Time (hours)	Amount dissolved
2	not more than 25%
4	between 20% and 40%
8	between 45% and 75%
12	not less than 80%

Loss on drying ⟨731⟩—Dry a portion of powdered T ablets in vacuum at a pressure not exceeding 5 mm of mer cury at 110° for 3 hours: it loses not more than 5.0% of its weight.

Uniformity of dosage units ⟨905⟩**:** meet the requirements.

Assay—

Mobile phase, Resolution solution, and *Chromatographic sys-tem*—Proceed as directed in the *Assay* under *Clarithromycin Tablets.*

Standard preparation—Prepare as directed for *Standard prep-aration* in the *Assay* under *Clarithromycin Tablets.*

Assay preparation—Finely powder an accurately counted number of Tablets, equivalent to about 2000 mg of clarithro-mycin. With the aid of methanol quantitatively transfer the powder to a 500-mL volumetric flask, add about 350 mL of methanol, and shake by mechanical means for 30 minutes. Di-lute with methanol to volume, and mix. Sonicate for 30 min-utes. Cool to room temperature, and allow to stand for at least 16 hours. Mix, and allow any insoluble matter to settle. T ransfer 3.0 mL of the supernatant to a 100-mL volumetric flask, dilute with *Mobile phase* to volume, and mix. Pass a portion of this solution through a filter having a 0.5- μm or finer porosity, and use the filtrate as the *Assay preparation.*

Procedure—Proceed as directed for *Procedure* in the *Assay* under *Clarithromycin Tablets.* Calculate the quantity, in mg, of clarithromycin ($C_{38}H_{69}NO_{13}$) in each Extended-Release T ablet taken by the formula:

$$(50/3)(C/N)(r_U / r_S)$$

in which *N* is the number of T ablets taken, and the other terms are as defined therein.

Clavulanate Potassium
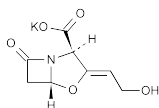
$C_8H_8KNO_5$ 237.25

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

Potassium (*Z*)-(2R,5R)-3-(2-hydroxyethylidene)-7-oxo-4-oxa-1-azabicyclo[3.2.0]heptane-2-carboxylate [61177-45-5].

DEFINITION

Clavulanate Potassium contains the equivalent of NL T 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 in the *Sample solution* corresponds to that in the *Standard solution*, as obtained in the *Assay.*
- **B. IDENTIFICATION TESTS—GENERAL,** *Potassium* ⟨191⟩**:** 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 hydrox-ide 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 dis-solved 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 size: 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 clavu-lanic acid peaks, *System suitability solution*
  Column efficiency: NLT 550 theoretical plates, *Standard 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 per centage of $C_8H_9NO_5$ in each mg of Clavu-lanate Potassium taken:

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

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 = nominal 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
Organic 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)
  Mobile phase: See the gradient table below.

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*
  System suitability solution: 0.1 mg/mL each of USP Clavulanate Lithium RS and amoxicillin 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
Temperature: 40°
Flow rate: 1 mL/min
 [NOTE—The system is equilibrated for 15 min with 100% *Solution A*.]
Injection size: 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 peak and the amoxicillin peak, *System suitability solution*
 Column efficiency: NLT 2000 theoretical plates from the clavulanic acid peak, *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, in terms of clavulanate potassium equivalent, of each impurity in the Clavulanate Potassium taken:

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

r_U = peak response of an individual impurity peak 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 = nominal concentration of Clavulanate Potassium from 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 size: 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
 Column efficiency: NLT 4000 theoretical plates
 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 sample taken:

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

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of the *Standard solution* (µg/mL)

C_U = nominal 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, tetramethylethyl-enediamine, 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 isopropyl 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 isopropyl 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 column that contains a 5-µm film coating of stationary phase G41
 Temperature
 Injector: 200°
 Detector: 250°
 Column: See the temperature program table below.

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
 Split ratio: 1:10
 Injection size: 1 µL
 Analysis
 Samples: *Standard solution* and *Sample solution*
 [NOTE—See the table below for relative retention times.]

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 impurity in the Clavulanate Potassium taken:

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

r_U = peak response for an 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*

C_U = nominal concentration of Clavulanate Potassium in the *Standard solution*

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 use 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-cyclohexyl-propionic 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
Temperature
Injector temperature: 200°
Detector temperature: 300°
Column temperature: See the temperature program table below.

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 size: 1 μL
System suitability
Sample: *Standard solution*
Suitability requirements
Resolution: NLT 2.0 between the 2-ethylhexanoic acid peak and the 3-cyclohexylpropionic acid peak
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of 2-ethylhexanoic acid in the Clavulanate Potassium taken:

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

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

R_S = peak area 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 = nominal 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 Unit/mg.
• STERILITY TESTS ⟨71⟩: Where the label states that Clavulanate Potassium is sterile, it meets the requirements when tested as directed under *Test for Sterility of the Product to Be Examined, Membrane Filtration*.
• PH ⟨791⟩: 5.5–8.0, in a 10 mg/mL solution
• WATER DETERMINATION, *Method I* ⟨921⟩: 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
USP Endotoxin RS

Clemastine Fumarate
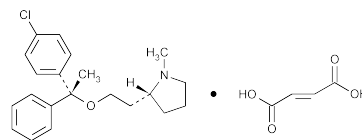
$C_{21}H_{26}ClNO \cdot C_4H_4O_4$ 459.96
Pyrrolidine, 2-[2-[1-(4-chlorophenyl)-1-phenylethoxy]ethyl]-1-methyl-, [R-(R*,R*)]-, (E)-2-butenedioate (1:1).
(+)-(2R)-2-[2-[[[(R)-p-Chloro-α-methyl-α-phenylbenzyl]-oxy]ethyl]-1-methylpyrrolidine fumarate (1:1)   [14976-57-9].

» Clemastine Fumarate contains not less than 98.0 percent and not more than 102.0 per cent of $C_{21}H_{26}ClNO \cdot C_4H_4O_4$, calculated on the dried basis.

Packaging and storage—Preserve in tight, light-resistant containers, at a temperature not exceeding 25 °.

USP Reference standards ⟨11⟩—
USP Clemastine Fumarate RS

Clarity and color of solution—Dissolve 100 mg of Clemastine Fumarate in 10.0 mL of methanol, and mix to obtain the *Test solution*. Prepare a *Comparison solution* by mixing 2.5 mL of 0.00002 M sodium chloride, 2.5 mL of water, 5.0 mL of 2.5 N nitric acid, and 1.0 mL of 0.1 N silver nitrate, and use this solution within 5 minutes. Prepare a *Color matching fluid* by mixing 1 volume of *Matching Fluid C* (see *Color and Achromicity* ⟨631⟩) with 3 volumes of water. Transfer the *Test solution*, the *Comparison solution*, and 10 mL of *Color matching fluid* to separate test tubes having the same nominal diameter (about 12 mm). View the *Test solution* and the *Comparison solution* horizontally against a dull black background: the *Test solution* is clear or not more opalescent than the *Comparison solution*. View the *Test solution* and *Color matching fluid* horizontally against a dull white background: the *Test solution* is colorless or not more intensely colored than *Color matching fluid*.