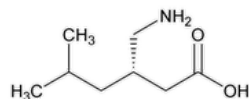


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Pregabalin



$C_8H_{17}NO_2$ 159.23

(S)-3-(Aminomethyl)-5-methylhexanoic acid CAS RN®: 148553-50-8.

DEFINITION

Pregabalin contains NLT 98.0% and NMT 102.0% of pregabalin ($C_8H_{17}NO_2$), calculated on the dried basis.

IDENTIFICATION

Change to read:

- **A.** [SPECTROSCOPIC IDENTIFICATION TESTS \(197\), Infrared Spectroscopy](#): (197K)▲ or (197A)▲ (USP 1-Aug-2020)
- **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the Assay.

ASSAY

PROCEDURE

Mobile phase: [Acetonitrile](#) and [water](#) (5:95)

Standard solution: 2.0 mg/mL of [USP Pregabalin RS](#) in *Mobile phase*

Sample solution: 2.0 mg/mL of Pregabalin in *Mobile phase*

Chromatographic system

(See [Chromatography \(621\), System Suitability](#).)

Mode: LC

Detector: UV 205 nm

Column: 4.6-mm × 25-cm; 5-μm packing [L1](#)

Temperatures

Autosampler: 10°

Column: 25°

Flow rate: 1.0 mL/min

Injection volume: 20 μL

Run time: NLT 2.5 times the retention time of pregabalin

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 1.5

Relative standard deviation: NMT 0.73%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of pregabalin ($C_8H_{17}NO_2$) in the portion of Pregabalin taken:

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

r_U = peak response of pregabalin from the *Sample solution*

r_S = peak response of pregabalin from the *Standard solution*

C_s = concentration of [USP Pregabalin RS](#) in the *Standard solution* (mg/mL)

C_u = concentration of Pregabalin in the *Sample solution* (mg/mL)

Acceptance criteria: 98.0%–102.0% on the dried basis

IMPURITIES

- [RESIDUE ON IGNITION \(281\)](#): NMT 0.1%

Change to read:

- [CHLORIDE AND SULFATE \(221\)](#), *Chloride*

Standard solution: Prepare as directed in the chapter using ▲1.4 mL.▲ (USP 1-Aug-2020)

Sample solution: Prepare as directed in the chapter using ▲1.0 g▲ (USP 1-Aug-2020) of Pregabalin.

Acceptance criteria: The turbidity produced in the *Sample solution* is NMT that produced in the *Standard solution* (0.1%).

Change to read:

- **ORGANIC IMPURITIES**

Buffer: 0.04 M [dibasic ammonium phosphate](#). Adjust with [phosphoric acid](#) to a pH of 6.5.

Solution A: [Methanol](#) and *Buffer* (20:80)

Solution B: [Methanol](#) and [acetonitrile](#) (10:90)

Mobile phase: See [Table 1](#).

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	98	2
5	98	2
16	80	20
33	80	20
34	98	2
45	98	2

▲**Sensitivity solution:** 0.005 mg/mL of [USP Pregabalin RS](#) in [water](#)▲ (USP 1-Aug-2020)

Standard solution: 0.01 mg/mL of [USP Mandelic Acid RS](#) and 0.05 mg/mL each of [USP Pregabalin RS](#) and [USP Pregabalin Related Compound C RS](#) in [water](#)

Sample solution: 10.0 mg/mL of Pregabalin in [water](#)

Chromatographic system

(See [Chromatography \(621\)](#), *System Suitability*.)

Mode: LC

Detector: UV 210 nm

Column: 4.6-mm × 25-cm; 5-μm packing [L1](#)

Column temperature: 35°

Flow rate: 1.0 mL/min

Injection volume: 20 μL

System suitability

Samples: ▲*Sensitivity solution* and ▲ (USP 1-Aug-2020) *Standard solution*

Suitability requirements

Relative standard deviation: NMT 5% for mandelic acid, pregabalin, and pregabalin related compound C, ▲*Standard solution*

Signal-to-noise ratio: NLT 10, *Sensitivity solution*▲ (USP 1-Aug-2020)

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of mandelic acid and pregabalin related compound C in the portion of Pregabalin taken:

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

r_U = peak response of mandelic acid or pregabalin related compound C from the *Sample solution*

r_S = peak response of mandelic acid or pregabalin related compound C from the *Standard solution*

C_S = concentration of [USP Mandelic Acid RS](#) or [USP Pregabalin Related Compound C RS](#) in the *Standard solution* (mg/mL)

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

Calculate the percentage of any individual unspecified impurity in the portion of Pregabalin taken:

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

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

r_S = peak response of pregabalin from the *Standard solution*

C_S = concentration of [USP Pregabalin RS](#) in the *Standard solution* (mg/mL)

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

F = relative response factor (see [Table 2](#))

Acceptance criteria: See [Table 2](#). The reporting threshold is 0.05%.

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Mandelic acid	0.66	—	0.10
Isobutylglutaric acid ^a	0.85	2.1	0.15
Pregabalin	1.0	1.0	—
Isobutylglutaramonoamide ^b	1.52	3.3	0.15
Pregabalin related compound C	3.95	—	0.15
Any unspecified impurity	—	1.0	0.10
Total impurities	—	—	0.8

^a 3-Isobutylpentanedioic acid.

^b 3-(2-Amino-2-oxoethyl)-5-methylhexanoic acid.

Change to read:

• **ENANTIOMERIC PURITY**

Buffer: [Triethylamine](#) and [water](#) (7.2:1000). Adjust with 50% (v/v) [phosphoric acid](#) to a pH of 3.0.

Mobile phase: [Acetonitrile](#) and *Buffer* (38:62)

Derivatizing reagent solution: 3 mg/mL of [Marfey's reagent](#) in [acetone](#)

▲ **Sensitivity stock solution:** 0.5 µg/mL of [USP Pregabalin RS](#) prepared as follows. Transfer an appropriate amount of [USP Pregabalin RS](#) to a suitable volumetric flask. Dissolve in 50% of the final volume of [water](#) and dilute with [acetone](#) to volume.

Sensitivity solution: Transfer 1.0 mL of the *Sensitivity stock solution* to a 10.0-mL volumetric flask, add 0.6 mL of the *Derivatizing reagent solution* and 100 µL of 1 M [sodium bicarbonate](#), and heat at 55° for about 1 h. Allow to cool to room temperature and dilute with [water](#) to volume. ▲ (USP 1-Aug-2020)

Standard stock solution: 1 mg/mL of [USP Pregabalin RS](#) and 0.05 mg/mL of [USP Pregabalin Related Compound A RS](#) prepared as follows.

Transfer appropriate amounts of [USP Pregabalin RS](#) and [USP Pregabalin Related Compound A RS](#) to a suitable volumetric flask. Dissolve in 50% of the final volume of [water](#) and dilute with [acetone](#) to volume.

Standard solution: Transfer 0.5 mL of the *Standard stock solution* to a 5.0-mL volumetric flask, add 0.3 mL of the *Derivatizing reagent solution* and 50 µL of 1 M [sodium bicarbonate](#), and heat at 55° for about 1 h. Allow to cool to room temperature and dilute with [water](#) to volume.

Sample stock solution: 1 mg/mL of Pregabalin prepared as follows. Transfer an appropriate amount of Pregabalin to a suitable volumetric flask. Dissolve in 50% of the final volume of [water](#) and dilute with [acetone](#) to volume.

Sample solution: Transfer 0.5 mL of the *Sample stock solution* to a 5.0-mL volumetric flask, add 0.3 mL of the *Derivatizing reagent solution* and 50 µL of 1 M [sodium bicarbonate](#), and heat at 55° for about 1 h. Allow to cool to room temperature and dilute with [water](#) to volume.

Chromatographic system

(See [Chromatography \(621\)](#), *System Suitability*.)

Mode: LC

Detector: UV 340 nm

Column: 4.6-mm × 25-cm; 5-µm packing [L1](#)

Temperatures

Autosampler: 10°

Column: 25°

Flow rate: 2.0 mL/min

Injection volume: 20 µL

Run time: NLT 3.8 times the retention time of pregabalin

System suitability

Samples: ▲ *Sensitivity solution* and ▲ (USP 1-Aug-2020) *Standard solution*

▲ [NOTE—The relative retention times for pregabalin and pregabalin related compound A are 1.0 and 1.2, respectively.] ▲ (USP 1-Aug-2020)

Suitability requirements

Resolution: NLT 3.0 between pregabalin and pregabalin related compound A, ▲ *Standard solution* ▲ (USP 1-Aug-2020)

Relative standard deviation: NMT 5.0% for pregabalin related compound A, ▲ *Standard solution*

Signal-to-noise ratio: NLT 10, *Sensitivity solution* ▲ (USP 1-Aug-2020)

Analysis

Sample: *Sample solution*

Calculate the percentage of pregabalin related compound A in the portion of Pregabalin taken:

$$\text{Result} = (r_U/r_T) \times 100$$

r_U = peak response of pregabalin related compound A from the *Sample solution*

r_T = sum of the peak responses of pregabalin and pregabalin related compound A from the *Sample solution*

Acceptance criteria: NMT 0.15%

SPECIFIC TESTS

• [Loss on Drying \(731\)](#)

Analysis: Dry at 105° for 3 h.

Acceptance criteria: NMT 0.5%

ADDITIONAL REQUIREMENTS

• **PACKAGING AND STORAGE:** Preserve in tight containers. Protect from light and store at NMT 25°.

• [USP REFERENCE STANDARDS \(11\)](#)

[USP Mandelic Acid RS](#)

[USP Pregabalin RS](#)

[USP Pregabalin Related Compound A RS](#)

(*R*)-3-(Aminomethyl)-5-methylhexanoic acid.

$C_8H_{17}NO_2$ 159.23

[USP Pregabalin Related Compound C RS](#)

4-Isobutylpyrrolidin-2-one.

$C_8H_{15}NO$ 141.21

Auxiliary Information - Please [check for your question in the FAQs](#) before contacting USP.

Topic/Question	Contact	Expert Committee
PREGABALIN	Documentary Standards Support	SM22020 Small Molecules 2
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM22020 Small Molecules 2

Chromatographic Database Information: [Chromatographic Database](#)

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