Special Feature: Pharmaceutical Analysis (4)

Pharmaceutical raw material inspection with handheld Raman spectrometer

Taro Nogami* and Fumihito Muta*

1. Introduction

Many Japanese pharmaceutical companies are now intensively investigating methods for inspection of starting materials[1]. One of the reasons is the PIC/S (Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme) accession of Japan in the near future. Since samples taken from all containers must be tested, speed of identification is strongly required.

Another requirement is the protection of the materials. There are contamination risks for opening the packages, and direct material identification through a glass bottle or a transparent bag is often required.

Handheld Raman spectrometers are recently recognized as an effective tool for starting material inspection. In the past, near infrared absorption spectroscopy was often used in this field. However, Raman spectroscopy, which supplies us much more information for samples, has a higher capability of material identification. The direct material identification through a glass bottle or a transparent bag is possible by Raman spectroscopy only.

Raman spectrometers used for pharmaceutical inspections must have performance characteristics described in USP <1120>[2]. The portable Raman spectrometer reported here meets the requirements of USP <1120>.

2. Portable Raman spectrometers

There are two types of handheld Raman spectrometers. Rigaku's FirstGuard spectrometers are usually held by one hand so that the optical probe tip touches the sample. Rigaku's Xantus spectrometers are held by both hands or the Xantus spectrometer is placed on a table, and the sample is set to the position of the optical probe tip by hand. Between the two types, there is no basic difference in performance or software.

There are many kinds of materials such as principal agents, excipients, disintegrators, binders, lubricants, diluents, preservatives and pigments. Most of the materials emit not only Raman scatter but also fluorescence. The intensity of the fluorescence depends on the material and also the excitation wavelength. Generally, excitation by a short wavelength creates stronger Raman intensity than excitation by a long wavelength. However, some materials have very strong intrinsic fluorescence when excited by a short wavelength of light, and the fluorescence background interferes with the analysis of Raman peaks. To solve this problem, long wavelength light, such as a near infrared light, are required for exciting those materials.

Both the FirstGuard series and the Xantus series have three types of excitation wavelength, 532 nm, 785 nm and 1064 nm. The optimum excitation wavelength is selected depending on the category of samples. Xantus-2 is a dual wavelength Raman spectrometer that can be used for many different sample categories. The excitation wavelength can be changed on the spot.

The maximum laser power for 785 nm and 1064 nm is 490 mW, which is high for a portable Raman spectrometer, and often advantageous. The laser power can be continuously changed, and an operator selects the

Fig. 1. FirstGuard 1064 nm.

Fig. 2. Xantus-2 785/1064 nm.

* Portable Analyzer Division, Rigaku Corporation.

power considering both necessity of signal enhancement and risk of heat degeneration of samples. It is easy to archive the data to either the instrument or a PC.

The position of the optical probe tip is continuously adjustable. Usually, the optical focal point is the same as the tip position. When you analyze the contents of glass bottles through the glass, the optical probe is screwed in, in order to increase the distance between the tip position and the focal point so that the focal point is inside the bottle.

Fast substance identification is done by an automatic library search. There are three types of libraries.

Factory Library: Installed at the factory before shipment
User Library: Built by users from known samples
Third party library: Third party specialty databases (Optional)

The identification results are displayed together with the HQI (Hit Quality Index), which is a correlation coefficient between the measured spectrum and the spectrum in the library.

3. Reduction of fluorescence background by 1064 nm excitation

Figure 3 shows spectra of L-Isoleucine, which has higher fluorescence background than that of other amino acids. The 785 nm excitation with a baseline correction can be used, because the fluorescence background has a broad and simple shape.

Figure 4 shows spectra of brown sugar, a sucrose sugar product with a distinctive brown color due to the presence of molasses. Since the fluorescence background from 785 nm excitation is too high, the baseline correction doesn't work. The 1064 nm excitation is the only way to get a reasonable Raman spectrum of brown sugar.

Since the spectrum of 1064 nm excitation in Fig. 4 has low background, the ordinate can be expanded. Figure 5 shows the expanded spectrum of brown sugar excited by 1064 nm. Although it is raw data without a baseline correction, peaks can be clearly observed.

Highly fluorescent glass bottles are also troublesome for the excitation by 785 nm or shorter wavelengths when analyzing a substance in such bottles. This problem also can be minimized by 1064 nm excitation.

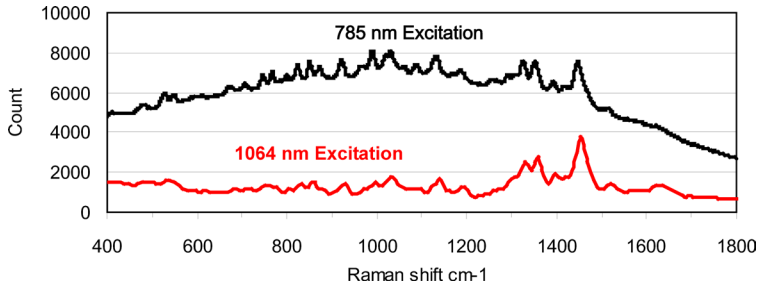

Fig. 3. Raman spectra of L-Isoleucine.

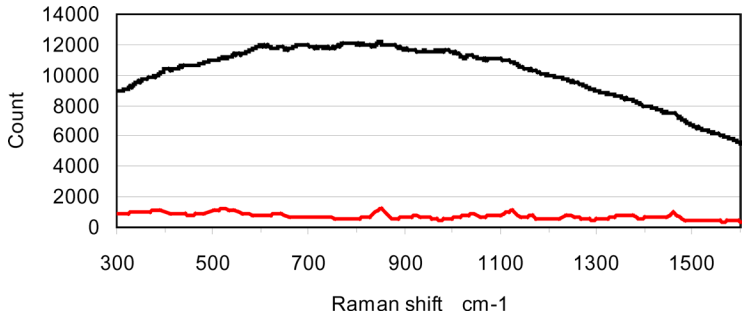

Fig. 4. Example of extreme fluorescence background. Raman spectra of brown sugar.

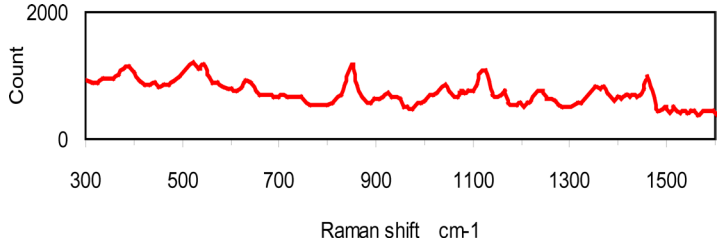

Fig. 5. Raman spectrum of brown sugar excited by 1064 nm. After the ordinate expansion of Fig. 4.

4. Optimum excitation wavelength for each category of material

The following are categories of starting materials and optimum excitation wavelengths for them.

(1) Sugar and starch

Sugars and starches are often used as excipients, disintegrators or binders. Usually, they can be analyzed by any excitation wavelength. However, sucrose sugar with brown color due to the presence of molasses needs to be analyzed by 1064 nm excitation.

(2) Amino acids

Amino acids are materials for transfusion fluids and supplements. Most of the essential amino acids and semi-essential amino acids such as Phenylalanine, Tryptophan, Isoleucine, Leucine, and Tyrosine can be analyzed by any excitation wavelength. However, as described previously, a 1064 nm excitation is recommended for analyzing Isoleucine.

(3) Cellulose

Cellulose is used as a disintegrator or binder.

All of Microcrystalline Cellulose, Methylcellulose and Cellulose Acetate Phthalate have some level of fluorescence background. It is possible to analyze them by 785 nm excitation if an appropriate baseline correction algorithm is used. However, the most recommended procedure is to use 1064 nm excitation.

(4) Organic pigments

Most organic pigments cannot be analyzed by 785 nm or a shorter wavelength. 1064 nm excitation is the only recommended way.

(5) Materials derived from animals or plants

Many materials such as shellac and gelatin need to be analyzed by 1064 nm excitation. Most amino sugars and natural plant extracts also need to be analyzed by 1064 nm excitation. Acacia gum and plant oils can be analyzed by 785 nm excitation to some extent, but 1064 nm excitation is normally recommended.

(6) Inorganic materials

Many kinds of inorganic materials are used as principal agents, additives or pigments, and it is not easy to recommend a generalized specific excitation wavelength. For instance, precipitated calcium carbonate, talc and titanium oxide can be analyzed by any excitation wavelength. On the other hand, however, iron oxide pigments are rather difficult to analyze by using any excitation wavelength.

5. FDA compliance

FirstGuard series and Xantus-2 series comply with FDA requirements. The hardware and software for the Raman analyzers were developed specifically for use in regulated environments.

The design qualification (DQ) document was written following the guidance of USP Chapter <1158> Analytical Instrument Qualification.

The DQ contains specific hardware and software requirements of 21 CRF part 11.

IQ/OQ/PQ protocols were written to test the completed product.

The IQ/OQ/PQ includes hardware, software and functional testing of the instrument.

The protocols include detailed test plans with expected and actual outcomes.

6. Summary

Unlike conventional handheld Raman Spectrometers, FirstGuard series and Xantus series have three different types of excitation wavelength. Depending on the category of materials, the optimum excitation wavelength should be designated. The dual wavelength Raman spectrometer Xantus-2 has the same capability as two spectrometers that each have a different wavelength, and can be used for many different sample categories, thus extending the usefulness of the instrument.

References

(1) PIC/S Guideline, Annex 8.
(2) USP Chapter <1120> Raman Spectroscopy.