 1*.

[Note—The system is equilibrated for 15 min with 100% *Solution A*.]

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	100	0
4	100	0
15	50	50
18	50	50
24	100	0

Standard solution: 0.1 mg/mL of USP Clavulanate Lithium RS in *Solution A*

Sample solution: 10.0 mg/mL of Clavulanate Potassium in *Solution A*

Chromatographic system

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

Mode: LC

Detector: UV 230 nm

Column: 4.6-mm × 10-cm; 5-µm packing L1

Column temperature: 40°

Flow rate: 1 mL/min

Injection volume: 20 µL

System suitability

Samples: *Standard solution* and *System suitability solution*

[Note—The relative retention times for clavulanic acid and amoxicillin are about 1.0 and 2.5, respectively.]

Suitability requirements

Resolution: NLT 13 between the clavulanic acid and amoxicillin peaks, *System suitability solution*

Tailing factor: NMT 2.0 for the clavulanic acid peak, *System suitability solution*

Relative standard deviation: NMT 2%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each individual impurity in the Clavulanate Potassium taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

r_U = peak response of an individual impurity from the *Sample solution*

r_S = peak response of clavulanic acid from the *Standard solution*

C_S = concentration of the *Standard solution* (mg/mL)

C_U = concentration of Clavulanate Potassium in the *Sample solution* (mg/mL)

M_{r1} = molecular weight of clavulanate potassium, 237.3

M_{r2} = molecular weight of clavulanate lithium, 205.1

Acceptance criteria

Total impurities: NMT 2%

- **Procedure 2: Limit of Clavam-2-carboxylate Potassium**

Mobile phase: 0.1 M monobasic sodium phosphate. Adjust with phosphoric acid to a pH of 4.0 ± 0.1.

Standard solution: 5 µg/mL of USP Clavam-2-carboxylate Potassium RS in water

Sample solution: 10 mg/mL of Clavulanate Potassium in water

Chromatographic system

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

Mode: LC

Detector: UV 210 nm

Column: 4-mm × 30-cm; 3- to 10-µm packing L1

Flow rate: 0.5 mL/min

Injection volume: 20 µL

System suitability

Sample: *Standard solution*

[Note—The relative retention times for clavam-2-carboxylic acid and clavulanic acid are about 0.7 and 1.0, respectively.]

Suitability requirements

Tailing factor: NMT 1.5

Relative standard deviation: NMT 5%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of clavam-2-carboxylate potassium in the portion of Clavulanate Potassium taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times F \times 100$$

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of USP Clavam-2-carboxylate Potassium RS in the *Standard solution* (µg/mL)

C_U = concentration of Clavulanate Potassium in the *Sample solution* (mg/mL)

F = unit conversion factor, 0.001 mg/µg

Acceptance criteria: NMT 0.01%

- **Procedure 3: Limit of Aliphatic Amines**

Internal standard solution: 50 µL of 3-methyl-2-pentanone in water to 100 mL

Standard solution: Dissolve 80.0 mg of each of the following amines in 2 N hydrochloric acid: 1,1-dimethylethylamine, diethylamine, tetramethylethylenediamine, 1,1,3,3-tetramethylbutylamine, and *N,N'*-diisopropylethylenediamine. Dilute with 2 N hydrochloric acid to 200.0 mL. Transfer 5.0 mL of this solution to a centrifuge tube. Add 5.0 mL of *Internal standard solution*, 10.0 mL of 2 N sodium hydroxide, 5.0 mL of isobutyl alcohol, and 5 g of sodium chloride. Shake for 1 min, and centrifuge to separate the layers. Use the upper layer.

Sample solution: Transfer 1.0 g of Clavulanate Potassium to a centrifuge tube, add 5.0 mL of *Internal standard solution*, 5.0 mL of 2 N sodium hydroxide, 10.0 mL of water, 5.0 mL of isobutyl alcohol, and 5 g of sodium chloride. Shake for 1 min, and centrifuge to separate the layers. Use the upper layer.

Chromatographic system

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

Mode: GC

Detector: Flame ionization

Column: 0.53-mm × 50-m capillary fused silica; 5-µm film coating of stationary phase G41

Temperatures

Injection port: 200°

Detector: 250°

Column: See *Table 2*.

Table 2

Initial Temperature (°)	Temperature Ramp (°/min)	Final Temperature (°)	Hold Time at Final Temperature (min)
35	—	35	7
35	30	150	15

Carrier gas: Helium

Flow rate: 8 mL/min

Injection type: Split ratio, 1:10

Injection volume: 1 µL

Analysis

Samples: *Standard solution* and *Sample solution*

[NOTE—See *Table 3* for relative retention times.]

Table 3

Name	Relative Retention Time
1,1-Dimethylethylamine	0.55
Diethylamine	0.76
3-Methyl-2-pentanone (internal standard)	1.0
Tetramethylethylenediamine	1.07
1,1,3,3-Tetramethylbutylamine	1.13
N,*N*'-Diisopropylethylenediamine	1.33
Bis(2-methylamino)ethyl ether[a]	1.57

[a] The relative retention time for this compound is provided for information only; bis(2-methylamino)ethyl ether is not a component of the *Standard solution*.

Calculate the percentage of each individual impurity in the portion of Clavulanate Potassium taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response for each individual impurity from the *Sample solution*

r_S = peak response for the relevant analyte from the *Standard solution*

C_S = concentration of the relevant analyte in the *Standard solution* (mg/mL)

C_U = concentration of Clavulanate Potassium in the *Sample solution* (mg/mL)

Calculate the percentage of any individual impurity for which no relevant reference compound is provided in the *Standard solution* by the same formula, except for r_S, using the peak response corresponding to the 1,1-dimethylethylamine peak.

Acceptance criteria

Total of all aliphatic amines: NMT 0.2%

• **Procedure 4: Limit of 2-Ethylhexanoic Acid**

Internal standard solution: 1 mg/mL of 3-cyclohexylpropionic acid in cyclohexane

Standard solution: 1.5 mg/mL of 2-ethylhexanoic acid in *Internal standard solution*. Transfer 1.0 mL of this solution to a centrifuge tube, and add 4.0 mL of 4 N hydrochloric acid. Shake for 1 min, and allow the phases to separate, centrifuging if necessary. Withdraw the lower phase, and reserve the upper phase. To the lower phase add 1.0 mL of *Internal standard solution*, and shake for 1 min. Allow the phases to separate, centrifuging if necessary. Withdraw the upper phase, and combine with the reserved upper layer.

Sample solution: Transfer 300 mg of Clavulanate Potassium to a centrifuge tube. Add 4.0 mL of 4 N hydrochloric acid, and shake with two successive 1.0-mL portions of the *Internal standard solution*. Allow the phases to separate, centrifuging if necessary. Use the combined upper phases.

Chromatographic system

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

Mode: GC

Detector: Flame ionization

Column: 0.53-mm × 25-m capillary fused silica; 1-µm film coating of stationary phase G35

Temperatures

Injection port: 200°

Detector: 300°

Column: See *Table 4*.

Table 4

Initial Temperature (°)	Temperature Ramp (°/min)	Final Temperature (°)	Hold Time at Final Temperature (min)
40	—	40	2
40	30	200	3

Carrier gas: Hydrogen

Flow rate: 100 cm/s

Injection volume: 1 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Resolution: NLT 2.0 between the 2-ethylhexanoic acid and 3-cyclohexylpropionic acid peaks

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of 2-ethylhexanoic acid in the portion of Clavulanate Potassium taken:

$$\text{Result} = (R_U/R_S) \times (C_S/C_U) \times 100$$

R_U = peak response ratio of 2-ethylhexanoic acid to 3-cyclohexylpropionic acid from the *Sample solution*

R_S = peak response ratio of 2-ethylhexanoic acid to 3-cyclohexylpropionic acid from the *Standard solution*

C_S = concentration of 2-ethylhexanoic acid in the *Standard solution* (mg/mL)

C_U = concentration of Clavulanate Potassium in the *Sample solution* (mg/mL)

Acceptance criteria: NMT 0.8%

SPECIFIC TESTS

• **Bacterial Endotoxins Test ⟨85⟩:** Where the label states that Clavulanate Potassium is sterile or must be subjected to further processing during the preparation of injectable dosage forms, it contains NMT 0.03 USP Endotoxin Units/mg.

• **Sterility Tests ⟨71⟩, *Test for Sterility of the Product to Be Examined*, *Membrane Filtration*:** Where the label states that Clavulanate Potassium is sterile, it meets the requirements when tested as directed.

• **pH ⟨791⟩**

Sample: 10 mg/mL

Acceptance criteria: 5.5–8.0

• **Water Determination** ⟨921⟩, *Method I*: NMT 1.5%

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in tight containers.

• **Labeling:** Where it is intended for use in preparing injectable dosage forms, the label states that it is sterile or must be subjected to further processing during the preparation of injectable dosage forms.

• **USP Reference Standards** ⟨11⟩

USP Clavam-2-carboxylate Potassium RS

USP Clavulanate Lithium RS

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
CLAVULANATE POTASSIUM	Documentary Standards Support	SM12020 Small Molecules 1

Chromatographic Database Information: Chromatographic Database

Most Recently Appeared In:
Pharmacopeial Forum: Volume No. PF 42(3)

Current DocID: GUID-A984DC58-903F-4577-B7E4-A108B988F1E0_3_en-US
Previous DocID: GUID-A984DC58-903F-4577-B7E4-A108B988F1E0_1_en-US
DOI: https://doi.org/10.31003/USPNF_M18000_03_01
DOI ref: 94sn9