

High-speed in-line use Spectrometer using the highly integrated original array sensor

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The fine chemical field, especially the pharmaceutical industry, is introducing advanced sensing technologies into the process line to improve safety and quality in accordance with PAT (Process Analytical Technology) promoted by FDA (Food and Drug Administration). For measuring powders without preparation during the drug formulation process, a near-infrared spectroscopic analyzer is the most promising sensing device. We are developing the key devices and fundamental technologies for a spectroscopic analyzer that has the required detection mechanism and high sensitivity for powder measurement, as well as a high-speed measuring function for blenders and 100% inspection.

INTRODUCTION

We, Advanced Technology Research Center of Corporate R&D Headquarters, have developed an interference measuring technology, which is the fundamental technology of Fourier Transform (FT) type spectroscopy, and have been supporting the commercialization of spectroscopic analyzers by the business division. ⁽¹⁾ Our commercialized near-infrared spectroscopic analyzer, the NR800, primarily focuses on liquid measurement and has achieved excellent results in the process industry such as petrochemicals.

On the other hand, in fine chemicals where many powders are used, manufacturers are considering introducing sophisticated sensing devices into process lines. Especially, the pharmaceutical industry is investigating introducing analyzers into process lines in accordance with Process Analytical Technology (PAT) ⁽²⁾, a guideline which aims to improve safety and quality advocated by the Food and Drug Administration (FDA), and “Pharmaceutical Development Q8” ⁽³⁾ by the International Conference on Harmonization of Technical Requirements (ICH).

We aim to create a high-speed in-line use compact spectroscopic analyzer with high resolution capable of directly measuring powders in the pharmaceutical production line. This paper describes our spectroscopic analysis methods, the original key devices we developed, and the features of our prototype spectroscopic analyzer.

SPECTROSCOPIC ANALYZER

What is spectroscopic analysis?

Absorption spectroscopic analysis is a technique for obtaining the composition of a sample by applying light to it and detecting the spectrum absorbed when the light penetrates or is reflected. States such as electronic state and molecular vibration specific to components in a sample are reflected in the absorption spectrum depending on the range of wavelength (frequency) of the light applied.

Since we aim to measure from powders (solid) to liquid and major measuring items are the components of the sample and its composition, the wavelength range for detecting its molecular vibration is between near-infrared (NIR) and infrared (IR).

In the IR region, a large absorbance due to the resonance of light with basic vibrations of molecules of the sample causes the light-penetrating distance to be short, only tens of μm . This makes it difficult to handle samples, and it is less suitable for in-line measurement consequently.

On the other hand, since the frequency of the NIR region we selected corresponds to the harmonic overtone of basic vibrations of the molecules, the absorbance is relatively small and the light-penetrating distance is of the order of millimeters, making it easy to handle samples. Thus, the NIR region is more suitable for in-line measurement with no pre-processing for many samples.

Various spectroscopic methods

Table 1 shows typical spectroscopic methods and their features.

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Table 1 Spectroscopic methods and their features

Method (type)	Wavelength characteristics			Power characteristics		Functions		
	Range	Accuracy	Resolution	Dynamic range	Photo-receptive efficiency	Measuring time	Size	Maintainability
Fourier transform (FT) type	3	3	2	2	3	1	1	3 - 2
Monochromator type	2	2	3	3	1	1	1	2 - 1
Polychromator type	2	2	1	2	3	3	3	3
Laser scanning type	1	2	3 - 2	3	3	2	3 - 1	3 - 1

3 : Excellent, 2 : Good, 1 : Poor

1) FT type: Interference method

This is a method that determines wavelengths by transforming interference signal data with the Fourier transform acquired while changing optical path lengths. It requires a wavelength standard in principle, but wavelength accuracy is high accordingly. Although this method has disadvantages such as long measuring time or vulnerability to shot noise or disturbing signal intensity fluctuations, it is widely used in the field of spectroscopic analysis with various countermeasures such as optical path length adjusting mechanisms or data processing.

2) Monochromator type: Filtering method

With this method, a specific wavelength is extracted using a diffraction grating, an etalon filter or other instrument, and its power is measured. A wavelength is selected by rotating the angle of the grating or changing the distance between two parallel surfaces of the etalon. With the method utilizing a diffraction grating generated by an acoustic optic effect, an ultrasonic sound frequency is modulated. Various structures have been developed aiming at a wide dynamic range as well as high wavelength resolution, and this is one of the most popular methods adopted in versatile spectrum analyzers.⁽⁴⁾

3) Polychromator type

With this method, a spectrum is created using a diffraction grating or other instrument, and multiple wavelengths in a specific wavelength range are measured at the same time by placing multiple sensors to cover the range. The wavelength resolution depends predominantly on the number of sensors. This method has an advantage of a large signal-to-noise ratio due to its high optical-use efficiency when measuring in a short period. A configuration with no mechanically movable parts is possible.

4) Laser scanning (wavelength scanning) type

This method measures the intensity of light from a sample while sweeping the wavelength of irradiating light. With a laser beam, high resolution and wide dynamic range can be obtained easily, but the measurable range of wavelength depends on the laser oscillation band.

Selection of spectroscopic method and design of basic structure

The features required for an in-line use analyzer include high-speed measurement, compact size, and ease of maintenance (preferably no maintenance). In terms of

these features, a polychromator type or a laser scanning type without a mechanical actuator is appropriate, however, with the laser scanning type it is not easy to expand the measurable wavelength range, while the polychromator type is usually inferior in terms of wavelength resolution.

Table 1 suggests that the polychromator type is the most suitable for the in-line use spectroscopic method if the wavelength resolution is improved. Based on this, to improve the wavelength resolution, we developed an array sensor achieving high sensitivity with world-class high density. Figure 1 illustrates the basic structure of the polychromator using the highly integrated array sensor.

The light to be measured is collimated and the grating is irradiated with it. The irradiated light is diffracted differently over a range of wavelengths, and the diffracted light is collected by a focusing lens at different positions depending on the diffraction angle. The collection points and their optical intensities are detected by an array sensor, and eventually spectral data is obtained through signal processing.

The key part of the passive elements is the diffraction grating. In order to achieve high durability, uniformity of wavelength dispersion characteristics, transformation of beam diameter, and flexibility of design, we used a prism. We tilted the prism slightly in a direction perpendicular to wavelength dispersion to secure a wide range of wavelength band and to avoid high-order diffraction beams and stray light.

As for the frame material of the spectroscope, to reduce the fluctuation of optical characteristics caused by changes of surrounding temperature, we used a special cast iron with low thermal expansion characteristics equivalent to that of optical materials.

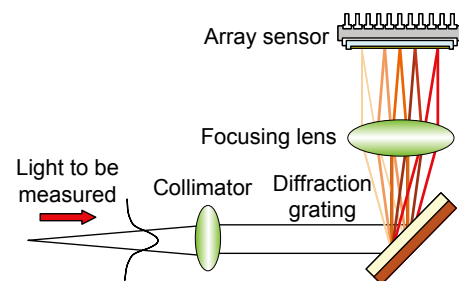


Figure 1 Basic structure of polychromator type spectroscopic analyzer

DEVELOPMENT OF HIGHLY-INTEGRATED HIGH-SENSITIVE ARRAY SENSOR

The array sensor is the most critical part in the polychromator type spectroscope, and the sensitivity depends on its characteristics. In particular, the wavelength resolution depends greatly on the number of its elements. The density of the array is the factor that determines the size of the instrument.

Development of charge amplifier

The Corporate R&D has developed an array sensor device with the world's highest density on which InGaAs-PDs (PD:

photo-diode) are integrated. This has enabled our business division to commercialize our products such as a Wavelength Division Multiplex (WDM) monitor. As this is designed to measure WDM signals for optical fiber communications (laser beam), even a tap split light has sufficient power. Thus, an I-V converter was attached externally and Si-IC (Silicon IC) primarily in charge of multiplexing functions was integrated into a photo-diode array (PDA).

When measuring powders, the photoreceptive power of the array sensor is quite weak, of the order of pW. Detecting such very weak light by a combination of multiplexer and I-V converter takes a long time due to restrictions such as time constant, requiring several milliseconds to read the data per element. Consequently, we have developed an Si-IC with a charge amplifier (integration type) array to realize high-speed measurement and measure weak light of sub-pW order. Figure 2 shows a block diagram of the circuit.

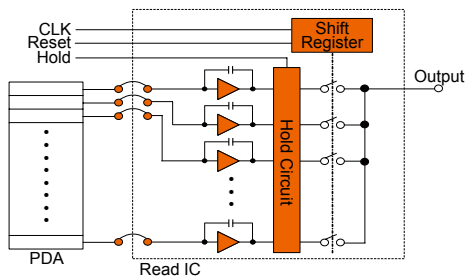


Figure 2 Block diagram of Si-IC with charge amplifier array

We made the capacitances of the charge amplifiers selectable, and designed dedicated circuits to reduce the charge injection during switching and compensate the drift, and incorporated them into the charge amplifier array. Charging behavior is clock synchronized so that the chargings to all the elements will advance simultaneously. The charging time, which requires dynamic control, is controlled by a pulse width externally input. The charged signals are held and read at high speed sequentially.

Figure 3 shows a layout of the Si-IC prototype employing the 2P3M (double-poly, triple-metal) process.

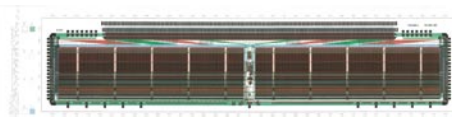


Figure 3 Layout of Si-IC with charge amplifier array

Development of array sensor

Figure 4 is an external view of the array sensor. In the center of the aluminum nitride (AlN) substrate, which was selected in view of heat conduction and other features, is the PDA consisting of 640 InGaAs-PD elements with 20- μ m pitch, the highest density in the world. On both sides of the substrate, the newly developed Si-IC with charge amplifier array is mounted. The substrate is mounted on a ceramic package via a thermo electric cooler and is sealed with a cap with a sapphire

window after filling with N₂.

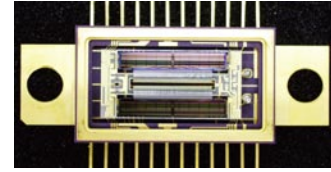


Figure 4 Highly-integrated and high-sensitive array sensor (without a window cap)

The evaluated characteristics of the sensor showed clearly that it satisfies the specifications required for a high-speed spectroscopic analyzer, such as a minimum photoreceptive sensitivity of -100 dBm and maximum operating clock frequency of 1 MHz or more.

DEVELOPMENT OF IN-LINE USE SPECTROSCOPIC ANALYZER

System configuration and design for high-speed operation

Figure 5 illustrates the configuration of the high-speed in-line use spectroscopic analyzer, and Figure 6 is an external view of the prototype spectroscopic analyzer and a diffuse reflection detecting probe.

Near-infrared light is guided by a large-diameter fiber from the source to the probe and the sample is irradiated. In the case of powders, the light is reflected and diffuses, penetrating deep into the sample, and is detected by the probe after wavelengths peculiar to the sample are absorbed. The detected light enters the spectroscope via a small-diameter fiber, and is guided to the array sensor.

The output from the array sensor is converted by an 18-bit A/D (analog-to-digital) converter, and transmitted externally as spectral data after arithmetical processing.

The goal for high-speed operation was a measurement interval of 10 msec assuming 100% inspection in production lines. To achieve this, we used an A/D converter capable of 1 M samplings/sec and calculation with a digital signal processor (DSP), and optimized codes incorporating parallel and pipeline processing into some data processing part. The result showed that our goal of 10 msec is feasible provided an appropriate amount of light power is secured.

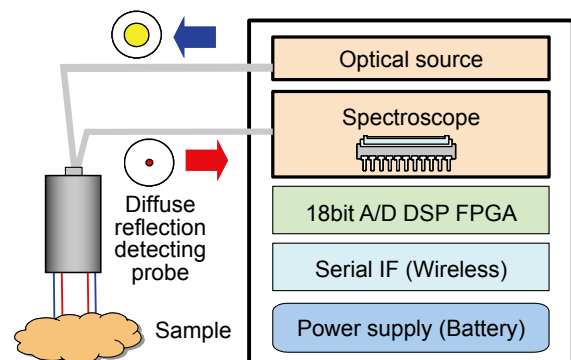


Figure 5 Spectroscopic analyzer configuration



Figure 6 Spectroscopic analyzer and diffuse reflection detecting probe (approx. 65 mm in diameter)

Table 2 lists the major specifications of the spectroscopic analyzer. It includes features required when applied to a rotary type blender such as wireless data interface, battery power supply, and synchronized sampling by external signals.

Table 2 Major specifications of spectroscopic analyzer

Item	Specification	Remarks
Wavelength range	1.0 - 1.7 μm	10000 - 6000 waves / cm
Wavelength resolution	1.0 nm	Reading resolution
Level characteristic	40 dB	Dynamic range
Absorption resolution	0.0001 Abs ^{*1}	Abs ^{*1}
Measuring time	10 msec minimum	Periodic measuring
Communications IF ^{*2}	RS232/wireless	USB available
Sample IF ^{*2}	FC/SMA optical connector	Direct IF ^{*2} available
Size	120 x 220 x 20 mm	Excluding projections
Power consumption	Less than 10 W	Battery power supply: 3 hours

*1 : Absorbance *2 : Interface

High efficient diffuse reflection detection and system interface

To increase the efficiency of the diffuse reflection detecting probe, we examined a area being irradiated and a light detecting area, and then designed optical layout including fibers. We obtained satisfactory results for a remote diffuse reflection detecting type probe, with an efficiency of approximately -30 dB, compared with a transmission-detection type probe.

Prototyping of a direct-interfacing type model, instead of a separately attached probe shown in Figure 6, is also under way. It is structured so that an analyzer is attached directly to a sampling port or some part of process equipment to detect diffuse-reflected light, and so it can easily be applied to a blender, etc.

When an analyzer is to be used in-line, connectivity with other control systems and compatibility of spectral data formats are important. We are currently working on connection with a standard system bus and introduction of general-purpose data formats.

Results of sample measurement

Figure 7 shows the measurement results of powder samples: cellulose, mannitol, magnesium stearate (Mg-St) and talc. These are widely used in tablets and powdered drugs as non-active ingredients.

The measurement conditions are 50 mm working-distance and 30 msec charging time, and 10 measurements are

averaged. The optical source is a 5-W halogen lamp.

The absorption spectra of each sample was successfully acquired in a short time of 300msec in total. Especially in the case of talc, we observed the sharp absorption spectrum peak around 1400 nm and proved high wavelength resolution of the prototype.

We will introduce a chemometrics function, which is very useful when analyzing an absorption spectrum of multiple ingredients. We will also explore the possibility of real-time analysis.

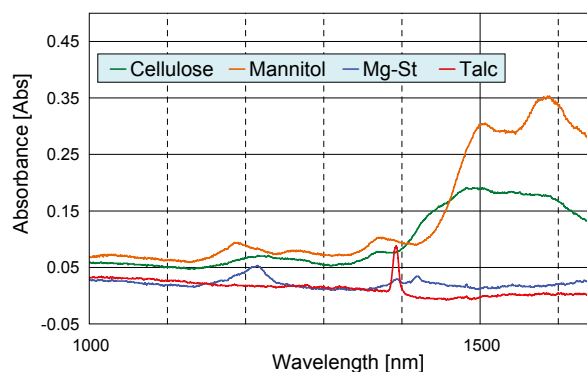


Figure 7 Measurement results of powder samples

CONCLUSION

We have developed our own key device, a highly sensitive array sensor with world-class high density, and achieved the minimum photoreceptive sensitivity of -100 dBm. Using this device, we achieved high wavelength resolution and high sensitivity of a polychromator type spectroscope. Through mechanical investigation and prototyping of a remote diffuse reflection detection mechanism required for powder measurement, introduction of high-speed data processing, and addition of functions such as a wireless interface, we completed the prototype model of a high-speed in-line use spectroscopic analyzer and confirmed its performance.

The spectroscopic analyzer described here is primarily for the fine chemical market, especially for a newly emerging sector of the pharmaceutical market. It is necessary to identify the needs in order to finalize the specifications and develop corresponding technologies, therefore we will improve the prototype model and advance to field tests for responding to the needs in the market.

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