Status: Currently Official on 17-Feb-2025
Official Date: Official as of 01-Aug-2016
Document Type: USP Monographs
DocId: GUID-2A4BE547-D9D3-4AD6-8105-F6624FFAEA74_1_en-US
DOI: https://doi.org/10.31003/USPNF_M4974_01_01
DOI Ref: bo54z

Amoxicillin and Clavulanic Acid Extended-Release Tablets

DEFINITION

Amoxicillin and Clavulanic Acid Extended-Release Tablets contain NLT 90.0% and NMT 110.0% of the labeled amounts of amoxicillin ($C_{16}H_{19}N_3O_5S$) and clavulanic acid ($C_8H_9NO_5$).

IDENTIFICATION

• **A.** The retention times of the major peaks of the *Sample solution* correspond to those of the *Standard solution*, as obtained in the *Assay*.

ASSAY

• **Procedure**

Buffer: 6.9 g/L of monobasic sodium phosphate adjusted with phosphoric acid to a pH of 4.2

Mobile phase: Methanol and *Buffer* (5:95)

Standard solution: 1 mg/mL of USP Amoxicillin RS and 62.5 µg/mL of USP Clavulanate Lithium RS in water. Store the solution at 4°, and inject within 10 h.

Sample solution: Equivalent to 1 mg/mL of amoxicillin and 62.5 µg/mL of clavulanic acid from finely powdered Tablets (NLT 6) in water. Stir for about 60 min. Store the solution at 4°, and inject within 12 h.

Chromatographic system

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

Mode: LC

Detector: UV 229 nm

Column: 8-mm × 10-cm; 5-µm packing L1

Flow rate: 2 mL/min

Injection volume: 20 µL

Autosampler temperature: 4°

System suitability

Sample: *Standard solution*

Suitability requirements

Resolution: NLT 2.0 between the amoxicillin and clavulanic acid peaks

Tailing factor: NMT 1.8 for the amoxicillin and clavulanic acid peaks

Relative standard deviation: NMT 1.0% for the amoxicillin and clavulanic acid peaks

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of amoxicillin ($C_{16}H_{19}N_3O_5S$) in the portion of Tablets taken:

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

r_U = response of amoxicillin from the *Sample solution*

r_S = response of amoxicillin from the *Standard solution*

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

C_U = nominal concentration of amoxicillin in the *Sample solution* (mg/mL)

P = potency of amoxicillin in USP Amoxicillin RS (µg/mg)

F = conversion factor, 0.001 mg/µg

Calculate the percentage of the labeled amount of clavulanic acid ($C_8H_9NO_5$) in the portion of Tablets taken:

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

r_U = response of clavulanic acid from the *Sample solution*

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

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

C_U = nominal concentration of clavulanic acid in the *Sample solution* (µg/mL)

P = potency of clavulanic acid in USP Clavulanate Lithium RS (mg/mg)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

• **Dissolution** ⟨711⟩

Test 1

Medium: Water; 900 mL

Apparatus 2: 75 rpm

Times

Amoxicillin: 1, 3, and 5 h

Clavulanic acid: 1 h

Mobile phase, Chromatographic system, and **System suitability:** Proceed as directed in the *Assay*.

Standard solution: USP Amoxicillin RS and USP Clavulanate Lithium RS in *Medium* at known concentrations similar to those expected in the *Sample solution*

Sample solution: Pass a portion of the solution under test through a suitable filter, and dilute with *Medium*, if necessary.

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the amounts of amoxicillin ($C_{16}H_{19}N_3O_5S$) and clavulanic acid ($C_8H_9NO_5$) dissolved.

Tolerances

Amoxicillin: The percentage of the labeled amount of amoxicillin ($C_{16}H_{19}N_3O_5S$) dissolved at the times specified conforms to *Table 1*.

Table 1

Time (h)	Amount Dissolved (%)
1	50–65
3	65–85
5	NLT 85

Clavulanic acid: NLT 80% (*Q*) of the labeled amount of clavulanic acid ($C_8H_9NO_5$) is dissolved in 1 h.

Test 2

Medium: Water; 900 mL

Apparatus 2: 75 rpm

Times

Amoxicillin: 1, 3, and 5 h

Clavulanic acid: 45 min

Mobile phase, Chromatographic system, and **System suitability:** Proceed as directed in the *Assay*.

Standard solution: USP Amoxicillin RS and USP Clavulanate Lithium RS in *Medium* at known concentrations similar to those expected in the *Sample solution*

Sample solution: Pass a portion of the solution under test through a suitable filter, and dilute with *Medium*, if necessary.

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the amounts of amoxicillin ($C_{16}H_{19}N_3O_5S$) and clavulanic acid ($C_8H_9NO_5$) dissolved.

Tolerances

Amoxicillin: The percentage of the labeled amount of amoxicillin ($C_{16}H_{19}N_3O_5S$) dissolved at the times specified conforms to *Table 2*.

Table 2

Time (h)	Amount Dissolved (%)
1	50–70
3	65–90

Time (h)	Amount Dissolved (%)
5	NLT 85

Clavulanic acid: NLT 85% (*Q*) of the labeled amount of clavulanic acid ($C_8H_9NO_5$) is dissolved in 45 min.

• **Uniformity of Dosage Units ⟨905⟩:** Meet the requirements

IMPURITIES

• **Organic Impurities**

Buffer: 13.8 g/L of monobasic sodium phosphate in water adjusted with phosphoric acid to a pH of 4.2

Solution A: Methanol and *Buffer* (1:199)

Solution B: Methanol and *Buffer* (10:90)

Mobile phase: See *Table 3*.

Table 3

Time (min)	Solution A (%)	Solution B (%)
0	100	0
8	70	30
13	70	30
13.01	40	60
18	40	60
18.01	100	0
25	100	0
30	100	0

[Note—These gradient elution times are established on an HPLC system with a dwell volume of approximately 5 mL. The gradient elution times in *Table 3* can be adjusted as necessary to achieve the separation described.]

System suitability solution: 0.4 mg/mL of USP Amoxicillin RS and 30 µg/mL of USP Amoxicillin Related Compound D RS in water. Store the solution at 4°.

Standard solution: 0.4 mg/mL of USP Amoxicillin RS in water. Store the solution at 4°, and inject within 24 h.

Sample solution: 1 mg/mL of amoxicillin and 62.5 µg/mL of clavulanic acid from finely powdered Tablets (NLT 2) in water. Stir for about 60 min. Store the solution at 4°, and use within 24 h.

Chromatographic system

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

Mode: LC

Detector: UV 230 nm

Column: 4.6-mm × 5-cm; 3-µm packing L1

Flow rate: 1.5 mL/min

Injection volume: 20 µL

Autosampler temperature: 4°

System suitability

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

Suitability requirements

Resolution: NLT 1.25 between the amoxicillin and amoxicillin related compound D peaks at a relative retention time of 0.83, *System suitability solution*

Tailing factor: NMT 1.8 for the amoxicillin peak, *Standard solution*

Relative standard deviation: NMT 1.0% for the amoxicillin peak, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times P \times F_1 \times (1/F_2) \times 100$$

r_U = response of each impurity from the *Sample solution*

r_S = response of amoxicillin from the *Standard solution*

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

C_U = nominal concentration of amoxicillin in the *Sample solution* (mg/mL)

P = potency of amoxicillin in USP Amoxicillin RS (µg/mg)

F_1 = conversion factor, 0.001 mg/µg

F_2 = relative response factor (see *Table 4*)

Acceptance criteria: See *Table 4*. The reporting limit is 0.003%.

Table 4

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Amoxicillin related compound I (D-hydroxyphenyl glycine)[a,b]	0.15	—	—
Amoxicillin related compound A (6-aminopenicillanic acid)[a,c]	0.30	—	—
Clavulanic acid	0.39	—	—
Amoxicillin related compound D (amoxicillin open ring)[a,d,e]	0.63	0.74	—
Amoxicillin related compound B (L-amoxicillin)[a,f]	0.78	—	—
Amoxicillin related compound D (amoxicillin open ring)[d,e]	0.83	0.74	2.5
Amoxicillin	1.0	—	—
Amoxicillin related compound G (D-hydroxyphenyl glycylamoxicillin)[a,g]	2.57	—	—
Amoxicillin related compound E (amoxicillin penilloic derivatives)[a,h,i]	2.63 3.00	—	—
Amoxicillin related compound C (amoxicillin rearrangement product)[j]	3.22	1.1	2.5
Amoxicillin open ring methyl ester[a,k]	3.38	—	—

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Amoxicillin related compound J (amoxicillin open ring dimer)[l]	4.07	1.0	4.5
Any individual unspecified impurity	—	—	0.5

[a] These are synthetic process impurities, which are controlled in the drug substance. They are listed here for reference only and are not to be reported.

[b] (*R*)-2-Amino-2-(4-hydroxyphenyl)acetic acid.

[c] (2*S*,5*R*,6*R*)-6-Amino-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0] heptane-2-carboxylic acid.

[d] The chromatographic system resolves two isomers of amoxicillin open ring.

[e] (4*S*)-2-{[(*R*)-2-Amino-2-(4-hydroxyphenyl)acetamido](carboxy)methyl}-5,5-dimethylthiazolidine-4-carboxylic acid.

[f] (2*S*,5*R*,6*R*)-6-[(*S*)-2-Amino-2-(4-hydroxyphenyl)acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid.

[g] (2*S*,5*R*,6*R*)-6-{(*R*)-2-[(*R*)-2-Amino-2-(4-hydroxyphenyl)acetamido]-2-(4-hydroxyphenyl)acetamido}-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo [3.2.0]heptane-2-carboxylic acid.

[h] The chromatographic system resolves two amoxicillin penilloic derivatives.

[i] (4*S*)-2-{[(*R*)-2-Amino-2-(4-hydroxyphenyl)acetamido]methyl}-5,5-dimethylthiazolidine-4-carboxylic acid.

[j] (4*S*)-2-[5-(4-Hydroxyphenyl)-3,6-dioxopiperazin-2-yl]-5,5-dimethylthiazolidine-4-carboxylic acid.

[k] (4*S*)-2-{[(*R*)-2-Amino-2-(4-hydroxyphenyl)acetamido]methoxycarbonylmethyl}-5,5-dimethylthiazolidine-4-carboxylic acid.

[l] (2*S*,5*R*,6*R*)-6-((2*R*)-2-{2-[(*R*)-2-Amino-2-(4-hydroxyphenyl)acetamido]-2-[(4*S*)-4-carboxy-5,5-dimethylthiazolidin-2-yl]acetamido}-2-(4-hydroxyphenyl)acetamido)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid.

SPECIFIC TESTS

• **Microbial Enumeration Tests ⟨61⟩** and **Tests for Specified Microorganisms ⟨62⟩:** The total aerobic microbial count does not exceed 10^3 cfu/g, and the total combined molds and yeasts count does not exceed 10^2 cfu/g.

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in tight containers and store at controlled room temperature.

• **Labeling:** When more than one *Dissolution* test is given, the labeling states the test used only if *Test 1* is not used.

• **USP Reference Standards ⟨11⟩**

USP Amoxicillin RS

USP Amoxicillin Related Compound D RS

(4*S*)-2-{[(*R*)-2-Amino-2-(4-hydroxyphenyl)acetamido](carboxy)methyl}-5,5-dimethylthiazolidine-4-carboxylic acid.

$C_{16}H_{21}N_3O_6S$ 383.42

USP Clavulanate Lithium RS

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

Topic/Question	Contact	Expert Committee
AMOXICILLIN AND CLAVULANIC ACID EXTENDED-RELEASE TABLETS	Documentary Standards Support	SM12020 Small Molecules 1
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM12020 Small Molecules 1

Chromatographic Database Information: Chromatographic Database

Most Recently Appeared In:
Pharmacopeial Forum: Volume No. PF 38(2)

Current DocID: GUID-2A4BE547-D9D3-4AD6-8105-F6624FFAEA74_1_en-US

DOI: https://doi.org/10.31003/USPNF_M4974_01_01

DOI ref: bo54z