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BRAVO - Accuracy is crucial: The starting point for a robust transfer of methods

Handheld devices nowadays make Raman spectroscopy available for various routine applications operated with a high degree of automation. Some decades ago this could not be imagined as for example it often was a challenge to ensure and achieve the required Raman shift accuracy during operation. With new arising developments, i.e. very stable diode lasers, Raman spectroscopy is getting more and more robust and user-friendly.

An important issue for handheld Raman spectrometers is the capability of a robust transfer of libraries between different instruments of the same type. In other words it is required that the same results are obtained with a common set of library data for various instruments. Prerequisite is a thorough calibration which guarantees a high accuracy and sets every spectrometer to a well-defined state. Of course, the second requirement is the capability of a spectrometer maintaining its performance during operation which is related to a high precision. Especially this issue is of high importance as handheld instruments are not operated under laboratory conditions but instead being exposed to manifold varying environmental conditions. Thus, a high accuracy combined with a high precision form the basis for a reliable in field operation using library data being generated in a centralized manner on multiple spectrometers.

With BRAVO special care is taken to make the highest standards only common for benchtop instrumentation available in handheld Raman spectroscopy. X-axis calibration is based on measurements of the emission of a neon lamp and Raman shift standards as defined by the ASTM [1]. Multiple Raman lines are evaluated to ensure a comprehensive calibration valid across the entire spectral range. To demonstrate the high level of accuracy achieved table 1 compares peak positions of cyclohexane to ASTM literature values based on measurements performed at multiple BRAVO spectrometers.

Notably, all Raman lines match very closely their literature values and the individual deviations are well below 1 cm^{-1} which is exceptional for handheld spectrometers. To emphasize this results it needs to be mentioned that cyclohexane was not used for spectrometer calibration. For the Pharmaceutical industry the chapters USP 1120 by the United States and EP 2.2.48 by the European Pharmacopeia define the minimum system requirements and guidelines for Raman instrumentation being operated in validated environments [2, 3].For example the EP 2.2.48 as well defines acceptable tolerances for the x-axis accuracy which are given in table 1 for benchtop and handheld instrumentation. It is obvious that the BRAVO spectrometer

Cyclohexane - ASTM values [1]	Cyclohexane – BRAVO (average +/- std. dev.)	Deviation to ASTM	Allowed deviations according to EP 2.2.48 (benchtop/handheld)
801.3	801.2 +/- 0.20	0.08	1.5 / 2.5
1028.3	1027.9 +/- 0.20	0.35	1.0 / 2.0
1266.4	1266.3 +/- 0.19	0.07	1.0 / 2.0
1444.4	1443.9 +/- 0.22	0.61	1.0 / 2.5
2852.9	2853.6 +/- 0.29	-0.66	2.0 / 3.0

Table 1: Comparison of Raman peak positions (unit: cm^{-1}) of cyclohexane to ASTM literature values as determined by BRAVO. The positions are shown as average values and standard deviation based on single measurements at 20 different BRAVO spectrometers, respectively.

is capable to be operated in line to requirements for benchtop instrumentation and easily exceeds the softened values for handheld instrumentation.

A common way to compare spectral data for library matching is to calculate the correlation coefficient between the measured spectrum and reference data. The correlation coefficient calculates to a number ranging from 1 to -1 representing a qualitative measure of identity in which 1 represents a perfect match. In reality this parameter is not only influenced by the similarity of the reference and analyzed material but depends as well on other parameters such as background signals, i.e. fluorescence. In general it is aimed to add as much as possible significance to this value in means of selectivity towards other materials, for example an adequate data pretreatment is recommended [4]. Regarding this aspect BRAVO's patented SSE™ mitigates fluorescence signals in an active manner [5].

A further influence on the correlation is given by the accuracy of a spectrometer which is illustrated in figure 1. Here the correlation coefficient of two Raman spectra of calcite is calculated in the range of 400 cm^{-1} to 1800 cm^{-1} as function of a constant deviation in x-axis accuracy across the entire spectral range. It is evident that for a deviation of 2 cm^{-1} the typically applied threshold of 0.95 is barely reached.

To ensure the required x-axis accuracy for BRAVO not only at an instrument test but continuously during operation a neon spectrum is generated with every Raman spectrum measured using an inbuilt neon lamp. Of course, the same care is taken at y-axis calibration stage using a NIST SRM relative intensity correction standard for Raman spectroscopy. Finally, with the spectroscopy software OPUS the overall performance of the spectrometer can be easily monitored running comprehensive system tests according to current Pharmaceutical regulations.

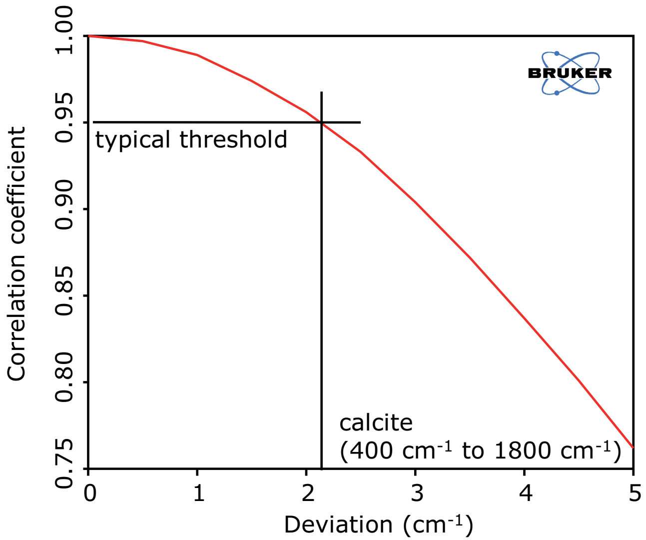

Figure 1: Correlation coefficient of two spectra of calcite in the range of 400 cm^{-1} to 1800 cm^{-1} as function of their relative deviation in x-axis accuracy (constant shift across the spectral range).

References

[1] ASTM E1840-96(2014), Standard Guide for Raman Shift Standards for Spectrometer Calibration.

[2] <1120> Raman Spectroscopy, United States Pharmacopeia.

[3] 2.2.48. Raman Spectroscopy, EUROPEAN PHARMACOPEIA 8.7.

[4] J. Kauffman et al., „Spectral Processing for Raman Library Searching", Amer. Pharm. Rev. 14, (2011).

[5] Bruker Product Note T29 12/15, "Efficient mitigation of fluorescence in Raman spectroscopy using SSE™".

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