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Application News

Fourier Transform Infrared Spectrophotometer IRSpirit™-X

Identification Test of the Ibuprofen Active Ingredient Compliant with European Pharmacopoeia and United States Pharmacopeia and Analysis of Final Product (Commercial Pharmaceutical) by ATR Method

Shoko Iwasaki, Yasushi Suzuki, and Takahide Hiramatsu

User Benefits

- A variety of infrared spectroscopy techniques can be used to easily perform identification tests for not only ibuprofen drug substances but also final products (commercial drugs).
- Identification tests compliant with European Pharmacopoeia and United States Pharmacopeia requirements can be easily performed using an IRSpirit-ZX spectrophotometer.
- The IRSpirit-ZX offers high humidity resistance for worry-free operations even in high-temperature and high-humidity environments.

■ Introduction

Infrared spectrophotometers are commonly used in combination with ultraviolet-visible spectrophotometers to perform identification tests of pharmaceuticals. The infrared spectroscopy method measures the degree of light absorption at each wavenumber as infrared light passes through the sample. The infrared spectrum shows the wavenumbers where light is absorbed and the intensity of that absorption, which are determined by the chemical structure and concentration of the target substances. Consequently, it can be used to identify or quantitate substances.

The pharmacopoeia of a country usually specifies the same measurement techniques for the same samples, but in a few rare cases, they specify different measurement techniques. This article describes differences in results obtained using the different identification test techniques specified for ibuprofen active ingredients in the European Pharmacopoeia (EP)[1] and the United States Pharmacopeia-National Formulary (USP-NF).[2] The article also describes using an ATR attachment to analyze not only the active ingredient but also the final drug product, which is the commercially marketed pharmaceutical.

■ Ibuprofen

Ibuprofen, which was used in this example is a type of non-steroidal anti-inflammatory pain reliever used to reduce symptoms of joint inflammation or fever and pain from inflamed areas. The market for ibuprofen and other nonsteroidal anti-inflammatory drugs (NSAID) is expected to expand due to continued global aging and increases in chronic pain.[3]

The chemical structure of ibuprofen is shown in Fig. 1. Due to its widespread use, the corresponding requirements are specified in the EP, USP-NF, and Japanese Pharmacopoeia (JP). They all specify using infrared spectroscopy for identification testing, but they recommend different measurement methods. The EP permits a variety of ATR and other techniques for analyzing potassium bromide (KBr) pellets, whereas the USP-NF specifies the paste (Nujol) method and the JP specifies analyzing KBr pellets.

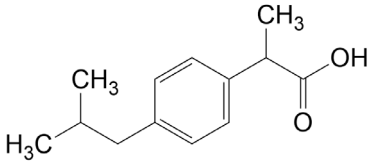

Fig. 1 Chemical Structure of Ibuprofen ($C_{13}H_{18}O_2$)

■ Instruments Used and Measurement Conditions

This article describes measuring the ibuprofen active ingredient using the KBr pellet method, the single reflection ATR method, and the paste method.

Samples were measured using an IRSpirit-ZX Fourier transform infrared spectrophotometer. The system is shown in Fig. 2, and the measurement parameters are listed in Table 1.

Fig. 2 IRSpirit™-X Series Fourier Transform Infrared Spectrophotometer

Table 1 Measurement Conditions

Instrument:	IRSpirit™-ZX spectrophotometer and QATR™-S (diamond) attachment
Resolution:	2 cm^{-1}
Number of scans:	45
Apodization function:	SqrTriangle
Detector:	DLATGS
Measurement wavenumber range:	4,000 to 550 cm^{-1}

Despite the compact case size (W390 × D250 × H210 mm) of the IRSpirit-X series systems, the TX model offers the highest sensitivity in its class. The ZX model features a ZnSe beam splitter that ensures worry-free operability even in high-temperature and high-humidity environments. However, due to the transmittance characteristics of its ZnSe beam splitter, the ZX model has a narrower measurable wavenumber range on the low-wavenumber end than the LX/TX models. Nevertheless, the ZX model is capable of measurements in the 4,000 to 650 cm^{-1} range, as specified in the EP, and the 3,800 to 650 cm^{-1} range, as specified in the USP-NF, for compliant measurements. But the ZX model is not capable of measuring the 4,000 to 400 cm^{-1} range, which is specified in the JP. To ensure identification tests are compliant with the JP, the LX or TX model should be used.

Due to the wide variety of instruments required for analyzing pharmaceuticals, laboratories tend to become cramped, so the extremely compact design of the IRSpirit-X series FTIR spectrophotometers makes them especially suitable for installation in sites with limited space.

■ EP-Compliant Identification Test (KBr Pellet Method)

Monographs 0721 in EP11.2 (in effect since July 1, 2023) specifies using the infrared spectroscopy method to compare the results of tested samples with ibuprofen CRS (CAS registration number (CAS RN®) 15687-27-1) in ibuprofen identification tests. Therefore, in this example, the infrared spectra from the tested ibuprofen reagent and the ibuprofen CRS reference sample were compared.

First, they were measured using the KBr pellet method, which is commonly used for identification testing. In the KBr pellet method, the sample is dispersed in KBr powder and formed into pellets with a pellet press. The pellet press used in this case was a Pixie mini-hydraulic press, which formed 7 mm diameter pellets. It is shown in Fig. 3.

The infrared spectra obtained are shown in Fig. 4. The test sample results closely match the standard reference sample results.

Fig. 3 Pixie Hydraulic Pellet Press

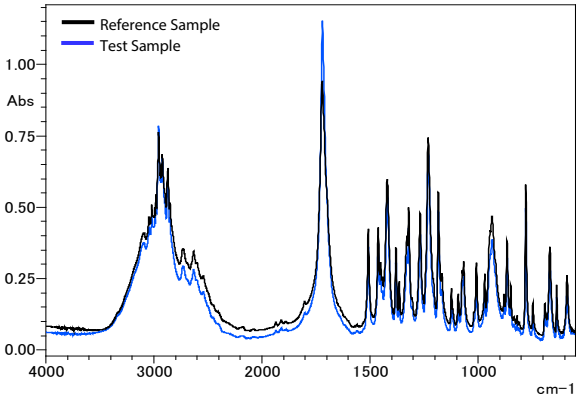

Fig. 4 Infrared Spectra of Ibuprofen (KBr Pellet Method)

■ EP-Compliant Identification Test (Single-Reflection ATR Method)

Aside from the KBr tablet method, a variety of other methods are also permitted for ibuprofen identification testing. Therefore, in this example, a diamond crystal was used to measure attenuated total reflectance (ATR). Ibuprofen reagent test samples were prepared in the same manner as in the KBr pellet method, and the results were compared with the results for ibuprofen CRS, the EP reference sample. The infrared spectra obtained are shown in Fig. 5.

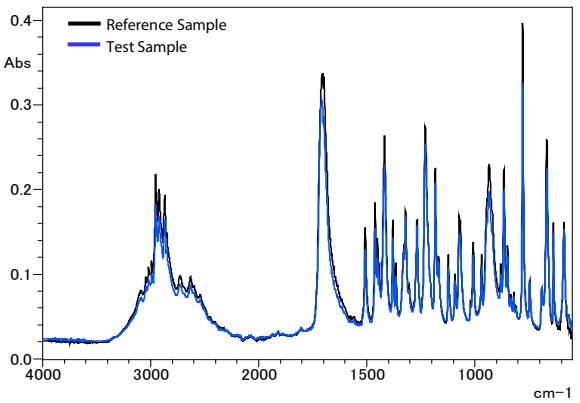

Fig. 5 Infrared Spectra of Ibuprofen (Single-Reflection ATR Method)

Just like the KBr pellet method results, the test sample results using the ATR method closely match the reference sample results.

Note that the ATR method offers the major advantage of not requiring pretreatment because the method involves positioning samples close to the crystal. However, the peak intensity obtained by the ATR method depends on the wavenumber, with higher peak intensities having lower wavenumbers.

Next, test sample spectra obtained from the KBr pellet and ATR methods were overlaid to identify the differences, as shown in Fig. 6. An enlarged view near 1,700 cm^{-1} is shown in Fig. 7. The intensity of peaks with the highest intensity is closely matched in both figures. A comparison of the spectra obtained by KBr pellet and ATR methods shows that the large absorption peak near 1,700 cm^{-1} shifted toward the low-wavenumber end in the ATR spectrum. Peak wavenumber positions are known to shift, particularly at peak positions with high absorption due to higher sample refractive index values.[4)-6)]

Thus, using different measurement techniques can result in different spectral intensity levels and peak positions, so it is essential to measure both the test sample and reference sample using the same technique.

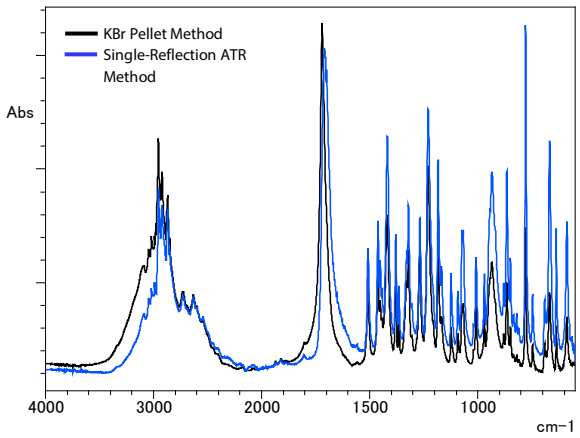

Fig. 6 Infrared Spectra of Ibuprofen
(KBr Pellet and Single-Reflection ATR Methods)

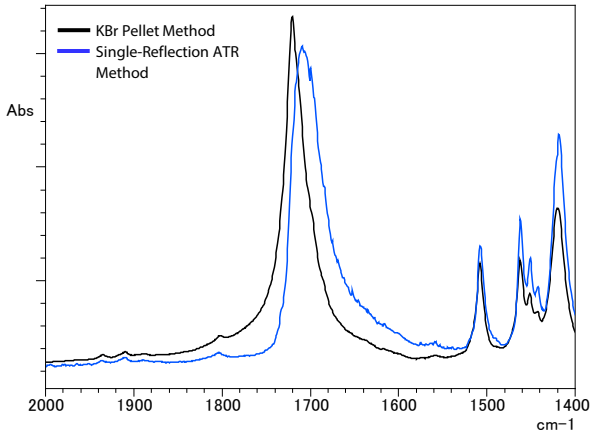

Fig. 7 Enlarged View of Spectra from 2,000 to 1,400 cm^{-1} in Fig. 6

■ USP-NF-Compliant Identification Test (Paste Method)

Monographs 206.28 in USP-NF 2023 Issue 2 (in effect since August 1, 2023) specifies the paste method for infrared spectroscopy used to compare results from test samples to ibuprofen CRS (CAS registration number (CAS RN) 15687-27-1) in ibuprofen identification tests.

Therefore, in this example, the paste method was used to obtain infrared spectra from the ibuprofen reagent test sample and the ibuprofen CRS reference sample and then the spectra were compared. The infrared spectra obtained are shown in Fig. 8. They show that the spectrum from the test sample closely matches the spectrum from the reference sample.

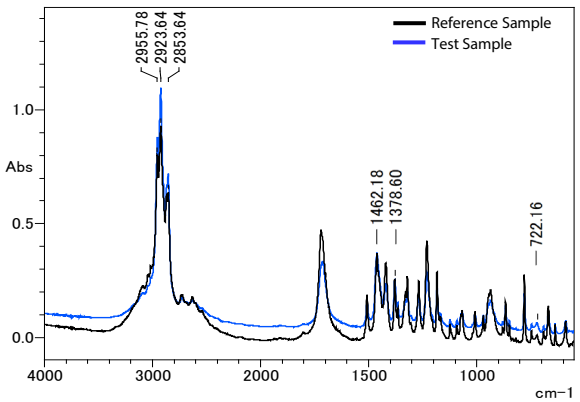

Fig. 8 Infrared Spectra of Ibuprofen (Paste Method)

Note that the paste method involves thoroughly mixing a small quantity of ground sample powder with a liquid paraffin (mineral oil) measuring spectra from that mixture sandwiched between two KBr window plates. Because the liquid paraffin absorbs light near 3,000 to 2,800 cm^{-1}, 1,500 to 1,350 cm^{-1}, and 720 cm^{-1} positions, the spectra obtained are for a mixture of ibuprofen and the liquid paraffin, as shown in Fig. 8.

■ Analysis of Final Product (Commercial Pharmaceutical) by ATR Method

The following describes measuring ingredients contained in commercial drug tablets as an example of identification testing of a final product. The surfaces of most commercial drugs are coated with a substance to protect them from humidity, etc., or to make them easier to swallow by masking their odor or taste. For this example, the results from directly analyzing the coating layer on the surface of a tablet and the results from measuring a powder obtained by grinding the tablet are presented below.

The results from directly measuring the tablet coating layer by the single-reflection ATR method are shown in Fig. 9. When using the ATR method, light only penetrates samples to the shallow depth of a few micrometers, which only enables measuring the coating layer on tablet surfaces. A library search detected cellulose and talc components.

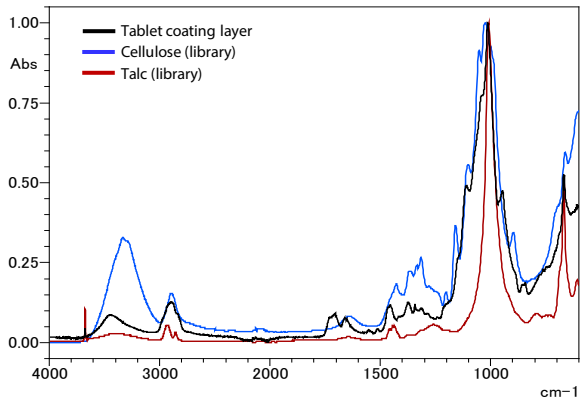

Fig. 9 Infrared Spectrum from a Tablet Coating Layer Overlaid with Library Search Results (Single-Reflection ATR Method)

Next, the tablet was ground to a powder, and the powder was measured by the single-reflection ATR method. Infrared spectra obtained from the powdered tablet and the ibuprofen CRS EP reference sample are shown overlaid in Fig. 10.

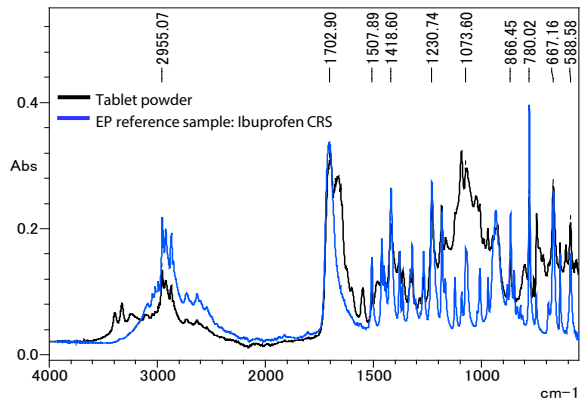

Fig. 10 Infrared Spectra of Powdered Tablet and Ibuprofen Reference Sample (Single-Reflection ATR Method)

The infrared spectrum from the tablet powder includes peaks that typically appear (at wavenumbers indicated at the top of Fig. 10) for ibuprofen, but also includes other peaks. To qualitatively analyze such non-ibuprofen ingredients, the infrared spectrum from the ibuprofen CRS was subtracted from the infrared spectrum from the tablet powder. The resulting difference spectrum is shown overlaid with library search results in Fig. 11. Based on that overlay, it can be inferred that the tablet analyzed in this case contains caffeine and silicate in addition to ibuprofen, cellulose, and talc.

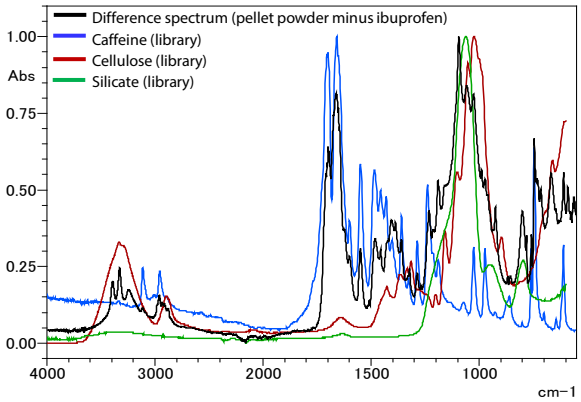

Fig. 11 Overlay of Ibuprofen Difference Spectrum with Library Search Results (Single-Reflection ATR Method)

■ Conclusion

Using the widely used drug ibuprofen, as a test sample, an IRSpirit-ZX FTIR spectrophotometer was used to perform EP and USP-NF-compliant identification tests based on the KBr pellet, ATR, and paste methods. For the EP-compliant identification test, results obtained by the KBr pellet and ATR methods were also compared. Since different measuring techniques will result in infrared spectra that do not match, it is essential to measure both test samples and reference samples using the same measuring techniques.

The system can also be used to qualitatively analyze surface coating layers or ingredients other than the main ingredient, ibuprofen, by using the ATR method to measure the commercial pharmaceutical, rather than only the active ingredient ibuprofen.

The IRSpirit-ZX model offers high humidity resistance for worry-free operations even in high-temperature and high-humidity environments. The LabSolutions™ IR software for data analysis and controlling IRSpirit-X series systems includes a program (IR Pilot™) designed specifically for easy identification testing, which has standard Spectral Advisor functionality that can suggest improvement measures that are based on comparing acquired data to measurement examples. With the IR Pilot program, procedural steps can be performed automatically, from performing operations by following instructions displayed in the window to correctly measuring samples, analyzing data, and printing results. It is highly recommended for users who intend to perform identification tests.

Reference Documents

1) EUROPEAN PHARMACOPOEIA SUPPLEMENT 11.2 (viewed August 2023)
2) The United States Pharmacopeia-National Formulary 2023 Issue2 (viewed August 2023)
3) A. Rastogi et al. A review on environmental occurrence, toxicity and microbial degradation of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs). *J. Environ. Manag.* 2021, 300, 113694.
4) FTIR TALK LETTER Vo.1
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