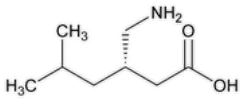
Printed on: Wed Nov 04 2020, 15:46:16 pm
Printed by: Shruti Kharidia
Official Status: Currently Official on 04-Nov-2020
Official Date: Official as of 1-Nov-2020
Document Type: USP
DocId: 1_GUID-C1E3DF2E-B4DA-4A71-9D65-176ADDD3F5FD_3_en-US
Printed from: https://online.uspnf.com/uspnf/document/1_GUID-C1E3DF2E-B4DA-4A71-9D65-176ADDD3F5FD_3_en-US

Pregabalin



$C_8H_{17}NO_2$ 159.23

(*S*)-3-(Aminomethyl)-5-methylhexanoic acid [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	—
Isobutylglutarmonoamide[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	Hillary Z Cai Senior Scientific Liaison	SM22020 Small Molecules 2

Chromatographic Database Information: Chromatographic Database

Most Recently Appeared In:
Pharmacopeial Forum: Volume No. 44(4)

Page Information:

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USP42-NF37 - 3645

Current DocID: GUID-C1E3DF2E-B4DA-4A71-9D65-176ADDD3F5FD_3_en-US