

Certificate of Analysis

CERTIFIED REFERENCE MATERIAL HRM-1016A

Carbamazepine

Batch Number

STY-0086-001

Description

A unit of the certified reference material (CRM) consists of 300 mg of carbamazepine in a screw-capped amber vial. The mass balance approach was adopted to determine the mass fractions (mg/g) of four classes of impurities; namely: structurally-related organic compounds, volatile organic compounds, total non-volatiles and water content, present in the CRM. The mass fraction value of carbamazepine was then obtained by subtracting the mass fraction values of the impurities from 1,000.

The reference material was produced with reference to the requirements set out in ISO/IEC 17025:2017 [1], ISO 17034:2016 [2] and ISO Guide 35:2017 [3].

Certified Mass Fraction Value

A certified value is a value for which a laboratory has the highest confidence in its accuracy. The certified mass fraction value given below is based on the results obtained by the mass balance approach:

Certified Mass Fraction Value: 997.2 ± 2.9 mg/g

The final result is expressed as the certified value $\pm$ the expanded uncertainty.

The uncertainty listed with the certified value is an expanded uncertainty about the mean, with coverage factor 2 (approximately 95 % confidence). It was estimated by combining uncertainties in the measurement of mass fractions of the four classes of impurities and the homogeneity and stability of the CRM, in accordance with ISO/IEC Guide 98-3:2008 [4].

Homogeneity

Homogeneity testing on carbamazepine and structurally-related organic compounds was performed on two sub-samples taken from eight bottles each using HPLC-DAD. The sample size taken was

approximately 2 mg. No significant differences in the between and within-bottle variances were found using one-way ANOVA at 95 % confidence level [3]. Thus, the material was regarded to be sufficiently homogeneous.

Stability

The short-term stability of carbamazepine and structurally-related organic compounds was studied. The material was stored at 50 °C (maximum allowable transportation temperature) for up to two weeks. The results showed that carbamazepine was stable over the study period.

The long-term stability of carbamazepine and structurally-related organic compounds at 4 °C was evaluated on three occasions over a period of up to three months after preparation. The results showed that carbamazepine was stable over the study period.

Validity of Certified Mass Fraction Value

The certified mass fraction value is valid within the specified measurement uncertainty until **20 Jul 2027**, provided that the CRM is subjected to the same handling and storage conditions as stated in this *Certificate of Analysis* (COA).

The CRM will be continuously monitored during the validity period to determine if any substantive change to the certified value has occurred. If necessary, its user will be advised if the CRM can continue to be used or an updated COA may be issued.

Analytical Methods

The sample was analysed by

- (i) high performance liquid chromatography with diode array detection (HPLC-DAD) to determine the structurally-related organic compounds;
- (ii) headspace gas chromatography with mass spectrometry (GC-MS) to determine the total volatile organic compounds;
- (iii) thermogravimetric analyser (TGA) to determine the total non-volatiles; and
- (iv) Karl Fisher coulometer to determine the water content.

The Table below summarises the results obtained from the above determinations:

Component(s)	Technique	Mass Fraction (mg/g)	Standard Uncertainty (mg/g)
Structurally-related organic compounds	HPLC-DAD	2.26	0.20
Total volatile organic compounds	GC-MS ¹	0.13	0.05
Total non-volatiles	TGA	< 5 (LOD ³)	1.44
Water	Karl Fisher coulometry ²	0.38	0.07

¹ Calibrated using ethanol CRM (NMIJ CRM 4001-b) from the National Metrology Institute of Japan (NMIJ).

² Validated with water saturated 1-octanol (SRM 2890) from NIST, USA.

³ LOD: limit of detection.

Metrological Traceability

The certified mass fraction value is traceable to the International System of Units (SI) through the mass balance method by the Health Sciences Authority (HSA).

Intended Use

The CRM is a primary measurement standard and is intended for use as a calibrant for the determination of carbamazepine for different purposes.

Instructions for Use

After use, the bottle must be tightly re-capped and protected from moisture and light. The minimum sample size for each use should be 10 mg.

Storage

The material should be properly sealed and stored at refrigerator temperature (2 to 8 °C) in its original bottle when not in use. Protect the material from moisture and light.

Safety Precautions for Users

Treat the material as hazardous substance. Use appropriate work practices when handling to avoid skin or eye contact, ingestion or inhalation of dust.

Further Information

Please direct all enquiries regarding this CRM to the contact in this COA.

References

- [1] ISO/IEC 17025:2017 General requirements for the competence of testing and calibration laboratories.
- [2] ISO 17034:2016 General requirements for the competence of reference material producers.
- [3] ISO Guide 35:2017 Reference materials – Guidance for characterisation and assessment for homogeneity and stability.
- [4] ISO/IEC Guide 98-3:2008 Uncertainty of measurement – Part 3: Guide to the expression of uncertainty in measurement (GUM:1995).

Certificate Revision Records

Certificate Ref. No.	Date of issue	Reason for issuance
CML-HRM-1016A/01	20 Jul 2017	Issuance of first certificate
CML-HRM-1016A/02	05 Jul 2018	Extension of expiry date
CML-HRM-1016A/03	18 Jun 2019	Extension of expiry date
CML-HRM-1016A/04	23 Jun 2020	Extension of expiry date
CML-HRM-1016A/05	24 May 2021	Extension of expiry date
CML-HRM-1016A/06	28 Jun 2021	Extension of expiry date
CML-HRM-1016A/07	17 Jan 2022	Addition of hierarchical position
CML-HRM-1016A/08	05 Jul 2023	Extension of expiry date
CML-HRM-1016A/09	01 Jul 2025	Extension of expiry date

Note

HSA does not assume any liability with respect to any loss caused by improper use and/or storage of the CRM by the customer.



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