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Lomustine Capsules

DEFINITION
Lomustine Capsules contain NLT 90.0% and NMT 110.0% of the labeled amount of lomustine ($C_9H_{16}ClN_3O_2$).

[**Caution**—Great care should be taken to prevent inhalation of particles of lomustine and to prevent exposure to the skin.]

IDENTIFICATION

• **A. Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*: 197K**

Sample: Transfer the contents of 2 Capsules to a stoppered Erlenmeyer flask containing 25 mL of methylene chloride. Shake vigorously, and filter. Evaporate the methylene chloride from the filtrate under a stream of dry nitrogen. Prepare a potassium bromide pellet of the residue.

Acceptance criteria: Meet the requirements

• **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**

[Note—Protect the solutions from light. Use freshly prepared solutions.]

Mobile phase: Acetonitrile and water (7:13)

Standard solution: 0.2 mg/mL of USP Lomustine RS in acetonitrile

Sample solution: 0.2 mg/mL of lomustine in acetonitrile prepared as follows. Transfer a portion of the Capsule fill (from NLT 20 Capsules) to a suitable volumetric flask, and add acetonitrile equivalent to 75% of the volume. Shake for 15 min, and dilute with acetonitrile to volume. Pass through a suitable filter, and discard the first few mL of filtrate.

Chromatographic system

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

Mode: LC

Detector: UV 230 nm

Column: 4.6-mm × 7.5-cm; 3-µm packing L1

Flow rate: 1.5 mL/min

Injection volume: 10 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Relative standard deviation: NMT 2.0%

Tailing factor: NMT 1.3

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of lomustine ($C_9H_{16}ClN_3O_2$) in the portion of Capsules taken:

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

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

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

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

Acceptance criteria: 90.0%–110.0%

IMPURITIES

• **Organic Impurities**

[Note—Protect the solutions from light. Use freshly prepared solutions.]

Solution A: Water

Solution B: Acetonitrile

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	90	10
3	90	10
40	65	35
47	65	35
52	50	50
55	50	50
55.1	5	95
60	5	95
60.1	90	10
65	90	10

Standard solution A: 0.032 mg/mL each of USP Carmustine Related Compound A RS, USP Lomustine Related Compound B RS, and USP Lomustine Related Compound C RS, and 0.04 mg/mL of USP Lomustine Related Compound D RS and 2 mg/mL of USP Lomustine RS in acetonitrile

Standard solution B: 8 µg/mL of USP Lomustine RS in acetonitrile

Sample solution: 8 mg/mL of lomustine in acetonitrile prepared as follows. Transfer a portion of the Capsule fill (from NLT 20 Capsules) to a suitable volumetric flask, and dilute with acetonitrile to volume. Sonicate for 30 min, and then stir for 30 min. Pass a portion of the solution through a suitable filter of 0.2-µm pore size.

Chromatographic system

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

Mode: LC

Detector: UV 195 and 230 nm

Column: 4.6-mm × 10-cm; 2.6-µm packing L43

Temperatures

Column: 35°

Sample: 15°

Flow rate: 0.8 mL/min

Injection volume: 4 µL

System suitability

Samples: *Standard solution A* and *Standard solution B*

Suitability requirements

Resolution: NLT 1.2 between the lomustine and lomustine related compound D peaks determined at 230 nm, *Standard solution A*

Relative standard deviation: NMT 10% for carmustine related compound A, lomustine related compounds B and C determined at 195 nm, *Standard solution A*; NMT 10% for lomustine determined at 230 nm, *Standard solution B*

Tailing factor: Between 0.7 and 1.3 for the lomustine peak determined at 230 nm, *Standard solution A*

Analysis

Samples: *Standard solution A*, *Standard solution B*, and *Sample solution*

Calculate the percentage of carmustine related compound A and lomustine related compounds B and C in the portion of Capsules taken:

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

r_U = peak area of each impurity from the *Sample solution*, determined at 195 nm

r_S = peak area of the corresponding related compound from *Standard solution A*, determined at 195 nm

C_S = concentration of the corresponding USP Carmustine Related Compound A RS, USP Lomustine Related Compound B RS, or USP Lomustine Related Compound C RS in *Standard solution A* (mg/mL)

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

Calculate the percentage of any unspecified impurity in the portion of Capsules taken:

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

r_U = peak area of any unspecified impurity from the *Sample solution*, determined at 195 nm or 230 nm. If the impurity is detected at both wavelengths, use the higher peak area in the formula.

r_S = peak area of lomustine from *Standard solution B*, determined at 230 nm

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

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

Acceptance criteria: See *Table 2*. Disregard any impurity peak less than 0.05%.

Table 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Carmustine related compound A[a]	0.11	0.4[b]
Lomustine related compound B[c]	0.39	0.4[b]
Lomustine related compound C[d]	0.73	0.4[b]
Lomustine	1.0	—
Lomustine related compound D[e]	1.02	—
Any individual unspecified impurity	—	0.2
Total impurities	—	2

[a] 1,3-Bis(2-chloroethyl)urea.

[b] No more than one such impurity (carmustine related compound A, lomustine related compound B, or lomustine related compound C) is greater than 0.2%.

[c] 1-(2-Chloroethyl)-3-cyclohexylurea.

[d] 1,3-Dicyclohexylurea.

[e] This process impurity is included in the table for identification only, and it is not to be reported or included in the *Total impurities*.

PERFORMANCE TESTS

• **Disintegration ⟨701⟩:** 20 min

Change to read:

• **Uniformity of Dosage Units ⟨905⟩:** ▲Meet the requirements▲ (CN 1-Aug-2023)

Procedure for content uniformity

Complete the analysis within 1 h after the preparation of *Sample solution*.

Standard solution: 0.02 mg/mL of USP Lomustine RS in methanol

Sample solution: Nominally equivalent to 0.02 mg/mL of lomustine in methanol prepared as follows. Transfer the content of a Capsule into a 100-mL volumetric flask, and dilute with methanol to volume. Allow the excipients to settle for at least 15 min. Transfer a measured volume of the clear supernatant to a suitable volumetric flask, and dilute to volume with methanol.

Instrumental conditions

(See *Ultraviolet-Visible Spectroscopy ⟨857⟩*.)

Mode: UV

Analytical wavelength: 230 nm

Cell length: 1 cm

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of lomustine ($C_9H_{16}ClN_3O_2$) in the Capsule taken:

$$\text{Result} = (A_U/A_S) \times (C_S/C_U) \times 100$$

A_U = absorbance from the *Sample solution*

A_S = absorbance from the *Standard solution*

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

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

▲▲ (CN 1-Aug-2023)

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in well-closed containers, and store at controlled room temperature.
- **USP Reference Standards** ⟨11⟩

USP Carmustine Related Compound A RS
1,3-Bis(2-chloroethyl)urea.
$C_5H_{10}Cl_2N_2O$ 185.05

USP Lomustine RS

USP Lomustine Related Compound B RS
1-(2-Chloroethyl)-3-cyclohexylurea.
$C_9H_{17}ClN_2O$ 204.70

USP Lomustine Related Compound C RS
1,3-Dicyclohexylurea.
$C_{13}H_{24}N_2O$ 224.34

USP Lomustine Related Compound D RS
3-(2-Chloroethyl)-1-cyclohexyl-1-nitrosourea.
$C_9H_{16}ClN_3O_2$ 233.70

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

Topic/Question	Contact	Expert Committee
LOMUSTINE CAPSULES	Documentary Standards Support	SM32020 Small Molecules 3

Chromatographic Database Information: Chromatographic Database

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